antibodies, soluble complement inhibitory compounds, proteins, protein fragments, peptides, small molecules, RNA aptamers, L-RNA aptamers, spiegelmers, antisense compounds, serine protease inhibitors, double stranded RNA, small interfering RNA, locked nucleic acid inhibitors, and peptide nucleic acid inhibitors.

90. A method as in claim 86 wherein the step of administering comprises administering a compound selected from the group consisting of CR1, LEX-CR1, MCP, DAF, CD59, Factor H, cobra venom factor, FUT-175, complestatin, and K76 COOH.

91. A method as in claim 86 wherein the proportion of type III red blood cells of the subject's total red blood cell content is greater than 10%.

92. A method as in claim 86 wherein the proportion of type III red blood cells of the subject's total red blood cell content is greater than 25%.

93. A method as in claim 86 wherein the proportion of type III red blood cells of the subject's total red blood cell content is greater than 50%.

94. A method as in claim 86 wherein the subject's platelet count is greater than 40,000 per microliter.

95. A method as in claim 86 wherein the subject's platelet count is greater than 75,000 per microliter.

96. A method as in claim 86 wherein the subject's platelet count is greater than 150,000 per microliter.

97. A method as in claim 86 wherein the subject's reticulocyte count is greater than 80 x 10^9 per liter.

98. A method as in claim 86 wherein the subject's reticulocyte count is greater than 120 x 10^9 per liter.

Samsung Bioepis Exhibit No. 1002
Page 10475

99. A method as in claim 86 wherein the subject's reticulocyte count is greater than 150 x 10^9 per liter.

100. A method as in claim 86 wherein said subject has a greater than 40% PNH type III granulocyte clone.

101. A method as in claim 86 wherein said subject has an LDH level greater than or equal to 1.5 times the upper limit of a normal LDH level in a person.

102. A method of reducing thrombosis in a subject comprising administering a compound to a subject, the compound being selected from the group consisting of compounds which bind to one or more complement components, compounds which block the generation of one or more complement components and compounds which block the activity of one or more complement components.

103. A method as in claim 102 wherein the step of administering comprises administering an anti-C5 antibody.

104. A method as in claim 102 wherein the compound is an anti-C5 antibody selected from the group consisting of h5G1.1-mAb, h5G1.1-scFv and functional fragments of h5G1.1.

105. A method as in claim 102 wherein the step of administering comprises administering an anti-C5a receptor antibody.

106. A method as in claim 102 wherein the step of administering comprises administering a compound selected from the group consisting of antibodies, soluble complement inhibitory compounds, proteins, protein fragments, peptides, small molecules, RNA aptamers, L-RNA aptamers, spiegelmers, antisense compounds, serine protease inhibitors, double

Samsung Bioepis Exhibit No. 1002
Page 10476

stranded RNA, small interfering RNA, locked nucleic acid inhibitors, and peptide nucleic acid inhibitors.

107. A method as in claim 102 wherein the step of administering comprises administering a compound selected from the group consisting of CR1, LEX-CR1, MCP, DAF, CD59, Factor H, cobra venom factor, FUT-175, complestatin, and K76 COOH.

108. A method as in claim 102 wherein the proportion of type III red blood cells of the subject's total red blood cell content is greater than 10%.

109. A method as in claim 102 wherein the proportion of type III red blood cells of the subject's total red blood cell content is greater than 25%.

110. A method as in claim 102 wherein the proportion of type III red blood cells of the subject's total red blood cell content is greater than 50%.

111. A method as in claim 102 wherein the subject's platelet count is greater than 40,000 per microliter.

112. A method as in claim 102 wherein the subject's platelet count is greater than 75,000 per microliter.

113. A method as in claim 102 wherein the subject's platelet count is greater than 150,000 per microliter.

114. A method as in claim 102 wherein the subject's reticulocyte count is greater than 80 x 10^9 per liter.

115. A method as in claim 102 wherein the subject's reticulocyte count is greater than 120 x 10^9 per liter.

116. A method as in claim 102 wherein the subject's reticulocyte count is greater than 150 x 10^9 per liter.

Samsung Bioepis Exhibit No. 1002
Page 10477

117. A method as in claim 102 wherein said subject has a greater than 40% PNH type III granulocyte clone.

118. A method as in claim 102 wherein said subject has an LDH level greater than or equal to 1.5 times the upper limit of a normal LDH level in a person.

119. A method of increasing proportion of type III red blood cells of a subject's total red blood cell content comprising administering a compound to the subject, the compound being selected from the group consisting of compounds which bind to one or more complement components, compounds which block the generation of one or more complement components and compounds which block the activity of one or more complement components.

120. A method as in claim 119 wherein the step of administering comprises administering an anti-C5 antibody.

121. A method as in claim 119 wherein the compound is an anti-C5 antibody selected from the group consisting of h5G1.1-mAb, h5G1.1-scFv and functional fragments of h5G1.1.

122. A method as in claim 119 wherein the step of administering comprises administering a compound selected from the group consisting of antibodies, soluble complement inhibitory compounds, proteins, protein fragments, peptides, small molecules, RNA aptamers, L-RNA aptamers, spiegelmers, antisense compounds, serine protease inhibitors, double stranded RNA, small interfering RNA, locked nucleic acid inhibitors, and peptide nucleic acid inhibitors.

123. A method as in claim 119 wherein the step of administering comprises administering a compound selected from the group consisting of

Samsung Bioepis Exhibit No. 1002
Page 10478

CR1, LEX-CR1, MCP, DAF, CD59, Factor H, cobra venom factor, FUT-175, complestatin, and K76 COOH.

124. A method as in claim 119 wherein the amount of PNH type III red blood cells is greater than about 10% of the subject's total red blood cell count.

125. A method as in claim 119 wherein the amount of PNH type III red blood cells is greater than about 25% of the subject's total red blood cell count.

126. A method as in claim 119 wherein the amount of PNH type III red blood cells is greater than about 50% of the subject's total red blood cell count.

127. A method as in claim 119 wherein the amount of PNH type III red blood cells is greater than about 75% of the subject's total red blood cell count.

128. A method as in claim 119 wherein the subject's platelet count is greater than 40,000 per microliter.

129. A method as in claim 119 wherein the subject's platelet count is greater than 75,000 per microliter.

130. A method as in claim 119 wherein the subject's platelet count is greater than 150,000 per microliter.

131. A method as in claim 119 wherein the subject's reticulocyte count is greater than 80 x 10^9 per liter.

132. A method as in claim 119 wherein the subject's reticulocyte count is greater than 120 x 10^9 per liter.

Samsung Bioepis Exhibit No. 1002
Page 10479

133. A method as in claim 119 wherein the subject's reticulocyte count is greater than 150 x 10^9 per liter.

134. A method as in claim 119 wherein said subject has a greater than 40% PNH type III granulocyte clone.

135. A method as in claim 119 wherein said subject has an LDH level greater than or equal to 1.5 times the upper limit of a normal LDH level in a person.

136. A method of reducing hemolysis in a subject comprising administering a compound to the subject, the compound being selected from the group consisting of compounds which bind to one or more complement components, compounds which block the generation of one or more complement components and compounds which block the activity of one or more complement components.

137. A method as in claim 136 wherein the step of administering comprises administering an anti-C5 antibody.

138. A method as in claim 136 wherein the compound is an anti-C5 antibody selected from the group consisting of h5G1.1-mAb, h5G1.1-scFv and functional fragments of h5G1.1.

139. A method as in claim 136 wherein the step of administering comprises administering a compound selected from the group consisting of antibodies, soluble complement inhibitory compounds, proteins, protein fragments, peptides, small molecules, RNA aptamers, L-RNA aptamers, spiegelmers, antisense compounds, serine protease inhibitors, double stranded RNA, small interfering RNA, locked nucleic acid inhibitors, and peptide nucleic acid inhibitors.

Samsung Bioepis Exhibit No. 1002
Page 10480

140. A method as in claim 136 wherein the step of administering comprises administering a compound selected from the group consisting of CR1, LEX-CR1, MCP, DAF, CD59, Factor H, cobra venom factor, FUT-175, complestatin, and K76 COOH.

141. A method as in claim 136 wherein the proportion of type III red blood cells of the subject's total red blood cell content is greater than 10%.

142. A method as in claim 136 wherein the proportion of type III red blood cells of the subject's total red blood cell content is greater than 25%.

143. A method as in claim 136 wherein the proportion of type III red blood cells of the subject's total red blood cell content is greater than 50%.

144. A method as in claim 136 wherein the subject's platelet count is greater than 40,000 per microliter.

145. A method as in claim 136 wherein the subject's platelet count is greater than 75,000 per microliter.

146. A method as in claim 136 wherein the subject's platelet count is greater than 150,000 per microliter.

147. A method as in claim 136 wherein the subject's reticulocyte count is greater than 80×10^9 per liter.

148. A method as in claim 136 wherein the subject's reticulocyte count is greater than 120×10^9 per liter.

149. A method as in claim 136 wherein the subject's reticulocyte count is greater than 150×10^9 per liter.

150. A method as in claim 136 wherein said subject has a greater than 40% PNH type III granulocyte clone.

Samsung Bioepis Exhibit No. 1002
Page 10481

151. A method as in claim 136 wherein said subject has an LDH level greater than or equal to 1.5 times the upper limit of a normal LDH level in a person.

152. A method of treating a nitric oxide (NO) deficiency in a subject afflicted with a hemolytic disease comprising administering a compound to the subject, the compound being selected from the group consisting of compounds which bind to one or more complement components, compounds which block the generation of one or more complement components and compounds which block the activity of one or more complement components.

153. A method as in claim 152 wherein the step of administering comprises administering an anti-C5 antibody.

154. A method as in claim 152 wherein the compound is an anti-C5 antibody selected from the group consisting of h5G1.1-mAb, h5G1.1-scFv and functional fragments of h5G1.1.

155. A method as in claim 152 wherein the step of administering comprises administering a compound selected from the group consisting of antibodies, soluble complement inhibitory compounds, proteins, protein fragments, peptides, small molecules, RNA aptamers, L-RNA aptamers, spiegelmers, antisense compounds, serine protease inhibitors, double stranded RNA, small interfering RNA, locked nucleic acid inhibitors, and peptide nucleic acid inhibitors.

156. A method as in claim 152 wherein the step of administering comprises administering a compound selected from the group consisting of CR1, LEX-CR1, MCP, DAF, CD59, Factor H, cobra venom factor, FUT-175, complestatin, and K76 COOH.

Samsung Bioepis Exhibit No. 1002
Page 10482

157. A method as in claim 152 wherein the proportion of type III red blood cells of the subject's total red blood cell content is greater than 10%.

158. A method as in claim 152 wherein the proportion of type III red blood cells of the subject's total red blood cell content is greater than 25%.

159. A method as in claim 152 wherein the proportion of type III red blood cells of the subject's total red blood cell content is greater than 50%.

160. A method as in claim 152 wherein the subject's platelet count is greater than 40,000 per microliter.

161. A method as in claim 152 wherein the subject's platelet count is greater than 75,000 per microliter.

162. A method as in claim 152 wherein the subject's platelet count is greater than 150,000 per microliter.

163. A method as in claim 152 wherein the subject's reticulocyte count is greater than 80×10^9 per liter.

164. A method as in claim 152 wherein the subject's reticulocyte count is greater than 120×10^9 per liter.

165. A method as in claim 152 wherein the subject's reticulocyte count is greater than 150×10^9 per liter.

166. A method as in claim 152 wherein said subject has a greater than 40% PNH type III granulocyte clone.

167. A method as in claim 152 wherein said subject has an LDH level greater than or equal to 1.5 times the upper limit of a normal LDH level in a person.

168. A method of rendering a subject afflicted with a hemolytic disease transfusion independent comprising administering a compound to the

Samsung Bioepis Exhibit No. 1002
Page 10483

subject, the compound being selected from the group consisting of compounds which bind to one or more complement components, compounds which block the generation of one or more complement components and compounds which block the activity of one or more complement components.

169. A method as in claim 168 wherein the step of administering comprises administering an anti-C5 antibody.

170. A method as in claim 168 wherein the compound is an anti-C5 antibody selected from the group consisting of h5G1.1-mAb, h5G1.1-scFv and functional fragments of h5G1.1.

171. A method as in claim 168 wherein the step of administering comprises administering a compound selected from the group consisting of antibodies, soluble complement inhibitory compounds, proteins, protein fragments, peptides, small molecules, RNA aptamers, L-RNA aptamers, spiegelmers, antisense compounds, serine protease inhibitors, double stranded RNA, small interfering RNA, locked nucleic acid inhibitors, and peptide nucleic acid inhibitors.

172. A method as in claim 168 wherein the step of administering comprises administering a compound selected from the group consisting of CR1, LEX-CR1, MCP, DAF, CD59, Factor H, cobra venom factor, FUT-175, complestatin, and K76 COOH.

173. A method as in claim 168 further comprising the step of administering one or more compounds that increase hematopoiesis in combination with said compound.

174. A method as in claim 173 wherein the one or more compounds that increase hematopoiesis is selected from the group consisting of steroids,

Samsung Bioepis Exhibit No. 1002
Page 10484

immunosuppressants, anti-coagulants, folic acid, iron, erythropoietin (EPO), antithymocyte globulin (ATG) and antilymphocyte globulin (ALG).

175. A method as in claim 173 wherein EPO is administered in combination with an anti-C5 antibody selected from the group consisting of h5G1.1-mAb, h5G1.1-scFv and functional fragments of h5G1.1.

176. A method as in claim 168 wherein the subject is transfusion independent for over six months from the first administration of said compound.

177. A method as in claim 168 wherein the subject is transfusion independent for over twelve months from the first administration of said compound.

178. A method as in claim 168 wherein the subject is transfusion independent for over two years from the first administration of said compound.

179. A method as in claim 168 wherein the proportion of type III red blood cells of the subject's total red blood cell content is greater than 10%.

180. A method as in claim 168 wherein the proportion of type III red blood cells of the subject's total red blood cell content is greater than 25%.

181. A method as in claim 168 wherein the proportion of type III red blood cells of the subject's total red blood cell content is greater than 50%.

182. A method as in claim 168 wherein the subject's platelet count is greater than 40,000 per microliter.

183. A method as in claim 168 wherein the subject's platelet count is greater than 75,000 per microliter.

184. A method as in claim 168 wherein the subject's platelet count is greater than 150,000 per microliter.

Samsung Bioepis Exhibit No. 1002
Page 10485

185. A method as in claim 168 wherein the subject's reticulocyte count is greater than 80 x 10^9 per liter.

186. A method as in claim 168 wherein the subject's reticulocyte count is greater than 120 x 10^9 per liter.

187. A method as in claim 168 wherein the subject's reticulocyte count is greater than 150 x 10^9 per liter.

188. A method as in claim 168 wherein said subject has a greater than 40% PNH type III granulocyte clone.

189. A method as in claim 168 wherein said subject has an LDH level greater than or equal to 1.5 times the upper limit of a normal LDH level in a person.

190. A method of treating a subject afflicted with a hemolytic disease comprising administering: 1) one or more compounds selected from the group consisting of compounds which bind to one or more complement components, compounds which block the generation of one or more complement components and compounds which block the activity of one or more complement components; in combination with 2) one or more compounds that increase hematopoiesis.

191. A method as in claim 190 wherein the one or more compounds that increase hematopoiesis are selected from the group consisting of steroids, immunosuppressants, anti-coagulants, folic acid, iron, erythropoietin (EPO), antithymocyte globulin (ATG) and antilymphocyte globulin (ALG).

192. A method as in claim 190 wherein EPO is administered in combination with an anti-C5 antibody selected from the group consisting of h5G1.1-mAb, h5G1.1-scFv and functional fragments of h5G1.1.

Samsung Bioepis Exhibit No. 1002
Page 10486

193. A method as in claim 190 wherein EPO is administered in combination with a compound selected from the group consisting of antibodies, soluble complement inhibitory compounds, proteins, protein fragments, peptides, small molecules, RNA aptamers, L-RNA aptamers, spiegelmers, antisense compounds, serine protease inhibitors, double stranded RNA, small interfering RNA, locked nucleic acid inhibitors, and peptide nucleic acid inhibitors.

194. A method as in claim 190 wherein EPO is administered in combination with a compound selected from the group consisting of CR1, LEX-CR1, MCP, DAF, CD59, Factor H, cobra venom factor, FUT-175, complestatin, and K76 COOH.

195. A method as in claim 190 wherein the proportion of type III red blood cells of the subject's total red blood cell content is greater than 10%.

196. A method as in claim 190 wherein the proportion of type III red blood cells of the subject's total red blood cell content is greater than 25%.

197. A method as in claim 190 wherein the proportion of type III red blood cells of the subject's total red blood cell content is greater than 50%.

198. A method as in claim 190 wherein the subject's platelet count is greater than 40,000 per microliter.

199. A method as in claim 190 wherein the subject's platelet count is greater than 75,000 per microliter.

200. A method as in claim 190 wherein the subject's platelet count is greater than 150,000 per microliter.

201. A method as in claim 190 wherein the subject's reticulocyte count is greater than 80 x 10^9 per liter.

Samsung Bioepis Exhibit No. 1002
Page 10487

202. A method as in claim 190 wherein the subject's reticulocyte count is greater than 120 x 10^9 per liter.

203. A method as in claim 190 wherein the subject's reticulocyte count is greater than 150 x 10^9 per liter.

204. A method as in claim 190 wherein said subject has a greater than 40% PNH type III granulocyte clone.

205. A method as in claim 190 wherein said subject has an LDH level greater than or equal to 1.5 times the upper limit of a normal LDH level in a person.

206. A method of reducing hemolysis in a subject having a hemolytic disease comprising administering an anti-C5 antibody, wherein hemolysis is reduced as evidenced by a reduction in lactate dehydrogenase (LDH) levels in the subject's bloodstream to within 20% of the upper limit of normal.

207. A method as in claim 206 wherein the anti-C5 antibody is selected from the group consisting of h5G1.1-mAb, h5G1.1-scFv and functional fragments of h5G1.1.

208. A method as in claim 206 wherein the proportion of type III red blood cells of the subject's total red blood cell content is greater than 10%.

209. A method as in claim 206 wherein the proportion of type III red blood cells of the subject's total red blood cell content is greater than 25%.

210. A method as in claim 206 wherein the proportion of type III red blood cells of the subject's total red blood cell content is greater than 50%.

211. A method as in claim 206 wherein the subject's platelet count is greater than 40,000 per microliter.

Samsung Bioepis Exhibit No. 1002
Page 10488

212. A method as in claim 206 wherein the subject's platelet count is greater than 75,000 per microliter.

213. A method as in claim 206 wherein the subject's platelet count is greater than 150,000 per microliter.

214. A method as in claim 206 wherein the subject's reticulocyte count is greater than 80 x 10^9 per liter.

215. A method as in claim 206 wherein the subject's reticulocyte count is greater than 120 x 10^9 per liter.

216. A method as in claim 206 wherein the subject's reticulocyte count is greater than 150 x 10^9 per liter.

217. A method as in claim 206 wherein said subject has a greater than 40% PNH type III granulocyte clone.

218. A method as in claim 206 wherein said subject has an LDH level greater than or equal to 1.5 times the upper limit of a normal LDH level in a person.

219. A method of reducing hemolysis in a subject having a hemolytic disease comprising administering to the subject a compound selected from the group consisting of antibodies, soluble complement inhibitory compounds, proteins, protein fragments, peptides, small molecules, RNA aptamers, L-RNA aptamers, spiegelmers, antisense compounds, serine protease inhibitors, double stranded RNA, small interfering RNA, locked nucleic acid inhibitors, and peptide nucleic acid inhibitors, wherein hemolysis is reduced as evidenced by a reduction in lactate dehydrogenase (LDH) levels in the subject's bloodstream to within 20% of the upper limit of normal.

Samsung Bioepis Exhibit No. 1002
Page 10489

220. A method as in claim 219 wherein the compound is selected from the group consisting of CR1, LEX-CR1, MCP, DAF, CD59, Factor H, cobra venom factor, FUT-175, complestatin, and K76 COOH.

221. A method as in claim 219 wherein said subject has a greater than 40% PNH type III granulocyte clone.

222. A method as in claim 219 wherein said subject has an LDH level greater than or equal to 1.5 times the upper limit of a normal LDH level in a person.

223. A method of reducing hemolysis in a subject having a hemolytic disease comprising administering an anti-C5 antibody, wherein serum complement hemolytic activity is reduced at least 80% as evidenced by a serum hemolytic assay.

224. A method as in claim 223 wherein the anti-C5 antibody is selected from the group consisting of h5G1.1-mAb, h5G1.1-scFv and functional fragments of h5G1.1.

225. A method as in claim 223 wherein the proportion of type III red blood cells of the subject's total red blood cell content is greater than 10%.

226. A method as in claim 223 wherein the proportion of type III red blood cells of the subject's total red blood cell content is greater than 25%.

227. A method as in claim 223 wherein the proportion of type III red blood cells of the subject's total red blood cell content is greater than 50%.

228. A method as in claim 223 wherein the subject's platelet count is greater than 40,000 per microliter.

229. A method as in claim 223 wherein the subject's platelet count is greater than 75,000 per microliter.

Samsung Bioepis Exhibit No. 1002
Page 10490

230. A method as in claim 223 wherein the subject's platelet count is greater than 150,000 per microliter.

231. A method as in claim 223 wherein the subject's reticulocyte count is greater than 80 x 10^9 per liter.

232. A method as in claim 223 wherein the subject's reticulocyte count is greater than 120 x 10^9 per liter.

233. A method as in claim 223 wherein the subject's reticulocyte count is greater than 150 x 10^9 per liter.

234. A method as in claim 223 wherein said subject has a greater than 40% PNH type III granulocyte clone.

235. A method as in claim 223 wherein said subject has an LDH level greater than or equal to 1.5 times the upper limit of a normal LDH level in a person.

236. A method of reducing hemolysis in a subject having a hemolytic disease comprising administering to the subject a compound selected from the group consisting of antibodies, soluble complement inhibitory compounds, proteins, protein fragments, peptides, small molecules, RNA aptamers, L-RNA aptamers, spiegelmers, antisense compounds, serine protease inhibitors, double stranded RNA, small interfering RNA, locked nucleic acid inhibitors, and peptide nucleic acid inhibitors, wherein serum complement hemolytic activity is reduced at least 80% as evidenced by a serum hemolytic assay.

237. A method as in claim 236 wherein the compound is selected from the group consisting of CR1, LEX-CR1, MCP, DAF, CD59, Factor H, cobra venom factor, FUT-175, complestatin, and K76 COOH.

Samsung Bioepis Exhibit No. 1002
Page 10491

238. A method as in claim 236 wherein said subject has a greater than 40% PNH type III granulocyte clone.

239. A method as in claim 236 wherein said subject has an LDH level greater than or equal to 1.5 times the upper limit of a normal LDH level in a person.

240. A method of reducing abdominal pain in a subject comprising administering a compound to the subject, the compound being selected from the group consisting of compounds which bind to one or more complement components, compounds which block the generation of one or more complement components and compounds which block the activity of one or more complement components.

241. A method as in claim 240 wherein the step of administering comprises administering an anti-C5 antibody.

242. A method as in claim 240 wherein the compound is an anti-C5 antibody selected from the group consisting of h5G1.1-mAb, h5G1.1-scFv and functional fragments of h5G1.1.

243. A method as in claim 240 wherein the step of administering comprises administering a compound selected from the group consisting of antibodies, soluble complement inhibitory compounds, proteins, protein fragments, peptides, small molecules, RNA aptamers, L-RNA aptamers, spiegelmers, antisense compounds, serine protease inhibitors, double stranded RNA, small interfering RNA, locked nucleic acid inhibitors, and peptide nucleic acid inhibitors.

244. A method as in claim 240 wherein the step of administering comprises administering a compound selected from the group consisting of

Samsung Bioepis Exhibit No. 1002
Page 10492

CR1, LEX-CR1, MCP, DAF, CD59, Factor H, cobra venom factor, FUT-175, complestatin, and K76 COOH.

245. A method as in claim 240 wherein the proportion of type III red blood cells of the subject's total red blood cell content is greater than 10%.

246. A method as in claim 240 wherein the proportion of type III red blood cells of the subject's total red blood cell content is greater than 25%.

247. A method as in claim 240 wherein the proportion of type III red blood cells of the subject's total red blood cell content is greater than 50%.

248. A method as in claim 240 wherein the subject's platelet count is greater than 40,000 per microliter.

249. A method as in claim 240 wherein the subject's platelet count is greater than 75,000 per microliter.

250. A method as in claim 240 wherein the subject's platelet count is greater than 150,000 per microliter.

251. A method as in claim 240 wherein the subject's reticulocyte count is greater than 80 x 10^9 per liter.

252. A method as in claim 240 wherein the subject's reticulocyte count is greater than 120 x 10^9 per liter.

253. A method as in claim 240 wherein the subject's reticulocyte count is greater than 150 x 10^9 per liter.

254. A method as in claim 240 wherein said subject has a greater than 40% PNH type III granulocyte clone.

255. A method as in claim 240 wherein said subject has an LDH level greater than or equal to 1.5 times the upper limit of a normal LDH level in a person.

Samsung Bioepis Exhibit No. 1002
Page 10493

256. A method of decreasing the frequency of transfusions required by a subject afflicted with a hemolytic disease comprising administering a compound to the subject, the compound being selected from the group consisting of compounds which bind to one or more complement components, compounds which block the generation of one or more complement components and compounds which block the activity of one or more complement components.

257. The method of claim 256 wherein the frequency of transfusions is decreased by about 50%.

258. The method of claim 256 wherein the frequency of transfusions is decreased by about 70%.

259. The method of claim 256 wherein the frequency of transfusions is decreased by about 90%.

260. A method as in claim 256 wherein the step of administering comprises administering an anti-C5 antibody.

261. A method as in claim 256 wherein the step of administering comprises administering an anti-C5 antibody selected from the group consisting of h5G1.1-mAb, h5G1.1-scFv and functional fragments of h5G1.1.

262. A method as in claim 256 wherein the step of administering comprises administering a compound selected from the group consisting of antibodies, soluble complement inhibitory compounds, proteins, protein fragments, peptides, small molecules, RNA aptamers, L-RNA aptamers, spiegelmers, antisense compounds, serine protease inhibitors, double stranded RNA, small interfering RNA, locked nucleic acid inhibitors, and peptide nucleic acid inhibitors.

Samsung Bioepis Exhibit No. 1002
Page 10494

263. A method as in claim 256 wherein the step of administering comprises administering a compound selected from the group consisting of CR1, LEX-CR1, MCP, DAF, CD59, Factor H, cobra venom factor, FUT-175, complestatin, and K76 COOH.

264. A method as in claim 256 further comprising the step of administering one or more compounds that increase hematopoiesis in combination with said compound.

265. A method as in claim 264 wherein the one or more compounds that increase hematopoiesis is selected from the group consisting of steroids, immunosuppressants, anti-coagulants, folic acid, iron, erythropoietin (EPO), antithymocyte globulin (ATG) and antilymphocyte globulin (ALG).

266. A method as in claim 264 wherein EPO is administered in combination with an anti-C5 antibody selected from the group consisting of h5G1.1-mAb, h5G1.1-scFv and functional fragments of h5G1.1.

267. A method as in claim 256 wherein the proportion of type III red blood cells of the subject's total red blood cell content is greater than 10%.

268. A method as in claim 256 wherein the proportion of type III red blood cells of the subject's total red blood cell content is greater than 25%.

269. A method as in claim 256 wherein the proportion of type III red blood cells of the subject's total red blood cell content is greater than 50%.

270. A method as in claim 256 wherein the subject's platelet count is greater than 40,000 per microliter.

271. A method as in claim 256 wherein the subject's platelet count is greater than 75,000 per microliter.

Samsung Bioepis Exhibit No. 1002
Page 10495

272. A method as in claim 256 wherein the subject's platelet count is greater than 150,000 per microliter.

273. A method as in claim 256 wherein the subject's reticulocyte count is greater than 80 x 10^9 per liter.

274. A method as in claim 256 wherein the subject's reticulocyte count is greater than 120 x 10^9 per liter.

275. A method as in claim 256 wherein the subject's reticulocyte count is greater than 150 x 10^9 per liter.

276. A method as in claim 256 wherein said subject has a greater than 40% PNH type III granulocyte clone.

277. A method as in claim 256 wherein said subject has an LDH level greater than or equal to 1.5 times the upper limit of a normal LDH level in a person.

Samsung Bioepis Exhibit No. 1002
Page 10496

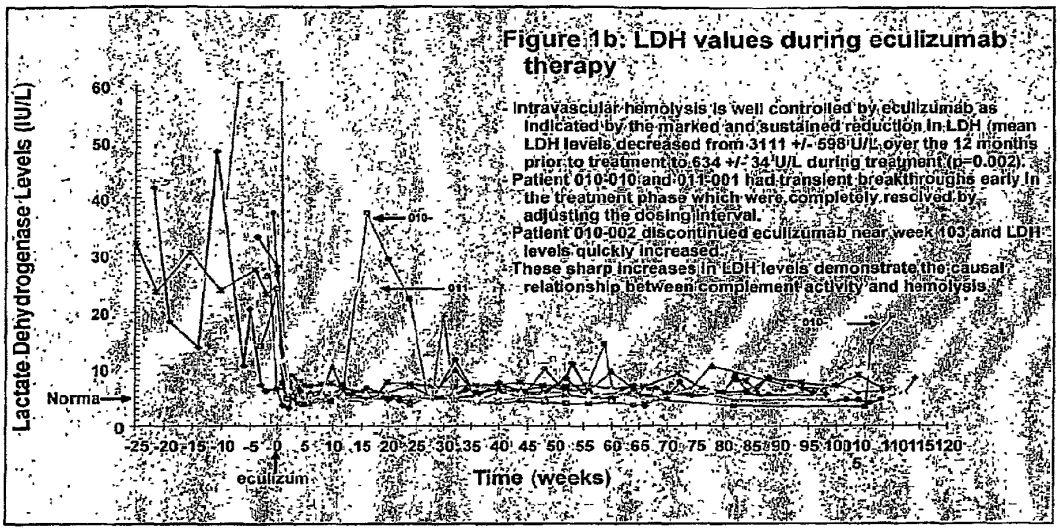
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457

Figure 1A.
Biochemical Parameters of Hemolysis During Eculizumab Treatment

Biochemical Marker	Normal range	Time of Analysis			p-value[a]
		Pre-study[b]	12 weeks	64 weeks	
LDH (IU/L)	150 - 480	3110.7 +/- 598.4	594.0 +/- 31.7	622.4 +/-41.1	0.002
AST (IU/L)	10 - 40	76.2 +/- 16.0	26.2 +/- 2.3	30.1 +/- 3.2	0.02
Haptoglobin (g/L)	0.5 - 2	<0.06	<0.06	0.14 +/- 0.07[c]	N.S.[d]
Hemoglobin (g/dL)	11.5 - 18	10.0 +/- 0.4	10.3 +/- 0.4	10.4 +/- 0.4	N.S.
Bilirubin	3 - 15	25.9 +/- 4.3	28.2 +/- 4.4	28.7 +/- 4.0	N.S.
Reticulocytes ($x10^{-3}/mm^3$)	20 - 80	161.4 +/- 25.9	191.2 +/- 23.6	189.6 +/- 21.8	N.S.

[a]from comparisons of mean change from pre-study to 64 weeks
[b]values represent means during 52 week period prior to treatment except for AST which represents the baseline mean
[c]10 of 11 patients were below the detectable limit of haptoglobin (<0.06 g/L); 1 patient had a value of 0.69 g/L.
[d]not significant

Figure 1b



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Page 10498

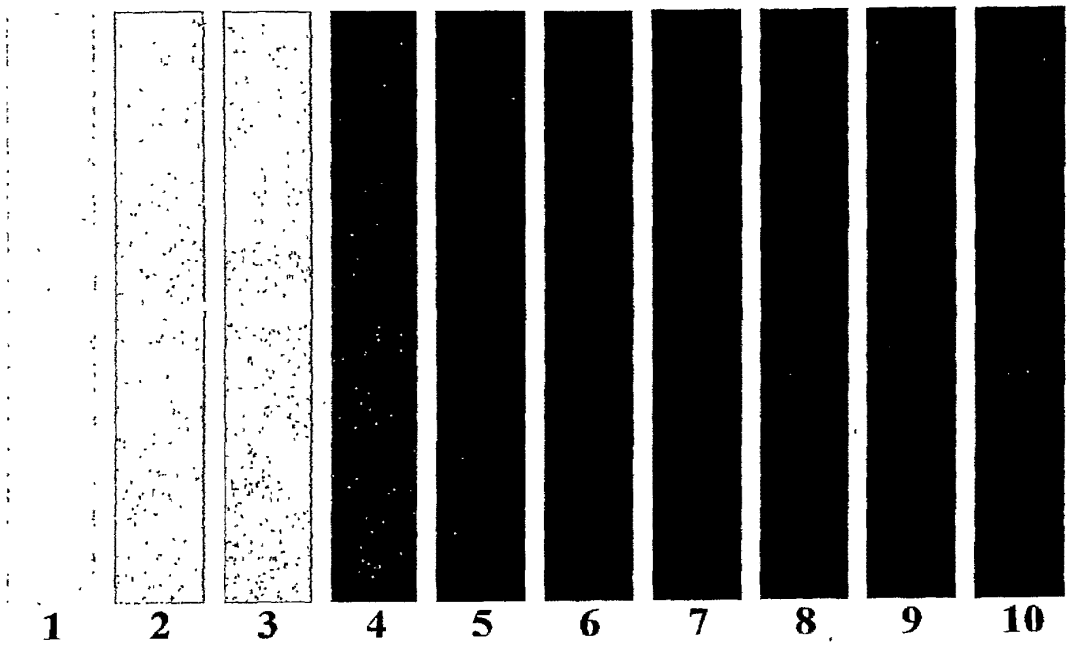
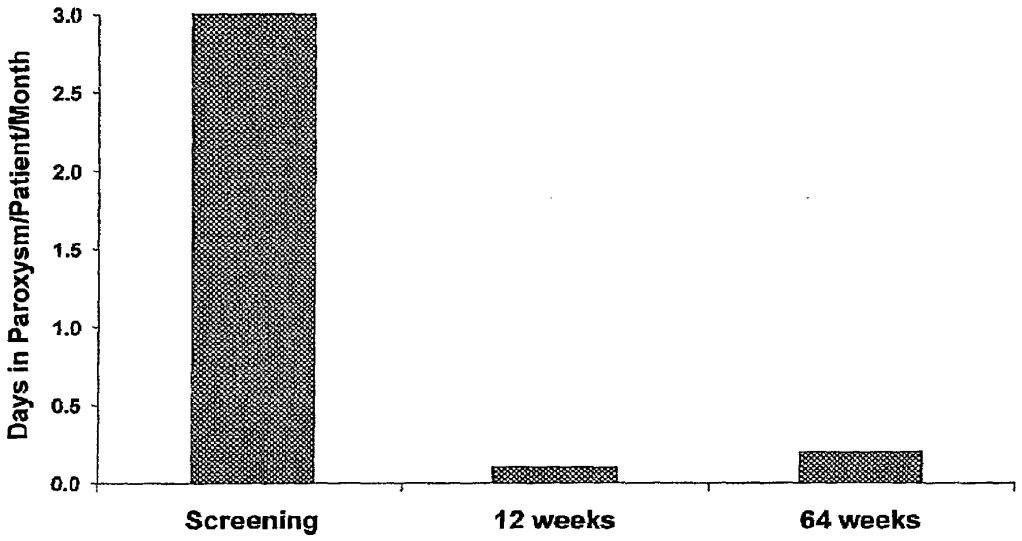


Figure 2

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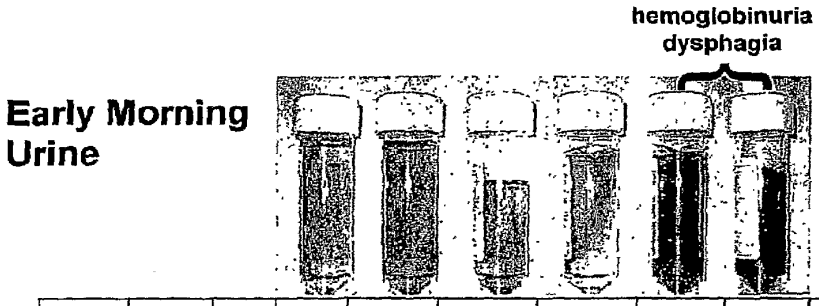
Figure 3.
Effect of Eculizumab on Paroxysm Rate (n=8)



Bars represent the paroxysm rates (number of paroxysms per patient per month) during the screening period (pre-eculizumab treatment), and during the first 12 weeks and the entire 64 weeks of eculizumab treatment. Three patients were not included in the analysis as either pretreatment urine scores were inadvertently not collected (2 patients) or an iron chelating agent that resulted in artificially colored urine was administered during the extension study (1 patient).

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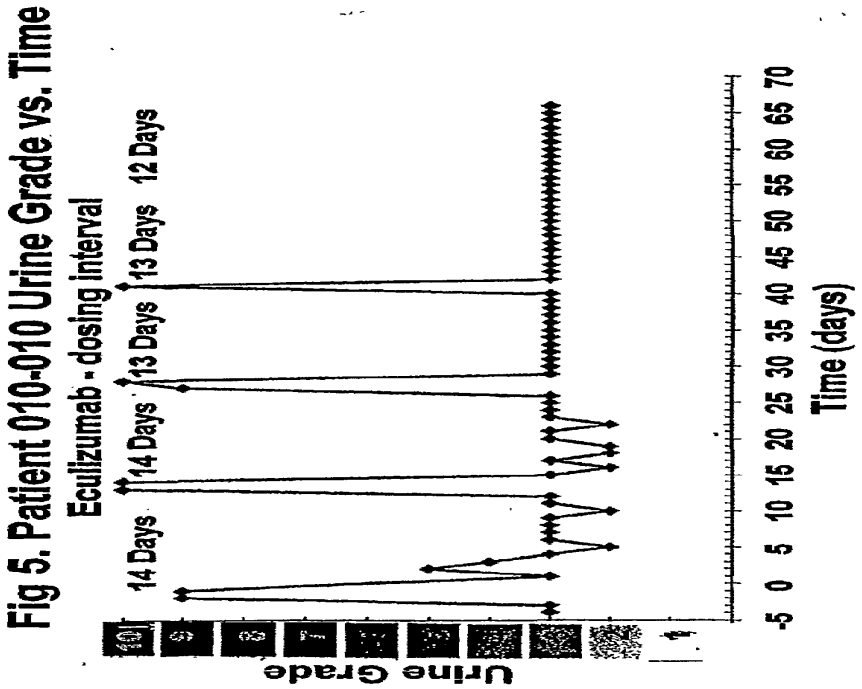
Figure 4.
Analysis of Complement Breakthrough



Visit	4							5			9
Day	0*	1-8	9	10	11	12	13	0*	1-2		0*
Urine	10	2-3	3	3	3	3	9	10	3		2
LDH	2624	–	784	–	–	697	1687	2917	–		495
AST	119	–	38	–	–	31	87	–	–		–
PK	28	–	51	–	–	35	31	23	–		51
PD	72	–	1	–	–	2	56	56	–		2

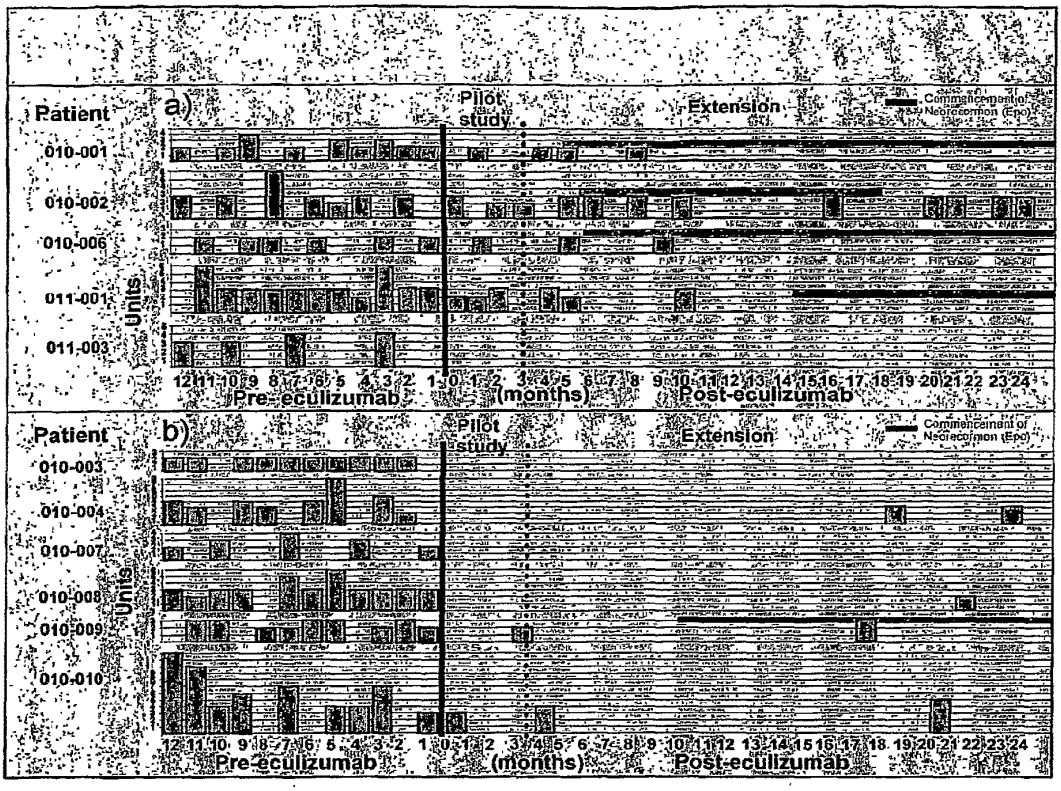
*Dose of eculizumab

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Page 10501



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Page 10502

Figure 6.
Units Transfused Pre- and Post-Eculizumab in (a) Cytopenic Patients and (b) Non-Cytopenic Patients



Samsung Bioepis Exhibit No. 1002
Page 10503

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464

Figure 7 Management of thrombocytopenic patient with erythropoietin

Patient 010-001 (hypoplastic; platelets 80 to 100 x 10^9/l)

Transfusions reduced with eculizumab and transfusion independence with combined eculizumab and erythropoietin (NeoRecormon 18,000U 3x/week)

Figure 8.
Eculizumab Pharmacodynamics Pre- and Post-dose

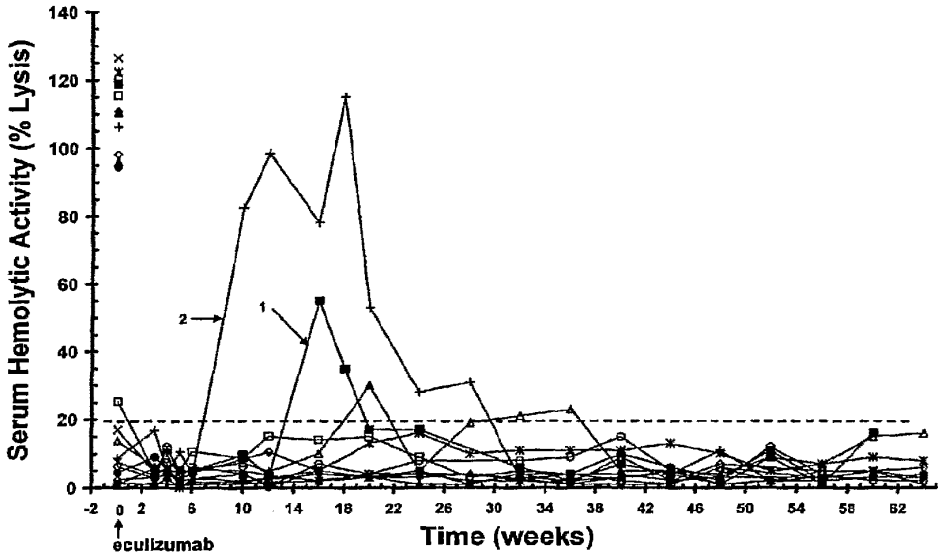


Figure 8 shows serum hemolytic activity (PD) during the 64 week treatment period as determined by the ability of serum to lyse antibody-presensitized chicken erythrocytes. The percentage of hemolytic activity at which complement is considered to be effectively inhibited (≤ 20 %) is indicated by dashed line. Two patients that demonstrated trough serum hemolytic activity values less than 20% are identified (patients 1 and 2).

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Page 10505

Figure 9.
Eculizumab Pharmacodynamics Pre- and Post-dose

Domain (a)	Mean Base-Line Score (b)	64 Week Change from Base-line (c)	p-value (d)
Global Health Status	56.1	13.8	0.009
Physical Functioning	70.9	14.3	<0.001
Emotional Functioning	70.5	12.5	<0.001
Role Functioning	66.7	14.5	0.003
Cognitive Functioning	77.3	10.3	0.001
Fatigue	47.5	-17.8	<0.001
Dyspnea	39.4	-16.6	0.002
Insomnia	30.3	-8.2	0.031
Pain	21.2	-8.2	0.023
Constipation	3.0	4.1	<0.001

a) the quality of life was assessed using the European Organization for Research and Treatment of Cancer QLQ-C30 instrument
b) numbers represent mean values of linearly transformed scores
c) values represent least-square means; positive change indicates improvement for Global Health Status and Functional Scales while a negative change indicates improvement for Symptom Scales
d) values are from a mixed analysis-of-covariance model with visit as a fixed effect, patient as a random effect, and baseline as a covariate

Samsung Bioepis Exhibit No. 1002
Page 10506

Figure 10.
Symptoms Pre- and 2 Years Post-Eculizumab

Patient	Pre-Eculizumab			Post-Eculizumab		
	Abdominal Pain	Dysphagia	Erectile Dysfunction	Abdominal Pain	Dysphagia	Erectile Dysfunction
010-001	Every 4 – 8 weeks	Every 4 – 8 weeks	Every 4 – 8 weeks	None	None	None
010-002	None	None	--	None	None	--
010-003	Every week	Every week	Every week	None	None	None
010-004	Every 4 – 6 weeks	None	--	None	None	--
010-006	None	None	None	None	None	None
010-007	None	At least every 4 weeks	--	None	None	--
010-008	None	Every 10 weeks	Every 10 weeks	None	None	Intermittent
010-009	None	None	None	None	None	None
010-010	Every 4 weeks	Every 4 weeks	None	None	2 episodes in 2 years*	None
011-001	None	None	--	None	None	--
011-003	None	None	--	None	None	--

*This patient experienced a transient breakthrough in complement blockade with a return of hemolysis and symptoms. Increasing the dosing frequency to 12 days re-established complete complement blockade and prevented further symptoms.

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Page 10507

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Art Unit	1644
Examiner Name	J. L. Rogers
Attorney Docket Number	AXJ-114BUSCN3

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Name/Print	Jill Gorny Sloper, Esq.	Registration Number	60,760

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
15/260,888	09/09/2016	Leonard BELL	AXJ-114BUSCN3	2558

133485 7590 10/27/2016

Nelson Mullins Riley & Scarborough LLP/Alexion
One Post Office Square
30th Floor
Boston, MA 02109-2127

EXAMINER	
ROGERS, JAMES L	

ART UNIT	PAPER NUMBER
1644	

NOTIFICATION DATE	DELIVERY MODE
10/27/2016	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

ipboston.docketing@nelsonmullins.com
chris.schlauch@nelsonmullins.com
ipqualityassuranceboston@nelsonmullins.com

Office Action Summary	Application No. 15/260,888	Applicant(s) BELL ET AL.	
	Examiner JAMES ROGERS	Art Unit 1644	AIA (First Inventor to File) Status No

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTHS FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *9/9/2016*.

☐ A declaration(s)/affidavit(s) under **37 CFR 1.130(b)** was/were filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ An election was made by the applicant in response to a restriction requirement set forth during the interview on _____; the restriction requirement and election have been incorporated into this action.

4)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims*

5)☒ Claim(s) *1-10* is/are pending in the application.

5a) Of the above claim(s) _____ is/are withdrawn from consideration.

6)☐ Claim(s) _____ is/are allowed.

7)☒ Claim(s) *1-10* is/are rejected.

8)☐ Claim(s) _____ is/are objected to.

9)☐ Claim(s) _____ are subject to restriction and/or election requirement.

* If any claims have been determined allowable, you may be eligible to benefit from the **Patent Prosecution Highway** program at a participating intellectual property office for the corresponding application. For more information, please see http://www.uspto.gov/patents/init_events/pph/index.jsp or send an inquiry to PPHfeedback@uspto.gov.

Application Papers

10)☐ The specification is objected to by the Examiner.

11)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

Certified copies:

a)☐ All b)☐ Some** c)☐ None of the:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

** See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)

2) ☒ Information Disclosure Statement(s) (PTO/SB/08a and/or PTO/SB/08b) Paper No(s)/Mail Date *10/21/2016*.

3) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .

4) ☐ Other: _____.

DETAILED ACTION

1. Claims 1-10 pending and under consideration in the instant examination.

2. The present application is being examined under the pre-AIA first to invent provisions.

Double Patenting

3. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., In re Berg, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); In re Goodman, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); In re Longi, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); In re Van Ornum, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); In re Vogel, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); In re Thorington, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on nonstatutory double patenting provided the reference application or patent either is shown to be commonly owned with the examined application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement. See MPEP § 717.02 for applications subject to examination under the first inventor to file provisions of the AIA as explained in MPEP § 2159. See MPEP §§ 706.02(l)(1) - 706.02(l)(3) for applications not subject to examination under the first inventor to file provisions of the AIA. A terminal disclaimer must be signed in compliance with 37 CFR 1.321(b).

The USPTO Internet website contains terminal disclaimer forms which may be used. Please visit www.uspto.gov/patent/patents-forms. The filing date of the application in which the form is filed determines what form (e.g., PTO/SB/25, PTO/SB/26, PTO/AIA/25, or PTO/AIA/26) should be used. A web-based eTerminal Disclaimer may be filled out completely online using web-screens. An eTerminal Disclaimer that meets all requirements is auto-processed and approved immediately upon submission. For more information about eTerminal Disclaimers, refer to www.uspto.gov/patents/process/file/efs/guidance/eTD-info-I.jsp.

4. Claims 1-10 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claim 1 of copending Application No. 15/148,839, in view of Hillmen et al. (N Engl J Med 2004; 350: 552-9).

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Although the conflicting claims are not identical, they are not patentably distinct from each other because the '839 application claims a pharmaceutical composition for use in treating a patient afflicted with PNH. The specification of the '516 at ¶158 defines eculizumab as having a heavy chain SEQ ID NO: 2 and light chain SEQ ID NO: 4 which is 100% identical in amino acid sequence to the currently claimed SEQ IDs NO: 2 and 4. (see alignment below).

SEQ ID NO: 2 alignment

```
Qy          1 QVQLVQSGAEVKKPGASVKVSCKASGYIFSNYWIQWVRQAPGQGLEWMGEILPGSGSTEY 60
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db          1 QVQLVQSGAEVKKPGASVKVSCKASGYIFSNYWIQWVRQAPGQGLEWMGEILPGSGSTEY 60

Qy         61 TENFKDRVTMTRDTSTSTVYMELSSLRSEDTAVYYCARYFFGSSPNWYFDVWGQGTLVTV 120
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db         61 TENFKDRVTMTRDTSTSTVYMELSSLRSEDTAVYYCARYFFGSSPNWYFDVWGQGTLVTV 120

Qy        121 SSASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQ 180
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        121 SSASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQ 180

Qy        181 SSGLYSLSSVVTVPSSNFGTQTYTCNVDHKPSNTKVDKTVERKCCVECPPCPAPPVAGPS 240
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        181 SSGLYSLSSVVTVPSSNFGTQTYTCNVDHKPSNTKVDKTVERKCCVECPPCPAPPVAGPS 240

Qy        241 VFLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQFNWYVDGVEVHNAKTKPREEQFNST 300
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        241 VFLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQFNWYVDGVEVHNAKTKPREEQFNST 300

Qy        301 YRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQVYTLPPSQEEMT 360
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        301 YRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQVYTLPPSQEEMT 360

Qy        361 KNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSRLTVDKSRWQE 420
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        361 KNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSRLTVDKSRWQE 420

Qy        421 GNVFSCSVMHEALHNHYTQKSLSLSLGK 448
              ||||||||||||||||||||||||||||
Db        421 GNVFSCSVMHEALHNHYTQKSLSLSLGK 448
```

SEQ ID NO: 4 alignment

```
Qy          1 MDMRVPAQLLGLLLLWLRGARCDIQMTQSPSSLSASVGDRVTITCGASENIYGALNWYQQ 60
```

```
                ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db          1 MDMRVPAQLLGLLLLWLRGARCDIQMTQSPSSLSASVGDRVTITCGASENIYGALNWYQQ 60

Qy         61 KPGKAPKLLIYGATNLADGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCQNVLNTPLTF 120
               ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db         61 KPGKAPKLLIYGATNLADGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCQNVLNTPLTF 120

Qy        121 GQGTKVEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGN 180
               ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        121 GQGTKVEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGN 180

Qy        181 SQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC 236
               |||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        181 SQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC 236
```

While the '839 does not specifically recite that the patient is anemic or that the antibody is administered to the patient at a dosage level of between 5-50 mg per kg per patient per treatment, in a single unit dosage form of the other various dosage schedules currently recited (e.g, 600 m/900/900 mg), Hillman teaches administration of the anti-C5 antibody eculizumab to an anemic patient (p. 555 under "demographic characteristics" at a dosing schedule of 600 mg for four weeks, followed one week later by a 900 mg dose and then by a dose of 900 mg every other week through week 12 (p. 554, under "treatment schedule"). In addition, [I]t is not inventive to discover the optimum or workable ranges by routine experimentation." In re Aller, 220 F.2d 454, 456 (CCPA 1955); see also In re Peterson, 315 F.3d 1325 (Fed. Cir. 2003). "Only if the 'results of optimizing a variable' are 'unexpectedly good' can a patent be obtained for the claimed critical range." In re Geisler, 116 F.3d 1465, 1469 (Fed. Cir. 1997) (quoting In re Antonie, 559 F.2d 618, 620 (CCPA 1977)). "[Discovery of an optimum value of a result effective variable in a known process is ordinarily within the skill of the art." In re Boesch, 617 F.2d 272, 276 (CCPA 1980). Given the teachings of Hillman one of skill in the art would regard administration of the anti-C5 antibody recited in '839 as an optimization variable.

5. Claims 1-10 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 91, 98, 100-106, 110-113, and 115 of copending Application No. 15/148,839.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Although the conflicting claims are not identical, they are not patentably distinct from each other because the '973 application claims a method for treating a patient afflicted with PNH by administration of an anti-C5 antibody in single unit dosage form and at a dosing schedule of 600 for the first 4 weeks, 900 mg for the fifth and 900 mg every 14 days thereafter. The specification of the '839 (¶s 20, 158) defines an anti-C5 antibody as having a heavy chain SEQ ID NO: 2 and light chain SEQ ID NO: 4 which is 100% identical in amino acid sequence to the currently claimed SEQ IDs NO: 2 and 4. (see alignment below).

SEQ ID NO: 2 alignment

```
Qy          1 QVQLVQSGAEVKKPGASVKVSCKASGYIFSNYWIQWVRQAPGQGLEWMGEILPGSGSTEY 60
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db          1 QVQLVQSGAEVKKPGASVKVSCKASGYIFSNYWIQWVRQAPGQGLEWMGEILPGSGSTEY 60

Qy         61 TENFKDRVTMTRDTSTSTVYMELSSLRSEDTAVYYCARYFFGSSPNWYFDVWGQGTLVTV 120
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db         61 TENFKDRVTMTRDTSTSTVYMELSSLRSEDTAVYYCARYFFGSSPNWYFDVWGQGTLVTV 120

Qy        121 SSASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQ 180
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        121 SSASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQ 180

Qy        181 SSGLYSLSSVVTVPSSNFGTQTYTCNVDHKPSNTKVDKTVERKCCVECPPCPAPPVAGPS 240
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        181 SSGLYSLSSVVTVPSSNFGTQTYTCNVDHKPSNTKVDKTVERKCCVECPPCPAPPVAGPS 240

Qy        241 VFLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQFNWYVDGVEVHNAKTKPREEQFNST 300
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        241 VFLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQFNWYVDGVEVHNAKTKPREEQFNST 300

Qy        301 YRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQVYTLPPSQEEMT 360
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        301 YRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQVYTLPPSQEEMT 360

Qy        361 KNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSRLTVDKSRWQE 420
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        361 KNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSRLTVDKSRWQE 420

Qy        421 GNVFSCSVMHEALHNHYTQKSLSLSLGK 448
              ||||||||||||||||||||||||||||
Db        421 GNVFSCSVMHEALHNHYTQKSLSLSLGK 448
```

SEQ ID NO: 4 alignment

```
Qy          1 MDMRVPAQLLGLLLLWLRGARCDIQMTQSPSSLSASVGDRVTITCGASENIYGALNWYQQ 60
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db          1 MDMRVPAQLLGLLLLWLRGARCDIQMTQSPSSLSASVGDRVTITCGASENIYGALNWYQQ 60

Qy         61 KPGKAPKLLIYGATNLADGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCQNVLNTPLTF 120
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db         61 KPGKAPKLLIYGATNLADGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCQNVLNTPLTF 120

Qy        121 GQGTKVEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGN 180
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        121 GQGTKVEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGN 180

Qy        181 SQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC 236
              |||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        181 SQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC 236
```

6. The closest prior art was regarded to be Hillmen et al. (N Engl J Med 2004; 350: 552-9). Hillmen teaches a method for treating a human patient that suffers from paroxysmal nocturnal hemoglobinuria (PNH) by administering to the patient an effective amount of

eculizumab (p. 552, "methods") which specifically binds to the terminal complement protein C5, inhibiting its cleavage into C5a and C5b (p. 553, 3rd ¶). Hillmen teaches that patients received infusions of 600 mg eculizumab weekly for four weeks, followed one week later by a 900 mg dose and then by a dose of 900 mg every other week through week 12 (p. 554 under “treatment schedule”). However, Hillmen does not teach the specific anti-C5 antibody recited by the current application. As evidenced by Report from Alexion Pharma K.K. eculizumab has a H and L chain sequence (p. 3 of the Report) which when compared to the H and L chains of the currently recited anti-C5 antibody are not the same (see sequence alignment below ExPASy (userSeq1 is the imputed sequence of eculizumab and userSeq2 is the amino acid sequence for the H chain of the currently recited claims).

```
98.9% identity in 448 residues overlap; Score: 2364.0; Gap frequency: 0.0%

UserSeq1       1 QVQLVQSGAEVKKPGASVKVSCKASGYIFSNYWIQWVRQAPGQGLEWMGEILPGSGSTEY
UserSeq2       1 QVQLVQSGAEVKKPGASVKVSCKASGYIFSNYWIQWVRQAPGQGLEWMGEILPGSGSTEY
                 ************************************************************

UserSeq1      61 TENFKDRVTMTRDTSTSTVYMELSSLRSEDTAVYYCARYFFGSSPNWYFDVWGQGTLVTV
UserSeq2      61 TENFKDRVTMTRDTSTSTVYMELSSLRSEDTAVYYCARYFFGSSPNWYFDVWGQGTLVTV
                 ************************************************************

UserSeq1     121 SSASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQ
UserSeq2     121 SSASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQ
                 ************************************************************

UserSeq1     181 SSGLYSLSSVVTVPSSNFGTQTYTCNVDHKPSNTKVDKTVERKCCVECPPCPAPPVAGPS
UserSeq2     181 SSGLYSLSSVVTVPSSNFGTQTYTCNVDHKPSNTKVDKTVERKCCVECPPCPAPPVAGPS
                 ************************************************************

UserSeq1     241 VFLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQFNWYVDGVEVHNAKTKPREEQFNST
UserSeq2     241 VFLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQFNWYVDGVEVHANKTKPREEQFNST
                 ********************************************  ************

UserSeq1     301 YRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQVYTLPPSQEEMT
UserSeq2     301 YRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQPEPEQVYTLPPSQEEMT
                 ******************************************   *************

UserSeq1     361 KNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSRLTVDKSRWQE
UserSeq2     361 KNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSRLTVDKSRWQE
                 ************************************************************

UserSeq1     421 GNVFSCSVMHEALHNHYTQKSLSLSLGK
UserSeq2     421 GNVFSCSVMHEALHNHYTQKSLSLSLGK
                 ****************************
```

One of skill in the art would not have been easily guided to using the currently claimed anti-C5 antibody for treating a patient suffering from PNH given the teachings of Hillmen.

7. No claim is allowed.

Samsung Bioepis Exhibit No. 1002
Page 10525

8. Any inquiry concerning this communication or earlier communications from the examiner should be directed to James Rogers whose telephone number is (571) 270-5374. The examiner can normally be reached Monday through Friday from 8:00 am to 5:30 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, **Daniel Kolker** can be reached on (571) 272-3181. The fax number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

October 20, 2016

/JAMES ROGERS/

/SHARON WEN/
Primary Examiner, Art Unit 1644

Samsung Bioepis Exhibit No. 1002
Page 10526

Notice of References Cited	Application/Control No. 15/260,888	Applicant(s)/Patent Under Reexamination BELL ET AL.	
	Examiner JAMES ROGERS	Art Unit 1644	Page 1 of 1

U.S. PATENT DOCUMENTS

*		Document Number Country Code-Number-Kind Code	Date MM-YYYY	Name	CPC Classification	US Classification
*	A	US-2016/0244516 A1	08-2016	BELL; Leonard	A61K31/7105	1/1
*	B	US-2012/0237515 A1	09-2012	Bell; Leonard	A61K31/7105	424/135.1
	C	US-				
	D	US-				
	E	US-				
	F	US-				
	G	US-				
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	N					
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*		Include as applicable: Author, Title Date, Publisher, Edition or Volume, Pertinent Pages)
	U	Hillmen et al. "Effect of eculizumab on hemolysis and transfusion requirements in patients with paroxysmal nocturnal hemoglobinuria" NEJM, 350(6), 2004, pp. 552-559
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	X	

*A copy of this reference is not being furnished with this Office action. (See MPEP § 707.05(a).)
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Search Notes	Application/Control No.	Applicant(s)/Patent Under Reexamination
	15260888	BELL ET AL.
	Examiner	Art Unit
	JAMES ROGERS	1644

CPC- SEARCHED		
Symbol	Date	Examiner

CPC COMBINATION SETS - SEARCHED		
Symbol	Date	Examiner

US CLASSIFICATION SEARCHED			
Class	Subclass	Date	Examiner

SEARCH NOTES		
Search Notes	Date	Examiner
STN: DISSABS MEETINGS BIOSCI CAPLUS MEDICINE	10/19/2016	JR
EAST: PGPUB, USPAT, JPO, EPO, INVENTOR SEARCH	10/19/2016	JR

INTERFERENCE SEARCH			
US Class/ CPC Symbol	US Subclass / CPC Group	Date	Examiner
	USPAT, USPAD, SEQ ID NO: 2, 4	10/19/2016	JR

/JAMES ROGERS/ Examiner.Art Unit 1644	

Doc code: IDS
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INFORMATION DISCLOSURE STATEMENT BY APPLICANT
(Not for submission under 37 CFR 1.99)

Application Number	15260888
Filing Date	2016-09-09
First Named Inventor	Leonard BELL
Art Unit	1644
Examiner Name	J. L. Rogers
Attorney Docket Number	AXJ-114BUSCN3

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	First Named Inventor	Leonard BELL
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	Examiner Name	J. L. Rogers
	Attorney Docket Number	AXJ-114BUSCN3

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EXAMINER SIGNATURE

Examiner Signature	/JAMES L ROGERS/	Date Considered	10/24/2016

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through a citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

[1] See Kind Codes of USPTO Patent Documents at www.USPTO.GOV or MPEP 901.04. [2] Enter office that issued the document, by the two-letter code (WIPO Standard ST.3). [3] For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. [4] Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16 if possible. [5] Applicant is to place a check mark here if English language translation is attached.

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	Attorney Docket Number	AXJ-114BUSCN3

CERTIFICATION STATEMENT

Please see 37 CFR 1.97 and 1.98 to make the appropriate selection(s):

That each item of information contained in the information disclosure statement was first cited in any communication from a foreign patent office in a counterpart foreign application not more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(1).

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A signature of the applicant or representative is required in accordance with CFR 1.33, 10.18. Please see CFR 1.4(d) for the form of the signature.

Signature	/Jill Gorny Sloper/	Date (YYYY-MM-DD)	2016-10-21
Name/Print	Jill Gorny Sloper, Esq.	Registration Number	60,760

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CONFIRMATION NO. 2558

SERIAL NUMBER	FILING or 371(c) DATE RULE	CLASS	GROUP ART UNIT	ATTORNEY DOCKET NO.
15/260,888	09/09/2016	424	1644	AXJ-114BUSCN3

APPLICANTS
Alexion Pharmaceuticals, Inc., New Haven, CT;

INVENTORS
Leonard BELL, Woodbridge, CT;
Russell P. Rother, Oklahoma City, OK;

**** CONTINUING DATA ***************************
This application is a CON of 15/148,839 05/06/2016
which is a CON of 13/426,973 03/22/2012
which is a CON of 12/225,040 05/13/2009 ABN
which is a 371 of PCT/US2007/006606 03/15/2007

**** FOREIGN APPLICATIONS ***************************

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Foreign Priority claimed ☐ Yes ☑ No 35 USC 119(a-d) conditions met ☐ Yes ☑ No Verified and Acknowledged /JAMES L ROGERS/ Examiner's Signature	☐ Met after Allowance JR Initials	STATE OR COUNTRY	SHEETS DRAWINGS	TOTAL CLAIMS	INDEPENDENT CLAIMS
		CT	4	10	1

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TITLE
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Attorney Docket Number	AXJ-114BUSCN3

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	42	ROTHER et al., Eculizumab, a C5 complement-blocking antibody, abolishes hemolysis and; reduces transfusion dependency in patients with paroxysmal nocturnal hemoglobinuria (PNH),; Molecular Immunology, Vol. 40(2-4), page 197; XP009163498, (2003).;	
	43	ROTHER et al., The clinical sequelae of intravascular hemolysis and extracellular plasma; hemoglobin, JAM A 293 (13):1653-1662 (2005);	
	44	ROTHER et al.. "Discovery and development of the complement inhibitor eculizumab for the treatment of paroxysmal nocturnal hemoglobinuria," Nature Biotechnology, 25 (11) 1256-1264 (2007)	

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /J.L.R/

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
	Application Number	15260888
	Filing Date	2016-09-09
	First Named Inventor	Leonard BELL
	Art Unit	1644
	Examiner Name	J. L. Rogers
	Attorney Docket Number	AXJ-114BUSCN3

	45	SIERRA, G. et al., "Vaccine against group B Neisseia meningitidis: Protection trial and mass vaccination results in Cuba," NIPH ANNALS 1991 NO, vol. 14(2), pages 195-210, ISSN: 0332-5652 (1991)	
	46	STEBLER et al., High-dose recombinant human erythropoietin for treatment of anemia in; myelodysplastic syndromes and paroxysmal nocturnal hemoglobinuria: a pilot study, Exp.; Hematol. 18: 1204-1208 (1990);	
	47	STRAUSS et al. "Alternative pathway of complement in sickle cell disease" Pediat. Res. 11, 285-289 (1997)	
	48	STUART et al. "Sickle-cell disease" Lancet, 364:1343-1360 (2004)	
	49	TANG et al., "Design of Freeze-Drying Process for Pharmaceuticals: Practical Advice" Pharmaceutical Research, vol. 21 (2):191-200 (2004)	
	50	The MERCK MANUAL of Diagnosis and Therapy, Seventeenth Edition, Chapter 127 Anemias,; pp. 849-883 (1999).;	

If you wish to add additional non-patent literature document citation information please click the Add button Add

EXAMINER SIGNATURE

Examiner Signature	/JAMES L ROGERS/	Date Considered	10/24/2016

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through a citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

[1] See Kind Codes of USPTO Patent Documents at www.USPTO.GOV or MPEP 901.04. [2] Enter office that issued the document, by the two-letter code (WIPO Standard ST.3). [3] For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. [4] Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16 if possible. [5] Applicant is to place a check mark here if English language translation is attached.

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /J.L.R/

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
	Application Number	15260888
	Filing Date	2016-09-09
	First Named Inventor	Leonard BELL
	Art Unit	1644
	Examiner Name	J. L. Rogers
	Attorney Docket Number	AXJ-114BUSCN3

CERTIFICATION STATEMENT

Please see 37 CFR 1.97 and 1.98 to make the appropriate selection(s):

That each item of information contained in the information disclosure statement was first cited in any communication from a foreign patent office in a counterpart foreign application not more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(1).

OR

☐ That no item of information contained in the information disclosure statement was cited in a communication from a foreign patent office in a counterpart foreign application, and, to the knowledge of the person signing the certification after making reasonable inquiry, no item of information contained in the information disclosure statement was known to any individual designated in 37 CFR 1.56(c) more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(2).

See attached certification statement.

The fee set forth in 37 CFR 1.17 (p) has been submitted herewith.

A certification statement is not submitted herewith.

SIGNATURE

A signature of the applicant or representative is required in accordance with CFR 1.33, 10.18. Please see CFR 1.4(d) for the form of the signature.

Signature	/Jill Gorny Sloper/	Date (YYYY-MM-DD)	2016-10-21
Name/Print	Jill Gorny Sloper, Esq.	Registration Number	60,760

This collection of information is required by 37 CFR 1.97 and 1.98. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 1 hour to complete, including gathering, preparing and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /J.L.R/

Privacy Act Statement

The Privacy Act of 1974 (P.L. 93-579) requires that you be given certain information in connection with your submission of the attached form related to a patent application or patent. Accordingly, pursuant to the requirements of the Act, please be advised that: (1) the general authority for the collection of this information is 35 U.S.C. 2(b)(2); (2) furnishing of the information solicited is voluntary; and (3) the principal purpose for which the information is used by the U.S. Patent and Trademark Office is to process and/or examine your submission related to a patent application or patent. If you do not furnish the requested information, the U.S. Patent and Trademark Office may not be able to process and/or examine your submission, which may result in termination of proceedings or abandonment of the application or expiration of the patent.

The information provided by you in this form will be subject to the following routine uses:

1. The information on this form will be treated confidentially to the extent allowed under the Freedom of Information Act (5 U.S.C. 552) and the Privacy Act (5 U.S.C. 552a). Records from this system of records may be disclosed to the Department of Justice to determine whether the Freedom of Information Act requires disclosure of these record s.

2. A record from this system of records may be disclosed, as a routine use, in the course of presenting evidence to a court, magistrate, or administrative tribunal, including disclosures to opposing counsel in the course of settlement negotiations.

3. A record in this system of records may be disclosed, as a routine use, to a Member of Congress submitting a request involving an individual, to whom the record pertains, when the individual has requested assistance from the Member with respect to the subject matter of the record.

4. A record in this system of records may be disclosed, as a routine use, to a contractor of the Agency having need for the information in order to perform a contract. Recipients of information shall be required to comply with the requirements of the Privacy Act of 1974, as amended, pursuant to 5 U.S.C. 552a(m).

5. A record related to an International Application filed under the Patent Cooperation Treaty in this system of records may be disclosed, as a routine use, to the International Bureau of the World Intellectual Property Organization, pursuant to the Patent Cooperation Treaty.

6. A record in this system of records may be disclosed, as a routine use, to another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c)).

7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (i.e., GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.

8. A record from this system of records may be disclosed, as a routine use, to the public after either publication of the application pursuant to 35 U.S.C. 122(b) or issuance of a patent pursuant to 35 U.S.C. 151. Further, a record may be disclosed, subject to the limitations of 37 CFR 1.14, as a routine use, to the public if the record was filed in an application which became abandoned or in which the proceedings were terminated and which application is referenced by either a published application, an application open to public inspections or an issued patent.

9. A record from this system of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /J.L.R/

I hereby certify that this paper (along with any paper referred to as being attached or enclosed) is being transmitted via the Office electronic filing system in accordance with 37 CFR § 1.6(a)(4).

Dated: October 21, 2016
Electronic Signature for Jill Gorny Sloper, Esq.: /Jill Gorny Sloper, /

Docket No.: AXJ-114BUSCN3
(PATENT)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of:
Leonard Bell *et al.*

Application No.: 15/260,888

Confirmation No.: 2558

Filed: September 9, 2016

Art Unit: 1644

For: TREATMENT OF PAROXYSMAL NOCTURNAL HEMOGLOBINURIA PATIENTS BY AN INHIBITOR OF COMPLEMENT

Examiner: J. L. Rogers

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

INFORMATION DISCLOSURE STATEMENT (IDS)

Dear Sir:

In compliance with 37 C.F.R. § 1.56, 1.97 and 1.98, the attention of the Patent and Trademark Office is hereby directed to the documents listed on the attached PTO/SB/08. It is respectfully requested that the documents listed on the PTO/SB/08 be expressly considered by the Examiner during the prosecution of this application, and that the documents be made of record therein and appear among the "References Cited" on any patent to issue therefrom.

The present application is a continuation of U.S. Application No. 15/148,839, filed May 6, 2016 (Atty. Docket No. AXJ-114BUSCN2). For the Examiner's convenience in reviewing this continuation application, Applicant submits a consolidated PTO Form SB/08, listing all references cited during the prosecution of the parent applications [U.S. Application No. 15/148,839, filed May 6, 2016 (Atty. Docket No. AXJ-114BUSCN2), U.S. Application No. 13/426,973, filed March 22, 2012 (Atty. Docket No. AXJ-114BUSCN), and U.S. Application No. 12/225,040, filed May 13, 2009 (Atty. Docket No. AXJ-0114BUS)].

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /J.L.R/

Copies of the references previously cited by or submitted to the Office in the parent applications are not enclosed, but will be provided upon request, in accordance with 37 CFR §1.98(d). In addition, Applicant submits herewith copies of foreign patents and non-patent literature references, but has not included copies of U.S. patents and U.S. patent applications, in accordance with 37 C.F.R. § 1.98(a)(2)(i)-(iv).

Additionally, Applicant calls to the attention of the Examiner the following Applications and Office Actions cited therein:

Applications				
Examiner's Initials	*Serial No.*	*Filing Date*	*First Named Inventor*	*Docket No.*
	15/284,015	10-03-2016	Leonard Bell	AXJ-114BUSCN4
	15/148,839	05-06-2016	Leonard Bell	AXJ-114BUSCN2
	13/426,973	03-22-2012	Leonard Bell	AXJ-114BUSCN
	12/225,040	05-13-2009	Leonard Bell	AXJ-114BUS
	12/621,792	11-19-2009	Leonard Bell	AXJ-114DV
	10/771,552	02-03-2004	Leonard Bell	AXJ-114RCE
	11/050,543	02-03-2005	Leonard Bell	AXJ-114CPRCE
	11/595,118	11-08-2006	Leonard Bell	AXJ-114CP2
	12/902,617	10-12-2010	Leonard Bell	AXJ-114CPCN
	13/335,518	12-22-2011	Leonard Bell	AXJ-114CPCN2RCE

Office Actions (copies enclosed)			
Examiner's Initials	Serial No.	Date Mailed from USPTO	Examiner
	15/148,839	08-16-2016	J. Rogers
	13/426,973	01-27-2014	J. Rogers
	13/426,973	05-31-2013	J. Rogers
	13/426,973	08-20-2012	J. Rogers
	12/225,040	09-22-2011	J. Rogers
	12/225,040	06-01-2011	J. Rogers
	12/225,040	04-11-2011	J. Rogers
	12/621,792	09-30-2010	P. Gambel
	10/771,552	12-22-2008	F. Vandervegt
	10/771,552	03-21-2008	F. Vandervegt
	10/771,552	08-10-2007	F. Vandervegt
	10/771,552	02-26-2007	F. Vandervegt
	10/771,552	09-26-2006	F. Vandervegt

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /J.L.R/

Samsung Bioepis Exhibit No. 1002
Page 10545

	11/050,543	07-09-2010	P. Gambel
	11/050,543	04-02-2008	F. Vandervegt
	11/050,543	10-10-2007	F. Vandervegt
	11/050,543	06-11-2007	F. Vandervegt
	11/595,118	01-21-2011	P. Gambel
	11/595,118	10-05-2010	P. Gambel
	11/595,118	07-07-2010	P. Gambel
	11/595,118	04-03-2009	F. Vandervegt
	12/902,617	06-23-2011	P. Gambel
	12/902,617	04-04-2011	P. Gambel
	13/335,518	08-22-2016	P. Gambel
	13/335,518	09-12-2014	P. Gambel
	13/335,518	02-06-2014	P. Gambel
	13/335,518	11-07-2013	P. Gambel

/JAMES L ROGERS/ 10/24/2016

The Examiner is requested to review the file histories of these applications, including cited references, Office Actions, Responses, etc., and is asked to contact Applicant's Attorney if the Examiner would like the Applicant to supply copies of any or all of the information included in any of these applications. For any of these applications, if Applicant's Attorney is not contacted by the Examiner with such a request, then it will be concluded that the Examiner has reviewed or will review the file content of these applications.

Applicant respectfully requests that the Examiner initial the blank columns next to the cited Applications and Office Actions, to indicate that the information has been considered by the Examiner. Alternatively, Applicant requests that the Examiner insert the phrase, "All references considered except where lined through," on each page of the Information Disclosure Statement, along with the Examiner's initials.

The filing of this Information Disclosure Statement is not to be interpreted as a representation that the cited documents are material, that an exhaustive search has been conducted, or that no other relevant information exists. Nor shall the citation of any documents herein be construed *per se* as a representation that such document is prior art. Moreover, Applicant understands the Examiner will make an independent evaluation of the cited documents.

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /J.L.R/

This Information Disclosure Statement is filed within three months of the U.S. filing date (37 C.F.R. § 1.97(b)(1)). The Director is hereby authorized to charge any deficiency in the fees filed, asserted to be filed or which should have been filed herewith (or with any paper hereafter filed in this application by this firm) to our Deposit Account No. 12-0080, under Order No. AXJ-114BUSCN3.

Dated: October 21, 2016

Respectfully submitted,

Electronic signature: /Jill Gorny Sloper, /
Jill Gorny Sloper, Esq.
Registration No.: 60,760
NELSON MULLINS RILEY & SCARBOROUGH LLP
One Post Office Square
Boston, Massachusetts 02109-2127
(617) 217-4630
(617) 742-4214 (Fax)
Attorney/Agent For Applicant

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /J.L.R/

I hereby certify that this paper (along with any paper referred to as being attached or enclosed) is being transmitted via the Office electronic filing system in accordance with 37 CFR § 1.6(a)(4).

Dated: November 4, 2016
Electronic Signature for Jill Gorny Sloper, Esq.: /Jill Gorny Sloper, Esq./

Docket No.: AXJ-114BUSCN3
(PATENT)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of:
Leonard Bell *et al.*

Application No.: 15/260,888 Confirmation No.: 2558

Filed: September 9, 2016 Art Unit: 1644

For: TREATMENT OF PAROXYSMAL NOCTURNAL HEMOGLOBINURIA PATIENTS BY AN INHIBITOR OF COMPLEMENT

Examiner: J. L. Rogers

MS Amendment
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

AMENDMENT IN RESPONSE TO

NON-FINAL OFFICE ACTION UNDER 37 C.F.R. § 1.111

Dear Sir:

In response to the Office Action dated October 27, 2016 (Paper No. 20161019), please amend the above-identified U.S. patent application as follows:

Amendments to the Specification begin on page 2 of this paper.

A Listing of the Claims begins on page 3 of this paper.

Remarks/Arguments begin on page 5 of this paper.

Samsung Bioepis Exhibit No. 1002
Page 10548

AMENDMENTS TO THE SPECIFICATION

In the Sequence Listing:

Please replace the Sequence Listing filed on September 9, 2016 with the replacement Sequence Listing submitted herewith.

In the Specification:

Please replace the "Sequence Listing" Paragraph on page 1 of the specification with the following paragraph:

SEQUENCE LISTING

The instant application contains a Sequence Listing which has been submitted electronically in ASCII format and is hereby incorporated by reference in its entirety. Said ASCII copy, created on ~~September 8, 2016~~ November 3, 2016, is named AXJ_114BUSCN3_Seq_Listing.txt and is ~~10,483~~ 10,282 bytes in size.

Please amend the paragraph beginning on page 44 (lines 24-29) as follows:

SEQ ID NO: 4 – Eculizumab Light Chain
~~MDMRVPAQLLGLLLLWLRGARC~~DIQMTQSPSSLSASVGDRVTITCGASENIYGAL
NWYQQKPGKAPKLLIYGATNLADGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCQ
NVLNTPLTFGQGTKVEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKV
QWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQG
LSSPVTKSFNRGEC

Samsung Bioepis Exhibit No. 1002
Page 10549

LISTING OF THE CLAIMS

1. **(Original)** A method of treating a patient suffering from paroxysmal nocturnal hemoglobinuria (PNH) comprising administering to the patient a pharmaceutical composition comprising an antibody that binds C5, wherein the antibody comprises a heavy chain consisting of SEQ ID NO: 2 and a light chain consisting of SEQ ID NO: 4.

2. **(Original)** The method of claim 1, wherein the pharmaceutical composition is administered by intravenous infusion.

3. **(Original)** The method of claim 1, wherein the antibody is administered to the patient at a dosage level of between 5 mg per kg and 50 mg per kg per patient per treatment.

4. **(Original)** The method of claim 1, wherein the pharmaceutical composition is in a single unit dosage form.

5. **(Original)** The method of claim 4, wherein the single unit dosage form is a 300 mg single unit dosage form.

6. **(Original)** The method of claim 1, wherein the pharmaceutical composition comprises a 300 mg single-use formulation of 30 ml of a 10 mg/ml sterile, preservative free solution.

7. **(Original)** The method of claim 1, wherein the patient is anemic.

8. **(Original)** The method of claim 1, wherein the patient is dosed as follows: 600 mg of the antibody via intravenous infusion every 7±1 days for 4 doses; followed by 900 mg of the antibody via intravenous infusion 7±1 days later; followed by a maintenance dose of 900 mg of the antibody via intravenous infusion every 14±2 days.

9. **(Original)** The method of claim 1, wherein administration of the antibody results in an immediate and sustained decrease in mean levels of lactate dehydrogenase (LDH).

10. **(Original)** The method of claim 9, wherein the immediate decrease occurs within one week of administration of the antibody.

REMARKS

Applicants acknowledge with appreciation the telephonic interview with the Examiner and his Supervisor on November 1, 2017, during which the rejections were discussed, as well as the fact that eculizumab was not in public use or publicly available as of March 15, 2007.

Claims 1-10 are pending. Applicants reserve the right to pursue claims to any canceled subject matter, or any subject matter which they are entitled to claim, in this or a separate application. *No new matter has been added.*

Information Disclosure Statement

Applicants acknowledge with appreciation the Examiner's indication that the Information Disclosure Statement submitted on October 21, 2016 has been considered. However, only three out of the four PTO/SB/08a Forms were formally acknowledged. Accordingly, Applicants respectfully request that the Examiner provide an initialed copy of the fourth PTO/SB/08a that was filed on October 21, 2016, to indicate that the listed references have been considered.

Additionally, Applicants submit herewith a Supplemental Information Disclosure Statement to make of record additional information for the Examiner's consideration.

Obviousness-Type Double Patenting

The Examiner has provisionally rejected claims 1-10 on the ground of non-statutory obviousness-type double patenting as being unpatentable over claim 1 of co-pending U.S. Patent Application No. 15/148,839.

While in no way acquiescing to the rejection, Applicants respectfully submit herewith a terminal disclaimer over U.S. Patent Application No. 15/148,839, as well as U.S. Patent Application No. 15/284,015. Accordingly, Applicants respectfully request that the Examiner withdraw the rejection.

Replacement Sequence Listing and Amendment to the Specification

It has come to Applicants' attention that the light chain recited in the specification and Sequence Listing as SEQ ID NO:4 inadvertently contains the precursor peptide leader sequence, as shown below:

SEQ ID NO: 4 (Light Chain)
MDMRVPAQLLGLLLLWLRGARCDIQMTQSPSSLSASVGDRVTITCGASE
NIYGALNWYQQKPGKAPKLLIYGATNLADGVPSRFSGSGSGTDFTLTIS
SLQPEDFATYYCQNVLNTPLTFGQGTKVEIKRTVAAPSVFIFPPSDEQL
KSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYS
LSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC

Accordingly, Applicants submit herewith a replacement Sequence Listing amending SEQ ID NO:4 to delete the leader sequence (underlined above), which is ultimately cleaved from the active light chain. Thus, as amended, SEQ ID NO:4 corresponds to the mature portion of the complete light chain sequence of eculizumab. Applicants have also amended the specification to update the "Sequences" summary on page 44 (lines 24-29) of the specification.

Applicants respectfully note that the mature light chain sequence is an inherent portion of the precursor sequence (*i.e.*, original SEQ ID NO:4), and could have been readily identified at the relevant filing date using well established rules and art-recognized techniques (see, for example, Figure 6 on page 734 of Adderson *et al.*, *J. Clin. Invest.* 89:729-738 (1992) (enclosed herewith as Exhibit A), which shows the characteristic mature N-terminus (DIQ) of a light V kappa antibody light chain, as well as Kabat *et al.*, Sequences of Immunological Interest 5th Edition, U.S. Public Health Service, Bethesda MD). Therefore, the amendment to SEQ ID NO:4 does not constitute new matter.

CONCLUSION

In view of the foregoing, entry of the amendments and remarks herein, reconsideration and withdrawal of all rejections, and allowance of the instant application with all pending claims is respectfully solicited. If a telephone conversation with the Applicants` attorney would help expedite the prosecution of the above-identified application, the Examiner is urged to call the Applicants` attorney at (617) 217-4630.

The Director is hereby authorized to charge any deficiency in the fees filed, asserted to be filed or which should have been filed herewith (or with any paper hereafter filed in this application by this firm) to our Deposit Account No. 12-0080, under Order No. AXJ-114BUSCN3.

Dated: November 4, 2016

Respectfully submitted,

Electronic signature: /Jill Gorny Sloper, Esq./
Jill Gorny Sloper, Esq.
Registration No.: 60,760
NELSON MULLINS RILEY & SCARBOROUGH LLP
One Post Office Square
Boston, Massachusetts 02109-2127
(617) 217-4630
(617) 742-4214 (Fax)
Attorney/Agent For Applicant

EXHIBIT A:
Adderson *et al*., *J. Clin. Invest*. 89:729-738 (1992)

Samsung Bioepis Exhibit No. 1002
Page 10555

Immunoglobulin Light Chain Variable Region Gene Sequences for Human Antibodies to *Haemophilus influenzae* Type b Capsular Polysaccharide Are Dominated by a Limited Number of V_κ and V_λ Segments and VJ Combinations

Elisabeth E. Adderson,* Penelope G. Shackelford,* Richard A. Insel,§ Anthony Quinn,* Patricia M. Wilson,‡ and William L. Carroll‖

*Division of Infectious Diseases and ‡Hematology Oncology, Mallinckrodt Department of Pediatrics, Washington University School of Medicine, St. Louis Children's Hospital, St. Louis, Missouri 63110; and §Department of Pediatrics, University of Rochester School of Medicine and Dentistry, Rochester, New York 14642

Abstract

The immune repertoire to *Haemophilus influenzae* type b capsular polysaccharide (Hib PS) appears to be dominated by certain light chain variable region genes (IgV_L). In order to examine the molecular basis underlying light chain bias, IgV_L genes have been cloned from a panel of heterohybridomas secreting human anti-Hib PS (antibody) (anti-Hib PS Ab). One hybridoma, representative of the predominant serum clonotype of anti-Hib PS Ab in older children and adults following immunization or Hib infection, uses a V_κII segment identical to the germline gene A2, and a JK3 segment. A second kappa hybridoma uses a member of the V_κI family and a JK4 segment. Four lambda antibodies, all cross-reactive with the structurally related antigen *Escherichia coli* K100 PS, use V_λVII segments which are 96–98% homologous to one another, and may originate from a single germline gene. Two additional lambda antibodies, not K100–cross-reactive, are encoded by members of the V_λII family. All lambda antibodies use highly homologous J_λ2 or J_λ3 segments. The VJ joints of all lambda antibodies and the V_κII–encoded antibody are notable for the presence of an arginine codon, suggesting an important role in antigen binding. Although more complex than heavy chain variable region gene usage, a significant portion of serum anti-Hib PS Ab is likely to be encoded by a limited number of V_κ and V_λ segments and VJ combinations, which may be selectively expressed during development, or following antigen exposure. (*J. Clin. Invest.* 1992: 89:729–738.) Key words: B-cell repertoire • somatic mutation • gene rearrangement • carbohydrate antigen

Introduction

The development of the antibody repertoire involves the recombination of individual members of two or three groups of germline segments, nucleotide insertion or deletion at these junctions, and somatic mutation of rearranged genes (1–4). The individual contributions of these molecular mechanisms to the generation of the immune repertoire against a specific antigen has been extensively studied in murine systems, but it is uncertain whether these findings can be extrapolated to humans. The chromosomal organization of the human heavy and light chain variable region segments within the immunoglobulin loci differ from those of mice (5–7). Furthermore, the response of highly inbred laboratory animal strains, and the use of simple haptens in most studies, may not be comparable with the human response to clinically relevant antigens, such as those presented by microbial pathogens.

The immune response to *Haemophilus influenzae* type b capsular polysaccharide (Hib PS)[1] is an excellent model to examine the immune repertoire to a functionally significant antigen. Hib is a major bacterial pathogen in young children and antibody directed against the capsular polysaccharide, a repetitive polymer of polyribosylribitol phosphate, protects against invasive infection (8). Similar to the response to other polysaccharide antigens, the immune response to Hib PS is age-dependent. Children under 5 yr have lower antibody responses and are at greatest risk of infection. Additionally, there appear to be variations in individual and ethnic susceptibilities to invasive Hib disease (9–11). Analysis of the immune response to Hib PS will contribute to our understanding of the development of the human antibody repertoire, and provide insight into age-related and possible genetic predisposition to infection caused by Hib.

Previous studies employing partial amino acid sequencing of anti-Hib PS serum antibody purified to clonality have shown that light chains of anti-Hib PS antibody are encoded by V_λ, and at least three V_κ gene families (12). Although highly informative, these studies have inherent technologic limitations. To obtain sufficient antibody for analysis, only individuals with antibody concentrations much higher than those elicited in young infants could be studied (12). Amino acid sequences were unobtainable on V_λ-encoded antibodies, and certain regions of V_κ-encoded antibodies (12, 13). Obtaining nucleic acid sequences of variable region genes encoding anti-Hib PS Abs would permit precise comparison of variable region genes obtained from different individuals, allowing classification of these genes into germline families and subfamilies, analysis of D- and J-segment usage, and assessment of the role of somatic mutation in the clonal evolution of this immune response. Additionally, this information could be applied to examination of the germline and expressed immune repertoire

Presented in part at the annual meeting of the Society for Pediatric Research, New Orleans, LA, 2 May 1991, and published in abstract form (*Pediatr. Res.* 29:155A).

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1. *Abbreviations used in this paper:* Ars, anti-p-azophenylarsonate; Hib, Haemophilus influenzae type b; Hib PS, Hib capsular polysaccharide; IgV_L, light chain variable region gene; PCR, polymerase chain reaction; SSC, standard saline citrate.

Samsung Bioepis Exhibit No. 1002
Page 10556

of individuals of various ages, and populations at high risk for invasive Hib infection.

Our previous work, and that of others, indicated that the heavy chains of anti-Hib PS Abs are encoded by a very restricted number of V_HIII gene segments, in combination with a variety of D and J_H segments (12, 14). We have extended our studies to examine light chain variable region gene (IgV_L) usage in the human anti-Hib PS response. A major component of serum anti-Hib PS Ab expresses a cross-reactive idiotype associated with the use of a V_κII gene (15, 16). Antibodies expressing this light chain account for the majority of anti-Hib PS antibody in older infants and adults following invasive Hib disease or immunization. Most lambda-encoded anti-Hib antibodies and some kappa-encoded (V_κI and V_κIII) anti-Hib PS Abs cross-react with the capsular polysaccharide of *E. coli* K100 (12, 17). Naturally acquired antibody of the majority of children expresses K100 PS cross-reactivity, and thus, colonization with this organism may provide protective immunity before exposure to Hib (18). Our results indicate that two important anti-Hib PS light chains, one associated with V_κII expression and the other with lambda antibodies cross-reactive with K100 PS, are encoded by two germline elements that may be expressed with little or no somatic mutation. Moreover, a nongermline-encoded arginine at the VJ joint is seen in the majority of anti-Hib PS Ab light chains, a result suggesting an essential role in antigen recognition.

Methods

Hybridomas. Heterohybridomas secreting human monoclonal anti-Hib PS antibody were obtained, as previously described (14). Volunteers were immunized with either plain Hib-PS vaccine (Praxis Biologicals, Rochester, NY) or Hib-PS diphtheria toxoid conjugate vaccine (Hib-PS-D) (Connaught Laboratories, Swiftwater, PA). 7 d following immunization, peripheral blood lymphocytes were harvested and fused to the nonsecreting mouse myeloma SP2/O-Ag14. Anti-Hib PS Ab was detected by binding to Hib PS in an ELISA, as previously described (14). Specificity was documented by antibody binding to ^{125}I-labeled antigen (19), and by inhibition of binding by 1.25 μg/ml of soluble Hib PS in an ELISA (20). Cross-reactivity with *E. coli* K100 PS was assayed by inhibition of binding to Hib PS-poly-L-lysine with 100 μg/ml of soluble K100 PS in an ELISA. An antibody concentration was selected that gave half-maximum absorbance in the ELISA. Greater than 15% inhibition was considered positive. The *E. coli* K100 PS was prepared from *E. coli* strain Easter, by the same method used to prepare Hib PS (19). The generation of hybridoma line 16M3C8 was described previously (21).

Cloning and sequencing of IgV_L genes. Total RNA was prepared from 10^6 hybridoma cells using the guanidine isothiocyanate method (22). 2 to 8 μg of total RNA served as template for first-strand cDNA synthesis, as previously described (14). 10 pmol of a consensus antisense primer corresponding to conserved sequences within the human kappa or lambda constant region (23) (C_κ codons 181-172:5'CAGCGTCAAGCTTCTGCTGTGGCTGTAGGT 3', C_λ codons 171-181:5'CAGGCTCAGGAAGCTTCTGGCCGCGTACTTGTT 3') was used to initiate cDNA synthesis by avian myeloblastosis virus (AMV) reverse transcriptase (RT; Life Sciences, St. Petersburg, FL). One half (10 μl) of the cDNA reaction was directly diluted into polymerase chain reactions (PCR), (24).

PCR conditions were as previously described, except that 70 pmol of an internal constant region consensus primer (C_κ codons 125-117:5'CAACGGATCCTCTGATGGCGGGAAGAT 3', C_λ codons 125-117:5'TGGGGATCCAGCTCCTCAGAGGAGGG 3') and 70 pmol of a degenerate 3' kappa or lambda leader sequence primer (kappa:5'GGGAATTCATGGACATG(GA)(GA)(GA)(GAT)(TC)CC-(ACT)(GAC)G(TC)(GT)CA(GC)CTT 3', lambda 5'GGGAATTCATG(GA)CCTG(GC)(AT)C(TC)CCTCTC(TC)T(TC)CT(GC)(AT)-(TC)C 3') were used to amplify rearranged variable region genes (14, 25).

PCR products were isolated from low melting-point agarose gels (FMC Bioproducts, Rockland, ME). Artificial restriction enzymes sites in each primer allowed directional cloning into M13mp18 and M13mp19 phage vectors (Boehringer Mannheim Corp., Indianapolis, IN). Sequencing of V_L genes was performed by the dideoxy technique (26). Two to five positive clones were obtained and sequenced for each hybridoma gene.

The 16M3C8 light chain was generated by amplification of first-strand cDNA, with primers corresponding to amino acid positions −7 of the leader, to position 6 of the lambda light chain (5'CTGCACAGGGTCCTGGGCCGAGCTCGTGGTGACTCA 3'), and the C_λ constant region (antisense, 5'GCATTCTAGACTATTATGAACATTCTGTAGGGGC3'). Blunt-ended PCR products were cloned into SmaI cut M13 mp18 and M13mp19 and sequencing was also performed by the dideoxy method.

Southern blot analysis of genomic DNA. Peripheral blood was obtained from 10 unrelated healthy adult volunteers, from L.S. (the donor of hybridoma LSF2), and from a parent of L.S. Lymphocytes were separated on a Ficoll-Hypaque gradient, and genomic DNA was prepared by Proteinase K digestion (27). 10 μg of each subject's genomic DNA was digested with BamHI (4 U/μg DNA) (Boehringer Mannheim Corp.) at 37°C for 16 h, according to manufacturer's specifications. Digested DNA was separated by electrophoresis in a 0.8% agarose gel using TAE buffer (0.04 M Tris-acetate/0.001 M EDTA), and was transferred to Duralon UV membranes (Stratagene Inc., La Jolla, CA), using a positive pressure blotting apparatus (Posiblotter; Stratagene, Inc.). To examine germline representation of anti-Hib PS Ig genes, genomic DNA was hybridized with a 320-bp EcoRI/SmaI V_λ segment from hybridoma LSF2 that lacked the associated J_λ and C_λ regions. Probe was radiolabeled to high specific activity using T7 DNA polymerase (28). Prehybridization and hybridizations were carried out in 5× standard saline citrate (SSC), 5× Denhardt's solution, and 200 μg/ml sheared and denatured salmon sperm DNA (Boehringer Mannheim Corp.) at 42°C overnight. Filters were washed with 2× SSC, 0.2% SDS at room temperature twice, then with 0.2× SSC, 0.2% SDS at 55 to 60°C twice, and exposed to X-OMAT AR film (Eastman Kodak Co., Rochester, NY) for 2–7 d.

In order to further localize germline candidates within V region families, an oligonucleotide probe corresponding to conserved sequences within the CDR-1 region (sense oligonucleotide: 5'GGCTCCAGCACTGGAGATGTCACCAGT 3', antisense oligonucleotide: 5'GTAGGGATAATGACCACTGGTGACATCTCC 3') was hybridized to genomic DNA using the method described by Hellman (29). 15 μg of BamHI-digested human genomic DNA was separated by electrophoresis in 0.8% agarose gel using TBE buffer (0.09 M Tris-borate/0.002 M EDTA). Agarose gels were dried under vacuum and hybridized in 5× saline/sodium phosphate/EDTA (SSPE), 0.1% SDS, and 10^6 μg/ml of sheared and denatured salmon sperm DNA with 2×10^6 cpm of probe/ml of hybridization solution at 60°C for 16 h (30, 31). Hybridization conditions were previously adjusted to minimize nonspecific binding. Gels were washed with 6× SSC at room temperature for 20 min twice, followed by a 4-h room temperature wash. The gel was finally washed in 6× SSC for 3 min at 64°C, and exposed to X-OMAT AR film for 4 d.

Results

Hybridomas

Eight hybridoma cell lines from seven individuals were initially selected from 20 cell lines. All individuals demonstrated substantial increases in serum anti-Hib PS Ab 1 mo after vaccination (Table I). Hybridomas were selected to exemplify serologic characteristics (kappa or lambda expression, and K100 PS

Samsung Bioepis Exhibit No. 1002
Page 10557

*Table I. Summary of Hybridoma Cell Lines**

Hybridoma	Isotype	Age	Vaccine Form	K100 Inh of mAb	Serum Anti-Hib PS Ab: Total Ab Pre	Total Ab Post	ΔK100 Inh Pre	ΔK100 Inh Post
RC3	IgA/k	Adult	PS-D	−	1.1	300	11	11
ED6.1	IgG_2/k	4 yr	PS-D	−	0.8	22	0	0
SB5/D6	IgA_1/λ	Adult	PS-D	+	2.0	688	30	27
RAY4	IgA_2/λ	Adult	PS-D	+	1.9	28	0	42
LSF2	IgA_1/λ	Adult	PS	+	ND	138	ND	29
JB32	IgA_1/λ	11 yr	PS	+	0.3	125	19	33
JB21	IgG_2/λ	11 yr	PS	−	0.3	125	19	33
16M3C8	IgG_2/λ	Adult‡	PS	−	ND	ND	ND	ND

* Columns show name of hybridoma cell line, isotype of anti-Hib PS Ab secreted, age of subject at immunization, type of vaccine (PS is plain polysaccharide, PS-D is Hib PS covalently linked to diphtheria toxoid), presence (+) or absence (−) of inhibition of binding of anti-Hib PS Ab by *E. coli* K100 PS, concentration of total serum anti-Hib PS AB pre- and 1 mo post-immunization, and percent inhibition of binding of serum lambda antibodies to Hib PS by *E. coli* K100 PS in pre- and 1 mo post-immunization sera. ‡ Pool of 3 adult donors. ND, not done.

cross-reactivity) and to represent the response to "T-independent" plain polysaccharide, or "T-dependent" polysaccharide-protein conjugate forms of antigen. (Table I).

Four lambda-expressing anti-Hib PS Ab, obtained from four different subjects, cross-reacted with K100 PS. One of these individuals, RAY4, had no detectable serum cross-reactivity before immunization. The Abs JB32 and JB21 were obtained from the same individual, and differed in heavy chain isotype and K100 cross-reactivity.

IgV_L genes. IgV_L nucleic acid sequences were obtained from two kappa and six lambda hybridomas. Candidate germline IgV_L sequences were sought by comparing hybridoma sequences to those registered with EMBL and GenBank (32).

Four lambda-expressing hybridomas, derived from four unrelated subjects, use V_λ segments which are 96–98% homologous to one another, and are members of the germline V_λVII family of which a single member, 4A, has been previously described (33) (Fig. 1). Notably, each of these four V_λVII-encoded hybridomas cross-reacts with K100 PS. The high degree of homology between these segments suggests that these genes may be encoded by a single, or group of, closely related germline elements. The four hybridoma genes share a number of nucleic acid differences (maximum nucleic acid sequence homology 89%) from the only previously sequenced V_λVII germline gene 4A, implying that these genes may be derived from another, as yet undescribed, V_λVII germline element.

The homology of the translated amino acid sequences of these 4 V_λVII sequences parallels the nucleic acid homology. The hybridoma V_λVII genes are 90 to 97% homologous at the amino acid level (Fig. 2). Framework regions are 94 to 100% homologous, whereas CDR regions are 72 to 96% homologous. Whether these minor differences reflect genetic polymorphisms, or somatic mutation, cannot be resolved from these data.

JB21 and 16M3C8, the lambda-expressing hybridomas which do not cross-react with K100 PS, are encoded by a V_λII gene family member (34), (Fig. 3). JB21 is 91% homologous to the germline V_λ2.1 gene (99% homologous in framework regions and 74% homologous in CDRs). 16M3C8 is 89% homologous to V_λ2.1 (95% in framework regions and 77% in CDRs). JB21 shares 87% amino acid homology with the translated V_λ2.1 germline sequence (99% in framework regions and 60% in CDR regions), and 16M3C8 shares 82% amino acid homology (92% in framework regions and 60% in CDRs) (Fig. 4).

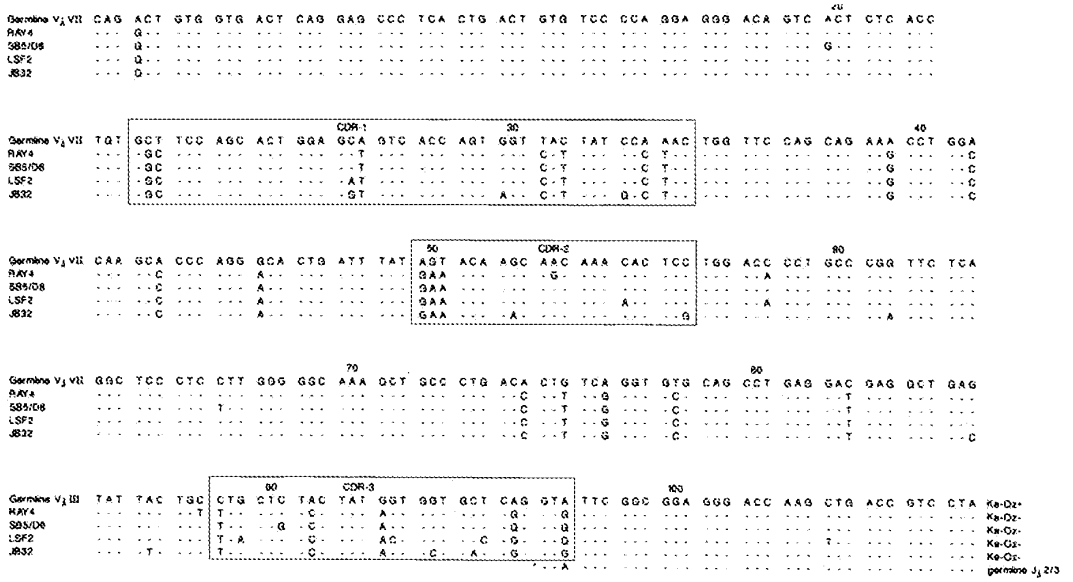


Figure 1. Nucleotide sequences of the V_λ and J_λ genes from four hybridoma cell lines (RAY4, SB5/D6, LSF2, JB32), and from the V_λVII germline gene, 4A (33). Numbering is according to Kabat (23). These sequence data are available from EMBL/GenBank Data Libraries under accession numbers M80917 (RAY4), M80918 (SB5/D6), M80915 (LSF2), and M80919 (JB32).

Samsung Bioepis Exhibit No. 1002
Page 10558

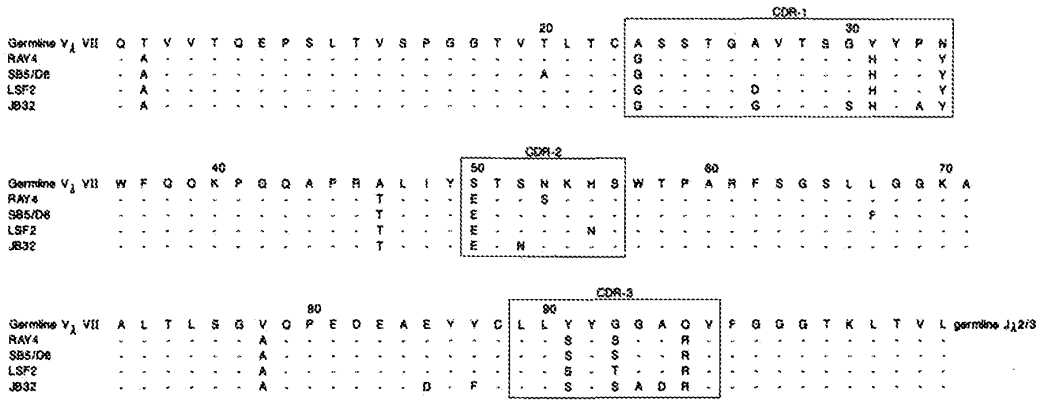


Figure 2. Translated amino acid sequences of V_λ and J_λ from four hybridoma cell lines (RAY4, SB5/D6, LSF2, JB32), and from the V_λVII germline gene, 4A (33). (See Fig. 1.)

These two V_λII-encoded gene segments are 91% homologous to one another, and have in common a number of nucleic acid differences from the V_λ2.1 germline gene (especially in CDRs). Whether they derive from another germline gene, or whether these differences reflect mutation, is unknown.

All four of the V_λVII-encoded antibodies are also encoded by V_HIII segments closely homologous to the germline gene 9.1 (5). Similar V_H segments also encode Ab utilizing other V_λ and V_κ gene segments (Table II) (manuscript in preparation). It is uncertain whether pairing of 9.1-like V_H and V_λVII-encoded heavy and light chains contributes to binding specificity or avidity. JB21 and RC3, also encoded by 9.1-like V_H gene segments, but paired with V_λII- and V_κII-encoded light chains, respectively, do not cross-react with K100 PS.

All six of the lambda light chains are encoded by a common J_λ segment closely homologous to both J_λ2 and J_λ3 germline genes (Fig. 1) (23). J_λ2 is associated with the use of the (Kern$^-$Oz$^-$)C_λ segment 2, and J_λ3 with the (Kern$^-$Oz$^+$)Cλ segment 3 (37). Each of these J_λ segments substitutes the codon GTG for the reported germline sequence GTA at amino acid position 97. Interestingly, this change does not result in an amino acid replacement, and is therefore not of importance in antigen binding. This minor sequence difference may reflect a shared genetic polymorphism, rather than somatic mutation.

The hybridoma RC3 uses a V_κII segment identical to the germline V_κII gene A2, and a J_κ3 segment closely homologous to the germline sequence (Fig. 5) (13). The second kappa hybridoma, ED6.1, is encoded by a member of the V_κI family

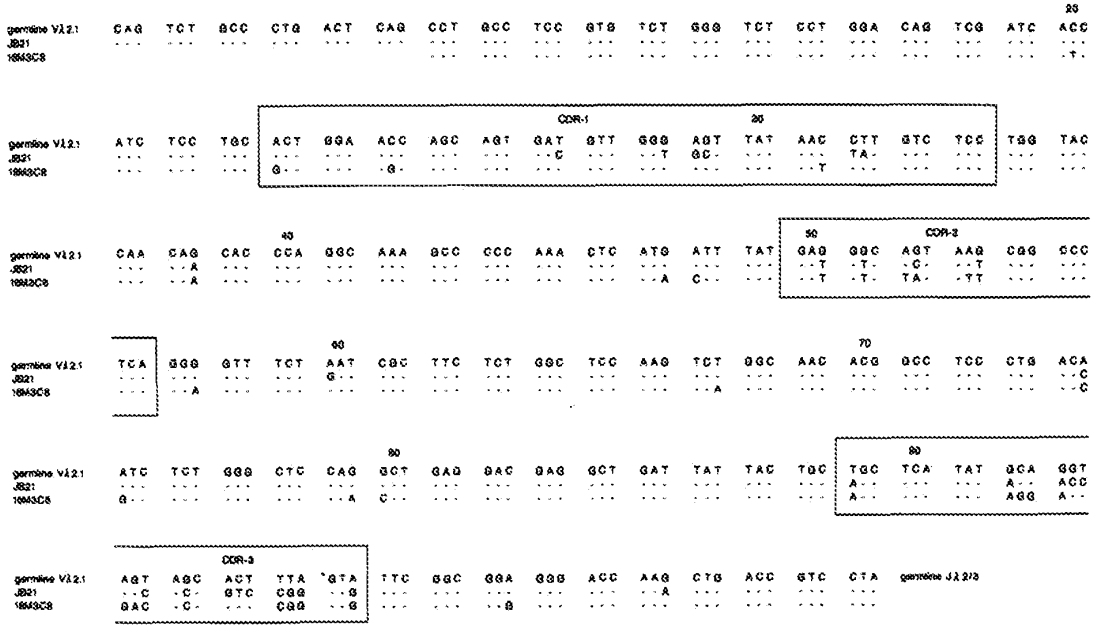


Figure 3. Nucleotide sequences of V_λ and J_λ genes from two hybridoma cell lines (JB21 and 16M3C8). Also shown is a germline gene V2.1 (34), and germline J_λ2/3 gene (23). An asterisk denotes the beginning of the J_λ segment. Numbering is according to Kabat (23). These sequence data are available from EMBL/GenBank Data Libraries under accession numbers M80916 (JB21) and M80921 (16M3C8).

Samsung Bioepis Exhibit No. 1002
Page 10559

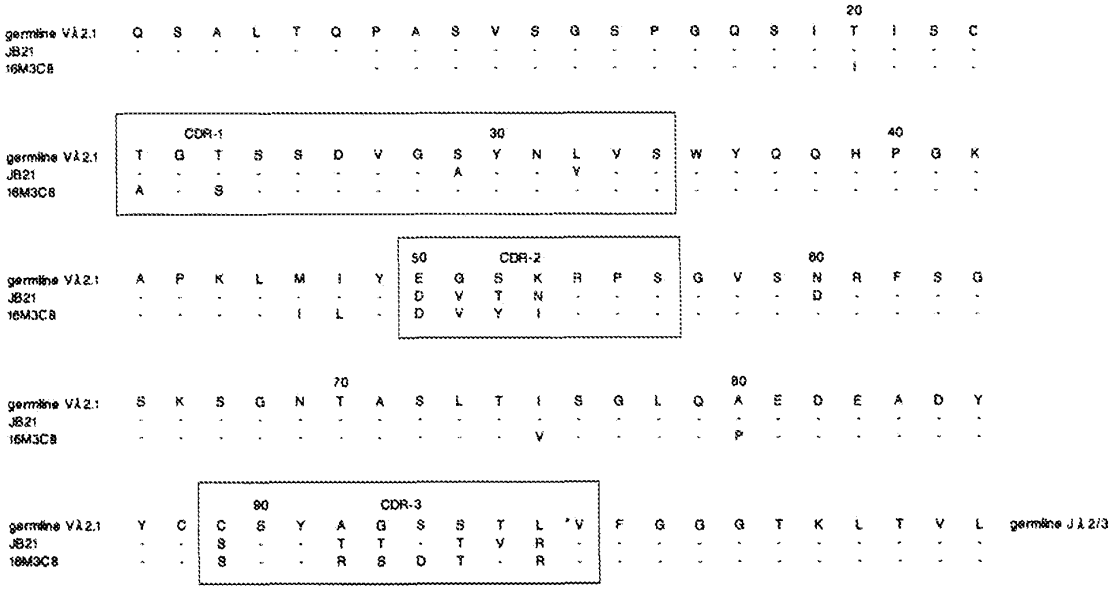


Figure 4. Translated amino acid sequences of V_λ and J_λ genes from two hybridoma cell lines (JB21 and 16M3C8). Shown for comparison is the translated sequence of the V_λ germline gene $V_\lambda 2.1$, and $J_\lambda 2/3$ germline gene. An asterisk denotes the beginning of the J_λ segment. (See Fig. 3.)

(36), and uses a $J_\kappa 4$ segment differing from the germline sequence by a single base (Fig. 6). The ED6.1 sequence is identical to the partial amino acid sequence reported previously for 2 kappa antibodies purified from serum (12).

VJ joints of seven of these eight hybridoma V_L genes are notable for the presence of an arginine codon (Fig. 7). Comparison of germline sequences indicates that in the RC3 V_L gene, the codon CGA could only have arisen by the addition of a non–germline-encoded G at the $V_\kappa J_\kappa$ joint. In the V_λVII-encoded antibodies, the relevant germline V_λ segment is unknown. The arginine codon may be germline-encoded, or result from either mutation or N sequence addition. The VJ splice junction in all lambda antibodies is identical, implying this V_λ/J_λ combination is a necessary prerequisite for generation of the arginine. Since the CDR-3 region encodes the third hypervariable region, the frequent finding of an arginine residue at this location, and particularly its presence in both kappa and lambda anti–Hib PS Ab clonotypes, implies this residue is of considerable importance in antigen binding.

*Table II. Summary of V_H and V_L Gene Segments**

Hybridoma	V_H Segment	V_L Segment
SB5/D6	V_HIII 9.1 (5)	V_λVII 4A (33)
RAY4	V_HIII 9.1	V_λVII 4A
JB32	V_HIII 9.1	V_λVII 4A
JB21	V_HIII 9.1	V_λII 2.1 (34)
RC3	V_HIII 9.1	V_κII A2 (13)
LSF2	V_HIII 9.1	V_λVII 4A
16M3C8	V_HIII VH26 (35)	V_λII 2.1
ED6.1	N.K.	V_κI clone KC-1 (36)

* Columns show name of hybridoma cell line and most closely homologous known germline V_H and V_L segments. Reference for germline shown in parentheses. NK, Not known.

Southern blots/analysis of germline V_λVII genes

The available repertoire of V_λVII family members was examined by hybridization of human genomic DNA with the V_λVII probe generated from LSF2. 10 prominent bands, as well as an additional 5 fainter bands, were demonstrated (Fig. 8). Notably, polymorphism such as the presence or absence of a 5.0-kb fragment, and varying intensity of the 3.5-kb fragment, was demonstrated even within this relatively small sample. The human lambda variable region locus is believed to contain about 60 members, of which 10 are members of the V_λVII family (33, 38). The five less prominent bands may represent members of other V_λ families sharing significant homology with the V_λVII family. To determine if the V_λVII-encoded antibodies derive from a single germline gene, an oligonucleotide probe corresponding to conserved V_λVII CDR-1 sequence was used to identify a single 3.7-kb genomic DNA fragment. Although more than one V gene may be present in a single restriction fragment, both the repeated isolation of highly homologous V_λVII genes, and the single prominant band detected with the oligonucleotide probe, suggests that a single V_λ gene may be responsible for the generation of lambda anti–Hib PS Ab that cross-reacts with K100 PS (Fig. 9). Less prominant higher molecular weight bands are also present, but hybridize weakly to the oligomer after subtraction of nonspecific background binding by high molecular weight DNA.

Discussion

To examine the molecular basis of the immune response to Hib PS, a panel of hybridomas secreting human monoclonal anti–Hib PS Ab has been developed. Our previous studies showed exclusive use of members of the V_HIII gene family in this im-

Samsung Bioepis Exhibit No. 1002
Page 10560

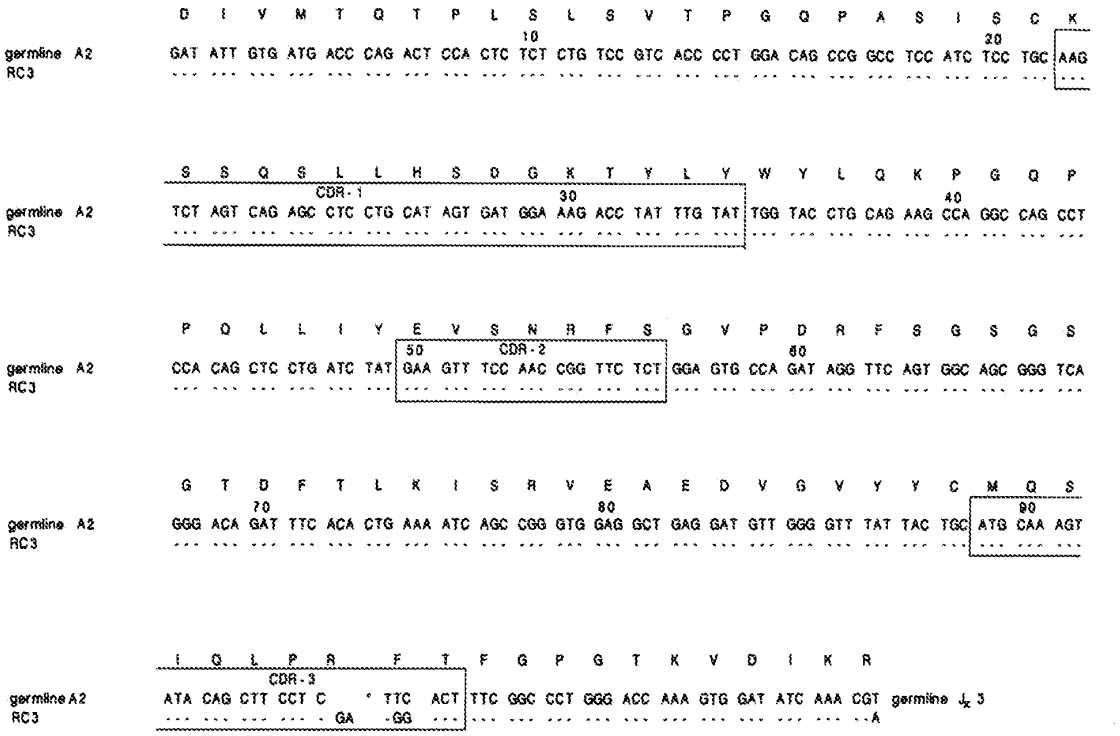


Figure 5. Nucleotide sequences of V_x and J_x genes from the hybridoma cell line RC3. Also shown is the translated amino acid sequence of the RC3 V_x gene. Shown for comparison is the nucleotide sequence of a germline V_x gene, A2 (13), and germline J_x3 gene. An asterisk denotes the beginning of the J_x segment. Numbering is according to Kabat (23). This sequence data is available from EMBL/GenBank Data Libraries under accession number M80914 (RC3).

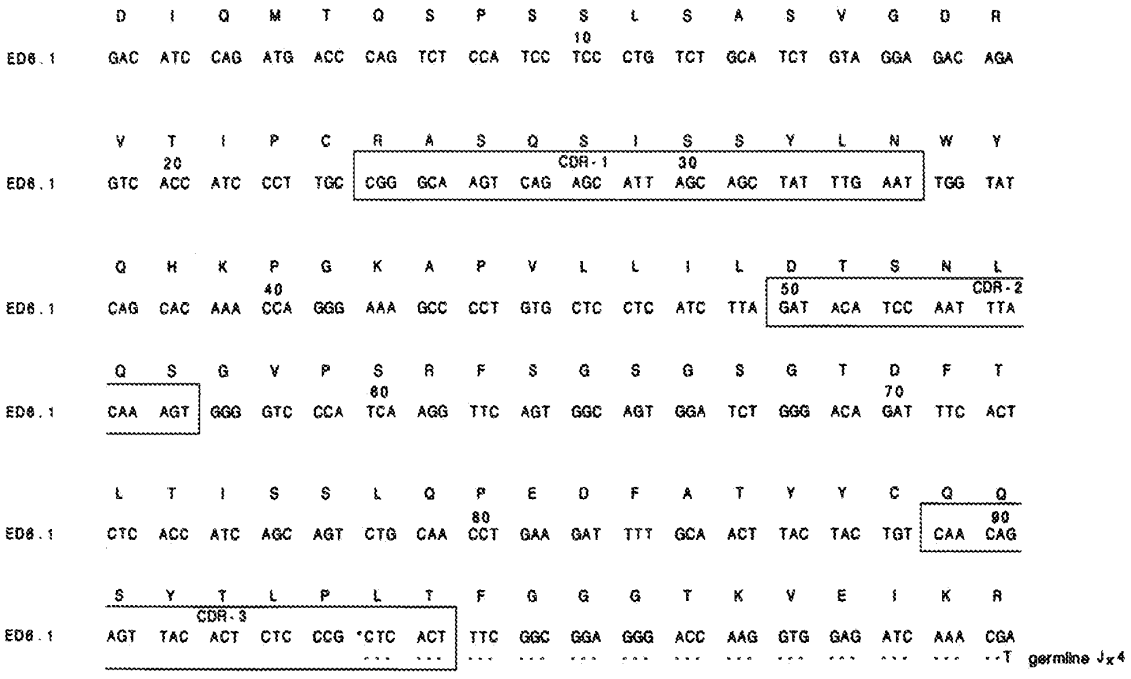


Figure 6. Nucleotide sequence of V_x and J_x genes from hybridoma cell line ED6.1. Also shown is the translated amino acid sequence of the ED6.1 V_x gene. An asterisk denotes the beginning of the J_x segment. Numbering is according to Kabat (23). This sequence data is available from EMBL/GenBank Data Libraries under accession number M80920 (ED6.1).

521

Samsung Bioepis Exhibit No. 1002
Page 10561

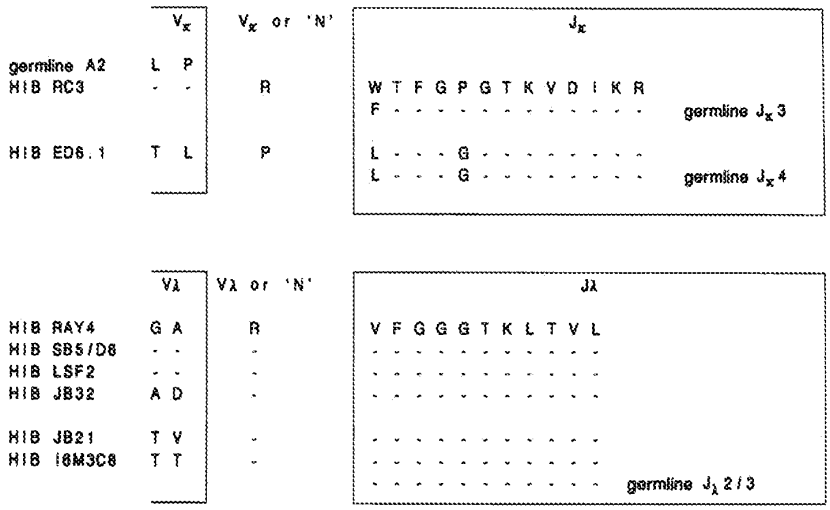


Figure 7. Translated amino acid sequences of VJ joints from seven hybridoma cell lines (RC3, ED6.1, RAY4, SB5/D6, LSF2, JB21, and 16M3C8). Also shown are translated amino acid sequences of the germline V_κ gene A2, and germline $J_\kappa 3$, $J_\kappa 4$, and $J_\lambda 2/3$ genes. (See Figs. 2, 4, and 6.)

mune response, and the apparent restriction to two or three germline V_H genes. In contrast, V_L gene usage is more complex, with antibody encoded by a number of V_λ and V_κ families (12). Analysis of light chain variable region genes obtained from cell lines selected to represent various characteristics of serum antibodies showed that despite diversity in the variety of light chain variable region gene segments utilized, most serum anti–Hib PS Abs may be encoded by a limited number of V_κ and V_λ germline genes.

The light chain distribution of anti–Hib PS Ab is characterized by a predominance of kappa light chains, although some individuals predominantly or exclusively express lambda light chains (39, 40). Scott et al. have shown that V_κII light chains are the most commonly expressed light chains among clonally purified serum anti–Hib PS antibodies from adults with high responses to immunization. Limited amino acid sequences of a number of these serum antibodies showed that greater than 60% of subjects immunized with plain Hib PS produce antibody encoded by a V_κII family member, and further, that a number of these antibodies show identical amino acid homology with the translated amino acid sequence of the germline V_κII gene A2 (12, 13). Lucas et al. have described an anti-idiotypic monoclonal antibody (Hibid-1) that identifies anti–Hib PS antibodies expressing this light chain (16). On average, 60%

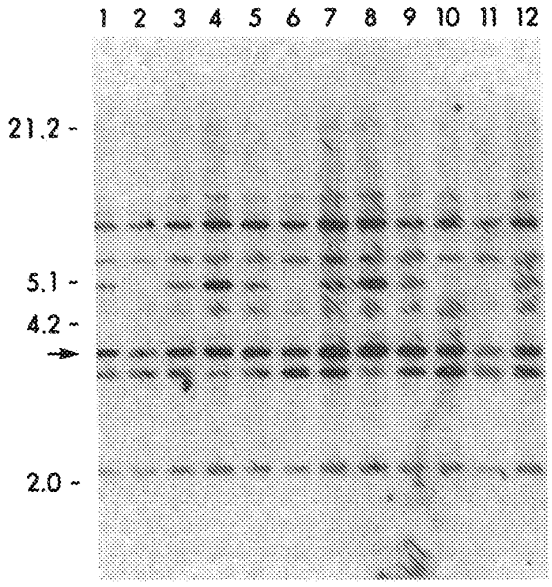


Figure 8. Southern blot analysis for V_λVII family members in BamHI-digested human genomic DNA. Lane *12* contains genomic DNA from the subject from whom hybridoma LSF2 was obtained. Lane *9* contains genomic DNA from a parent of LS. The remaining 10 donors are unrelated. An arrow indicates the 3.7-kb fragment which is identified by the oligonucleotide probe illustrated in Fig. 9.

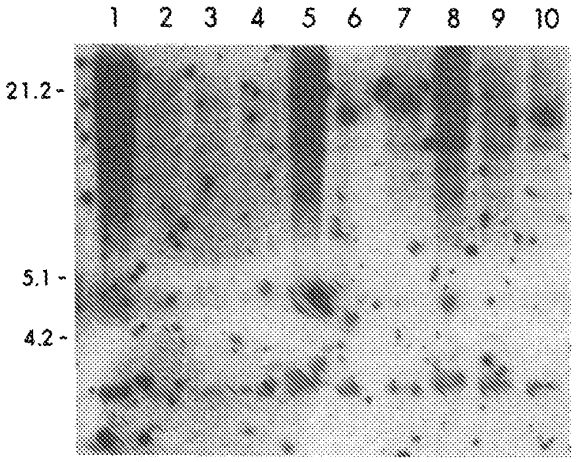


Figure 9. Dried gel hybridization of BamHI-digested human genomic DNA with an oligonucleotide probe corresponding to conserved V_λVII hybridoma CDR-1 sequences. Genomic DNA in lanes *1, 4, 5, 6, 7, 9* and *10* of Fig. 8 corresponds to that in lanes *2, 7, 4, 8, 10, 5* and *9* of Fig. 9, respectively.

Samsung Bioepis Exhibit No. 1002
Page 10562

of the total anti–Hib PS antibody of most children and adults immunized with either Hib PS or Hib PS-conjugate vacine expresses this idiotype (15, 16). Taken together, this suggests the most common clonotype of anti–Hib PS Ab is encoded by a single V_κII gene. The V_κ locus contains approximately 50 functional genes, of which 40% are members of the V_κII family (41). The V_κII A2 germline gene is known to be present in a single copy (13). Our findings definitively demonstrate that at least a portion of V_κII-encoded antibodies are encoded by unmutated germline elements. Our subject R.C. was immunized with PS-protein conjugate vaccine, whereas Scott's subjects were immunized with the plain PS vaccine. Thus it is possible that the unmutated V_κII A2 segment is utilized irrespective of antigen presentation in a T-independent or T-dependent form.

Lambda variable region gene usage appears similarly restricted. The majority of lambda-expressing anti–Hib PS Ab in adults with high antibody responses to vaccine cross-reacts with *E. coli* K100 PS (17). The capsular polysaccharides of Hib and *E. coli* K100 are structurally similar and gastrointestinal colonization with *E. coli* K100 induces antibody to Hib PS in humans (42). "Naturally occurring" anti–Hib PS Ab in children commonly cross-reacts with K100 PS, whereas Ab of individuals immunized with Hib PS or responding to Hib infection is less frequently cross-reactive (18). The kappa/lambda ratio of natural anti–Hib PS Ab is lower in infants than in older children, and in the vaccine-induced antibody of adults (39). Further, Hibid-1 (the CRI associated with expression of the V_κII light chain) is expressed less frequently and comprises a smaller proportion of total anti–Hib PS Ab in preimmune compared with postimmunization sera. Expression of Hibid-1 following immunization is similar in adults and children. These results imply that cross-reactive antigens may induce the natural antibody of children. K100 PS-cross-reactive antibody may provide protective immunity in young children upon first exposure to Hib. These cross-reactive antibodies appear to be subsequently replaced or dominated by antibody specific for Hib PS when individuals are exposed to this antigen by immunization, colonization, or infection. We demonstrate that cross reactivity of lambda antibodies may be mediated through a single light chain germline gene. The mechanism for the clonal dominance of the V_κII antibodies is unclear; the avidity for Hib PS of these K100 PS–cross-reactive antibodies from adults is similar to that of Hib specific PS antibodies (P. Shackelford, unpublished observation).

Lambda antibodies expressing the V_λII gene did not cross-react with *E. coli* K100 PS. Whether all noncross-reactive antibodies are encoded by closely related members of the V_λII gene family will require further characterization of additional antibodies.

By the age of about 5 yr most individuals have acquired protective anti–Hib PS Ab. All of the hybridomas in this study were derived from older children or adults, who had detectable preimmunization antibody. The B cells immortalized by fusion, therefore, most likely represent a secondary immune response. Despite this, V_H gene segments obtained from these hybridomas appear to be relatively unmutated (14), and it appears that some V_L genes are similarly conserved. The RC3 V_κ gene segment is identical to the A2 germline gene, and although the pertinent V_λVII germline gene is not known, the paucity of differences in V_λVII segments from four different subjects suggests these gene segments are relatively unmutated. J_κ and J_λ segments are also highly homologous to germline elements. Thus, at least a portion of the anti–Hib PS response represents the use of unmutated germline elements.

VJ joints of the majority of rearranged V_L genes also appear to be an additional source of restriction in the anti–Hib PS immune response. Although there is variability in the use of J_κ segments, V_κII-encoded V_L genes are characterized by the presence of an arginine at amino acid position 95a (13). In the RC3 V_L gene and at least one of the antibodies (B-G2a) described by Scott, this appears to have arisen by N sequence addition. In four other kappa antibodies described by Scott, alternative joining may have generated this invariant arginine (13). All of the lambda V_L genes in the present study are similarly characterized by an invariant arginine-96. The germline V_λVII segment is not known; therefore the mechanism used to generate this codon is uncertain. The invariant presence of this residue in many anti–Hib PS Abs supports the previous suggestion that it may be of great importance in antigen binding (13). This also is supported by studies of the murine anti-*p*-azophenylarsonate (Ars) response. Anti-Ars light chains also contain an invariant arginine at position 96, encoded by intracodonic splicing of a single V_κ (V_κ10-Ars) and a single J_κ (J_κ1) segment (43). This arginine is essential for Ars binding, and the substitution of tyrosine for arginine has been shown to abolish binding (44). The presence of arginine residues clustered within the CDR's of the heavy chains of murine anti–DNA antibodies correlates with increased affinity, and the arginine requirement in the anti–Hib PS response may indicate its participation in the recognition of the similar phosphate–ester linkage of the repeating carbohydrate moiety (45). Thus, although diversity exists in the use of a variety of V and J segments, certain VJ combinations, which produce arginine codons by junctional flexibility or N segment addition, may be strongly selected.

Does the restricted nature of V_H and V_L segment usage in the human anti–Hib PS response explain the age-related acquisition of immunity to this organism? In both mice and humans, preferential use of certain V_H gene segments is observed in early development. In mice, biased usage of J_H-proximal V_H gene segments occurs in fetal and neonatal animals (46, 47). Developmental regulation of V_L gene usage is less extensively studied than V_H genes. Teale and Morris noted preferential expression of certain V_κ families in LPS-stimulated murine fetal B cells compared to adult B cells, with no evidence for position-dependent bias (48). Kaushik et al. also described nonstochastic use of V_κ families in adult mice, suggesting molecular constraints may persist beyond the neonatal period (49). Two or three V_H gene segments, and a single V_κ and a single V_λ gene segments, appear to encode a large proportion of anti–Hib PS Ab in immune subjects. The use of highly conserved V gene segments in human anti–Hib PS response may place considerable restraints on the immune response. The inability to utilize these genes, whether due to chromosomal position or other molecular constraints, may be responsible for the age-related susceptibility to Hib infection. The lack of somatic hypermutation in a portion of these antibodies would also place greater dependence on the germline repertoire, in that it may be impossible to improve antibody affinity by antigen-driven selection of favorable mutations. The absence or polymorphism of these genes also may contribute to individual and ethnic susceptibility to invasive Hib disease. In addition, the repertoire differences detected in some individuals (such as the absence of kappa antibody, or the absence of the V_κII-associated CRI) may be explained by the use of other minor light chains. An individ-

Samsung Bioepis Exhibit No. 1002
Page 10563

ual missing the A2 germline gene has been described, although the functional implications of such a deletion are not known (13).

Expression of certain V_H gene family members in mice is correlated with B cell subpopulations (50). An alternative explanation for the poor response to plain Hib PS may be a maturational delay in recruitment of a critical B cell population that selectively expresses important variable region gene segments. We and others note that an arginine is expressed at the VJ joint in the great majority of anti-Hib PS light chains. In some circumstances N segment addition is required to generate this codon. The addition of these extra nucleotides is infrequent in light chain recombination, suggesting that these B cell precursors may be relatively infrequent (51). Moreover, N segment addition also appears to be developmentally regulated. Neonatal murine B cells lack N sequences, and their presence in heavy chain recombination increases with time (52). In addition, N sequence addition may also correlate with certain B cell subsets. N segments appear to be rare in Ly1-B cell-derived populations (53).

In contrast to plain polysaccharide vaccines, most young infants respond well to the newer Hib-PS protein conjugate vaccines (54). It is presently unknown if this antigen formulation recruits an alternative antibody repertoire, or if, by an uncertain mechanism, developmental restriction of a "dormant" B cell subset is overcome. To address this question, V gene expression in infants must be examined.

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Samsung Bioepis Exhibit No. 1002
Page 10564

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Samsung Bioepis Exhibit No. 1002
Page 10565

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Docket No.: AXJ-114BUSCN3
(PATENT)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of:
Leonard Bell *et al.*

Application No.: 15/260,888 Confirmation No.: 2558

Filed: September 9, 2016 Art Unit: 1644

For: TREATMENT OF PAROXYSMAL NOCTURNAL HEMOGLOBINURIA PATIENTS BY AN INHIBITOR OF COMPLEMENT

Examiner: J. L. Rogers

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

SUPPLEMENTAL INFORMATION DISCLOSURE STATEMENT (SIDS)

Dear Sir:

Applicant provides herewith a copy of an Office Action from an Application previously made of record:

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Examiner's Initials	Serial No.:	Date Mailed from USPTO	Atty. Docket No.	Examiner
	15/284,015	11-01-2016	AXJ-114BUSCN4	J. Rogers

The Examiner is requested to review the file history of this application, including cited references, Office Actions, Responses, etc., and is asked to contact Applicant's Attorney if the Examiner would like the Applicant to supply copies of any or all of the information included in this application. If Applicant's Attorney is not contacted by the Examiner with such a request, then it will be concluded that the Examiner has reviewed or will review the file content of this application.

Samsung Bioepis Exhibit No. 1002
Page 10566

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Page 10567

This Information Disclosure Statement is filed after the mailing date of a first Office Action on the merits, but before the mailing date of any of a Final Action under 37 C.F.R.§ 1.113, a Notice of Allowance under 37 C.F.R. § 1.311 or an action that otherwise closes prosecution in this application (37 C.F.R. § 1.97(c)). Accordingly, no fees are due with this submission (37 CFR § 1.97(b)(3)). However, the Director is hereby authorized to charge any fee deficiency which should have been filed herewith to our Deposit Account No. 12-0080, under Order No. AXJ-114BUSCN3.

Dated: November 4, 2016

Respectfully submitted,

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Electronic Patent Application Fee Transmittal

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Filing Date:	09-Sep-2016
Title of Invention:	TREATMENT OF PAROXYSMAL NOCTURNAL HEMOGLOBINURIA PATIENTS BY AN INHIBITOR OF COMPLEMENT
First Named Inventor/Applicant Name:	Leonard BELL
Filer:	Jill R. Gorny Sloper
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Filing Fees for Utility under 35 USC 111(a)

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Basic Filing:				
Pages:				
Claims:				
Miscellaneous-Filing:				
Petition:				
Patent-Appeals-and-Interference:				
Post-Allowance-and-Post-Issuance:				
Extension-of-Time:				

Samsung Bioepis Exhibit No. 1002
Page 10569

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Miscellaneous:				
STATUTORY OR TERMINAL DISCLAIMER	1814	1	160	160
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Samsung Bioepis Exhibit No. 1002
Page 10570

Electronic Acknowledgement Receipt	
EFS ID:	27408277
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Page 10571

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Samsung Bioepis Exhibit No. 1002
Page 10572

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Information:					
This is not an USPTO supplied IDS fillable form					
8	Other Reference-Patent/App/Search documents	15284015.pdf	297399 5ce401f4c66470c65ab8ad5f407ec6f4d0b9c717	no	6
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Warnings:					
Information:					
		Total Files Size (in bytes):	21610076		

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111
If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371
If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office
If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

Samsung Bioepis Exhibit No. 1002
Page 10573

PTO/AIA/96 (08-12)
Approved for use through 01/31/2013. OMB 0651-0031
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STATEMENT UNDER 37 CFR 3.73(c)

Applicant/Patent Owner: Alexion Pharmaceuticals, Inc.

Application No./Patent No.: 15/260,888 Filed/Issue Date: September 9, 2016

Titled: TREATMENT OF PAROXYSMAL NOCTURNAL HEMOGLOBINURIA PATIENTS BY AN INHIBITOR OF COMPLEMENT

Alexion Pharmaceuticals, Inc. (Name of Assignee) , a Corporation (Type of Assignee, e.g., corporation, partnership, university, government agency, etc.)

states that, for the patent application/patent identified above, it is (choose **one** of options 1, 2, 3 or 4 below):

1. [X] The assignee of the entire right, title, and interest.

2. [ ] An assignee of less than the entire right, title, and interest (check applicable box):

   [ ] The extent (by percentage) of its ownership interest is _____ %). Additional Statement(s) by the owners holding the balance of the interest must be submitted to account for 100% of the ownership interest.

   [ ] There are unspecified percentages of ownership. The other parties, including inventors, who together own the entire right, title and interest are:

   Additional Statement(s) by the owner(s) holding the balance of the interest must be submitted to account for the entire right, title, and interest.

3. [ ] The assignee of an undivided interest in the entirety (a complete assignment from one of the joint inventors was made). The other parties, including inventors, who together own the entire right, title, and interest are:

   Additional Statement(s) by the owner(s) holding the balance of the interest must be submitted to account for the entire right, title, and interest.

4. [ ] The recipient, via a court proceeding or the like (*e.g.*, bankruptcy, probate), of an undivided interest in the entirety (a complete transfer of ownership interest was made). The certified document(s) showing the transfer is attached.

The interest identified in option 1, 2 or 3 above (not option 4) is evidenced by either (choose **one** of options A or B below):

A. [ ] An assignment from the inventor(s) of the patent application/patent identified above. The assignment was recorded in the United States Patent and Trademark Office at Reel _____, Frame _____, or for which a copy thereof is attached.

B. [X] A chain of title from the inventor(s), of the patent application/patent identified above, to the current assignee as follows:

1. From: Leonard Bell To: Alexion Pharmaceuticals, Inc.
   The document was recorded in the United States Patent and Trademark Office at Reel 039718, Frame 0748, or for which a copy thereof is attached.

2. From: Russell P. Rother To: Alexion Pharmaceuticals, Inc.
   The document was recorded in the United States Patent and Trademark Office at Reel 039718, Frame 0748, or for which a copy thereof is attached.

PTO/AIA/96 (08-12)
Approved for use through 01/31/2013. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
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STATEMENT UNDER 37 CFR 3.73(c)

3. From: _____ To: _____
The document was recorded in the United States Patent and Trademark Office at
Reel _____, Frame _____, or for which a copy thereof is attached.

4. From: _____ To: _____
The document was recorded in the United States Patent and Trademark Office at
Reel _____, Frame _____, or for which a copy thereof is attached.

5. From: _____ To: _____
The document was recorded in the United States Patent and Trademark Office at
Reel _____, Frame _____, or for which a copy thereof is attached.

6. From: _____ To: _____
The document was recorded in the United States Patent and Trademark Office at
Reel _____, Frame _____, or for which a copy thereof is attached.

☐ Additional documents in the chain of title are listed on a supplemental sheet(s).

☒ As required by 37 CFR 3.73(c)(1)(i), the documentary evidence of the chain of title from the original owner to the assignee was, or concurrently is being, submitted for recordation pursuant to 37 CFR 3.11.

[NOTE: A separate copy (i.e., a true copy of the original assignment document(s)) must be submitted to Assignment Division in accordance with 37 CFR Part 3, to record the assignment in the records of the USPTO. See MPEP 302.08]

The undersigned (whose title is supplied below) is authorized to act on behalf of the assignee.

Signature	Date
11/2/16	
Todd Spalding	Vice President, Head of Intellectual Property
Printed or Typed Name	Title or Registration Number

PTO/AIA/25 (04-13)
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U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
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TERMINAL DISCLAIMER TO OBVIATE A PROVISIONAL DOUBLE PATENTING REJECTION OVER A PENDING "REFERENCE" APPLICATION	Docket Number (Optional) AXJ-114BUSCN3

In re Application of: Leonard BELL *et al.*

Application No.: 15/260,888-Conf. #2558

Filed: September 9, 2016

For: TREATMENT OF PAROXYSMAL NOCTURNAL HEMOGLOBINURIA PATIENTS BY AN INHIBITOR OF COMPLEMENT

The applicant, Alexion Pharmaceuticals, Inc., owner of 100 percent interest in the instant application hereby disclaims, except as provided below, the terminal part of the statutory term of any patent granted on the instant application which would extend beyond the expiration date of the full statutory term of any patent granted on pending **reference** Application Number (see attached), filed, _____, as the term of any patent granted on said **reference** application may be shortened by any terminal disclaimer filed prior to the grant of any patent on the pending **reference** application. The applicant hereby agrees that any patent so granted on the instant application shall be enforceable only for and during such period that it and any patent granted on the **reference** application are commonly owned. This agreement runs with any patent granted on the instant application and is binding upon the grantee, its successors or assigns.

In making the above disclaimer, the applicant does not disclaim the terminal part of any patent granted on the instant application that would extend to the expiration date of the full statutory term of any patent granted on said **reference** application, "as the term of any patent granted on said **reference** application may be shortened by any terminal disclaimer filed prior to the grant of any patent on the pending **reference** application," in the event that: any such patent granted on the pending **reference** application expires for failure to pay a maintenance fee, is held unenforceable, is found invalid by a court of competent jurisdiction, is statutorily disclaimed in whole or terminally disclaimed under 37 CFR 1.321, has all claims canceled by a reexamination certificate, is reissued, or is in any manner terminated prior to the expiration of its full statutory term as shortened by any terminal disclaimer filed prior to its grant.

Check either box 1 or 2 below, if appropriate.

1. [X] The undersigned is the applicant. If the applicant is an assignee, the undersigned is authorized to act on behalf of the assignee.

I hereby acknowledge that any willful false statements made are punishable under 18 U.S.C. 1001 by fine or imprisonment of not more than five (5) years, or both.

2. [ ] The undersigned is an attorney or agent of record. Reg. No. _____



Signature

11/2/2016
Date

Todd Spalding
Typed or printed name

Vice President, Head of Intellectual Property
Title

Telephone Number

[X] Terminal disclaimer fee under 37 CFR 1.20(d) is included.

WARNING: Information on this form may become public. Credit card information should not be included on this form. Provide credit card information and authorization on PTO-2038.

Samsung Bioepis Exhibit No. 1002
Page 10576

SUPPLEMENTAL SHEET FOR TERMINAL DISCLAIMER TO OBVIATE A PROVISIONAL DOUBLE PATENTING REJECTION OVER A PENDING "REFERENCE" APPLICATION	Docket Number (Optional) AXJ-114BUSCN3

Reference application Nos. applicable to this terminal disclaimer (referenced on first page):

15/148,839 (filed May 6, 2016)

15/284,015 (filed October 3, 2016)

Samsung Bioepis Exhibit No. 1002
Page 10577

I hereby certify that this paper (along with any paper referred to as being attached or enclosed) is being transmitted via the Office electronic filing system in accordance with 37 CFR § 1.6(a)(4).

Dated: November 4, 2016
Electronic Signature for Jill Gorny Sloper, Esq.: /Jill Gorny Sloper, Esq./

Docket No.: AXJ-114BUSCN3
(PATENT)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of:
Leonard Bell *et al.*

Application No.: 15/260,888 | Confirmation No.: 2558

Filed: September 9, 2016 | Art Unit: 1644

For: TREATMENT OF PAROXYSMAL NOCTURNAL HEMOGLOBINURIA PATIENTS BY AN INHIBITOR OF COMPLEMENT | Examiner: J. L. Rogers

MS Sequence
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

STATEMENT PURSUANT TO 37 CFR 1.821

Dear Sir:

Submitted herewith in connection with the above-referenced patent application and in full compliance with 37 C.F.R. §§1.821-1.825 is a computer readable copy and paper copy of the Sequence Listing (filed together as a .txt file via the United States Patent Office's Electronic Filing System).

I hereby state that I have reviewed the paper copy of the Sequence Listing, as required by 37 CFR 1.821(c), and have reviewed the computer readable form of the Sequence Listing, as required by 37 CFR 1.821(e), and that the content of the paper and computer readable copies for the above-referenced Patent application are the same as required by 37 CFR 1.821(f) (note that these documents are submitted as one electronic file). No new matter has been added to the Sequence Listing.

Samsung Bioepis Exhibit No. 1002
Page 10578

Dated: November 4, 2016

Respectfully submitted,

Electronic signature: /Jill Gorny Sloper, Esq./
Jill Gorny Sloper, Esq.
Registration No.: 60,760
NELSON MULLINS RILEY & SCARBOROUGH LLP
One Post Office Square
Boston, Massachusetts 02109-2127
(617) 217-4630
(617) 742-4214 (Fax)
Attorney/Agent For Applicant

DocCode – SEQ.TXT

SCORE Placeholder Sheet for IFW Content

Application Number: 15260888 Document Date: 11/04/2016

The presence of this form in the IFW record indicates that the following document type was received in electronic format on the date identified above. This content is stored in the SCORE database.

Since this was an electronic submission, there is no physical artifact folder, no artifact folder is recorded in PALM, and no paper documents or physical media exist. The TIFF images in the IFW record were created from the original documents that are stored in SCORE.

- Sequence Listing

At the time of document entry (noted above):

- USPTO employees may access SCORE content via eDAN using the Supplemental Content tab, or via the SCORE web page.
- External customers may access SCORE content via PAIR using the Supplemental Content tab.

Form Revision Date: August 26, 2013

Samsung Bioepis Exhibit No. 1002
Page 10580

PTO/SB/06 (09-11)
Approved for use through 1/31/2014. OMB 0651-0032
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
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PATENT APPLICATION FEE DETERMINATION RECORD Substitute for Form PTO-875	Application or Docket Number 15/260,888	Filing Date 09/09/2016	☐ To be Mailed

ENTITY: ☒ LARGE ☐ SMALL ☐ MICRO

APPLICATION AS FILED – PART I

FOR	(Column 1) NUMBER FILED	(Column 2) NUMBER EXTRA	RATE ($)	FEE ($)
☐ BASIC FEE (37 CFR 1.16(a), (b), or (c))	N/A	N/A	N/A	
☐ SEARCH FEE (37 CFR 1.16(k), (i), or (m))	N/A	N/A	N/A	
☐ EXAMINATION FEE (37 CFR 1.16(o), (p), or (q))	N/A	N/A	N/A	
TOTAL CLAIMS (37 CFR 1.16(i))	minus 20 =	*	X $ =	
INDEPENDENT CLAIMS (37 CFR 1.16(h))	minus 3 =	*	X $ =	
☐ APPLICATION SIZE FEE (37 CFR 1.16(s))	If the specification and drawings exceed 100 sheets of paper, the application size fee due is $310 ($155 for small entity) for each additional 50 sheets or fraction thereof. See 35 U.S.C. 41(a)(1)(G) and 37 CFR 1.16(s).			
☐ MULTIPLE DEPENDENT CLAIM PRESENT (37 CFR 1.16(j))				
* If the difference in column 1 is less than zero, enter "0" in column 2.			TOTAL	

APPLICATION AS AMENDED – PART II

AMENDMENT	11/04/2016	(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	RATE ($)	ADDITIONAL FEE ($)
	Total (37 CFR 1.16(i))	* 10	Minus	** 20	= 0	X $80 =	0
	Independent (37 CFR 1.16(h))	* 1	Minus	***3	= 0	X $420 =	0
	☐ Application Size Fee (37 CFR 1.16(s))						
	☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))						
						TOTAL ADD'L FEE	**0**

AMENDMENT		(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	RATE ($)	ADDITIONAL FEE ($)
	Total (37 CFR 1.16(i))	*	Minus	**	=	X $ =	
	Independent (37 CFR 1.16(h))	*	Minus	***	=	X $ =	
	☐ Application Size Fee (37 CFR 1.16(s))						
	☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))						
						TOTAL ADD'L FEE	

* If the entry in column 1 is less than the entry in column 2, write "0" in column 3.
** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 20, enter "20".
*** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 3, enter "3".
The "Highest Number Previously Paid For" (Total or Independent) is the highest number found in the appropriate box in column 1.

LIE
GYZELL P. JOHNSON SMITH

This collection of information is required by 37 CFR 1.16. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 12 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**
If you need assistance in completing the form, call 1-800-PTO-9199 and select option 2.

Samsung Bioepis Exhibit No. 1002
Page 10581

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Sequence Listing was accepted.
If you need help call the Patent Electronic Business Center at (866)
217-9197 (toll free).
Reviewer: Douglas, Keisha (ASRC)
Timestamp: [year=2016; month=11; day=10; hr=16; min=49; sec=12; ms=286;
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Samsung Bioepis Exhibit No. 1002
Page 10582

Validated By CRFValidator v 1.0.5

Application No: 15260888 Version No: 2.0

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Samsung Bioepis Exhibit No. 1002
Page 10583

SEQUENCE LISTING

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<120> TREATMENT OF PAROXYSMAL NOCTURNAL HEMOGLOBINURIA PATIENTS
BY AN INHIBITOR OF COMPLEMENT

<130> AXJ-114BUSCN3

<140> US 15/260,888
<141> 2016-09-09

<150> 15/148,839
<151> 2016-05-06

<150> 13/426,973
<151> 2012-03-22

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<151> 2009-05-13

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Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Ile Phe Ser Asn Tyr
20 25 30

Trp Ile Gln Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
35 40 45

Gly Glu Ile Leu Pro Gly Ser Gly Ser Thr Glu Tyr Thr Glu Asn Phe
50 55 60

Lys Asp Arg Val Thr Met Thr Arg Asp Thr Ser Thr Ser Thr Val Tyr
65 70 75 80

Samsung Bioepis Exhibit No. 1002
Page 10584

```
Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95

Ala Arg Tyr Phe Phe Gly Ser Ser Pro Asn Trp Tyr Phe Asp Val Trp
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Trp Ile Gln Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
        35                  40                  45

Gly Glu Ile Leu Pro Gly Ser Gly Ser Thr Glu Tyr Thr Glu Asn Phe
    50                  55                  60

Lys Asp Arg Val Thr Met Thr Arg Asp Thr Ser Thr Ser Thr Val Tyr
65                  70                  75                  80

Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95

Ala Arg Tyr Phe Phe Gly Ser Ser Pro Asn Trp Tyr Phe Asp Val Trp
            100                 105                 110

Gly Gln Gly Thr Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro
        115                 120                 125

Ser Val Phe Pro Leu Ala Pro Cys Ser Arg Ser Thr Ser Glu Ser Thr
    130                 135                 140
```


Samsung Bioepis Exhibit No. 1002
Page 10585

```
Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr
145                 150                 155                 160

Val Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro
                165                 170                 175

Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr
            180                 185                 190

Val Pro Ser Ser Asn Phe Gly Thr Gln Thr Tyr Thr Cys Asn Val Asp
        195                 200                 205

His Lys Pro Ser Asn Thr Lys Val Asp Lys Thr Val Glu Arg Lys Cys
    210                 215                 220

Cys Val Glu Cys Pro Pro Cys Pro Ala Pro Pro Val Ala Gly Pro Ser
225                 230                 235                 240

Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg
                245                 250                 255

Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser Gln Glu Asp Pro
            260                 265                 270

Glu Val Gln Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala
        275                 280                 285

Lys Thr Lys Pro Arg Glu Glu Gln Phe Asn Ser Thr Tyr Arg Val Val
    290                 295                 300

Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr
305                 310                 315                 320

Lys Cys Lys Val Ser Asn Lys Gly Leu Pro Ser Ser Ile Glu Lys Thr
                325                 330                 335

Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu
            340                 345                 350

Pro Pro Ser Gln Glu Glu Met Thr Lys Asn Gln Val Ser Leu Thr Cys
        355                 360                 365
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Samsung Bioepis Exhibit No. 1002
Page 10586

```
Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser
    370                 375                 380

Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp
385                 390                 395                 400

Ser Asp Gly Ser Phe Phe Leu Tyr Ser Arg Leu Thr Val Asp Lys Ser
                405                 410                 415

Arg Trp Gln Glu Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala
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            20                  25                  30

Leu Ser Ala Ser Val Gly Asp Arg Val Thr Ile Thr Cys Gly Ala Ser
        35                  40                  45

Glu Asn Ile Tyr Gly Ala Leu Asn Trp Tyr Gln Gln Lys Pro Gly Lys
    50                  55                  60

Ala Pro Lys Leu Leu Ile Tyr Gly Ala Thr Asn Leu Ala Asp Gly Val
65                  70                  75                  80

Pro Ser Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr
                85                  90                  95

Ile Ser Ser Leu Gln Pro Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Asn
            100                 105                 110
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Samsung Bioepis Exhibit No. 1002
Page 10587

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Val Leu Asn Thr Pro Leu Thr Phe Gly Gln Gly Thr Lys Val Glu Ile
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Lys Arg Thr
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Leu Asn Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
        35                  40                  45


Tyr Gly Ala Thr Asn Leu Ala Asp Gly Val Pro Ser Arg Phe Ser Gly
    50                  55                  60


Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65                  70                  75                  80


Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Asn Val Leu Asn Thr Pro Leu
                85                  90                  95


Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Arg Thr Val Ala Ala
            100                 105                 110


Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln Leu Lys Ser Gly
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Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr Pro Arg Glu Ala
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Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser Gly Asn Ser Gln
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Samsung Bioepis Exhibit No. 1002
Page 10588

145 150 155 160

Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr Tyr Ser Leu Ser
165 170 175

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Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro Val Thr Lys Ser
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Phe Asn Arg Gly Glu Cys
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Asp

<210> 7
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Samsung Bioepis Exhibit No. 1002
Page 10589

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1 5

Samsung Bioepis Exhibit No. 1002
Page 10590

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
15/260,888	09/09/2016	Leonard BELL	AXJ-114BUSCN3	2558

133485 7590 11/14/2016

Nelson Mullins Riley & Scarborough LLP/Alexion
One Post Office Square
30th Floor
Boston, MA 02109-2127

EXAMINER	
ROGERS, JAMES L	

ART UNIT	PAPER NUMBER
1644	

NOTIFICATION DATE	DELIVERY MODE
11/14/2016	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

ipboston.docketing@nelsonmullins.com
chris.schlauch@nelsonmullins.com
ipqualityassuranceboston@nelsonmullins.com

Applicant-Initiated Interview Summary	Application No.	Applicant(s)	
	15/260,888	BELL ET AL.	
	Examiner	Art Unit	
	JAMES ROGERS	1644	

All participants (applicant, applicant's representative, PTO personnel):

(1) *JAMES ROGERS*.

(2) *DANIEL KOLKER, SPE*.

(3) *JANE REMILLARD*.

(4) *DARRELL FONTENOT*.

Date of Interview: *01 November 2016*.

Type: ☒ Telephonic ☐ Video Conference
☐ Personal [copy given to: ☐ applicant ☐ applicant's representative]

Exhibit shown or demonstration conducted: ☐ Yes ☒ No.
If Yes, brief description: _____.

Issues Discussed ☐101 ☐112 ☐102 ☐103 ☒Others
(For each of the checked box(es) above, please describe below the issue and detailed description of the discussion)

Claim(s) discussed: *1*.

Identification of prior art discussed: _____.

Substance of Interview
(For each issue discussed, provide a detailed description and indicate if agreement was reached. Some topics may include: identification or clarification of a reference or a portion thereof, claim interpretation, proposed amendments, arguments of any applied references etc...)

Proposed possible amendments to claim 1 were discussed. No agreement was reached but applicant agreed to submit an amendment/response to the prior office action.

Applicant recordation instructions: The formal written reply to the last Office action must include the substance of the interview. (See MPEP section 713.04). If a reply to the last Office action has already been filed, applicant is given a non-extendable period of the longer of one month or thirty days from this interview date, or the mailing date of this interview summary form, whichever is later, to file a statement of the substance of the interview

Examiner recordation instructions: Examiners must summarize the substance of any interview of record. A complete and proper recordation of the substance of an interview should include the items listed in MPEP 713.04 for complete and proper recordation including the identification of the general thrust of each argument or issue discussed, a general indication of any other pertinent matters discussed regarding patentability and the general results or outcome of the interview, to include an indication as to whether or not agreement was reached on the issues raised.

☐ Attachment

/JAMES ROGERS/ Examiner, Art Unit 1644	/DANIEL E. KOLKER/ Supervisory Patent Examiner, Art Unit 1644

Summary of Record of Interview Requirements

Manual of Patent Examining Procedure (MPEP), Section 713.04, Substance of Interview Must be Made of Record
A complete written statement as to the substance of any face-to-face, video conference, or telephone interview with regard to an application must be made of record in the application whether or not an agreement with the examiner was reached at the interview.

Title 37 Code of Federal Regulations (CFR) § 1.133 Interviews
Paragraph (b)

In every instance where reconsideration is requested in view of an interview with an examiner, a complete written statement of the reasons presented at the interview as warranting favorable action must be filed by the applicant. An interview does not remove the necessity for reply to Office action as specified in §§ 1.111, 1.135. (35 U.S.C. 132)

37 CFR §1.2 Business to be transacted in writing.
All business with the Patent or Trademark Office should be transacted in writing. The personal attendance of applicants or their attorneys or agents at the Patent and Trademark Office is unnecessary. The action of the Patent and Trademark Office will be based exclusively on the written record in the Office. No attention will be paid to any alleged oral promise, stipulation, or understanding in relation to which there is disagreement or doubt.

The action of the Patent and Trademark Office cannot be based exclusively on the written record in the Office if that record is itself incomplete through the failure to record the substance of interviews.

It is the responsibility of the applicant or the attorney or agent to make the substance of an interview of record in the application file, unless the examiner indicates he or she will do so. It is the examiner's responsibility to see that such a record is made and to correct material inaccuracies which bear directly on the question of patentability.

Examiners must complete an Interview Summary Form for each interview held where a matter of substance has been discussed during the interview by checking the appropriate boxes and filling in the blanks. Discussions regarding only procedural matters, directed solely to restriction requirements for which interview recordation is otherwise provided for in Section 812.01 of the Manual of Patent Examining Procedure, or pointing out typographical errors or unreadable script in Office actions or the like, are excluded from the interview recordation procedures below. Where the substance of an interview is completely recorded in an Examiners Amendment, no separate Interview Summary Record is required.

The Interview Summary Form shall be given an appropriate Paper No., placed in the right hand portion of the file, and listed on the "Contents" section of the file wrapper. In a personal interview, a duplicate of the Form is given to the applicant (or attorney or agent) at the conclusion of the interview. In the case of a telephone or video-conference interview, the copy is mailed to the applicant's correspondence address either with or prior to the next official communication. If additional correspondence from the examiner is not likely before an allowance or if other circumstances dictate, the Form should be mailed promptly after the interview rather than with the next official communication.

The Form provides for recordation of the following information:
- Application Number (Series Code and Serial Number)
- Name of applicant
- Name of examiner
- Date of interview
- Type of interview (telephonic, video-conference, or personal)
- Name of participant(s) (applicant, attorney or agent, examiner, other PTO personnel, etc.)
- An indication whether or not an exhibit was shown or a demonstration conducted
- An identification of the specific prior art discussed
- An indication whether an agreement was reached and if so, a description of the general nature of the agreement (may be by attachment of a copy of amendments or claims agreed as being allowable). Note: Agreement as to allowability is tentative and does not restrict further action by the examiner to the contrary.
- The signature of the examiner who conducted the interview (if Form is not an attachment to a signed Office action)

It is desirable that the examiner orally remind the applicant of his or her obligation to record the substance of the interview of each case. It should be noted, however, that the Interview Summary Form will not normally be considered a complete and proper recordation of the interview unless it includes, or is supplemented by the applicant or the examiner to include, all of the applicable items required below concerning the substance of the interview.

A complete and proper recordation of the substance of any interview should include at least the following applicable items:
1) A brief description of the nature of any exhibit shown or any demonstration conducted,
2) an identification of the claims discussed,
3) an identification of the specific prior art discussed,
4) an identification of the principal proposed amendments of a substantive nature discussed, unless these are already described on the Interview Summary Form completed by the Examiner,
5) a brief identification of the general thrust of the principal arguments presented to the examiner,
   (The identification of arguments need not be lengthy or elaborate. A verbatim or highly detailed description of the arguments is not required. The identification of the arguments is sufficient if the general nature or thrust of the principal arguments made to the examiner can be understood in the context of the application file. Of course, the applicant may desire to emphasize and fully describe those arguments which he or she feels were or might be persuasive to the examiner.)
6) a general indication of any other pertinent matters discussed, and
7) if appropriate, the general results or outcome of the interview unless already described in the Interview Summary Form completed by the examiner.

Examiners are expected to carefully review the applicant's record of the substance of an interview. If the record is not complete and accurate, the examiner will give the applicant an extendable one month time period to correct the record.

Examiner to Check for Accuracy

If the claims are allowable for other reasons of record, the examiner should send a letter setting forth the examiner's version of the statement attributed to him or her. If the record is complete and accurate, the examiner should place the indication, "Interview Record OK" on the paper recording the substance of the interview along with the date and the examiner's initials.

Samsung Bioepis Exhibit No. 1002
Page 10593

Application Number	Application/Control No.	Applicant(s)/Patent under Reexamination	
	15/260,888	BELL ET AL.	

Document Code - DISQ	Internal Document – DO NOT MAIL

TERMINAL DISCLAIMER	☒ APPROVED	☐ DISAPPROVED
Date Filed : 11/4/16	This patent is subject to a Terminal Disclaimer	

Approved/Disapproved by:
JEAN PROCTOR

U.S. Patent and Trademark Office

Samsung Bioepis Exhibit No. 1002
Page 10594

UNITED STATES PATENT AND TRADEMARK OFFICE

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15/260,888	09/09/2016	Leonard BELL	AXJ-114BUSCN3	2558

133485 7590 12/22/2016

Nelson Mullins Riley & Scarborough LLP/Alexion
One Post Office Square
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EXAMINER	
ROGERS, JAMES L	

ART UNIT	PAPER NUMBER
1644	

NOTIFICATION DATE	DELIVERY MODE
12/22/2016	ELECTRONIC

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Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

ipboston.docketing@nelsonmullins.com
chris.schlauch@nelsonmullins.com
ipqualityassuranceboston@nelsonmullins.com

Office Action Summary	Application No. 15/260,888	Applicant(s) BELL ET AL.	
	Examiner JAMES ROGERS	Art Unit 1644	AIA (First Inventor to File) Status No

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTHS FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *11/4/2016*.

☐ A declaration(s)/affidavit(s) under **37 CFR 1.130(b)** was/were filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ An election was made by the applicant in response to a restriction requirement set forth during the interview on _____; the restriction requirement and election have been incorporated into this action.

4)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims*

5)☒ Claim(s) *1-10* is/are pending in the application.

5a) Of the above claim(s) _____ is/are withdrawn from consideration.

6)☐ Claim(s) _____ is/are allowed.

7)☒ Claim(s) *1-10* is/are rejected.

8)☐ Claim(s) _____ is/are objected to.

9)☐ Claim(s) _____ are subject to restriction and/or election requirement.

* If any claims have been determined allowable, you may be eligible to benefit from the **Patent Prosecution Highway** program at a participating intellectual property office for the corresponding application. For more information, please see http://www.uspto.gov/patents/init_events/pph/index.jsp or send an inquiry to PPHfeedback@uspto.gov.

Application Papers

10)☐ The specification is objected to by the Examiner.

11)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

Certified copies:

a)☐ All b)☐ Some** c)☐ None of the:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

** See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)

2) ☒ Information Disclosure Statement(s) (PTO/SB/08a and/or PTO/SB/08b) Paper No(s)/Mail Date *10/21/2016, 11/4/2016*.

3) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .

4) ☐ Other: _____.

DETAILED ACTION

1. Claims 1-10 pending and under consideration in the instant examination.

2. The present application is being examined under the pre-AIA first to invent provisions.

3. Applicant's IDSs filed on 10/21/2016 and 11/4/2016 are acknowledged and have been considered.

4. Applicant has overcome the ODP rejections which were in the prior OA mailed on 11/4/2016 given applicant's approved TD over US Patent Application 15/148,839 (Note: applicant's has also filed an approved TD over US Patent application 15/284,015).

Claim Rejections - 35 USC § 102

5. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) *the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.*

6. Claims 1-2 and 7-10 are rejected under 35 U.S.C. 102(b) as being anticipated by Hillmen et al. (N Engl J Med 2004; 350: 552-9, IDS Ref. of 10/21/2016), as is evidenced by applicant's specification as filed at p.44 and Thomas et al. (Molecular Immunology, 33(17/18), pp.1389-1401, 1996).

With respect to base claim 1, Hillmen teaches a method for treating a human patient that suffers from paroxysmal nocturnal hemoglobinuria (PNH) by administering to the patient an effective amount of eculizumab (p. 552, "methods") which specifically binds to the terminal complement protein C5, inhibiting its cleavage into C5a and C5b (p. 553, 3rd ¶).

While Hillmen does not specifically recite that the antibody that binds C5 comprises a heavy chain consisting of SEQ ID NO: 2 and a light chain consisting of SEQ ID NO:4, the specification as filed at p. 44 discloses that SEQ ID NO: 2 and SEQ ID NO: 4 constitute the H and L chains for "eculizumab" and Hillmen, as noted supra, teaches administering "eculizumab". Hillmen further teaches that "eculizumab" is a recombinant humanized antibody that binds to C5 (p. 553, 3rd ¶) and cites Thomas which in turn describes in detail humanization of the clone referred to as "5G1.1" arrive at the humanized h5G1.1 which retain both the affinity and blocking functions of the murine 5g1.1 antibody (abstract). Accordingly and in absence of evidence to the contrary, the

currently recited SEQ ID NO: 2 and SEQ ID NO: 4 which constitute the L and H chains of "eculizumab" are considered to be inherent properties of the "eculizumab" anti-C5 humanized monoclonal antibody taught by Hillmen.

Claim 2 is included because Hillmen teaches that the patients received eculizumab by infusion (p. 554 under "Treatment Schedule").

Claim 7 is included because Hillmen teaches that the patients had previously been diagnosed of aplastic anemia (p. 555, 1st ¶).

Claim 8 is included because Hillmen teaches that patients received infusions of eculizumab (600 mg) every week for four weeks, followed one week later by a 900 mg dose and then by a dose of 900 mg every other week through week 12 (p. 552 under "methods" and p. 554 under "treatment schedule").

Claims 9-10 are included because Hillmen teaches that a decrease in lactate dehydrogenase began after a single dose of eculizumab (immediate decrease occurs within 1 week of administration of the antibody) in all patients and remained within or just above the normal range for the duration of the study (sustained decrease in mean levels of LDH) (p. 555, last ¶).

The reference teachings anticipate the claimed invention.

Claim Rejections - 35 USC § 103

7. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained even though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

8. Claims 1-4 and 7-10 rejected under 35 U.S.C. 103(a) as being unpatentable over Hillmen et al. (N Engl J Med 2004; 350: 552-9), in view of Thomas et al. (Molecular Immunology, 33(17/18), pp.1389-1401, 1996) and of Evans et al. (US 6,355,245 B1, issued 3/12/2002).

The prior art teachings of Hillmen are discussed above.

To the extent that applicant intends to argue that Hillmen on its own does not constitute an enabling references because it does not explicitly place the eculizumab antibody in the public domain by not enabling one of ordinary skill in the art to make and use eculizumab comprising SEQ ID NO: 2 and 4 as currently claimed, Hillmen discloses (p. 553, 3rd¶) that eculizumab is a recombinant human antibody that binds to C5, and refers to reference number 15 (Thomas) as disclosing more information about eculizumab. Thomas in turn discloses that eculizumab is the humanized antibody h5G1.1. The '245 patent further discloses and claims the antibody made by hybridoma 5G1.1 (see for example claims 20-21) and thus places the 5G1.1 hybridoma and the antibody produced by it into the public domain.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to follow the teachings of Hillmen, Thomas and the ‘245 patent to arrive at the currently claimed invention. Hillmen and Thomas collectively teach that the 5G1.1 antibody can be used to treat PNH, and the ‘245 patent provides the public with this antibody. Thus one of ordinary skill in the art would have found it obvious to use this publicly available antibody in the methods disclosed by Hillmen.

From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

9. Claims 1-10 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hillmen et al. (N Engl J Med 2004; 350: 552-9), in view of Thomas et al. (Molecular Immunology, 33(17/18), pp.1389-1401, 1996) and of Evans et al. (US 6,355,245 B1, issued 3/12/2002), as applied to claims 1-4 and 7-10 above, and further in view of Wang (US 2005/0271660).

The prior art teachings of Hillmen, Thomas and the ‘245 patent are discussed supra.

The prior art teachings differ from the claimed invention in the recitation that the antibody is administered at a dosage level of between 5-50 mg/kg per patient per

treatment as in claim 3, that the composition is in a single unit dosage form as in claim 4 and that the single unit dosage form is a 300 mg single unit dosage form as in claim 5.

The prior art teachings further differ in the recitation that the pharmaceutical composition comprises a 300 mg single-use formulation of 30 ml of a 10 mg/ml sterile, preservative free solution as in claim 6.

The ‘245 patent further teaches antibody 5G1.1, which is the same as eculizumab (discussion supra), is effective at doses of 2.2, 3, or 5 mg per kg body weight; this corresponds to 154, 210, or 350 mg of antibody for a 70kg adult human (‘245 patent, column 16 lines 10-30). Evans (the ‘245 patent) also teaches that eculizumab is therapeutically effective when as little as 210 mg are present (column 16 lines 10-15). Evans teaches that the antibodies are particularly advantageous in that they are highly active even when administered in low doses (col 8 lines 25-32), providing a reasonable expectation of success in treating PHN with a dose less than what was disclosed by Hillmen. The reference teaches that it is within the skill of an artisan, particularly a physician, to determine the optimal dose (column 18 lines 15-30). Evans teaches formulations of the anti-C5 antibodies may be formulated in a pharmaceutically effective carrier such saline, which is considered to be a "preservative free solution". (col 18 lines 30-45).

Neither Hillmen nor the ‘245 patent (Evans) teaches a 300 mg single unit dosage as recited in the claims.

Nevertheless it would have been obvious to one of ordinary skill in the art to modify the teachings of Hillmen to administer 300 mg single unit dosages. Hillmen teaches that both 600 and 900 mg dosages can be used, and since Evans patent teaches that 210 or 350 mg of antibody would be expected to be therapeutically effective, arriving at the 300 mg dosage would be routine, convenient and obvious. One of ordinary skill in the art would have a reasonable expectation of success, as Evans teaches that the antibody exerts its effect at low doses.

It is further noted, [I]t is not inventive to discover the optimum or workable ranges by routine experimentation.” In re Aller, 220 F.2d 454, 456 (CCPA 1955); see also In re Peterson, 315 F.3d 1325 (Fed. Cir. 2003). “Only if the ‘results of optimizing a variable’ are ‘unexpectedly good’ can a patent be obtained for the claimed critical range.” In re Geisler, 116 F.3d 1465, 1469 (Fed. Cir. 1997) (quoting In re Antonie, 559 F.2d 618, 620 (CCPA 1977)). “[Discovery of an optimum value of a result effective variable in a known process is ordinarily within the skill of the art.” In re Boesch, 617 F.2d 272, 276 (CCPA 1980).

Finally, **Wang** teaches that eculizumab is highly soluble, including at up to 30 mg per ml (paragraph 0171, Figure 10). Wang further teaches that pharmaceutically acceptable carriers include pyrogen-free water may be used in formulation of the antibody (¶71)

(sterile, preservative free solution). Therefore the artisan of ordinary skill would have had a reasonable expectation of success in making a 10 mg / ml solution of the antibody sterile, preservative free solution.

From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

10. No claim is allowed.

11. Any inquiry concerning this communication or earlier communications from the examiner should be directed to James Rogers whose telephone number is (571) 270-5374. The examiner can normally be reached Monday through Friday from 8:00 am to 5:30 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, **Daniel Kolker** can be reached on (571) 272-3181. The fax number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

December 5, 2016 /JAMES ROGERS/
Art Unit 1644

/DANIEL E. KOLKER/

Supervisory Patent Examiner, Art Unit 1644

Notice of References Cited	Application/Control No. 15/260,888	Applicant(s)/Patent Under Reexamination BELL ET AL.	
	Examiner JAMES ROGERS	Art Unit 1644	Page 1 of 1

U.S. PATENT DOCUMENTS

*		Document Number Country Code-Number-Kind Code	Date MM-YYYY	Name	CPC Classification	US Classification
*	A	US-6,355,245 B1	03-2002	Evans; Mark J.	C07K14/472	424/130.1
*	B	US-2005/0271660 A1	12-2005	Wang, Yi	C07K16/18	424/144.1
	C	US-				
	D	US-				
	E	US-				
	F	US-				
	G	US-				
	H	US-				
	I	US-				
	J	US-				
	K	US-				
	L	US-				
	M	US-				

FOREIGN PATENT DOCUMENTS

*		Document Number Country Code-Number-Kind Code	Date MM-YYYY	Country	Name	CPC Classification
	N					
	O					
	P					
	Q					
	R					
	S					
	T					

NON-PATENT DOCUMENTS

*		Include as applicable: Author, Title Date, Publisher, Edition or Volume, Pertinent Pages)
	U	Thomas et al. "Inhibition of complement activity by humanized anti-C5 antibody and single-chain Fv" Molecular Immunology, 33(17/18), pp. 1389-1401, 1996
	V	
	W	
	X	

*A copy of this reference is not being furnished with this Office action. (See MPEP § 707.05(a).)
Dates in MM-YYYY format are publication dates. Classifications may be US or foreign.

supplemental STN search

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     (FILE 'HOME' ENTERED AT 09:40:36 ON 14 NOV 2016)

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L27            0 FILE ESBIOBASE
L28            0 FILE FOMAD
L29            0 FILE FROSTI
L30            0 FILE FSTA
L31            0 FILE GENBANK
L32            0 FILE IFIALL
L33            0 FILE IMSRESEARCH
L34            0 FILE KOSMET
L35            0 FILE MEDLINE
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L44            0 FILE USPATOLD
L45            0 FILE USPAT2
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L47            0 FILE VETU
L48            0 FILE IPA
L49            0 FILE NAPRALERT
     TOTAL FOR ALL FILES
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Samsung Bioepis Exhibit No. 1002
Page 10603

supplemental STN search

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L101            7 DUP REM L100 (0 DUPLICATES REMOVED)
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(Not for submission under 37 CFR 1.99)

Application Number	15260888
Filing Date	2016-09-09
First Named Inventor	Leonard BELL
Art Unit	1644
Examiner Name	J. L. Rogers
Attorney Docket Number	AXJ-114BUSCN3

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	2	5135916		1992-08-04	Sims et al.	
	3	5660825		1997-08-26	Sims et al.	
	4	6355245		2002-03-12	Evans et al.	
	5	7361339		2008-04-22	Bell	
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	1	2007005612	WO	A2	2007-01-11	Medimmune, Inc		
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Search Notes	Application/Control No.	Applicant(s)/Patent Under Reexamination
	15260888	BELL ET AL.
	Examiner	Art Unit
	JAMES ROGERS	1644

CPC- SEARCHED		
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CPC COMBINATION SETS - SEARCHED		
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US CLASSIFICATION SEARCHED			
Class	Subclass	Date	Examiner

SEARCH NOTES		
Search Notes	Date	Examiner
STN: DISSABS MEETINGS BIOSCI CAPLUS MEDICINE	10/19/2016	JR
EAST: PGPUB, USPAT, JPO, EPO, INVENTOR SEARCH	10/19/2016	JR

INTERFERENCE SEARCH			
US Class/ CPC Symbol	US Subclass / CPC Group	Date	Examiner
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/JAMES ROGERS/ Examiner.Art Unit 1644	

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EAST Search History (Prior Art)

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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of:
Leonard Bell *et al.*

Application No.: 15/260,888

Confirmation No.: 2558

Filed: September 9, 2016

Art Unit: 1644

For: TREATMENT OF PAROXYSMAL NOCTURNAL HEMOGLOBINURIA PATIENTS BY AN INHIBITOR OF COMPLEMENT

Examiner: J. L. Rogers

Commissioner for Patents
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SUPPLEMENTAL INFORMATION DISCLOSURE STATEMENT (SIDS)

Dear Sir:

Applicant provides herewith a copy of an Office Action from an Application previously made of record:

Office Action (copy enclosed)				
Examiner's Initials	Serial No.:	Date Mailed from USPTO	Atty. Docket No.	Examiner
	15/284,015	11-01-2016	AXJ-114BUSCN4	J. Rogers

/JAMES L ROGERS/ 11/23/2016

The Examiner is requested to review the file history of this application, including cited references, Office Actions, Responses, etc., and is asked to contact Applicant's Attorney if the Examiner would like the Applicant to supply copies of any or all of the information included in this application. If Applicant's Attorney is not contacted by the Examiner with such a request, then it will be concluded that the Examiner has reviewed or will review the file content of this application.

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /J.L.R/

Applicant respectfully requests that the Examiner initial the blank column next to the cited Office Action, to indicate that the information has been considered by the Examiner. Alternatively, Applicant requests that the Examiner insert the phrase, "All references considered except where lined through," on each page of the Information Disclosure Statement, along with the Examiner's initials.

Pursuant to 37 C.F.R. § 1.97(e)(2), no item of information contained in this Information Disclosure Statement was cited in a communication from a foreign patent office in a counterpart foreign application and, to my knowledge after making reasonable inquiry, no item of information contained in this Information Disclosure Statement was known to any individual designated in 37 C.F.R. § 1.56(c) more than three months prior to the filing of this Information Disclosure Statement.

In accordance with 37 C.F.R. § 1.704(d)(1), the item of information contained in this Information Disclosure Statement is a communication that was issued by the United States Patent and Trademark Office, and this communication was not received by any individual designated in § 1.56(c) more than thirty days prior to the filing of this Information Disclosure Statement.

The filing of this Information Disclosure Statement is not to be interpreted as a representation that the cited document is material, that an exhaustive search has been conducted, or that no other relevant information exists. Nor shall the citation of any document herein be construed *per se* as a representation that such document is prior art. Moreover, Applicant understands the Examiner will make an independent evaluation of the cited document.

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /J.L.R/

This Information Disclosure Statement is filed after the mailing date of a first Office Action on the merits, but before the mailing date of any of a Final Action under 37 C.F.R.§ 1.113, a Notice of Allowance under 37 C.F.R. § 1.311 or an action that otherwise closes prosecution in this application (37 C.F.R. § 1.97(c)). Accordingly, no fees are due with this submission (37 CFR § 1.97(b)(3)). However, the Director is hereby authorized to charge any fee deficiency which should have been filed herewith to our Deposit Account No. 12-0080, under Order No. AXJ-114BUSCN3.

Dated: November 4, 2016

Respectfully submitted,

Electronic signature: /Jill Gorny Sloper, Esq./
Jill Gorny Sloper, Esq.
Registration No.: 60,760
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Attorney/Agent For Applicant

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /J.L.R/

UNITED STATES PATENT AND TRADEMARK OFFICE

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APPLICATION NUMBER	FILING OR 371(C) DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO./TITLE
15/260,888	09/09/2016	Leonard BELL	AXJ-114BUSCN3

CONFIRMATION NO. 2558

133485
Nelson Mullins Riley & Scarborough LLP/Alexion
One Post Office Square
30th Floor
Boston, MA 02109-2127

PUBLICATION NOTICE

OC00000088177142

Title:TREATMENT OF PAROXYSMAL NOCTURNAL HEMOGLOBINURIA PATIENTS BY AN INHIBITOR OF COMPLEMENT

Publication No.US-2016-0376355-A1
Publication Date:12/29/2016

NOTICE OF PUBLICATION OF APPLICATION

The above-identified application will be electronically published as a patent application publication pursuant to 37 CFR 1.211, et seq. The patent application publication number and publication date are set forth above.

The publication may be accessed through the USPTO's publically available Searchable Databases via the Internet at www.uspto.gov. The direct link to access the publication is currently http://www.uspto.gov/patft/.

The publication process established by the Office does not provide for mailing a copy of the publication to applicant. A copy of the publication may be obtained from the Office upon payment of the appropriate fee set forth in 37 CFR 1.19(a)(1). Orders for copies of patent application publications are handled by the USPTO's Office of Public Records. The Office of Public Records can be reached by telephone at (571) 272-3150 or (800) 972-6382, by facsimile at (571) 273-3250, by mail addressed to the United States Patent and Trademark Office, Office of Public Records, Alexandria, VA 22313-1450 or via the Internet.

In addition, information on the status of the application, including the mailing date of Office actions and the dates of receipt of correspondence filed in the Office, may also be accessed via the Internet through the Patent Electronic Business Center at www.uspto.gov using the public side of the Patent Application Information and Retrieval (PAIR) system. The direct link to access this status information is currently http://pair.uspto.gov/. Prior to publication, such status information is confidential and may only be obtained by applicant using the private side of PAIR.

Further assistance in electronically accessing the publication, or about PAIR, is available by calling the Patent Electronic Business Center at 1-866-217-9197.

Office of Data Managment, Application Assistance Unit (571) 272-4000, or (571) 272-4200, or 1-888-786-0101

PTO/SB/06 (09-11)
Approved for use through 1/31/2014. OMB 0651-0032
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
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PATENT APPLICATION FEE DETERMINATION RECORD Substitute for Form PTO-875	Application or Docket Number 15/260,888	Filing Date 09/09/2016	☐ To be Mailed

ENTITY: ☒ LARGE ☐ SMALL ☐ MICRO

APPLICATION AS FILED – PART I

FOR	(Column 1) NUMBER FILED	(Column 2) NUMBER EXTRA	RATE ($)	FEE ($)
☐ BASIC FEE (37 CFR 1.16(a), (b), or (c))	N/A	N/A	N/A	
☐ SEARCH FEE (37 CFR 1.16(k), (i), or (m))	N/A	N/A	N/A	
☐ EXAMINATION FEE (37 CFR 1.16(o), (p), or (q))	N/A	N/A	N/A	
TOTAL CLAIMS (37 CFR 1.16(i))	minus 20 =	*	X $ =	
INDEPENDENT CLAIMS (37 CFR 1.16(h))	minus 3 =	*	X $ =	
☐ APPLICATION SIZE FEE (37 CFR 1.16(s))	If the specification and drawings exceed 100 sheets of paper, the application size fee due is $310 ($155 for small entity) for each additional 50 sheets or fraction thereof. See 35 U.S.C. 41(a)(1)(G) and 37 CFR 1.16(s).			
☐ MULTIPLE DEPENDENT CLAIM PRESENT (37 CFR 1.16(j))				
* If the difference in column 1 is less than zero, enter "0" in column 2.			TOTAL	

APPLICATION AS AMENDED – PART II

AMENDMENT	01/09/2017	(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	RATE ($)	ADDITIONAL FEE ($)
	Total (37 CFR 1.16(i))	* 10	Minus	** 20	= 0	X $80 =	0
	Independent (37 CFR 1.16(h))	* 1	Minus	***3	= 0	X $420 =	0
	☐ Application Size Fee (37 CFR 1.16(s))						
	☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))						
						TOTAL ADD'L FEE	0

AMENDMENT		(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	RATE ($)	ADDITIONAL FEE ($)
	Total (37 CFR 1.16(i))	*	Minus	**	=	X $ =	
	Independent (37 CFR 1.16(h))	*	Minus	***	=	X $ =	
	☐ Application Size Fee (37 CFR 1.16(s))						
	☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))						
						TOTAL ADD'L FEE	

* If the entry in column 1 is less than the entry in column 2, write "0" in column 3.
** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 20, enter "20".
*** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 3, enter "3".
The "Highest Number Previously Paid For" (Total or Independent) is the highest number found in the appropriate box in column 1.

SLIE
HELENA PAYTON

This collection of information is required by 37 CFR 1.16. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 12 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**
If you need assistance in completing the form, call 1-800-PTO-9199 and select option 2.

Samsung Bioepis Exhibit No. 1002
Page 10622

I hereby certify that this paper (along with any paper referred to as being attached or enclosed) is being transmitted via the Office electronic filing system in accordance with 37 CFR § 1.6(a)(4).

Dated: January 19, 2017
Electronic Signature for Jill Gorny Sloper, Esq.: /Jill Gorny Sloper, Esq./

Docket No.: AXJ-114BUSCN3
(PATENT)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of:
Leonard Bell *et al.*

Application No.: 15/260,888 Confirmation No.: 2558

Filed: September 9, 2016 Art Unit: 1644

For: TREATMENT OF PAROXYSMAL NOCTURNAL HEMOGLOBINURIA PATIENTS BY AN INHIBITOR OF COMPLEMENT

Examiner: J. L. Rogers

MS Amendment
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

AMENDMENT IN RESPONSE TO NON-FINAL OFFICE ACTION UNDER 37 C.F.R. § 1.111

Dear Sir:

In response to the Office Action dated December 22, 2016 (Paper No. 20161123), please amend the above-identified U.S. patent application as follows:

A Listing of the Claims is reflected on page 2 of this paper.

Remarks/Arguments begin on page 4 of this paper.

Samsung Bioepis Exhibit No. 1002
Page 10623

LISTING OF THE CLAIMS

1. **(Original)** A method of treating a patient suffering from paroxysmal nocturnal hemoglobinuria (PNH) comprising administering to the patient a pharmaceutical composition comprising an antibody that binds C5, wherein the antibody comprises a heavy chain consisting of SEQ ID NO: 2 and a light chain consisting of SEQ ID NO: 4.

2. **(Original)** The method of claim 1, wherein the pharmaceutical composition is administered by intravenous infusion.

3. **(Original)** The method of claim 1, wherein the antibody is administered to the patient at a dosage level of between 5 mg per kg and 50 mg per kg per patient per treatment.

4. **(Original)** The method of claim 1, wherein the pharmaceutical composition is in a single unit dosage form.

5. **(Original)** The method of claim 4, wherein the single unit dosage form is a 300 mg single unit dosage form.

6. **(Original)** The method of claim 1, wherein the pharmaceutical composition comprises a 300 mg single-use formulation of 30 ml of a 10 mg/ml sterile, preservative free solution.

7. **(Original)** The method of claim 1, wherein the patient is anemic.

8. **(Original)** The method of claim 1, wherein the patient is dosed as follows: 600 mg of the antibody via intravenous infusion every 7±1 days for 4 doses; followed by 900 mg of the antibody via intravenous infusion 7±1 days later; followed by a maintenance dose of 900 mg of the antibody via intravenous infusion every 14±2 days.

9. **(Original)** The method of claim 1, wherein administration of the antibody results in an immediate and sustained decrease in mean levels of lactate dehydrogenase (LDH).

10. **(Original)** The method of claim 9, wherein the immediate decrease occurs within one week of administration of the antibody.

REMARKS

Claims 1-10 are pending. Applicants reserve the right to pursue claims to any subject matter which they are entitled to claim in this or a separate application.

Information Disclosure Statement

Applicants acknowledge with appreciation the Examiner's indication that the Information Disclosure Statements submitted on October 21, 2016 and November 4, 2016 have been considered.

Rejection Under 35 U.S.C. § 102

Claims 1-2 and 7-10 are rejected under 35 U.S.C. § 102(b) as being anticipated by Hillmen *et al.* (*N. Engl. J. Med.* 2004; 350:552-9), as evidenced by the specification as filed (page 44) and Thomas *et al.* (Molecular Immunology, 33(17/18), pp. 1389, 1996). Specifically, the Examiner asserts that "the currently recited SEQ ID NO:2 and SEQ ID NO:4 which constitute the L and H chains of 'eculizumab' are considered to be inherent properties of the 'eculizumab' anti-C5 humanized antibody taught by Hillmen." The Examiner further states:

> [t]o the extent that applicant intends to argue that Hillmen on its own does not constitute an enabling reference because it does not explicitly place the eculizumab antibody in the public domain by not enabling one of ordinary skill in the art to make and use eculizumab comprising SEQ ID NO:2 and 4 as currently claimed, Hillmen discloses (p. 553, 3rd ¶) that eculizumab is a recombinant human antibody that binds to C5, and refers to reference number 15 (Thomas) as disclosing more information about eculizumab. Thomas in turn discloses that eculizumab is the humanized antibody h5G1.1. The '245 patent [US 6,355,245] further discloses and claims the antibody made by hybridoma 5G1.1 (see for example claims 20-21) and thus places the 5G1.1 hybridoma and the antibody produced by it into the public domain.

Applicants respectfully traverse the rejection. As described in the enclosed Declaration Pursuant to 37 C.F.R. § 1.132 by Dr. Leonard Bell (hereinafter "Declaration"), prior to the March 15, 2007 effective filing date of the present application, the complete structure of eculizumab was not disclosed in the prior art; nor was it available to the public. Specifically, Hillmen *et al.* fails to teach any part of the sequence of eculizumab, and U.S. Patent 6,355,245 (the '245 patent) fails to teach or in any way suggest the unique, non-naturally occurring, protein-

engineered full heavy chain of eculizumab (including the CH1-hinge-CH2-CH3 regions), which confers important, unexpected functional effects.

Nor does Thomas *et al.* describe eculizumab. Although Thomas *et al.* describes an antibody comprising the humanized variable region of eculizumab, the authors do not disclose, teach or suggest the full unique, protein-engineered heavy chain of eculizumab. The antibody described by Thomas *et al.* contains a *naturally-occurring* IgG4 heavy chain and is therefore not eculizumab, but rather another antibody that is structurally and functionally different from eculizumab.

Specifically, as evidenced by the sequence alignment within the Declaration, the heavy chain constant regions of eculizumab and the antibody described by Thomas *et al.* differ in fourteen amino acid residues (*i.e.*, four different residues in the CH1 domain, six different residues in the hinge region, and four different residues in the CH2 domain). Moreover, as discussed in the accompanying Declaration, these structural differences confer eculizumab with advantageous functional features over the antibody described by Thomas *et al.*, including decreased effector function, reduced immunogenicity and increased half-life.

In sum, the complete structure of eculizumab was not disclosed prior to the March 15, 2007 effective filing date of the present application. Moreover, as described in the accompanying Declaration, eculizumab was not publicly available prior to March 15, 2007. Therefore, prior to the effective filing date of the present application, the complete structure of eculizumab was neither taught nor suggested in the cited prior art; nor was it obtainable by way of public availability.

Accordingly, for at the least the above-discussed reasons, claims 1-2 and 7-10 are patentable, and the Examiner is respectfully requested to reconsider and withdraw this rejection.

Rejections Under 35 U.S.C. § 103

Claims 1-4 and 7-10 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Hillmen *et al.* in view of Thomas *et al.* and Evans *et al.* (U.S. Patent No. 6,355,245). Claims 1-10 are further rejected under 35 U.S.C. § 103(a) as being unpatentable over Hillmen *et al.* in view of Thomas *et al.* and Evans *et al.*, as applied to claims 1-4 and 7-10, and in further view of Wang (U.S. Patent Publication No. 2005/0271660). The Examiner relies on Hillmen *et al.*,

Thomas *et al.* and Evans *et al.* for the reasons discussed above. The Examiner relies on Wang for teaching that eculizumab is highly soluble and that pharmaceutically acceptable carriers (*e.g.*, pyrogen-free water) can be used in formulating the antibody.

Applicants respectfully traverse these rejections. As discussed above, none of Hillmen *et al.*, Thomas *et al.* or Evans *et al.* teaches the complete structure of eculizumab. Importantly, none of these references even suggests the unique non-naturally occurring, protein-engineered heavy chain of eculizumab, which confers important, unexpected functional effects.

Wang fails to cure this deficiency. Indeed, Wang fails to teach any part of the sequence of eculizumab, let alone its unique heavy chain.

Accordingly, for at the least the above-discussed reasons, claims 1-10 are patentable, and the Examiner is respectfully requested to reconsider and withdraw this rejection.

CONCLUSION

In view of the foregoing, entry of the amendments and remarks herein, reconsideration and withdrawal of all rejections, and allowance of the instant application with all pending claims is respectfully solicited. If a telephone conversation with the Applicants` attorney would help expedite the prosecution of the above-identified application, the Examiner is urged to call the Applicants` attorney at (617) 217-4630.

The Director is hereby authorized to charge any deficiency in the fees filed, asserted to be filed or which should have been filed herewith (or with any paper hereafter filed in this application by this firm) to our Deposit Account No. 12-0080, under Order No. AXJ-114BUSCN3.

Dated: January 19, 2017

Respectfully submitted,

Electronic signature: /Jill Gorny Sloper, Esq./
Jill Gorny Sloper, Esq.
Registration No.: 60,760
NELSON MULLINS RILEY & SCARBOROUGH LLP
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Attorney/Agent For Applicant

I hereby certify that this paper (along with any paper referred to as being attached or enclosed) is being transmitted via the Office electronic filing system in accordance with 37 CFR § 1.6(a)(4).

Dated: January 19, 2017
Electronic Signature for Jill Gorny Sloper, Esq.: /Jill Gorny Sloper, Esq./

Docket No.: AXJ-114BUSCN3
(PATENT)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of:
Leonard Bell *et al.*

Application No.: 15/260,888

Confirmation No.: 2558

Filed: September 9, 2016

Art Unit: 1644

For: TREATMENT OF PAROXYSMAL NOCTURNAL HEMOGLOBINURIA PATIENTS BY AN INHIBITOR OF COMPLEMENT

Examiner: J. L. Rogers

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

DECLARATION PURSUANT TO 37 CFR 1.132 BY DR. LEONARD BELL

I, Leonard Bell, M.D., a co-inventor of the subject invention, declare that:

1. I founded Alexion Pharmaceuticals, Inc. and served as its Chief Executive Officer from 1992 until 2015. In that role, I was closely involved in the development of eculizumab and in the administration and monitoring of all clinical trials involving eculizumab.

2. Prior to March 15, 2007, which is the date the subject patent application was filed, eculizumab was not available to the public. In order to be approved for marketing, eculizumab was used in clinical trials before March 15, 2007, but only under strict control and conditions of confidentiality. Patients in clinical trials of eculizumab received intravenous infusions of eculizumab at hospitals and infusion clinics and never themselves possessed samples of eculizumab. Researchers and staff involved in clinical trials of eculizumab were not permitted to use or distribute eculizumab for

Samsung Bioepis Exhibit No. 1002
Page 10630

purposes other than conducting the clinical trials, and were strictly accountable to Alexion for the inventory of eculizumab and for information about eculizumab.

3. Moreover, prior to March 15, 2007, the complete structure of eculizumab was not disclosed to the public. For example, the Hillmen reference (Hillmen et al., N. ENGL. J. MED., 350, pp. 552-59 (2004)) does not disclose any parts of the sequence of eculizumab and the '245 patent (U.S. Pat. No. 6,355,245) does not disclose or even hint at the unique non-naturally occurring, protein-engineered heavy chain (including the CH1-hinge-CH2-CH3 regions) of eculizumab.

4. Nor does the Thomas reference (Thomas et al., MOLECULAR IMMUNOLOGY, 33 (17/18), pp. 1389-1401 (1996)) describe eculizumab. The Thomas reference describes an antibody comprising the humanized variable region of eculizumab, but does not disclose or hint at the unique non-naturally occurring, protein-engineered heavy chain of eculizumab, which confers important functional effects (as discussed below). Rather, the antibody described in the Thomas reference contains a *naturally-occurring* IgG4 heavy chain. The antibody described in the Thomas reference therefore is not eculizumab. It is both structurally and functionally different from eculizumab.

5. As shown below, a sequence alignment of the heavy chain constant regions and hinge of eculizumab (shown in bold on the top line below) and that of the antibody described in the Thomas reference (shown on the bottom line below) demonstrates that the two antibodies are structurally very different, with fourteen different amino acid residues in the constant regions (underlined and highlighted) (four different residues in the CH1 domain, six different residues in the hinge region and four different residues in the CH2 domain):

```
----------------------------CH1-----------------------
ASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHT
ASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHT
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Samsung Bioepis Exhibit No. 1002
Page 10631

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----------CH1-------------------------------|Hinge-
FPAVLQSSGLYSLSSVVTVPSSNFGTQTYTCNVDHKPSNTKVDKTVERKCCV
FPAVLQSSGLYSLSSVVTVPSSSLGTKTYTCNVDHKPSNTKVDKRVESKYGP

-Hinge--|----------------CH2-----------------
ECPPCPAPP-VAGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSQEDP
PCPSCPAPEFLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSQEDP

---------CH2-------------------------------------
EVQFNWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKC
EVQFNWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKC

--------CH2-------|-------------CH3---------------
KVSNKGLPSSIEKTISKAKGQPREPQVYTLPPSQEEMTKNQVSLTCLVKG
KVSNKGLPSSIEKTISKAKGQPREPQVYTLPPSQEEMTKNQVSLTCLVKG

-------------------------CH3---------------------
FYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSRLTVDKSRWQEGNV
FYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSRLTVDKSRWQEGNV

---------CH3-------------
FSCSVMHEALHNHYTQKSLSLSLGK
FSCSVMHEALHNHYTQKSLSLSLGK
```

6. Also, the functional properties of eculizumab and the antibody described in the Thomas reference are very different. For example, eculizumab does not bind as strongly to Fcγ receptors as the Thomas antibody. Binding to the Fcγ receptors initiates and amplifies immune responses that are undesirable for an antibody intended to shut down the terminal complement pathway. Thus, engineering eculizumab to minimize binding to these receptors provided important advantages over the antibody described in the Thomas reference.

7. Eculizumab also has a much longer plasma half-life than the antibody described in the Thomas reference. It is advantageous for an antibody like eculizumab to remain in the circulation longer so that it does not need to be administered to patients as frequently.

8. Accordingly, as demonstrated by comparative data between eculizumab and the antibody described in the Thomas reference, the non-natural, protein-engineered, heavy chain of eculizumab reduces effector function activation, minimizes immunogenicity, and contributes to a longer half-life of eculizumab compared to the antibody described in the Thomas reference. These properties were surprising and unpredictable, and made eculizumab a better drug candidate than the antibody described in the Thomas reference.

9. In sum: the complete structure of eculizumab was not available to the public on or before March 15, 2007; eculizumab was not available to the public or being used by the public prior to that time; the unique protein-engineered heavy chain of eculizumab was not described in the Hillmen reference, the Thomas reference or the '245 patent; and the unique protein-engineered heavy chain of eculizumab could not be derived from the combined disclosures of the Hillmen reference, the Thomas reference and/or the '245 patent.

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or of any patent issued thereon.

Leonard Bell, M.D. 1/18/2017 Date

Electronic Acknowledgement Receipt

EFS ID:	28107744
Application Number:	15260888
International Application Number:	
Confirmation Number:	2558
Title of Invention:	TREATMENT OF PAROXYSMAL NOCTURNAL HEMOGLOBINURIA PATIENTS BY AN INHIBITOR OF COMPLEMENT
First Named Inventor/Applicant Name:	Leonard BELL
Customer Number:	133485
Filer:	Jill R. Gorny Sloper/Danielle Gamache
Filer Authorized By:	Jill R. Gorny Sloper
Attorney Docket Number:	AXJ-114BUSCN3
Receipt Date:	19-JAN-2017
Filing Date:	09-SEP-2016
Time Stamp:	16:07:39
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	no

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1		Response.pdf	150489 a0d98da3ac2ef6e19de75390ebb9b0b50a450e88	yes	7

Samsung Bioepis Exhibit No. 1002
Page 10634

	Multipart Description/PDF files in .zip description		
	Document Description	**Start**	**End**
	Amendment/Req. Reconsideration-After Non-Final Reject	1	1
	Claims	2	3
	Applicant Arguments/Remarks Made in an Amendment	4	7

Warnings:					
Information:					
2	Miscellaneous Incoming Letter	Bell_Declaration.pdf	3135451 72f899c4b9ebb134cbc750ee90c7d8018e7d2208	no	4
Warnings:					
Information:					
		Total Files Size (in bytes):	3285940		

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New Applications Under 35 U.S.C. 111
If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371
If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office
If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

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Page 10635

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Dated: January 24, 2017
Electronic Signature for Jill Gorny Sloper, Esq.: /Jill Gorny Sloper, Esq./

Docket No.: AXJ-114BUSCN3
(PATENT)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of:
Leonard Bell *et al.*

Application No.: 15/260,888 Confirmation No.: 2558

Filed: September 9, 2016 Art Unit: 1644

For: TREATMENT OF PAROXYSMAL NOCTURNAL HEMOGLOBINURIA PATIENTS BY AN INHIBITOR OF COMPLEMENT

Examiner: J. L. Rogers

Office of Initial Patent Examination's Filing Receipt Corrections
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

REQUEST FOR CORRECTED FILING RECEIPT

Dear Sir:

Applicant hereby requests that a corrected Filing Receipt be issued in the above-identified patent application to reflect an update to the Inventor information.

Please correct the Inventor(s) information from:

Leonard BELL, Woodbridge, CT;
Russell P. ROTHER, Oklahoma City, OK;

to:

Leonard BELL, Woodbridge, CT;
Russell P. ROTHER, Oklahoma City, OK;
Mark J. EVANS, Radnor, PA;

Samsung Bioepis Exhibit No. 1002
Page 10636

Applicant additionally requests that all pertinent U.S. Patent and Trademark Office records relating to the subject application be changed to reflect this correction.

The Director is hereby authorized to charge any deficiency in the fees filed, asserted to be filed or which should have been filed herewith (or with any paper hereafter filed in this application by this firm) to our Deposit Account No. 12-0080, under Order No. AXJ-114BUSCN3.

Dated: January 24, 2017

Respectfully submitted,

Electronic signature: /Jill Gorny Sloper, Esq./
Jill Gorny Sloper, Esq.
Registration No.: 60,760
NELSON MULLINS RILEY & SCARBOROUGH LLP
One Post Office Square
Boston, Massachusetts 02109-2127
(617) 217-4630
(617) 217-4699 (Fax)
Attorney/Agent For Applicant

Electronic Patent Application Fee Transmittal

Application Number:	15260888
Filing Date:	09-Sep-2016
Title of Invention:	TREATMENT OF PAROXYSMAL NOCTURNAL HEMOGLOBINURIA PATIENTS BY AN INHIBITOR OF COMPLEMENT
First Named Inventor/Applicant Name:	Leonard BELL
Filer:	Jill R. Gorny Sloper
Attorney Docket Number:	AXJ-114BUSCN3

Filed as Large Entity

Filing Fees for Utility under 35 USC 111(a)

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Basic Filing:				
Pages:				
Claims:				
Miscellaneous-Filing:				
LATE FILING FEE FOR OATH OR DECLARATION	1051	1	140	140
PROCESSING FEE, EXCEPT PROV. APPLS.	1830	1	140	140
Petition:				
Patent-Appeals-and-Interference:				

Samsung Bioepis Exhibit No. 1002
Page 10638

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Post-Allowance-and-Post-Issuance:				
Extension-of-Time:				
Miscellaneous:				
		Total in USD ($)		**280**

Samsung Bioepis Exhibit No. 1002
Page 10639

Electronic Acknowledgement Receipt

EFS ID:	28145796
Application Number:	15260888
International Application Number:	
Confirmation Number:	2558
Title of Invention:	TREATMENT OF PAROXYSMAL NOCTURNAL HEMOGLOBINURIA PATIENTS BY AN INHIBITOR OF COMPLEMENT
First Named Inventor/Applicant Name:	Leonard BELL
Customer Number:	133485
Filer:	Jill R. Gorny Sloper/Danielle Gamache
Filer Authorized By:	Jill R. Gorny Sloper
Attorney Docket Number:	AXJ-114BUSCN3
Receipt Date:	24-JAN-2017
Filing Date:	09-SEP-2016
Time Stamp:	15:17:03
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	yes
Payment Type	DA
Payment was successfully received in RAM	$280
RAM confirmation Number	012517INTEFSW00001795120080
Deposit Account	120080
Authorized User	Jill Sloper
The Director of the USPTO is hereby authorized to charge indicated fees and credit any overpayment as follows: 37 CFR 1.16 (National application filing, search, and examination fees) 37 CFR 1.17 (Patent application and reexamination processing fees)	

37 CFR 1.19 (Document supply fees)

37 CFR 1.20 (Post Issuance fees)

37 CFR 1.21 (Miscellaneous fees and charges)

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Application Data Sheet	AXJ_114BUSCN3_Corrected_ADS.pdf	63084 c217b624f8d4835bf39fb9c864a7a02046d8a8d2	no	3
Warnings:					
Information:					
This is not an USPTO supplied ADS fillable form					
2	Oath or Declaration filed	Evans_Declaration.pdf	1266858 9ba0498a444335560b764fa8f9d6da0eddaa7951	no	1
Warnings:					
Information:					
3	Request under Rule 48 correcting inventorship	AXJ_114BUSCN3_Request_to_correct_inventorship.pdf	109059 660761a4c159701e19e72e9cfebab29c77c99b69	no	2
Warnings:					
Information:					
4	Request for Corrected Filing Receipt	AXJ_114BUSCN3_Request_for_corrected_FR.pdf	110739 d0779b728c4220cfaaac6da4bf42fb222aa85fd4	no	2
Warnings:					
Information:					
5	Fee Worksheet (SB06)	fee-info.pdf	32085 66e1ad130ef8268741b2e2f052f71baddbd1c39b	no	2
Warnings:					
Information:					
		Total Files Size (in bytes):	1581825		

Samsung Bioepis Exhibit No. 1002
Page 10641

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111

If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371

If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office

If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

Samsung Bioepis Exhibit No. 1002
Page 10642

Corrected Application Data Sheet

Inventor Information

Inventor Number::	1
Given Name::	Leonard
Family Name::	BELL
City of Residence::	Woodbridge
State or Province of Residence::	CT
Country of Residence::	US
Street of mailing address::	59 Tumblebrook Road
City of mailing address::	Woodbridge
State or Province of mailing address::	CT
Country of mailing address::	US
Postal or Zip Code of mailing address::	06525

Inventor Number::	2
Given Name::	Russell
Middle Name::	P.
Family Name::	ROTHER
City of Residence::	Oklahoma City
State or Province of Residence::	OK
Country of Residence::	US
Street of mailing address::	10325 Forest Meadow Drive
City of mailing address::	Oklahoma City
State or Province of mailing address::	OK
Country of mailing address::	US

Postal or Zip Code of mailing address::	73151
Inventor Number::	3
Given Name::	Mark
Middle Name::	J.
Family Name::	EVANS
City of Residence::	Radnor
State or Province of Residence::	PA
Country of Residence::	US
Street of mailing address::	617 Twinbridge Drive
City of mailing address::	Radnor
State or Province of mailing address::	PA
Country of mailing address::	US
Postal or Zip Code of mailing address::	19087

Correspondence Information

Correspondence Customer Number::	133485
E-Mail address::	IPBoston.Docketing@nelsonmullins.com

Application Information

Application Number::	15/260,888
Filing Date::	09/09/16
Title::	TREATMENT OF PAROXYSMAL NOCTURNAL HEMOGLOBINURIA

PATIENTS BY AN INHIBITOR OF COMPLEMENT

Attorney Docket Number:: AXJ-114BUSCN3

Signature:

NOTE: This Application Data Sheet must be signed in accordance with 37 CFR 1.33(b). **However, if this Application Data Sheet is submitted with the INITIAL filing of the application and either box A or B is not checked in subsection 2 of the "Authorization or Opt-Out of Authorization to Permit Access" section, then this form must also be signed in accordance with 37 CFR 1.14(c).**

This Application Data Sheet **must** be signed by a patent practitioner if one or more of the applicants is a **juristic entity** (e.g., corporation or association). If the applicant is two or more joint inventors, this form must be signed by a patent practitioner, **all** joint inventors who are the applicant, or one or more joint inventor-applicants who have been given power of attorney (e.g., see USPTO Form PTO/AIA/81) on behalf of **all** joint inventor-applicants.

See 37 CFR 1.4(d) for the manner of making signatures and certifications.

Signature	/Jill Gorny Sloper, Esq./	Date (YYYY-MM-DD)	2017-01-24
Name	Jill Gorny Sloper, Esq.	Registration Number	60,760

PTO/AIA/01 (06-12)
Approved for use through 01/31/2014. OMB 0651-0032
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number.

DECLARATION (37 CFR 1.63) FOR UTILITY OR DESIGN APPLICATION USING AN APPLICATION DATA SHEET (37 CFR 1.76)

Title of Invention	TREATMENT OF PAROXYSMAL NOCTURNAL HEMOGLOBINURIA PATIENTS BY AN INHIBITOR OF COMPLEMENT

As the below named inventor, I hereby declare that:

This declaration is directed to:

- [ ] The attached application, or
- [x] United States application or PCT international application number 15/260,888 filed on 09/09/2016.

The above-identified application was made or authorized to be made by me.

I believe that I am the original inventor or an original joint inventor of a claimed invention in the application.

I hereby acknowledge that any willful false statement made in this declaration is punishable under 18 U.S.C. 1001 by fine or imprisonment of not more than five (5) years, or both.

WARNING:

Petitioner/applicant is cautioned to avoid submitting personal information in documents filed in a patent application that may contribute to identity theft. Personal information such as social security numbers, bank account numbers, or credit card numbers (other than a check or credit card authorization form PTO-2038 submitted for payment purposes) is never required by the USPTO to support a petition or an application. If this type of personal information is included in documents submitted to the USPTO, petitioners/applicants should consider redacting such personal information from the documents before submitting them to the USPTO. Petitioner/applicant is advised that the record of a patent application is available to the public after publication of the application (unless a non-publication request in compliance with 37 CFR 1.213(a) is made in the application) or issuance of a patent. Furthermore, the record from an abandoned application may also be available to the public if the application is referenced in a published application or an issued patent (see 37 CFR 1.14). Checks and credit card authorization forms PTO-2038 submitted for payment purposes are not retained in the application file and therefore are not publicly available.

LEGAL NAME OF INVENTOR

Inventor: Mark J. Evans Date (Optional): 22 Jan 2017

Signature: Mark J. Evans

Note: An application data sheet (PTO/SB/14 or equivalent), including naming the entire inventive entity, must accompany this form or must have been previously filed. Use an additional PTO/AIA/01 form for each additional inventor.

I hereby certify that this paper (along with any paper referred to as being attached or enclosed) is being transmitted via the Office electronic filing system in accordance with 37 CFR § 1.6(a)(4).

Dated: January 24, 2017
Electronic Signature for Jill Gorny Sloper, Esq.: /Jill Gorny Sloper, Esq./

Docket No.: AXJ-114BUSCN3
(PATENT)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of:
Leonard Bell *et al.*

Application No.: 15/260,888 | Confirmation No.: 2558

Filed: September 9, 2016 | Art Unit: 1644

For: TREATMENT OF PAROXYSMAL NOCTURNAL HEMOGLOBINURIA PATIENTS BY AN INHIBITOR OF COMPLEMENT | Examiner: J. L. Rogers

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

REQUEST TO CORRECT INVENTORSHIP UNDER 37 C.F.R. 1.48(a)

Dear Sir:

This request under 37 CFR § 1.48(a) is to add the following inventor to the above-referenced patent application:

Mark J. EVANS

This inventor was erroneously omitted from the above-referenced patent application at the time of filing.

Enclosed is a Corrected Application Data Sheet reflecting the names of all inventors in this application. A Request for Corrected Filing Receipt is also being submitted with this Request.

Samsung Bioepis Exhibit No. 1002
Page 10647

Submitted herewith is the processing fee of $140.00 pursuant to 37 CFR § 1.17(i)(1). Please charge any additional fees to our Deposit Account No. 12-0080, under Order No. AXJ-114BUSCN3, from which the undersigned is authorized to draw.

Dated: January 24, 2017

Respectfully submitted,

Electronic signature: /Jill Gorny Sloper, Esq./
Jill Gorny Sloper, Esq.
Registration No.: 60,760
NELSON MULLINS RILEY & SCARBOROUGH LLP
One Post Office Square
Boston, Massachusetts 02109-2127
(617) 217-4630
(617) 217-4699 (Fax)
Attorney/Agent For Applicant

PATENT ASSIGNMENT COVER SHEET

Electronic Version v1.1
Stylesheet Version v1.2

EPAS ID: PAT4240219

SUBMISSION TYPE:	NEW ASSIGNMENT
NATURE OF CONVEYANCE:	ASSIGNMENT

CONVEYING PARTY DATA

Name	Execution Date
MARK J. EVANS	01/23/2017

RECEIVING PARTY DATA

Name:	ALEXION PHARMACEUTICALS, INC.
Street Address:	100 COLLEGE ST.
City:	NEW HAVEN
State/Country:	CONNECTICUT
Postal Code:	06510

PROPERTY NUMBERS Total: 1

Property Type	Number
Application Number:	15260888

CORRESPONDENCE DATA

Fax Number: (617)217-4699

Correspondence will be sent to the e-mail address first; if that is unsuccessful, it will be sent using a fax number, if provided; if that is unsuccessful, it will be sent via US Mail.

Phone: (617) 217-4700
Email: IPBoston.Docketing@nelsonmullins.com, danielle.gamache@nelsonmullins.com
Correspondent Name: NELSON MULLINS RILEY & SCARBOROUGH LLP
Address Line 1: ONE POST OFFICE SQUARE
Address Line 4: BOSTON, MASSACHUSETTS 02109-2127

ATTORNEY DOCKET NUMBER:	AXJ-114BUSCN3
NAME OF SUBMITTER:	JILL GORNY SLOPER, ESQ.
SIGNATURE:	/Jill Gorny Sloper, Esq./
DATE SIGNED:	01/24/2017
	This document serves as an Oath/Declaration (37 CFR 1.63).

Total Attachments: 2
source=Evans_Assignment#page1.tif
source=Evans_Assignment#page2.tif

ASSIGNMENT BY INVENTOR

I, Mark J. EVANS, of Radnor, Pennsylvania, for good and valuable consideration paid to me by

Alexion Pharmaceuticals, Inc.

a Corporation of Delaware, having its principal place of business at 100 College St., New Haven, Connecticut 06510, the receipt of which is hereby acknowledged, do hereby sell, assign and transfer unto said

Alexion Pharmaceuticals, Inc.

its successors and assigns, the entire interest for the United States of America and all foreign countries including all rights of priority under the International Convention for the Protection of Industrial Property in a certain invention or improvement in

TREATMENT OF PAROXYSMAL NOCTURNAL HEMOGLOBINURIA PATIENTS BY AN INHIBITOR OF COMPLEMENT

described in an application

[ ] Executed by me of even date herewith and about to be filed

or

[x] Application No. 15/260888, filed on September 9, 2016

in the United States Patent and Trademark Office, and in all Letters Patent of the United States and all foreign countries which may or shall be granted on said invention, or any parts thereof, or on said application, or any divisional, continuing, reissue or other applications based in whole or in part thereon. And I agree, for myself and my executors and administrators, with said Corporation and its successors and assigns but at its or their expense and charges, hereafter to execute all applications, amended specifications, deed or other instrument, and to do all acts necessary or proper to secure the grant of Letters Patent in the United States and in all other countries to said Corporation, with specifications and claims in such form as shall be approved by the counsel of said Corporation and to vest and confirm in said Corporation, its successors and assigns, the legal title to all such patents.

And I do hereby authorize and request the Commissioner of Patents and Trademarks of the United States to issue such Letters Patent as shall be granted upon said application or applications based thereon to said Corporation, its successors and assigns.

And I do further hereby grant the attorneys/agents of Nelson Mullins Riley & Scarborough LLP, the power to insert on this Assignment the filing date and/or application number of said application.

Samsung Bioepis Exhibit No. 1002
Page 10650

Mark J. Evans

Date: Jan 23, 2017

United States of America)
State of Pennsylvania) ss.:
County of Chester)

On this 23 day of January, 2017 before me, the the undersigned notary public, personally appeared Mark J Evans (name of document signer), proved to me through satisfactory evidence of identification, which was PA Drivers License, to be the person whose name is signed on the preceding or attached document in my presence.

Susanne B Martin (official signature and seal of notary)

My commission expires 10-04-2017

COMMONWEALTH OF PENNSYLVANIA
NOTARIAL SEAL
SUSANNE B. MARTIN, Notary Public
Easttown Twp., Chester County
My Commission Expires October 4, 2017

Samsung Bioepis Exhibit No. 1002
Page 10651

Document code: WFEE

United States Patent and Trademark Office
Sales Receipt for Accounting Date: 01/26/2017

MTEKLEMI SALE #00000011 Mailroom Dt: 01/24/2017 120080 15260888
01 FC : 1819 600.00 DA

Samsung Bioepis Exhibit No. 1002
Page 10652

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NUMBER	FILING OR 371(C) DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO./TITLE
15/260,888	09/09/2016	Leonard BELL	AXJ-114BUSCN3

CONFIRMATION NO. 2558

133485
Nelson Mullins Riley & Scarborough LLP/Alexion
One Post Office Square
30th Floor
Boston, MA 02109-2127

37 CFR 1.48 ACKNOWLEDGEMENT LETTER

OC00000008747435

Date Mailed: 01/30/2017

NOTICE OF ACCEPTANCE OF REQUEST UNDER 37 CFR 1.48(a)

This is in response to the applicant's request under 37 CFR 1.48(a) submitted on 01/24/2017.

The request under 37 CFR 1.48(a) to correct the inventorship, to correct or update the name of an inventor, or to correct the order of names of joint inventors is accepted.

Questions about the contents of this notice and the requirements it sets forth should be directed to the Office of Data Management, Application Assistance Unit, at **(571) 272-4000** or **(571) 272-4200** or **1-888-786-0101**.

/ctuazon/

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NUMBER	FILING or 371(c) DATE	GRP ART UNIT	FIL FEE REC'D	ATTY.DOCKET.NO	TOT CLAIMS	IND CLAIMS
15/260,888	09/09/2016	1644	1740	AXJ-114BUSCN3	10	1

CONFIRMATION NO. 2558

UPDATED FILING RECEIPT

133485
Nelson Mullins Riley & Scarborough LLP/Alexion
One Post Office Square
30th Floor
Boston, MA 02109-2127

OC000000088747434

Date Mailed: 01/30/2017

Receipt is acknowledged of this non-provisional patent application. The application will be taken up for examination in due course. Applicant will be notified as to the results of the examination. Any correspondence concerning the application must include the following identification information: the U.S. APPLICATION NUMBER, FILING DATE, NAME OF APPLICANT, and TITLE OF INVENTION. Fees transmitted by check or draft are subject to collection. Please verify the accuracy of the data presented on this receipt. **If an error is noted on this Filing Receipt, please submit a written request for a Filing Receipt Correction. Please provide a copy of this Filing Receipt with the changes noted thereon. If you received a "Notice to File Missing Parts" for this application, please submit any corrections to this Filing Receipt with your reply to the Notice. When the USPTO processes the reply to the Notice, the USPTO will generate another Filing Receipt incorporating the requested corrections**

Inventor(s)

Leonard BELL, Woodbridge, CT;
Russell P. ROTHER, Oklahoma City, OK;
Mark J. EVANS, Radnor, PA;

Applicant(s)

Alexion Pharmaceuticals, Inc., New Haven, CT;

Power of Attorney: The patent practitioners associated with Customer Number 133485

Domestic Priority data as claimed by applicant

This application is a CON of 15/148,839 05/06/2016
which is a CON of 13/426,973 03/22/2012 ABN
which is a CON of 12/225,040 05/13/2009 ABN
which is a 371 of PCT/US2007/006606 03/15/2007

Foreign Applications for which priority is claimed (You may be eligible to benefit from the **Patent Prosecution Highway** program at the USPTO. Please see http://www.uspto.gov for more information.) - None.
Foreign application information must be provided in an Application Data Sheet in order to constitute a claim to foreign priority. See 37 CFR 1.55 and 1.76.

Permission to Access Application via Priority Document Exchange: Yes

Permission to Access Search Results: Yes

Applicant may provide or rescind an authorization for access using Form PTO/SB/39 or Form PTO/SB/69 as appropriate.

Samsung Bioepis Exhibit No. 1002
Page 10654

If Required, Foreign Filing License Granted:

The country code and number of your priority application, to be used for filing abroad under the Paris Convention, is **US 15/260,888**

Projected Publication Date: Not Applicable

Non-Publication Request: No

Early Publication Request: No

Title

TREATMENT OF PAROXYSMAL NOCTURNAL HEMOGLOBINURIA PATIENTS BY AN INHIBITOR OF COMPLEMENT

Preliminary Class

424

Statement under 37 CFR 1.55 or 1.78 for AIA (First Inventor to File) Transition Applications: No

PROTECTING YOUR INVENTION OUTSIDE THE UNITED STATES

Since the rights granted by a U.S. patent extend only throughout the territory of the United States and have no effect in a foreign country, an inventor who wishes patent protection in another country must apply for a patent in a specific country or in regional patent offices. Applicants may wish to consider the filing of an international application under the Patent Cooperation Treaty (PCT). An international (PCT) application generally has the same effect as a regular national patent application in each PCT-member country. The PCT process **simplifies** the filing of patent applications on the same invention in member countries, but **does not result** in a grant of "an international patent" and does not eliminate the need of applicants to file additional documents and fees in countries where patent protection is desired.

Almost every country has its own patent law, and a person desiring a patent in a particular country must make an application for patent in that country in accordance with its particular laws. Since the laws of many countries differ in various respects from the patent law of the United States, applicants are advised to seek guidance from specific foreign countries to ensure that patent rights are not lost prematurely.

Applicants also are advised that in the case of inventions made in the United States, the Director of the USPTO must issue a license before applicants can apply for a patent in a foreign country. The filing of a U.S. patent application serves as a request for a foreign filing license. The application's filing receipt contains further information and guidance as to the status of applicant's license for foreign filing.

Applicants may wish to consult the USPTO booklet, "General Information Concerning Patents" (specifically, the section entitled "Treaties and Foreign Patents") for more information on timeframes and deadlines for filing foreign patent applications. The guide is available either by contacting the USPTO Contact Center at 800-786-9199, or it can be viewed on the USPTO website at http://www.uspto.gov/web/offices/pac/doc/general/index.html.

For information on preventing theft of your intellectual property (patents, trademarks and copyrights), you may wish to consult the U.S. Government website, http://www.stopfakes.gov. Part of a Department of Commerce initiative, this website includes self-help "toolkits" giving innovators guidance on how to protect intellectual property in specific countries such as China, Korea and Mexico. For questions regarding patent enforcement issues, applicants may call the U.S. Government hotline at 1-866-999-HALT (1-866-999-4258).

LICENSE FOR FOREIGN FILING UNDER

Title 35, United States Code, Section 184

Title 37, Code of Federal Regulations, 5.11 & 5.15

GRANTED

The applicant has been granted a license under 35 U.S.C. 184, if the phrase "IF REQUIRED, FOREIGN FILING LICENSE GRANTED" followed by a date appears on this form. Such licenses are issued in all applications where the conditions for issuance of a license have been met, regardless of whether or not a license may be required as set forth in 37 CFR 5.15. The scope and limitations of this license are set forth in 37 CFR 5.15(a) unless an earlier license has been issued under 37 CFR 5.15(b). The license is subject to revocation upon written notification. The date indicated is the effective date of the license, unless an earlier license of similar scope has been granted under 37 CFR 5.13 or 5.14.

This license is to be retained by the licensee and may be used at any time on or after the effective date thereof unless it is revoked. This license is automatically transferred to any related applications(s) filed under 37 CFR 1.53(d). This license is not retroactive.

The grant of a license does not in any way lessen the responsibility of a licensee for the security of the subject matter as imposed by any Government contract or the provisions of existing laws relating to espionage and the national security or the export of technical data. Licensees should apprise themselves of current regulations especially with respect to certain countries, of other agencies, particularly the Office of Defense Trade Controls, Department of State (with respect to Arms, Munitions and Implements of War (22 CFR 121-128)); the Bureau of Industry and Security, Department of Commerce (15 CFR parts 730-774); the Office of Foreign AssetsControl, Department of Treasury (31 CFR Parts 500+) and the Department of Energy.

NOT GRANTED

No license under 35 U.S.C. 184 has been granted at this time, if the phrase "IF REQUIRED, FOREIGN FILING LICENSE GRANTED" DOES NOT appear on this form. Applicant may still petition for a license under 37 CFR 5.12, if a license is desired before the expiration of 6 months from the filing date of the application. If 6 months has lapsed from the filing date of this application and the licensee has not received any indication of a secrecy order under 35 U.S.C. 181, the licensee may foreign file the application pursuant to 37 CFR 5.15(b).

SelectUSA

The United States represents the largest, most dynamic marketplace in the world and is an unparalleled location for business investment, innovation, and commercialization of new technologies. The U.S. offers tremendous resources and advantages for those who invest and manufacture goods here. Through SelectUSA, our nation works to promote and facilitate business investment. SelectUSA provides information assistance to the international investor community; serves as an ombudsman for existing and potential investors; advocates on behalf of U.S. cities, states, and regions competing for global investment; and counsels U.S. economic development organizations on investment attraction best practices. To learn more about why the United States is the best country in the world to develop technology, manufacture products, deliver services, and grow your business, visit http://www.SelectUSA.gov or call +1-202-482-6800.

Samsung Bioepis Exhibit No. 1002
Page 10656

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
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Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
15/260,888	09/09/2016	Leonard BELL	AXJ-114BUSCN3	2558

133485 7590 02/02/2017

Nelson Mullins Riley & Scarborough LLP/Alexion
One Post Office Square
30th Floor
Boston, MA 02109-2127

EXAMINER	
ROGERS, JAMES L	

ART UNIT	PAPER NUMBER
1644	

NOTIFICATION DATE	DELIVERY MODE
02/02/2017	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

ipboston.docketing@nelsonmullins.com
chris.schlauch@nelsonmullins.com
ipqualityassuranceboston@nelsonmullins.com

Applicant-Initiated Interview Summary	**Application No.** 15/260,888	**Applicant(s)** BELL ET AL.	
	Examiner JAMES ROGERS	**Art Unit** 1644	

All participants (applicant, applicant's representative, PTO personnel):

(1) *JAMES ROGERS*.

(2) *DANIEL KOLKER, SPE*.

(3)*JILL SLOPER, JANE REMILLARD*.

(4)*Todd Spaldin*
(5) Darrell Fontenot
(6) Tara Rahemb
.

Date of Interview: *25 January 2017*.

Type: ☒ Telephonic ☐ Video Conference
☐ Personal [copy given to: ☐ applicant ☐ applicant's representative]

Exhibit shown or demonstration conducted: ☐ Yes ☒ No.
If Yes, brief description: _____.

Issues Discussed ☐101 ☐112 ☒102 ☒103 ☐Others
(For each of the checked box(es) above, please describe below the issue and detailed description of the discussion)

Claim(s) discussed: *1*.

Identification of prior art discussed: _____.

Substance of Interview
(For each issue discussed, provide a detailed description and indicate if agreement was reached. Some topics may include: identification or clarification of a reference or a portion thereof, claim interpretation, proposed amendments, arguments of any applied references etc...)

The outstanding 102(b) and 103(a) rejections of record were discussed. Applicant pointed out that the heavy chain sequence disclossed in the secondary reference Thomas is not the same as the currently claimed SEQ ID NO: 2 and pointed to the declaration of Leonard Bell, item (5) which provides a sequence alignment. No agreement was reached.

Applicant recordation instructions: The formal written reply to the last Office action must include the substance of the interview. (See MPEP section 713.04). If a reply to the last Office action has already been filed, applicant is given a non-extendable period of the longer of one month or thirty days from this interview date, or the mailing date of this interview summary form, whichever is later, to file a statement of the substance of the interview

Examiner recordation instructions: Examiners must summarize the substance of any interview of record. A complete and proper recordation of the substance of an interview should include the items listed in MPEP 713.04 for complete and proper recordation including the identification of the general thrust of each argument or issue discussed, a general indication of any other pertinent matters discussed regarding patentability and the general results or outcome of the interview, to include an indication as to whether or not agreement was reached on the issues raised.

☐ Attachment

Samsung Bioepis Exhibit No. 1002
Page 10658

/JAMES ROGERS/ Examiner, Art Unit 1644	/DANIEL E. KOLKER/ Supervisory Patent Examiner, Art Unit 1644

Summary of Record of Interview Requirements

Manual of Patent Examining Procedure (MPEP), Section 713.04, Substance of Interview Must be Made of Record
A complete written statement as to the substance of any face-to-face, video conference, or telephone interview with regard to an application must be made of record in the application whether or not an agreement with the examiner was reached at the interview.

Title 37 Code of Federal Regulations (CFR) § 1.133 Interviews
Paragraph (b)

In every instance where reconsideration is requested in view of an interview with an examiner, a complete written statement of the reasons presented at the interview as warranting favorable action must be filed by the applicant. An interview does not remove the necessity for reply to Office action as specified in §§ 1.111, 1.135. (35 U.S.C. 132)

37 CFR §1.2 Business to be transacted in writing.
All business with the Patent or Trademark Office should be transacted in writing. The personal attendance of applicants or their attorneys or agents at the Patent and Trademark Office is unnecessary. The action of the Patent and Trademark Office will be based exclusively on the written record in the Office. No attention will be paid to any alleged oral promise, stipulation, or understanding in relation to which there is disagreement or doubt.

The action of the Patent and Trademark Office cannot be based exclusively on the written record in the Office if that record is itself incomplete through the failure to record the substance of interviews.

It is the responsibility of the applicant or the attorney or agent to make the substance of an interview of record in the application file, unless the examiner indicates he or she will do so. It is the examiner's responsibility to see that such a record is made and to correct material inaccuracies which bear directly on the question of patentability.

Examiners must complete an Interview Summary Form for each interview held where a matter of substance has been discussed during the interview by checking the appropriate boxes and filling in the blanks. Discussions regarding only procedural matters, directed solely to restriction requirements for which interview recordation is otherwise provided for in Section 812.01 of the Manual of Patent Examining Procedure, or pointing out typographical errors or unreadable script in Office actions or the like, are excluded from the interview recordation procedures below. Where the substance of an interview is completely recorded in an Examiners Amendment, no separate Interview Summary Record is required.

The Interview Summary Form shall be given an appropriate Paper No., placed in the right hand portion of the file, and listed on the "Contents" section of the file wrapper. In a personal interview, a duplicate of the Form is given to the applicant (or attorney or agent) at the conclusion of the interview. In the case of a telephone or video-conference interview, the copy is mailed to the applicant's correspondence address either with or prior to the next official communication. If additional correspondence from the examiner is not likely before an allowance or if other circumstances dictate, the Form should be mailed promptly after the interview rather than with the next official communication.

The Form provides for recordation of the following information:
- Application Number (Series Code and Serial Number)
- Name of applicant
- Name of examiner
- Date of interview
- Type of interview (telephonic, video-conference, or personal)
- Name of participant(s) (applicant, attorney or agent, examiner, other PTO personnel, etc.)
- An indication whether or not an exhibit was shown or a demonstration conducted
- An identification of the specific prior art discussed
- An indication whether an agreement was reached and if so, a description of the general nature of the agreement (may be by attachment of a copy of amendments or claims agreed as being allowable). Note: Agreement as to allowability is tentative and does not restrict further action by the examiner to the contrary.
- The signature of the examiner who conducted the interview (if Form is not an attachment to a signed Office action)

It is desirable that the examiner orally remind the applicant of his or her obligation to record the substance of the interview of each case. It should be noted, however, that the Interview Summary Form will not normally be considered a complete and proper recordation of the interview unless it includes, or is supplemented by the applicant or the examiner to include, all of the applicable items required below concerning the substance of the interview.

A complete and proper recordation of the substance of any interview should include at least the following applicable items:
1) A brief description of the nature of any exhibit shown or any demonstration conducted,
2) an identification of the claims discussed,
3) an identification of the specific prior art discussed,
4) an identification of the principal proposed amendments of a substantive nature discussed, unless these are already described on the Interview Summary Form completed by the Examiner,
5) a brief identification of the general thrust of the principal arguments presented to the examiner,
   (The identification of arguments need not be lengthy or elaborate. A verbatim or highly detailed description of the arguments is not required. The identification of the arguments is sufficient if the general nature or thrust of the principal arguments made to the examiner can be understood in the context of the application file. Of course, the applicant may desire to emphasize and fully describe those arguments which he or she feels were or might be persuasive to the examiner.)
6) a general indication of any other pertinent matters discussed, and
7) if appropriate, the general results or outcome of the interview unless already described in the Interview Summary Form completed by the examiner.

Examiners are expected to carefully review the applicant's record of the substance of an interview. If the record is not complete and accurate, the examiner will give the applicant an extendable one month time period to correct the record.

Examiner to Check for Accuracy

If the claims are allowable for other reasons of record, the examiner should send a letter setting forth the examiner's version of the statement attributed to him or her. If the record is complete and accurate, the examiner should place the indication, "Interview Record OK" on the paper recording the substance of the interview along with the date and the examiner's initials.

Samsung Bioepis Exhibit No. 1002
Page 10660

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
15/260,888	09/09/2016	Leonard BELL	AXJ-114BUSCN3	2558

133485 7590 04/11/2017

Nelson Mullins Riley & Scarborough LLP/Alexion
One Post Office Square
30th Floor
Boston, MA 02109-2127

EXAMINER	
ROGERS, JAMES L	

ART UNIT	PAPER NUMBER
1644	

NOTIFICATION DATE	DELIVERY MODE
04/11/2017	ELECTRONIC

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ipboston.docketing@nelsonmullins.com
chris.schlauch@nelsonmullins.com
ipqualityassuranceboston@nelsonmullins.com

Office Action Summary	Application No. 15/260,888	Applicant(s) BELL ET AL.	
	Examiner JAMES ROGERS	Art Unit 1644	AIA (First Inventor to File) Status No

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTHS FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *1/19/2017*.

☐ A declaration(s)/affidavit(s) under **37 CFR 1.130(b)** was/were filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ An election was made by the applicant in response to a restriction requirement set forth during the interview on _____; the restriction requirement and election have been incorporated into this action.

4)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims*

5)☒ Claim(s) *1-10* is/are pending in the application.

5a) Of the above claim(s) _____ is/are withdrawn from consideration.

6)☐ Claim(s) _____ is/are allowed.

7)☒ Claim(s) *1-10* is/are rejected.

8)☐ Claim(s) _____ is/are objected to.

9)☐ Claim(s) _____ are subject to restriction and/or election requirement.

* If any claims have been determined allowable, you may be eligible to benefit from the **Patent Prosecution Highway** program at a participating intellectual property office for the corresponding application. For more information, please see http://www.uspto.gov/patents/init_events/pph/index.jsp or send an inquiry to PPHfeedback@uspto.gov.

Application Papers

10)☐ The specification is objected to by the Examiner.

11)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

Certified copies:

a)☐ All b)☐ Some** c)☐ None of the:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

** See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)

2) ☐ Information Disclosure Statement(s) (PTO/SB/08a and/or PTO/SB/08b) Paper No(s)/Mail Date _____.

3) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .

4) ☐ Other: _____.

DETAILED ACTION

1. Claims 1-10 pending and under consideration in the instant examination.

2. The present application is being examined under the pre-AIA first to invent provisions.

In view of the Response filed 1/19/2017, the following rejections are maintained.

Response to Arguments

Claim Rejections - 35 USC § 102

3. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) *the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.*

4. Claims 1-2 and 7-10 are rejected under 35 U.S.C. 102(b) as being anticipated by Hillmen et al. (N Engl J Med 2004; 350: 552-9, IDS Ref. of 10/21/2016), as is evidenced by applicant's specification as filed at p.44 and Thomas et al. (Molecular Immunology, 33(17/18), pp.1389-1401, 1996).

With respect to base claim 1, Hillmen teaches a method for treating a human patient that suffers from paroxysmal nocturnal hemoglobinuria (PNH) by administering to the patient an effective amount of eculizumab (p. 552, "methods") which specifically binds to the terminal complement protein C5, inhibiting its cleavage into C5a and C5b (p. 553, 3rd ¶).

While Hillmen does not specifically recite that the antibody that binds C5 comprises a heavy chain consisting of SEQ ID NO: 2 and a light chain consisting of SEQ ID NO:4, the specification as filed at p. 44 discloses that SEQ ID NO: 2 and SEQ ID NO: 4 constitute the H and L chains for "eculizumab" and Hillmen, as noted supra, teaches administering "eculizumab". Hillmen further teaches that "eculizumab" is a recombinant humanized antibody that binds to C5 (p. 553, 3rd ¶) and cites Thomas which in turn describes in detail humanization of the clone referred to as "5G1.1" arrive at the humanized h5G1.1 which retain both the affinity and blocking functions of the murine 5g1.1 antibody (abstract). Accordingly and in absence of evidence to the contrary, the currently recited SEQ ID NO: 2 and SEQ ID NO: 4 which constitute the L and H chains of "eculizumab" are considered to be inherent properties of the "eculizumab" anti-C5 humanized monoclonal antibody taught by Hillmen.

Claim 2 is included because Hillmen teaches that the patients received eculizumab by infusion (p. 554 under “Treatment Schedule").

Claim 7 is included because Hillmen teaches that the patients had previously been diagnosed of aplastic anemia (p. 555, 1st ¶).

Claim 8 is included because Hillmen teaches that patients received infusions of eculizumab (600 mg) every week for four weeks, followed one week later by a 900 mg dose and then by a dose of 900 mg every other week through week 12 (p. 552 under “methods” and p. 554 under “treatment schedule”).

Claims 9-10 are included because Hillmen teaches that a decrease in lactate dehydrogenase began after a single dose of eculizumab (immediate decrease occurs within 1 week of administration of the antibody) in all patients and remained within or just above the normal range for the duration of the study (sustained decrease in mean levels of LDH) (p. 555, last ¶).

The reference teachings anticipate the claimed invention.

Applicant’s arguments submitted on 1/19/2017 were fully considered but were not considered persuasive.

Applicant has submitted a declaration by Dr. Leonard Bell that prior to March 15, 2007 effective filing date of the present application, the complete structure of eculizumab was not disclosed in the prior art; nor was it available to the public and that Hillmen fails to teach any part of the sequence of eculizumab (p. 4 of the Response).

This argument was not considered persuasive for the following reasons:

The Bell declaration submitted on 1/19/2017 states that clinical trials were conducted “but only under strict control and conditions of confidentiality”. However the declaration does not provide any evidence that the experiments conducted in the HILLMEN reference were under any condition of confidentiality, nor does it provide any evidence that the authors of that study were working under the direction of the present inventors.

It remains the examiner’s position that there is substantial evidence that eculizumab was in use more than a year before applicant filed for the patent.

As noted supra, 35 USC 102(b) states:

A person shall be entitled to a patent unless —

(b) the invention was patented or described in a printed publication in this or a foreign country **or in public use or on sale in this country**, more than one year prior to the date of the application for patent in the United States,

While it is true that if the antibody was unknown prior, then a reference which names it does not enable that antibody. See MPEP 2121.02 sections I and II. See also 2121.01, "the stated test is whether a reference contains an 'enabling disclosure'... ." In re Hoeksema, 399 F.2d 269, 158 USPQ 596 (CCPA 1968). The disclosure in an asserted anticipating reference must provide an enabling disclosure of the desired subject matter; mere naming or description of the subject matter is insufficient, if it cannot be produced without undue experimentation." And … "Such possession is effected if one of ordinary skill in the art could have combined the publication's description of the invention with his [or her] own knowledge to make the claimed invention." In re Donohue, 766 F.2d 531, 226 USPQ 619 (Fed. Cir. 1985)."

In the instant case, applicant's position is that the mere naming is insufficient. However, the extensive number of both patent literature and NPL documents as well as clinical trials indicates that eculizumab was widespread and well-known. As evidence of the availability and use of eculizumab the examiner refers applicant to the following documents, some of which (exhibits A-E) are part of the Request for additional Information which is also part of this OA:

A) **Exhibit A:** from ClinicalTrails.gov (studies 41-60).
B) **Exhibit B:** Clinicaltrials.gov from 6/23/2005 for NCT00098280
C) **Exhibit C:** "Safety and Effectiveness of h5G1.1-mAb for dermatomyositis" clinical Trials.gov identifier NCT00005571
D) **Exhibit D:** Kaplan 2002. Current Opinion in Investigational Drugs 3(7):1017-1023.
E) **Exhibit E:** Appel et al. Kidney International 2006 70:S45-S50, in particular the paragraph spanning pp. S48-S49 (http://www.kidney-international.org/article/S0085-2538(15)51857-7/pdf)
F) **Wang (US 2005/0271660)**, which references pexelizumab or eculizumab as an antibody therapeutic (¶s4 , claim 7) and is presumed to be enabled.
G) **Rother (WO 2005/110481)**. See for example claims 10, 44-45, 79-80, 123, 125, 130 as well as page 17 line 26 – p. 18 line 12 (noting that the antibody from US Patent 6355245 is now named eculizumab).
H) **Rother (US 2009/0028850)**. This is the publication of the national-stage entry of the '481 application above. Note that the underlying application (11/596382) contains claims to methods of using eculizumab; the office has considered these claims to be enabled. Note that the case recently was decided by the PTAB, and the Board agreed that claims drawn to administering eculizumab were obvious (and thus presumably enabled and operative) as of the filing date of that underlying application, 5/16/2005.

In re Antor Media Corp (CAFC, 2012) states that subject matter disclosed in a reference, whether it is a patent claim, other parts of a patent, or non-patent literature, is presumed to be enabling absent evidence to the contrary.

It remains the examiner's position that eculizumab was effectively in the public domain over a year prior to the filing of this application, as indicated by the preponderance of evidence.

Claim Rejections - 35 USC § 103

5. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained even though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

6. Claims 1-10 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hillmen et al. (N Engl J Med 2004; 350: 552-9), in view of Thomas et al. (Molecular Immunology, 33(17/18), pp.1389-1401, 1996) and of Evans et al. (US 6,355,245 B1, issued 3/12/2002), and further in view of Wang (US 2005/0271660).

The prior art teachings of Hillmen are discussed supra. The prior art teachings of Thomas and the '245 patent were discussed in the prior OA.

The prior art teachings differ from the claimed invention in the recitation that the antibody is administered at a dosage level of between 5-50 mg/kg per patient per treatment as in claim 3, that the composition is in a single unit dosage form as in claim 4 and that the single unit dosage form is a 300 mg single unit dosage form as in claim 5.

The prior art teachings further differ in the recitation that the pharmaceutical composition comprises a 300 mg single-use formulation of 30 ml of a 10 mg/ml sterile, preservative free solution as in claim 6.

The ‘245 patent further teaches antibody 5G1.1, which is the same as eculizumab (discussion supra), is effective at doses of 2.2, 3, or 5 mg per kg body weight; this corresponds to 154, 210, or 350 mg of antibody for a 70kg adult human (‘245 patent, column 16 lines 10-30). Evans (the ‘245 patent) also teaches that eculizumab is therapeutically effective when as little as 210 mg are present (column 16 lines 10-15). Evans teaches that the antibodies are particularly advantageous in that they are highly active even when administered in low doses (col 8 lines 25-32), providing a reasonable expectation of success in treating PHN with a dose less than what was disclosed by Hillmen. The reference teaches that it is within the skill of an artisan, particularly a physician, to determine the optimal dose (column 18 lines 15-30). Evans teaches formulations of the anti-C5 antibodies may be formulated in a pharmaceutically effective carrier such saline, which is considered to be a "preservative free solution". (col 18 lines 30-45).

Neither Hillmen nor the ‘245 patent (Evans) teaches a 300 mg single unit dosage as recited in the claims.

Nevertheless it would have been obvious to one of ordinary skill in the art to modify the teachings of Hillmen to administer 300 mg single unit dosages. Hillmen teaches that both 600 and 900 mg dosages can be used, and since Evans patent teaches that 210 or 350 mg of antibody would be expected to be therapeutically effective, arriving at the 300 mg dosage would be routine, convenient and obvious. One of ordinary skill in the art would have a reasonable expectation of success, as Evans teaches that the antibody exerts its effect at low doses.

It is further noted, [I]t is not inventive to discover the optimum or workable ranges by routine experimentation.” In re Aller, 220 F.2d 454, 456 (CCPA 1955); see also In re Peterson, 315 F.3d 1325 (Fed. Cir. 2003). “Only if the ‘results of optimizing a variable’ are ‘unexpectedly good’ can a patent be obtained for the claimed critical range.” In re Geisler, 116 F.3d 1465, 1469 (Fed. Cir. 1997) (quoting In re Antonie, 559 F.2d 618, 620 (CCPA 1977)). “[Discovery of an optimum value of a result effective variable in a known process is ordinarily within the skill of the art.” In re Boesch, 617 F.2d 272, 276 (CCPA 1980).

Finally, **Wang** teaches that eculizumab is highly soluble, including at up to 30 mg per ml (paragraph 0171, Figure 10). Wang further teaches that pharmaceutically acceptable carriers include pyrogen-free water may be used in formulation of the antibody (¶71) (sterile, preservative free solution). Therefore the artisan of ordinary skill would have had a reasonable expectation of success in making a 10 mg / ml solution of the antibody sterile, preservative free solution.

From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

Applicant's arguments filed on 1/19/2017 were fully considered but were not considered persuasive.

Applicant's arguments mirror applicant's arguments with respect to the 35 USC 102(b) rejection over Hillmen supra. Accordingly, the examiner refers applicant to the examiner's rebuttal supra.

Request for Additional Information Under 37 CFR 1.105

7. Applicant and the assignee of this application are required under 37 CFR 1.105 to provide the following information that the examiner has determined is reasonably necessary to the examination of this application.

8. In response to this requirement, please provide answers to each of the following interrogatories eliciting factual information:

(A) **Studies #41-60 in the attached Exhibit A** provide prima facie evidence that the methods now claimed were in use in this country more than a year before the application for patent was filed. Therefore for each of studies #41-60 in the attached document Exhibit A, please answer the following questions:

(i) Whether any of the trials (#s41-60) used the same sequences for eculizumab as currently claimed (i.e., SEQ ID 2 and 4).

(ii) Whether any of the researcher(s) at each of the study sites identified in (i) above for which the same sequences currently claimed was under any confidentiality agreement?

(iii) What was the nature of such confidentiality agreement in (ii) above?

(iv) Were the researchers for those trials identified in (i) acting solely at the direction of the present inventors?

(B) **the study entitled "Safety and Effectiveness of h5G1.1-mAb for Dermatomyositis" listed on the attached Exhibit B** please answer the following questions:

(i) Whether the trial used the same sequences for eculizumab as currently claimed (i.e., SEQ ID 2 and 4).

(ii) Whether any of the researcher(s) at each the study sites was under any confidentiality agreement?

(ii) What was the nature of such confidentiality agreement in (ii) above?

(iii) Were the researchers acting solely at the direction of the present inventors?

(C) **Exhibit D: "Eculizumab Alexion –Mariana Kaplan**: please answer the following questions with respect to the study (445382) reference on p. 1018, 2nd ¶:

(i) Whether the trial used the same sequences for eculizumab as currently claimed (i.e., SEQ ID 2 and 4).

(ii) Whether any of the researcher(s) at the study site was under any confidentiality agreement?

(iii) What was the nature of such confidentiality agreement in (i) above?

(iv) Were the researchers acting solely at the direction of the present inventors?

(D) **Exhibit E (Appel "new approaches to the treatment of glomerular diseases)**, please answer the following questions with respect to the randomized, placebo-controlled trial in 200 patients referenced at the end of p. S48:

(i) Whether the trial used the same sequences for eculizumab as currently claimed (i.e., SEQ ID 2 and 4).

(ii) Whether any of the researcher(s) at study site was under any confidentiality agreement?

(iii) What was the nature of such confidentiality agreement in (ii) above?

(iv) Were the researchers acting solely at the direction of the present inventors?

(E) On what date was eculizumab as encompassed by the currently claimed invention (i.e., H chains SEQ ID NO: 2 and L chain SEQ ID NO: 4) first offered for sale?

9. The applicant is reminded that the reply to this requirement must be made with candor and good faith under 37 CFR 1.56. Where the applicant does not have or cannot readily obtain an item of required information, a statement that the item is unknown or cannot be readily obtained may be accepted as a complete reply to the requirement for that item.

Double Patenting

10. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *Jn re Berg,* 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *Jn re Goodman,* 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi,* 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum,* 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel,* 422 F.2d 438, 164 USPQ 619 (CCPA 1970); *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321 (c) or 1.321 (d) may be used to overcome an actual or provisional rejection based on nonstatutory double patenting provided the reference application or patent either is shown to be commonly owned with the examined application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement. See MPEP § 717.02 for applications subject to examination under the first inventor to file provisions of the AIA as explained in MPEP § 2159. See MPEP §§ 706.02(1)(1) - 706.02(1)(3) for applications not subject to examination under the first inventor to file provisions of the AIA. A terminal disclaimer must be signed in compliance with 37 CFR 1.321 (b).

The USPTO Internet website contains terminal disclaimer forms which may be used. Please visit www.uspto.gov/patent/patents-forms. The filing date of the application in which the form is filed determines what form (e.g., PTO/SB/25, PTO/SB/26, PTO/AIA/25, or PTO/AIA/26) should be used. A web-based eTerminal Disclaimer may be filled out completely online using web-screens. An eTerminal Disclaimer that meets all requirements is auto-processed and approved immediately upon submission. For more information about eTerminal Disclaimers, refer to www.uspto.gov/patents/process/file/efs/guidance/eTD-info-I.jsp.

11. Claims 1-10 are rejected on the ground of nonstatutory double patenting as being unpatentable over claims 1-19 of **US Patent No. 9,494,601,** view of Hillmen et al. (N Engl J Med 2004; 350: 552-9), Thomas et al. (Molecular Immunology, 33 (17/18), pp. 1389-1401), Evans et al. (US 6,355,245 81, issued 3/12/2002) and Wang (US 2005/0271660)**.**

Although the conflicting claims are not identical, they are not patentably distinct from each other because both the current application and '601 claim eculizumab (see claim 10 of the '601).

Samsung Bioepis Exhibit No. 1002
Page 10670

The differences between the claimed invention and ‘601 (treatment of a patient suffering from PNH and recited doses) would be obvious in view of Hillmen, Thomas, Evan and Wang as discussed supra.

12. Claims 1-10 are rejected on the ground of nonstatutory double patenting as being unpatentable over claims 1-17 of **US Patent No. 9,409,980,** in view of Hillmen et al. (N Engl J Med 2004; 350: 552-9), Thomas et al. (Molecular Immunology, 33 (17/18), pp. 1389-1401), Evans et al. (US 6,355,245 81, issued 3/12/2002) and Wang (US 2005/0271660).

Although the conflicting claims are not identical, they are not patentably distinct from each other because both the current application and '980 claim eculizumab (see claim 5 of the '980).

The differences between the claimed invention and ‘980 (treatment of a patient suffering from PNH and recited doses) would be obvious in view of Hillmen, Thomas, Evan and Wang as discussed supra.

13. Claims 1-10 are rejected on the ground of nonstatutory double patenting as being unpatentable over claims 1-14 of **US Patent No. 9,556,263,** view of Hillmen et al. (N Engl J Med 2004; 350: 552-9), Thomas et al. (Molecular Immunology, 33 (17/18), pp. 1389-1401), Evans et al. (US 6,355,245 81, issued 3/12/2002) and Wang (US 2005/0271660).

Although the conflicting claims are not identical, they are not patentably distinct from each other because both the current application and '263 claim eculizumab (see claims 2 and 4 of the '263).

The differences between the claimed invention and ‘263 (treatment of a patient suffering from PNH and recited doses) would be obvious in view of Hillmen, Thomas, Evan and Wang as discussed supra.

14. No claim is allowed.

15. Any inquiry concerning this communication or earlier communications from the examiner should be directed to James Rogers whose telephone number is (571) 270-5374. The examiner can normally be reached Monday through Friday from 8:00 am to 5:30 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, **Daniel Kolker** can be reached on (571) 272-3181. The fax number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you

have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

March 30, 2017 /JAMES ROGERS/
Art Unit 1644

/DANIEL E. KOLKER/

Supervisory Patent Examiner, Art Unit 1644

Notice of References Cited	Application/Control No. 15/260,888	Applicant(s)/Patent Under Reexamination BELL ET AL.	
	Examiner JAMES ROGERS	Art Unit 1644	Page 1 of 3

U.S. PATENT DOCUMENTS

*		Document Number Country Code-Number-Kind Code	Date MM-YYYY	Name	CPC Classification	US Classification
*	A	US-2005/0271660 A1	12-2005	Wang, Yi	C07K16/18	424/144.1
*	B	US-2009/0028850 A1	01-2009	Rother; Russell P.	C07K16/18	424/133.1
	C	US-				
	D	US-				
	E	US-				
	F	US-				
	G	US-				
	H	US-				
	I	US-				
	J	US-				
	K	US-				
	L	US-				
	M	US-				

FOREIGN PATENT DOCUMENTS

*		Document Number Country Code-Number-Kind Code	Date MM-YYYY	Country	Name	CPC Classification
	N	WO 2005110481 A2	11-2005	CANADA	ZHONG ZHEN	C07K16/18
	O					
	P					
	Q					
	R					
	S					
	T					

NON-PATENT DOCUMENTS

*		Include as applicable: Author, Title Date, Publisher, Edition or Volume, Pertinent Pages)
	U	Appel et al. "New approaches to the treatment of glomerular diseases" Kidney International 70, S45-S50 2006
	V	Hillmen et al. "Effect of Eculizumab on Hemolysis and Transfusion Requirements in Patients with Paroxysmal Nocturnal hemoglobinuria" NEJM, 350: 6, 2004
	W	69 Studies for eculizumab for clinicaltrials.gov, printed 2/28/2017, pp. 1-3
	X	Clinical Trials Identifier: NCT0098280, "Eculizumab to Treat Paroxysmal Nocturnal Hemoglobinuria" 6/23/2005, pp. 1-4

*A copy of this reference is not being furnished with this Office action. (See MPEP § 707.05(a).)
Dates in MM-YYYY format are publication dates. Classifications may be US or foreign.

Notice of References Cited	Application/Control No. 15/260,888	Applicant(s)/Patent Under Reexamination BELL ET AL.	
	Examiner JAMES ROGERS	Art Unit 1644	Page 2 of 3

U.S. PATENT DOCUMENTS

*		Document Number Country Code-Number-Kind Code	Date MM-YYYY	Name	CPC Classification	US Classification
	A	US-				
	B	US-				
	C	US-				
	D	US-				
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	L	US-				
	M	US-				

FOREIGN PATENT DOCUMENTS

*		Document Number Country Code-Number-Kind Code	Date MM-YYYY	Country	Name	Classification
	N					
	O					
	P					
	Q					
	R					
	S					
	T					

NON-PATENT DOCUMENTS

*		Include as applicable: Author, Title Date, Publisher, Edition or Volume, Pertinent Pages)
	U	Safety and Effectiveness of h5G1.1-mAb for dermatomyositis" clinicaltrials.gov identifier NCT00005571, April 25, 2000, pp. 1-4
	V	Alexion Mariana Kaplan "Eculizumab" Current Opinion in Investigational Drugs 2002 (3(7): 10107-1023
	W	
	X	

*A copy of this reference is not being furnished with this Office action. (See MPEP § 707.05(a).)
Dates in MM-YYYY format are publication dates. Classifications may be US or foreign.

Notice of References Cited	Application/Control No. 15/260,888	Applicant(s)/Patent Under Reexamination BELL ET AL.	
	Examiner JAMES ROGERS	Art Unit 1644	Page 3 of 3

U.S. PATENT DOCUMENTS

*		Document Number Country Code-Number-Kind Code	Date MM-YYYY	Name	CPC Classification	US Classification
	A	US-				
	B	US-				
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FOREIGN PATENT DOCUMENTS

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NON-PATENT DOCUMENTS

*		Include as applicable: Author, Title Date, Publisher, Edition or Volume, Pertinent Pages)
	U	
	V	
	W	
	X	

*A copy of this reference is not being furnished with this Office action. (See MPEP § 707.05(a).)
Dates in MM-YYYY format are publication dates. Classifications may be US or foreign.

ClinicalTrials.gov
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Trial record **1 of 1** for: nct00005571
Previous Study | Return to List | Next Study

Safety and Effectiveness of h5G1.1-mAb for Dermatomyositis

This study has been completed.

Sponsor:
National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS)

Information provided by:
National Institutes of Health Clinical Center (CC)

ClinicalTrials.gov Identifier:
NCT00005571

First received: April 25, 2000
Last updated: March 3, 2008
Last verified: December 2001
History of Changes

Full Text View | Tabular View | No Study Results Posted | Disclaimer | How to Read a Study Record

Purpose

This study will evaluate the safety and effectiveness of the experimental drug h5G1.1-mAb in treating patients with dermatomyositis. This disease, which causes skin rash, muscle weakness, and sometimes various other symptoms, may be due to an immune system abnormality. Drugs currently used to treat dermatomyositis, such as prednisone and various anticancer drugs, often have serious side effects and may not work in all patients. h5G1.1-mAb is a genetically engineered antibody that blocks the activity of certain proteins involved in the immune reaction that produces inflammation.

Patients age 18 years and older who have had dermatomyositis for at least 6 months and who have not improved with prednisone or other therapies, or who cannot tolerate prednisone or other therapies, may be eligible for this 12-week study. Candidates will have a history and physical examination, including blood and urine tests, throat culture, and muscle strength testing. Participants will be randomly assigned to receive either h5G1.1-mAb or placebo (an inactive substance). The drug or placebo will be given intravenously (through a thin tube inserted into a vein) once a week for five doses and then every other week for two more doses.

Participants will undergo the following additional tests at various intervals during the study as follows:

1. Complete physical examination (visit 9)
2. Blood and urine tests (various intervals)
3. Muscle strength testing, assessment of ability to perform daily tasks, and completion of questionnaire regarding functional abilities (visits 2, 6 and 9)
4. Ultrasound imaging of muscle (during certain muscle exercises) (visits 2, 6 and 9)
5. Electrocardiogram (EKG) (visits 2 and 9)
6. Throat swab (culture) (visit 6)
7. Examination and photography of skin lesions (visits 2 and 9)
8. Skin biopsy - removal of small sample of skin tissue under local anesthetic (visits 2 and 9)
9. Magnetic resonance imaging (MRI) scan of muscles (visits 2 and 9)
10. Possible muscle biopsy - removal of small sample of muscle tissue under local anesthetic (visits 2 and 9).

Condition	Intervention	Phase
Dermatomyositis	Drug: h5G1.1-mAb	Phase 2

Study Type: Interventional
Study Design: Primary Purpose: Treatment

Official Title: A Randomized, Third-Party-Blind, Placebo-Controlled Pilot Study of the Effect of h5G1.1-mAb on Dermatomyositis Patients

Resource links provided by NLM:

Drug information available for: Eculizumab

Samsung Bioepis Exhibit No. 1002
Page 10676

Genetic and Rare Diseases Information Center resources: Idiopathic Inflammatory Myopathy Dermatomyositis Polymyositis

U.S. FDA Resources

Further study details as provided by National Institutes of Health Clinical Center (CC):

Estimated Enrollment:	17
Study Start Date:	April 2000
Estimated Study Completion Date:	December 2001

Detailed Description:

This is a randomized, third-party, placebo-controlled pilot study of h5G1.1-mAb, an antibody directed at the complement component C5, administered to patients with dermatomyositis with persistent disease. We are one of the four groups taking part in a multicenter trial under the sponsorship of Alexion Pharmaceuticals, Inc.

In dermatomytosis, humorally-mediated damage to muscle and skin microvasculature appears very important. The deposition of the membrane attack complex (C5-9) on the capillaries has been shown to precede the destruction of muscle fibers and to be a specific finding in the skin lesion. These observations, along with the recent discovery of the effectiveness of intravenous gammaglobulin (IVIG) in dermatomyositis, support the role of complement activation in the pathogenesis of dermatomyositis. Among the activated components of the complement system, the products that are generated after cleavage of C5, namely, C5a and C5b-9, are potent inflammatory mediators with pleiotropic activities. Inhibition of complement activation at C5 would prevent the formation of these pro-inflammatory molecules while allowing the generation of C3b, which is critical for opsonization and immune complex clearance. C5 inhibition therefore represents a potentially effective therapeutic modality for dermatomyositis.

Anti-C5 monoclonal antibodies are designed to prevent the cleavage of C5. A murine monoclonal antibody to human C5, m5G1.1-mAb, was humanized (h5G1.1-mAb) by grafting the antibody's antigen-binding CDR regions onto human antibody-derived framework and constant domains. This antibody is being made available by Alexion Pharmaceuticals, and will be used under their IND.

There will be 15 patients entered (with the goal of 12 evaluable patients) distributed among two treatment groups. Patients will be randomized at a 3 to 1 ratio between h5G1.1-mAb and placebo. Following a screening period of no less than 7 days, a 2 month double-blind, randomized treatment period will commence. Patients will receive an active (h5G1.1-mAb, 8mg/kg) bolus infusion every week X 5, then every 2 weeks X 2, or a placebo bolus infusion every week X 5, then every 2 weeks X 2. All patients will be receiving 7 infusions of h5G1.1-mAb or placebo.

The objective is to determine the safety and tolerability of h5G1.1-mAb and to evaluate the pharmacokinetics and pharmacodynamics of this antibody as well as its efficacy in the target population. Safety will be assessed via the collection of adverse events and the evaluation of pre- and post-treatment laboratory data. Efficacy will be assessed by the change in the manual muscle testing score relative to placebo at 2.25 months (one week following the end of the active treatment period) (primary efficacy value), and the change in the muscle enzyme level, MRI findings, skin examination findings and biopsy, and SF-36 (secondary efficacy values).

Eligibility

Ages Eligible for Study:	Child, Adult, Senior
Sexes Eligible for Study:	All
Accepts Healthy Volunteers:	No

Criteria

Patients age greater than or equal to 18 years.

Patients with a diagnosis of definite or probable dermatomyositis by criteria of Bohan et. al., with either active rash typical of dermatomyositis, history of rash typical of dermatomyositis, or Gottron's papules.

Patients with a manual muscle testing score less than or equal to 136/170.

Patients with a disease duration greater than or equal to 6 months.

Patients with persistent disease (defined as active rash plus CK greater than or equal to 2 times ULN), or rapidly progressive disease, or response to steroids with inability to taper dose, or unacceptable side effects of steroids.

Patients may be on stable (times 28 days prior to Visit 2) dose of MTX or AZA.

No other immunosuppressive agents times 84 days prior to first dose.

Patients on stable oral steroid use for 28 days prior to Visit 2.

Patients with adequate hematologic function, defined as hemoglobin greater than or equal to 8.5 g/dl, WBC greater than or equal to 3,000 mm(3), neutrophils greater than or equal to 1,200 mm(3), platelets greater than or equal to 100,000 mm(3).

Patients must be willing and able to give informed consent.

Women must be post-menopausal, surgically sterile or practicing a medically approved method of contraception.

Patients with liver disease will be excluded.

Patients with history of alcohol or drug abuse within two years of screening, or a history of positive Hepatitis B or Hepatitis C serology, unless vaccinated will be excluded.

Samsung Bioepis Exhibit No. 1002
Page 10677

Patients with renal insufficiency, defined as creatinine greater than or equal to 2.0 mg/dl will be excluded.

Patients with history of malignancy, except basal cell carcinoma and remote (greater than or equal to 5 years) malignancies in complete remission will be excluded.

Patients with history of poorly controlled diabetes will be excluded.

Patients with presence or suspicion of active infection, recent serious infection, or chronic/recurrent viral or bacterial infection will be excluded.

Patients with throat culture positive for pathogenic Neisseria species (meningitidis or gonorrhoeae) will be exluded. Subjects with a positive culture may be treated with appropriate antibiotic therapy and retested.

Patients with joint disease or replacement that would interfere with patient's ability to perform muscle testing will be excluded.

Patients with any clinically significant medical condition that is likely to interfere with the participation in the study or the evaluation of the study medication's safety profile will be excluded.

No patients with known or suspected hereditary complement deficiency will be excluded.

Patients with history of allergic reaction to murine proteins will be excluded.

Patients participating in any other investigational drug trial, or exposure to other investigational agent or device within thirty days prior to screening will be excluded.

Pregnant or breastfeeding patients will be excluded.

Women intending to conceive during the course of the study, including follow-up period will be excluded.

Patients with history of HIV, Lyme disease, or other environmentally induced myositis will be excluded.

Contacts and Locations

Choosing to participate in a study is an important personal decision. Talk with your doctor and family members or friends about deciding to join a study. To learn more about this study, you or your doctor may contact the study research staff using the Contacts provided below. For general information, see Learn About Clinical Studies.

Please refer to this study by its ClinicalTrials.gov identifier: NCT00005571

Locations

United States, Maryland

National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS)
Bethesda, Maryland, United States, 20892

Sponsors and Collaborators

National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS)

More Information

Publications:

Pearson CM, Bohan A. The spectrum of polymyositis and dermatomyositis. Med Clin North Am. 1977 Mar;61(2):439-57. Review.

Love LA, Leff RL, Fraser DD, Targoff IN, Dalakas M, Plotz PH, Miller FW. A new approach to the classification of idiopathic inflammatory myopathy: myositis-specific autoantibodies define useful homogeneous patient groups. Medicine (Baltimore). 1991 Nov;70(6):360-74.

Adams EM, Pucino F, Yarboro C, Hicks JE, Thornton B, McGarvey C, Sonies BC, Bartlett ML, Villalba ML, Fleisher T, Plotz PH. A pilot study: use of fludarabine for refractory dermatomyositis and polymyositis, and examination of endpoint measures. J Rheumatol. 1999 Feb;26(2):352-60.

ClinicalTrials.gov Identifier:	NCT00005571 History of Changes
Other Study ID Numbers:	000117 00-AR-0117
Study First Received:	April 25, 2000
Last Updated:	March 3, 2008

Keywords provided by National Institutes of Health Clinical Center (CC):

Skin	Complement
Humoral Immunity	Antibody
Myositis	Dermatomyositis

Additional relevant MeSH terms:

Dermatomyositis	Neuromuscular Diseases
Polymyositis	Nervous System Diseases
Myositis	

Samsung Bioepis Exhibit No. 1002
Page 10678

Muscular Diseases
Musculoskeletal Diseases
Connective Tissue Diseases
Skin Diseases

ClinicalTrials.gov processed this record on February 24, 2017

Samsung Bioepis Exhibit No. 1002
Page 10679

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69 studies found for: eculizumab

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List | By Topic | On Map | Search Details

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Only show open studies

Rank	Status	Study
41	Terminated	Safety & Efficacy of Eculizumab to Prevent AMR in Living Donor Kidney Transplant Recipients Requiring Desensitization **Condition:** Antibody Mediated Rejection **Intervention:** Drug: Eculizumab **Study Start:** September 2011 **First Received:** July 19, 2011
42	Withdrawn	Targeting Complement Activation in Antineutrophil Cytoplasmic Autoantibodies (ANCA)-Vasculitis - Eculizumab **Condition:** Anti-Neutrophil Cytoplasmic Antibody-Associated Vasculitis **Interventions:** Drug: Standard of care treatment; Drug: eculizumab **Study Start:** May 2011 **First Received:** December 13, 2010
43	Completed	Safety and Efficacy Study of Eculizumab in Shiga-Toxin Producing Escherichia Coli Hemolytic-Uremic Syndrome (STEC-HUS) **Condition:** Shiga-like Toxin-producing Escherichia Coli **Intervention:** Drug: Eculizumab (Soliris®) **Study Start:** July 2011 **First Received:** August 3, 2011
44	Completed	Extension Study of Eculizumab in Patients With Transfusion Dependent Paroxysmal Nocturnal Hemoglobinuria (PNH) **Condition:** Paroxysmal Hemoglobinuria, Nocturnal **Intervention:** Drug: eculizumab **Study Start:** May 2005 **First Received:** July 20, 2005
45	Recruiting	Complement Inhibition Using Eculizumab to Overcome Platelet Transfusion Refractoriness in Patients With Severe Thrombocytopenia **Conditions:** Thrombocytopenia; Alloimmune Platelet Refractoriness **Intervention:** Drug: Eculizumab **Study Start:** November 4, 2014 **First Received:** November 21, 2014
46	Recruiting	Eculizumab in Shiga-toxin Related Hemolytic and Uremic Syndrome Pediatric Patients - ECULISHU **Condition:** Hemolytic Uremic Syndrome of Childhood **Interventions:** Drug: Eculizumab; Drug: Placebo **Study Start:** June 2015 **First Received:** July 28, 2014
47	Completed	Eculizumab to Treat Paroxysmal Nocturnal Hemoglobinuria

Condition: Hemoglobinuria, Paroxysmal
Intervention: Drug: Eculizumab
Study Start: December 2004
First Received: December 3, 2004

48 Completed — Eculizumab to Treat Paroxysmal Nocturnal Hemoglobinuria
Condition: Paroxysmal Hemoglobinuria, Nocturnal
Intervention: Drug: Eculizumab
Study Start: August 9, 2005
First Received: August 11, 2005

49 Completed — Study Using Eculizumab in Transfusion Dependent Paroxysmal Nocturnal Hemoglobinuria (PNH) Patients
Condition: Hemoglobinuria, Paroxysmal
Intervention: Drug: eculizumab
Study Start: October 2004
First Received: July 18, 2005

50 Completed — Study of Safety in Hemolytic Paroxysmal Nocturnal Hemoglobinuria (PNH) Patients Treated With Eculizumab
Condition: Hemoglobinuria, Paroxysmal
Intervention: Drug: eculizumab
Study Start: December 2004
First Received: July 19, 2005

51 Completed — Eculizumab in Treating Patients With Paroxysmal Nocturnal Hemoglobinuria
Condition: Leukemia
Intervention: Biological: eculizumab
Study Start: November 2004
First Received: June 2, 2005

52 Completed — Safety and Efficacy Study of Eculizumab in Patients With Mild Allergic Asthma
Condition: Allergic Asthma
Intervention: Drug: eculizumab
Study Start: September 2007
First Received: June 12, 2007

53 Completed — A Retrospective, Observational, Non-interventional Trial to Assess Eculizumab Treatment Effect in Patients With Atypical Hemolytic Uremic Syndrome (aHUS)
Condition: Atypical Hemolytic Uremic Syndrome (aHUS)
Intervention:
Study Start: August 2009
First Received: November 13, 2012

54 Unknown † — The Safety and Efficacy of Eculizumab in Japanese Patients With Atypical Hemolytic Uremic Syndrome (aHUS)
Condition: Atypical Hemolytic Uremic Syndrome (aHUS)
Intervention: Drug: Eculizumab
Study Start: May 2012
First Received: December 4, 2012

55 Completed — Safety and Effectiveness of h5G1.1-mAb for Dermatomyositis
Condition: Dermatomyositis
Intervention: Drug: h5G1.1-mAb
Study Start: April 2000
First Received: April 25, 2000

56 Completed — To Characterize the Safety and Tolerability of Eculizumab in Two Japanese aHUS Patients
Condition: ATYPICAL HEMOLYTIC UREMIC SYNDROME (AHUS)
Intervention:
Study Start: May 2012
First Received: December 4, 2012

Samsung Bioepis Exhibit No. 1002
Page 10681

57	Not yet recruiting	Phase 2 Safety and Efficacy Study of RA101495 to Treat PNH Patients Who Have an Inadequate Response to Eculizumab **Condition:** Paroxysmal Nocturnal Hemoglobinuria (PNH) **Intervention:** Drug: RA101495 **Study Start:** February 2017 **First Received:** January 20, 2017
58	Recruiting	Identification and Treatment of Thrombotic Microangiopathies in Allogeneic Stem Cell Transplants **Conditions:** Thrombotic Microangiopathy; Disorder Related to Bone Marrow Transplantation **Intervention:** Drug: eculizumab **Study Start:** September 2014 **First Received:** October 15, 2015
59	Active, not recruiting	Paroxysmal Nocturnal Hemoglobinuria (PNH) Registry **Condition:** Paroxysmal Nocturnal Hemoglobinuria **Intervention:** **Study Start:** January 2007 **First Received:** April 15, 2011
60	Terminated	aHUS Observational Long Term Follow-Up **Condition:** Atypical Hemolytic Uremic Syndrome **Intervention:** **Study Start:** March 2012 **First Received:** January 18, 2012

TO TOP

⏮ ◀ Previous Page (21-40) Studies Shown (41-60) Next Page (61-69) ▶ ⏭

† Study has passed its completion date and status has not been verified in more than two years.

Samsung Bioepis Exhibit No. 1002
Page 10682

EAST Search History

EAST Search History (Prior Art)

Ref #	Hits	Search Query	DBs	Default Operator	Plurals	Time Stamp
L1	188	(alexion near3 pharmaceuticals).as.	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2017/03/02 09:06
L2	180	(leonard near3 bell).in.	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2017/03/02 09:08
L3	399	(russell near3 rother).in.	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2017/03/02 09:08
L4	200	(eculizumab).clm.	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2017/03/02 09:10
L5	292	((paroxysmal near3 nocturnal) or PNH).clm.	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2017/03/02 09:10
L6	22	L4 and L5	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2017/03/02 09:10
L7	5	L1 and L6	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2017/03/02 09:11
L8	6	L2 and L6	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2017/03/02 09:17
L9	4	L3 and L6	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2017/03/02 09:19

EAST Search History (Interference)

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(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
24 November 2005 (24.11.2005)

PCT

(10) International Publication Number
WO 2005/110481 A2

(51) International Patent Classification[7]: A61K 45/06

(21) International Application Number:
PCT/US2005/017048

(22) International Filing Date: 16 May 2005 (16.05.2005)

(25) Filing Language: English

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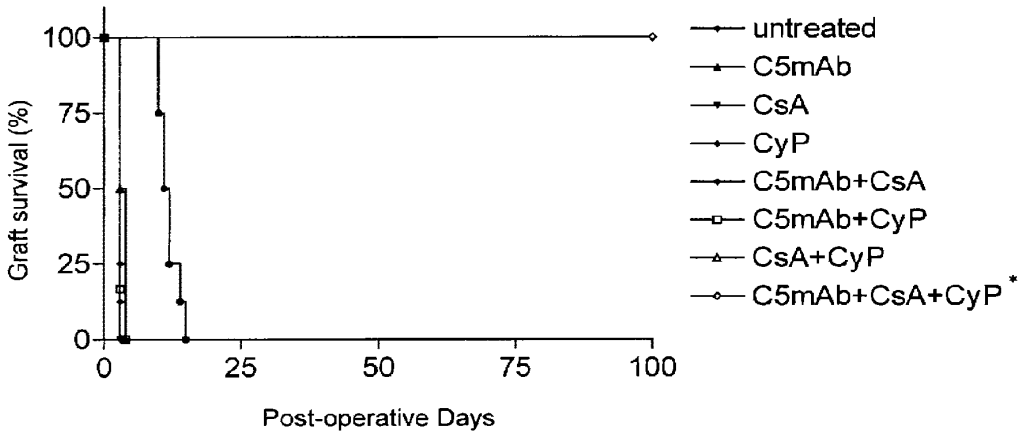
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(54) Title: PROLONGATION OF SURVIVAL OF AN ALLOGRAFT BY INHIBITING COMPLEMENT ACTIVITY



(57) Abstract: Methods of prolonging survival of allotransplanted cells, tissues or organs are presented. These methods are directed to administering to the allotransplant recipient an inhibitor of complement activity together with one or more immunosuppressants. The inhibitor of complement activity is administered chronically. These methods have been determined to aid in preventing chronic rejection of allografts. These methods can additionally be used in cases in which the recipient has been presensitized to the allograft or in which there is an ABO mismatch between the allograft and the recipient.

WO 2005/110481 A2

Samsung Bioepis Exhibit No. 1002
Page 10684

PROLONGATION OF SURVIVAL OF AN ALLOGRAFT BY INHIBITING COMPLEMENT ACTIVITY

RELATED APPLICATIONS

This application claims the benefit of and priority to U.S. Provisional Patent Application No. 60/571,444, filed May 14, 2004, the disclosure of which is incorporated herein by reference in its entirety.

TECHNICAL FIELD

The present disclosure relates to methods for prolonging survival of an allograft in a mammal. In particular, the present disclosure relates to prolonging survival of an allograft by administering an inhibitor of complement or terminal complement formation, especially an inhibitor of complement C5 cleavage, in addition to one or more drugs that are immunosuppressant.

BACKGROUND

Organ transplantation is the preferred treatment for most patients with chronic organ failure. Although transplantation of kidney, liver, lung, and heart offers an excellent opportunity for rehabilitation as recipients return to a more normal lifestyle, it is limited by the medical/surgical suitability of potential recipients, an increasing shortage of donors, and premature failure of transplanted organ function.

Transplantation of cells, tissues and organs has become very common and is often a life-saving procedure. Organ transplantation is the preferred treatment for most patients with chronic organ failure. Despite great improvement in treatments to inhibit rejection, rejection continues to be the single largest impediment to successful organ transplantation. Rejection includes not only acute rejection but also chronic rejection. One-year survival rates for transplanted kidneys average 88.3% with kidneys from deceased donors and 94.4% with kidneys received from living donors. The corresponding five year survival rates for the transplanted kidneys are 63.3% and 76.5% (OPTN/SRTR Annual Report, 2002). For livers the one year survival rates are 80.2% and 76.5% for livers from deceased and living donors, respectively. The corresponding five year liver graft survival rates are 63.5% and 73.0% (OPTN/SRTR Annual Report, 2002). The use of immunosuppressant drugs, especially cyclosporin A and more recently tacrolimus, has dramatically improved the success rate of organ transplantation especially by preventing acute rejection. But as the numbers above

Samsung Bioepis Exhibit No. 1002
Page 10685

show, there is still a need to improve the success rates, both short-term and especially long-term. As seen from the above numbers for kidney and liver transplants, the five year failure rates for these transplanted organs are on the order of 25-35%. In the year 2001 alone there were more than 23,000 patients who received an organ transplant of which approximately 19,000 were kidney or liver (OPTN/SRTR Annual Report, 2002). For this one year of transplants alone, with present techniques it can be expected that approximately 5,000-6,000 of these transplanted kidneys and livers will fail within 5 years. These numbers do not even include other transplanted organs or transplanted tissues or cells such as bone marrow.

There are multiple types of transplants. These are described in Abbas et al., 2000. A graft transplanted from one individual to the same individual is called an autologous graft or autograft. A graft transplanted between two genetically identical or syngeneic individual is called a syngeneic graft. A graft transplanted between two genetically different individuals of the same species is called an allogeneic graft or allograft. A graft transplanted between individuals of different species is called a xenogeneic graft or xenograft. The molecules that are recognized as foreign on allografts are called alloantigens and those on xenografts are called xenoantigens. The lymphocytes or antibodies that react with alloantigens or xenoantigens are described as being alloreactive or xenoreactive, respectively.

Currently more than 40,000 kidney, heart, lung, liver and pancreas transplants are performed in the United States each year (Abbas et al., 2000). Other possible transplants include, but are not limited to, vascular tissue, eye, cornea, lens, skin, bone marrow, muscle, connective tissue, gastrointestinal tissue, nervous tissue, bone, stem cells, islets, cartilage, hepatocytes, and hematopoietic cells. Unfortunately, there are many more candidates for a transplant than there are donors. To overcome this shortage, a major effort is being made to learn how to use xenografts. While progress is being made in this field, the fact is that at present most transplants are allografts. An allogeneic transplant, while presently being more likely to be successful than a xenogeneic transplant, must surmount numerous obstacles to be successful. There are several types of immunological attacks made by the recipient against the donor organ which can lead to rejection of the allograft. These include hyperacute rejection, acute vascular rejection (including accelerated humoral rejection and de novo acute humoral rejection), and chronic rejection. Rejection is normally a result of T-cell mediated or humoral antibody attack, but may include additional secondary factors such as the effects of complement and cytokines.

Samsung Bioepis Exhibit No. 1002
Page 10686

An ever growing gap between the number of patients requiring organ transplantation and the number of donor organs available has become a major problem throughout the world. Park et al., 2003. Individuals who have developed anti-HLA antibodies are said to be immunized or sensitized. Gloor, 2005. HLA sensitization is the major barrier to optimal utilization of organs from living donors in clinical transplantation (Warren et al., 2004) due to the development of severe antibody-mediated rejection (ABMR). For example, more than 50% of all individuals awaiting kidney transplantation are presensitized patients (Glotz et al., 2002) who have elevated levels of broadly reactive alloantibodies, resulting from multiple transfusions, prior failed allografts, or pregnancy (Kupiec-Weglinski, 1996). The role of ABMR is currently one of the most dynamic areas of study in transplantation, due to recognition that this type of rejection can lead to either acute or chronic loss of allograft function. Mehra et al., 2003. Numerous cases of ABMR, including hyperacute rejection (HAR) or accelerated humoral rejection (ACHR), have been reported that are characterized by acute allograft injury that is resistant to potent anti-T cell therapy, the detection of circulating donor specific antibodies, and the deposition of complement components in the graft. ABMR with elevated circulating alloantibodies and complement activation that occurs in 20-30% of acute rejection cases has a poorer prognosis than cellular rejection. Mauiyyedi et al., 2002.

Highly presensitized patients, who exhibit high levels of alloantibodies, usually suffer an immediate and aggressive HAR. In clinical practice, with great efforts and significant advances in technology, HAR is avoided by obtaining a pretransplant lymphocytotoxic cross-match to identify sensitized patients with antibodies specific for donor HLA antigens. However, circulating antibodies against donor HLA or other non-MHC endothelial antigens may also be responsible for a delayed form of acute humoral rejection, which is associated with an increased incidence of graft loss. Collins et al., 1999. Therefore, development of a novel presensitized animal model to mimic ABMR in clinical settings would be beneficial to studies on the mechanism, and to the much needed progress in the management of allograft rejection in presensitized hosts.

Some highly presensitized patients can benefit from intervention programs such as immunoadsorption (Palmer et al.,1989; Ross et al., 1993; Kriaa et al., 1995), plasmapheresis and intravenous immunoglobulin (Sonnenday et al., 2002; Rocha et al., 2003), that have been designed and implemented to temporarily eliminate anti-donor antibodies. However, in addition to their benefits, the aforementioned therapies carry with them numerous drawbacks

Samsung Bioepis Exhibit No. 1002
Page 10687

as some individuals are less susceptible to their effects (Kriaa et al., 1995; Hakim et al., 1990; Glotz et al., 1993; Tyan et al., 1994); they are extremely expensive, time-consuming, and risky (Salama et al., 2001). Moreover, the transient and variable effect of these protocols has limited their impact. Glotz et al., 2002; Kupin et al., 1991; Schweitzer et al., 2000. Therefore, developing novel strategies to reduce the risk and cost in prevention of ABMR would be beneficial to presensitized recipients receiving an allograft.

SUMMARY

Accordingly, methods of prolonging survival of transplanted cells, tissues or organs are provided. In particular, methods of prolonging survival of allotransplanted cells, tissues or organs are provided. These methods are directed to using one or more immunosuppressants in addition to an inhibitor of complement activity. Use of one or more immunosuppressants and an inhibitor of complement activity in the manufacture of one or more medicaments or medicament packages is also provided. Such medicaments or medicament packages are useful in prolonging survival of an allograft in a subject mammal.

In certain embodiments, the inhibition of complement activity is effected by chronic administration of a drug directed against complement C5. A preferred drug that inhibits complement activity is an antibody specific to one or more components of complement, for example, C5. In certain preferred embodiments, the antibody inhibits the cleavage of C5 and thereby inhibits the formation of both C5a and C5b-9. The antibody may be, e.g., a monoclonal antibody, a chimeric antibody (e.g., a humanized antibody), an antibody fragment (e.g., Fab), a single chain antibody, an Fv, or a domain antibody. The recipient is also treated with one or more immunosuppressive drugs, for example, cyclosporin A.

In certain embodiments, either an MHC mismatched recipient (i.e., a mammalian recipient of an MHC mismatched allograft), a presensitized recipient or an ABO mismatched recipient (i.e., a mammalian recipient of an AMB mismatched allograft) is treated. In this model, the recipient is again chronically treated with a complement inhibitor, preferably an anti-C5 monoclonal antibody, together with immunosuppressive drugs, preferably a chronic administration of cyclosporin A and a short-term administration of cyclophosphamide. This triple therapy results in extended graft survival in the presensitized allotransplant recipient.

The present disclosure also provides methods of prolonging survival of an allograft in a mammalian recipient by administering to the recipient agents that modulate the level and/or ratio of subclasses and/or isotypes of anti-donor immunoglobulins (Ig) in the recipient. In

Samsung Bioepis Exhibit No. 1002
Page 10688

certain embodiments, an agent that reduces the level of anti-donor IgG1 in the recipient is preferred. In certain embodiments, an agent that increases the level of anti-donor IgG2a and/or IgG2b in the recipient is preferred. In certain embodiments, an agent that reduces the ratio of anti-donor IgG1/anti-donor IgG2a or IgG2b in the recipient is preferred.

The present disclosure also provides a method of prolonging survival of an allograft in a second mammalian recipient using an allograft that has been accommodated in a first mammalian recipient (i.e., the allograft has prolonged survival in the first recipient). The present disclosure further provides an allograft that is resistant to anti-donor antibodies in a mammalian recipient, and the allograft is prepared from a first recipient that has accommodated the allograft. In preferred embodiments, the first recipient has accommodated the allograft by receiving a treatment as described herein, such a triple therapy treatment involving administering to the first recipient a drug that inhibits complement activity and two immunosuppressive agents.

Further provided are pharmaceutical packages. A pharmaceutical package of the present disclosure may comprise a drug that inhibits complement activity and at least one immunosuppressive agent. The pharmaceutical package may further comprise a label for chronic administration. The pharmaceutical package may also comprise a label for self-administration by a patient, for example, a recipient of a transplant graft, or instructions for a caretaker of a recipient of a transplant graft. In certain embodiments, the drug and the agent in the pharmaceutical package are in a formulation or separate formulations that are suitable for chronic administration and/or self-administration.

The present disclosure also provides lyophilized formulations and formulations suitable for injection. Certain embodiments provide a lyophilized antibody formulation comprising an antibody that inhibits complement activity and a lyoprotectant. In preferred embodiments, the antibody formulation is suitable for chronic administration, for example, the antibody formulation is stable. Alternative embodiments provide an injection system comprising a syringe; the syringe comprises a cartridge containing an antibody that inhibits complement activity and is in a formulation suitable for injection.

An antibody employed in various embodiments of the present disclosure preferably inhibits the formation of terminal complement or C5a. In certain embodiments, antibody inhibits formation of terminal complement or C5a is a whole antibody or an antibody fragment. The whole antibody or antibody fragment may be a human, humanized,

Samsung Bioepis Exhibit No. 1002
Page 10689

chimerized or deimmunized antibody or antibody fragment. In certain embodiments, the whole antibody or antibody fragment may inhibit cleavage of complement C5. In certain embodiments, the antibody fragment is a Fab, an F(ab')2, an Fv, a domain antibody, or a single-chain antibody. In preferred embodiments, the antibody fragment is pexelizumab. In alternative preferred embodiments, the whole antibody is eculizumab.

In certain embodiments, a drug, such as an antibody, that inhibits complement activity is present in unit dosage form, which can be particularly suitable for self-administration. Similarly, an immunosuppressive agent of the present disclosure may also be present in unit dosage form.

BRIEF DESCRIPTION OF THE DRAWINGS

Figures 1A-1D show anti-donor antibody levels in presensitized versus unsensitized recipients under different treatments.

Figures 2A and 2B show comparison between triple therapy using anti-C5 antibody, CsA and CyP in presensitized allograft recipients and combination therapy using only anti-C5 antibody and CsA in presensitized allograft recipients. Figure 2A compares heart-allograft survival in various recipients under different treatments as indicated. Figure 2B shows histology and immunohistology, for example, for lymphocyte infiltration in heart allografts of recipients in different groups.

Figure 3 shows blocked terminal complement activity by anti-C5 antibody as compared to immunosuppressive agents.

Figures 4A-4D compare levels of anti-donor antibodies in presensitized recipients of allografts under monotherapy with anti-C5 antibody alone, double combination therapy with anti-C5 antibody and CsA, and triple combination therapy with anti-C5 antibody, CsA and CyP.

Figures 5A and 5B show change of ratios of IgG isotypes in allograft recipients that were untreated or under different treatments.

Figure 6 shows high-level expression of Bcl-2 and Bcl-xl proteins in long-term surviving heart grafts as compared to heart grafts of untreated animals.

Figure 7 shows improved second transplantation (re-transplantation) of an accommodated graft from a first transplantation recipient.

Figure 8 shows results from re-transplantation experiments.

Samsung Bioepis Exhibit No. 1002
Page 10690

Figure 9 shows results from re-transplantation experiments.

DETAILED DESCRIPTION

Overview: Rejection of Transplants or Grafts

Hyperacute rejection occurs within minutes to hours after transplant and is due to preformed antibodies to the transplanted tissue antigens. It is characterized by hemorrhage and thrombotic occlusion of the graft vasculature. The binding of antibody to endothelium activates complement, and antibody and complement induce a number of changes in the graft endothelium that promote intravascular thrombosis and lead to vascular occlusion, the result being that the grafted organ suffers irreversible ischemic damage (Abbas et al., 2000). Hyperacute rejection is often mediated by preexisting IgM alloantibodies, e.g., those directed against the ABO blood group antigens expressed on red blood cells. This type of rejection, mediated by natural antibodies, is the main reason for rejection of xenotransplants. Hyperacute rejection due to natural IgM antibodies is no longer a major problem with allografts because allografts are usually selected to match the donor and recipient ABO type. Hyperacute rejection of an ABO matched allograft may still occur, usually mediated by IgG antibodies directed against protein alloantigens, such as foreign MHC molecules, or against less well defined alloantigens expressed on vascular endothelial cells. Such antibodies may arise as a result of prior exposure to alloantigens through blood transfusion, prior transplantation, or multiple pregnancies (this prior exposure being referred to as "presensitization"). Abbas et al., 2000.

Acute rejection is a process of vascular and parenchymal injury mediated by T cells, macrophages, and antibodies that usually begins after the first week of transplantation. Abbas et al., 2001. T lymphocytes play a central role in acute rejection by responding to alloantigens, including MHC molecules, present on vascular endothelial and parenchymal cells. The activated T cells cause direct lysis of graft cells or produce cytokines that recruit and activate inflammatory cells, which cause necrosis. Both $CD4^+$ and $CD8^+$ cells may contribute to acute rejection. The destruction of allogeneic cells in a graft is highly specific and a hallmark of $CD8^+$ cytotoxic T lymphocyte killing. Abbas et al., 2000. $CD4^+$ T cells may be important in mediating acute graft rejection by secreting cytokines and inducing delayed-type hypersensitivity-like reactions in grafts, with some evidence available that indicates that $CD4^+$ T cells are sufficient to mediate acute rejection. Abbas et al., 2000. Antibodies can also mediate acute rejection after a graft recipient mounts a humoral immune

Samsung Bioepis Exhibit No. 1002
Page 10691

response to vessel wall antigens and the antibodies that are produced bind to the vessel wall and activate complement. Abbas et al., 2000.

Chronic rejection is characterized by fibrosis with loss of normal organ structures occurring over a prolonged period. The pathogenesis of chronic rejection is less well understood than that of acute rejection. Graft arterial occlusion may occur as a result of the proliferation of intimal smooth muscle cells (Abbas et al., 2000). This process is called accelerated or graft arteriosclerosis and can develop in any vascularized organ transplant within 6 months to a year after transplantation.

For a transplant to be successful, the several modes of rejection must be overcome. Multiple approaches are utilized in preventing rejection. This may require administration of immunosuppressants, often several types to prevent the various modes of attack, e.g., inhibition of T-cell attack, antibodies, and cytokine and complement effects. Prescreening of donors to match them with recipients is also a major factor in preventing rejection, especially in preventing hyperacute rejection. Immunoadsorption of anti-HLA antibodies prior to grafting may reduce hyperacute rejection. Prior to transplantation the recipient or host may be administered anti-T cell reagents, e.g., the monoclonal antibody OKT3, Anti-Thymocyte Globulin (ATG), cyclosporin A, or tacrolimus (FK 506). Additionally, glucocorticoids and/or azathioprine may be administered to the host prior to transplant. Drugs used to aid in preventing transplant rejection include, but are not limited to, ATG or ALG, OKT3, daclizumab, basiliximab, corticosteroids, 15-deoxyspergualin, cyclosporins, tacrolimus, azathioprine, methotrexate, mycophenolate mofetil, 6-mercaptopurine, bredinin, brequinar, leflunamide, cyclophosphamide, sirolimus, anti-CD4 monoclonal antibodies, CTLA4-Ig, anti-CD154 monoclonal antibodies, anti-LFA1 monoclonal antibodies, anti-LFA-3 monoclonal antibodies, anti-CD2 monoclonal antibodies, and anti-CD45.

Allografts are rejected in part by the activation of T cells. The transplant recipient mounts a rejection response following $CD4^+$ T cell recognition of foreign antigens in the allograft. These antigens are encoded by the major histocompatibility complex (MHC). There are both Class I and Class II MHC molecules. In humans the class I MHC molecules are HLA-A, HLA-B, and HLA-C. The class II MHC molecules in humans are called HLA-DR, HLA-DQ and HLA-DP. In mice the class I MHC molecules are H-2K, H-2D and H-2L and the class II MHC molecules are I-A and I-E. When $CD4^+$ T cells bind the foreign MHC antigens they are activated and undergo clonal proliferation. The activated T cells secrete cytokines which aid in activating monocytes/macrophages, B cells and cytotoxic $CD8^+$ T

Samsung Bioepis Exhibit No. 1002
Page 10692

cells. The activated monocytes/macrophages release agents which result in tissue damage, the B cells produce alloantibodies which lead to complement mediated tissue destruction, and the $CD8^+$ T cells kill graft cells in an antigen-specific manner through induction of apoptosis and cell lysis.

Immunosuppressive Agents

The numerous drugs utilized to delay graft rejection (i.e., to prolong their survival) work in a variety of ways. Immunosuppressive agents are widely used. See Stepkowski, 2000, for a review of the mechanism of action of several immunosuppressive drugs. Cyclosporin A is one of the most widely used immunosuppressive drugs for inhibiting graft rejection. It is an inhibitor of interleukin-2 or IL-2 (it prevents mRNA transcription of interleukin-2). More directly, cyclosporin inhibits calcineurin activation that normally occurs upon T cell receptor stimulation. Calcineurin dephosphorylates NFAT (nuclear factor of activated T cells) enabling it to enter the nucleus and bind to interleukin-2 promoter. By blocking this process, cyclosporin A inhibits the activation of the $CD4^+$ T cells and the resulting cascade of events which would otherwise occur. Tacrolimus is another immunosuppressant that acts by inhibiting the production of interleukin-2.

Rapamycin (Sirolimus), SDZ RAD, and interleukin-2 receptor blockers are drugs that inhibit the action of interleukin-2 and therefore prevent the cascade of events described above.

Inhibitors of purine or pyrimidine biosynthesis are also used to inhibit graft rejection. These prevent DNA synthesis and thereby inhibit cell division including the ability of T cells to divide. The result is the inhibition of T cell activity by preventing the formation of new T cells. Inhibitors of purine synthesis include azathioprine, methotrexate, mycophenolate mofetil (MMF) and mizoribine (bredinin). Inhibitors of pyrimidine synthesis include brequinar sodium and leflunomide. Cyclophosphamide is an inhibitor of both purine and pyrimidine synthesis.

Yet another method for inhibiting T cell activation is to treat the recipient with antibodies to T cells. OKT3 is a murine monoclonal antibody against CD3 which is part of the T cell receptor. This antibody inhibits the T cell receptor and suppresses T cell activation.

Numerous other drugs and methods for delaying allotransplant rejection are known to and used by those of skill in the art. One approach has been to deplete T cells, e.g., by irradiation. This has often been used in bone marrow transplants, especially if there is a

Samsung Bioepis Exhibit No. 1002
Page 10693

partial mismatch of major HLA. Administration to the recipient of an inhibitor (blocker) of the CD40 ligand-CD40 interaction and/or a blocker of the CD28-B7 interaction has been used (U.S. Patent 6,280,957). Published PCT patent application WO 01/37860 teaches the administration of an anti-CD3 monoclonal antibody and IL-5 to inhibit the Th1 immune response. Published PCT patent application WO 00/27421 teaches a method for prophylaxis or treatment of corneal transplant rejection by administering a tumor necrosis factor-α antagonist. Glotz et al. (2002) show that administration of intravenous immunoglobulins (IVIg) can induce a profound and sustained decrease in the titers of anti-HLA antibodies thereby allowing a transplant of an HLA-mismatched organ. Similar protocols have included plasma exchanges (Taube et al., 1984) or immunoadsorption techniques coupled to immunosuppressive agents (Hiesse et al., 1992) or a combination of these (Montgomery et al., 2000). Changelian et al. (2003) teach a model in which immunosuppression is caused by an oral inhibitor of Janus kinase 3 (JAK3) which is an enzyme necessary for the proper signaling of cytokine receptors which use the common gamma chain (γc) (Interleukins-2, -4, -7, -9, -15, -21), the result being an inhibition of T cell activation. Antisense nucleic acids against ICAM-1 have been used alone or in combination with a monoclonal antibody specific for leukocyte-function associated antigen 1 (LFA-1) in a study of heart allograft transplantation (Stepkowski, 2000). Similarly, an anti-ICAM-1 antibody has been used in combination with anti-LFA-1 antibody to treat heart allografts (Stepkowski, 2000). Antisense oligonucleotides have additionally been used in conjunction with cyclosporin in rat heart or kidney allograft models, resulting in a synergistic effect to prolong the survival of the grafts (Stepkowski, 2000). Chronic transplant rejection has been treated by administering an antagonist of TGF-β which is a cytokine involved in differentiation, proliferation and apoptosis (U.S. Patent Application Publication US 2003/0180301).

Complement and Transplant/Graft Rejection

The role of complement in transplant rejection is well known. This is especially true in the case of xenotransplantation, but complement also plays a role in allotransplant rejection. For review, see Platt and Saadi, 1999. One aspect of complement's role is that ischemia-reperfusion injury may occur at the time that an organ graft is reperfused with the blood of the recipient. Complement may also cause some manifestations of allograft rejection.

The complement system is described in detail in U.S. Patent 6,355,245. The complement system acts in conjunction with other immunological systems of the body to

Samsung Bioepis Exhibit No. 1002
Page 10694

defend against intrusion of cellular and viral pathogens. There are at least 25 complement proteins, which are found as a complex collection of plasma proteins and membrane cofactors. The plasma proteins make up about 10% of the globulins in vertebrate serum. Complement components achieve their immune defensive functions by interacting in a series of intricate but precise enzymatic cleavage and membrane binding events. The resulting complement cascade leads to the production of products with opsonic, immunoregulatory, and lytic functions.

The complement cascade progresses via the classical pathway or the alternative pathway. These pathways share many components and, while they differ in their initial steps, they converge and share the same "terminal complement" components (C5 through C9) responsible for the activation and destruction of target cells.

The classical complement pathway is typically initiated by antibody recognition of and binding to an antigenic site on a target cell. The alternative pathway is usually antibody independent and can be initiated by certain molecules on pathogen surfaces. Both pathways converge at the point where complement component C3 is cleaved by an active protease (which is different in each pathway) to yield C3a and C3b. Other pathways activating complement attack can act later in the sequence of events leading to various aspects of complement function.

C3a is an anaphylatoxin. C3b binds to bacterial and other cells, as well as to certain viruses and immune complexes, and tags them for removal from the circulation. C3b in this role is known as opsonin. The opsonic function of C3b is considered to be the most important anti-infective action of the complement system. Patients with genetic lesions that block C3b function are prone to infection by a broad variety of pathogenic organisms, while patients with lesions later in the complement cascade sequence, i.e., patients with lesions that block C5 functions, are found to be more prone only to Neisseria infection, and then only somewhat more prone (Fearon, 1983).

C3b also forms a complex with other components unique to each pathway to form classical or alternative C5 convertase, which cleaves C5 into C5a and C5b. C3 is thus regarded as the central protein in the complement reaction sequence since it is essential to both the alternative and classical pathways (Wurzner et al., 1991). This property of C3b is regulated by the serum protease Factor I, which acts on C3b to produce iC3b. While still functional as opsonin, iC3b cannot form an active C5 convertase.

Samsung Bioepis Exhibit No. 1002
Page 10695

C5 is a 190 kDa beta globulin found in normal serum at approximately 75 μg/mL (0.4 μM). C5 is glycosylated, with about 1.5-3 percent of its mass attributed to carbohydrate. Mature C5 is a heterodimer of a 999 amino acid 115 kDa alpha chain that is disulfide linked to a 656 amino acid 75 kDa beta chain. C5 is synthesized as a single chain precursor protein product of a single copy gene (Haviland et al., 1991). The cDNA sequence of the transcript of this gene predicts a secreted pro-C5 precursor of 1659 amino acids along with an 18 amino acid leader sequence.

The pro-C5 precursor is cleaved after amino acid 655 and 659, to yield the beta chain as an amino terminal fragment (amino acid residues +1 to 655) and the alpha chain as a carboxyl terminal fragment (amino acid residues 660 to 1658), with four amino acids deleted between the two.

C5a is cleaved from the alpha chain of C5 by either alternative or classical C5 convertase as an amino terminal fragment comprising the first 74 amino acids of the alpha chain (i.e., amino acid residues 660-733). Approximately 20 percent of the 11 kDa mass of C5a is attributed to carbohydrate. The cleavage site for convertase action is at or immediately adjacent to amino acid residue 733. A compound that would bind at or adjacent to this cleavage site would have the potential to block access of the C5 convertase enzymes to the cleavage site and thereby act as a complement inhibitor.

C5 can also be activated by means other than C5 convertase activity. Limited trypsin digestion (Minta and Man, 1977; Wetsel and Kolb, 1982) and acid treatment (Yamamoto and Gewurz, 1978; Vogt et al., 1989) can also cleave C5 and produce active C5b.

C5a is another anaphylatoxin. C5b combines with C6, C7, and C8 to form the C5b-8 complex at the surface of the target cell. Upon binding of several C9 molecules, the membrane attack complex (MAC, C5b-9, terminal complement complex-TCC) is formed. When sufficient numbers of MACs insert into target cell membranes the openings they create (MAC pores) mediate rapid osmotic lysis of the target cells. Lower, non-lytic concentrations of MACs can produce other effects. In particular, membrane insertion of small numbers of the C5b-9 complexes into endothelial cells and platelets can cause deleterious cell activation. In some cases activation may precede cell lysis.

As mentioned above, C3a and C5a are anaphylatoxins. These activated complement components can trigger mast cell degranulation, which releases histamine and other mediators of inflammation, resulting in smooth muscle contraction, increased vascular

Samsung Bioepis Exhibit No. 1002
Page 10696

permeability, leukocyte activation, and other inflammatory phenomena including cellular proliferation resulting in hypercellularity. C5a also functions as a chemotactic peptide that serves to attract pro-inflammatory granulocytes to the site of complement activation.

Complement-binding recipient antibodies to donor alloantigens are considered to be the main cause of hyperacute graft rejection. Owing to pretransplant crossmatch testing, this prototype of humoral rejection is now rarely observed (Regele et al., 2001). Data are now showing that humoral immune mechanisms might contribute to other types of allograft rejection (Regele et al., 2001). High levels of panel reactive antibodies indicating humoral presensitization were found to be associated with inferior kidney graft survival (Opelz, 1992), the appearance of alloantibodies during the post-transplant period has been reported to predict poor graft outcome (Jeannet et al., 1970; Halloran et al., 1992), and selective removal of recipient IgG by immunoadsorption reversed some rejection episodes indicating the contribution of humoral immune mechanisms to rejection (Persson et al., 1995; Böhmig et al., 2000). Complement activation within a graft might indicate antibody-mediated graft injury. The complement cleavage product C4d is a marker for activation of the antibody-dependent classical pathway. Capillary C4d deposits in kidney allograft biopsies were associated with poor graft outcome.

Recently increasing evidence indicates that complement activation significantly contributes to the sensitization of allograft recipients and the development of tissue injury in allografts (Platt et al., 1999). Antibodies are the most thoroughly investigated mediators of activating the classical complement pathway. Clinically, alloantibodies are known to activate complement (Baldwin et al., 2001). Halloran and Collins indicate that C4d deposition in peritubular capillaries of renal allografts is a sensitive and diagnostic marker of acute humoral rejection that correlates strongly with the presence of circulating donor-specific antibodies (Collins et al., 1999; Halloran, 2003). Further supporting evidence is seen in animals with complement inhibition (Pratt et al., 1996; Pruitt et al., 1991; Forbes et al., 1978) or deficiency (Pratt et al., 2000; Baurer et al., 1995) which exhibit significantly reduced inflammatory injury and lowered anti-donor immune responses. In ABMR, complement is suggested to be activated by the classical pathway and to play a key role in the pathogenesis (Collard et al., 1997). Although the role of complement in HAR or acute vascular rejection (AVR) following xenotransplantation has been well documented (Platt et al., 1999), precise mechanisms of complement in the pathogenesis of ABMR following allotransplantation has not yet been elucidated.

Samsung Bioepis Exhibit No. 1002
Page 10697

The C5 component of complement is cleaved to form products with multiple proinflammatory effects and thus represents an attractive target for complement inhibition within the immune-mediated inflammatory response. As described above, C5a is a powerful anaphylatoxin and chemotactic factor. Cellular activation by C5a induces the release of multiple additional inflammatory mediators (Jose et al., 1983). The complement activation pathways (classical, alternative, or mannan-binding lectin pathway) ultimately lead to the formation of the cytolytic membrane attack complex C5b-9 (Kirschfunk, 2001), which can mediate both direct tissue injury by cell lysis, and proinflammatory cell activation at sublytic doses (Saadi et al., 1995; Papadimitriou et al., 1991). Therefore, blocking both C5a and C5b-9 generation may be required for the optimal inhibition of complement-mediated inflammatory response following transplantation. At the same time, inhibition of the complement cascade at C5 does not impair the generation of C3b, preserving C3b-mediated opsonization of pathogenic microorganisms as well as solubilization and clearance of immune complexes (Liszewski, 1993).

The beneficial effect of anti-C5 mAb has previously been reported in several experimental models including myocardial reperfusion (Vakeva et al., 1998), systemic lupus erythematosus (Wang et al., 1996) and rheumatoid arthritis (Wang et al., 1995); as well as in human clinical trials (Kirschfink, 2001) of autoimmune disease, cardiopulmonary bypass and acute myocardial infarction. In addition, complement inactivation by a functionally blocking anti-C5 monoclonal Ab (mAb) prevented HAR in xenotransplantation models (Kroshus et al., 1995; Wang et al., 1999).

Methods of delaying allotransplant rejection by administration of complement inhibitors have been tested. Published PCT patent application WO 92/10205 discloses the use of a combination of cyclosporin and a soluble complement receptor (sCR1) to inhibit rejection of a cardiac allotransplant in a presensitized rat model. Complement receptor 1 binds complements C3b and C4b. Soluble forms of complement receptor 1 occur naturally or can be generated via recombinant DNA procedures. These soluble complement receptors have inhibited in vitro the consequences of complement activation (U.S. Patent 6,057,131). In WO 92/10205, rats, which had been presensitized to the cardiac allograft they were receiving, were administered cyclosporin A intramuscularly at 10 mg/kg/day beginning two days prior to transplant and continued until the time of graft rejection. Additionally, soluble complement receptor 1 (sCR1) was administered as a single intravenous bolus at 15 mg/kg immediately prior to reperfusion of the graft. Control animals with no drug treatment had the

Samsung Bioepis Exhibit No. 1002
Page 10698

graft rejected at an average of 3.8 days. Those administered cyclosporin A alone rejected the grafts at an average of 57 days (this was quite variable with two rats rejecting quickly at 2 and 4 days and a third rat rejecting at 166 days). Rats administered sCR1 alone rejected the grafts at an average of 44 days. Those rats administered the combination of cyclosporin A and sCR1 rejected the grafts at an average of 147 days. The combination of chronic cyclosporin A and single bolus sCR1 was seen to result in a synergistic effect greatly prolonging the time until graft rejection. Earlier studies by Pruitt and Bollinger (1991) used a similar model of a presensitized rat allograft to show that administration of sCR1 alone to inactivate complement resulted in increased time before graft rejection.

Sims et al. (U.S. Patent 5,135,916) suggest using inhibitors of complement, e.g., CD59 or antibodies against C7 or C9 to block the formation of the C5b-9 complex, to treat the vascular endothelium of organs and tissues to be transplanted. This would prevent the C5b-9 initiated cell necrosis. The C5b-9 inactivators would be added to the perfusate or storage medium to protect the vascular lining cells from ongoing complement activation during in vitro storage. Additionally the organ or tissue would be protected from the cytolytic and thrombotic effects arising from complement activation initiated upon transplantation, thereby circumventing complement mediated acute rejection. Sims et al. (U.S. Patent 5,573,940 and U.S. Patent 6,100,443) also teach a method of expressing CD59 in the transplanted tissue or organ to protect the transplanted organ from rejection. This can be accomplished by transfecting the cells being transplanted.

Although the several drugs developed to date in combination with methods of prescreening donors and recipients to match the donor allograft to the recipient have over time increased the average length of time of survival of allografts, many allografts are nonetheless rejected during the life-time of the recipient. In general, the prior art advances have mainly been directed to overcoming acute graft rejection. Further, the role of activated terminal complement components in antibody-mediated allograft rejection has not been examined using inhibitors that specifically target the complement cascade at the C5 protein level. The methods described herein and as exemplified in the Examples advance the allotransplant art by inhibiting chronic rejection of allografts, in particular, allografts in a presensitized recipient. New methods are presented for further prolonging allograft survival by using a proper combination of immunosuppressive drugs in combination with a chronic administration of a complement inhibitor.

Samsung Bioepis Exhibit No. 1002
Page 10699

Methods and Uses

The methods disclosed herein are used to prolong allograft survival. The methods generally include administering an inhibitor of complement activity in combination with one or more immunosuppressants.

Suitable complement inhibitors are known to those of skill in the art. Antibodies can be made to individual components of activated complement, e.g., antibodies to C5a, C7, C9, etc. (see, e.g., U.S. Patent 6,534,058; published U.S. patent application US 2003/0129187; and U.S. Patent 5,660,825). Proteins are known which inhibit complement-mediated lysis, including CD59, CD55, CD46 and other inhibitors of C8 and C9 (see, e.g., U.S. Patent 6,100,443). U.S. Patent 6,355,245 teaches an antibody which binds to C5 and prevents it from being cleaved into C5a and C5b thereby preventing the formation not only of C5a but also the C5b-9 complex. Proteins known as complement receptors and which bind complement are also known (see, Published PCT Patent Application WO 92/10205 and U.S. Patent 6,057,131). Use of soluble forms of complement receptors, e.g., soluble CR1, can inhibit the consequences of complement activation such as neutrophil oxidative burst, complement mediated hemolysis, and C3a and C5a production. Those of skill in the art recognize the above as some, but not all, of the known methods of inhibiting complement and its activation.

Suitable immunosuppressants include, but are not limited to, ATG or ALG, OKT3, daclizumab, basiliximab, corticosteroids, 15-deoxyspergualin, cyclosporins, tacrolimus, azathioprine, methotrexate, mycophenolate mofetil, 6-mercaptopurine, bredinin, brequinar, leflunamide, cyclophosphamide, sirolimus, anti-CD4 monoclonal antibodies, CTLA4-Ig, anti-CD154 monoclonal antibodies, anti-LFA1 monoclonal antibodies, anti-LFA-3 monoclonal antibodies, anti-CD2 monoclonal antibodies, and anti-CD45.

An allograft can include a transplanted organ, part of an organ, tissue or cell. These include, but are not limited to, heart, kidney, lung, pancreas, liver, vascular tissue, eye, cornea, lens, skin, bone marrow, muscle, connective tissue, gastrointestinal tissue, nervous tissue, bone, stem cells, islets, cartilage, hepatocytes, and hematopoietic cells.

At least part of the reason for the failure of allografts is that one response by the recipient of an allograft is the activation of complement. This results in the formation of C5a and C5b-9 which are potent proinflammatory molecules which aid in causing graft failure. Without wishing to be bound by any proposed theory, Applicants theorized that inhibiting the

Samsung Bioepis Exhibit No. 1002
Page 10700

formation of C5a and C5b-9 or inhibiting C5a and C5b-9 which was present would aid in preventing graft failure. Furthermore, it was theorized that so long as the allograft is present, the recipient will continue to attempt to mount an immune response against the graft, and this response will include attempts to produce C5a and C5b-9. If not prevented, this complement response will lead to acute vascular rejection in the short term and could contribute to chronic graft rejection in the long term. Prior art methods of using inhibitors of complement activity were limited to administering these inhibitors only at the time of transplant. This was helpful in preventing acute rejection, but as the results disclosed herein illustrate, improved results are obtained by administration of such inhibitors for a longer term. This long-term administration aids in preventing a chronic rejection of the allograft as opposed to only aiding in preventing an acute rejection. The result is a longer term survival of the allograft as compared to either not administering an inhibitor of complement activity or administering such an inhibitor only at the time of transplant of the allograft. Although very commonly it is desirable that the allograft will survive for the remaining lifetime of the recipient, there are times when the allograft is needed only for a shorter length of time, e.g., a bridge organ to bridge the time until the recipient's own organ can recover on its own, at which time the allograft will no longer be needed. The length of time such a graft will be needed will vary, but will usually be longer than the time at which acute rejection would occur and may be long enough for chronic rejection to occur. This period of desired survival for a bridge graft may be several months, e.g., six months.

To prove that long-term inhibition of complement activity will prolong allograft survival, experiments were performed in which complement activation was inhibited in a chronic fashion and not merely at the time of transplant. Chronic treatment means treatment during an extended period up to the lifetime of the allograft. This can be daily treatment but is not limited to daily treatment. Chronic treatment will maintain an effective amount of the drug in the allograft recipient. For example, a preferred method is to include the anti-C5 monoclonal antibody eculizumab in the treatment. In studies of persons suffering from paroxysmal nocturnal hemoglobinuria (PNH), eculizumab has been administered at a dose of 900 mg/patient once every 12-14 days. This dosing has been found to completely and consistently block terminal complement activity and has greatly inhibited the symptoms of PNH (Hillmen et al., 2004). The administered dose is able to block the effects of complement for approximately two weeks before the eculizumab is inactivated or removed from the body. Therefore, a chronic treatment of eculizumab may be, e.g., the administration

Samsung Bioepis Exhibit No. 1002
Page 10701

of 900 mg to the allograft recipient once every two weeks for the remaining life-time of the patient. Similarly, other drugs can be delivered chronically as needed, whether this is on a daily basis or another schedule is required to maintain an effective amount of the drug in the allograft recipient. Because it is well known that graft rejection can be caused by more than just complement activation, e.g., by T cell activity, the experiments included immunosuppressants such as cyclosporin to further aid in preventing graft rejection.

A preferred method of inhibiting complement activity is to use a monoclonal antibody which binds to complement C5 and prevents C5 from being cleaved. This prevents the formation of both C5a and C5b-9 while at the same time allowing the formation of C3a and C3b which are beneficial to the recipient. Such antibodies that are specific to human complement are known (U.S. Patent 6,355,245). These antibodies disclosed in U.S. Patent 6,355,245 include both a whole or full-length antibody (now named eculizumab) and a single-chain antibody (now named pexelizumab). A similar antibody against mouse C5 is called BB5.1 (Frei et al., 1987). BB5.1 was utilized in the experiments set forth below. Antibodies to inhibit complement activity need not be monoclonal antibodies. They can be, e.g., polyclonal antibodies. They may additionally be antibody fragments. An antibody fragment includes, but is not limited to, an Fab, F(ab'), $F(ab')_2$, a single-chain antibody, a domain antibody and an Fv. Furthermore, it is well known by those of skill in the art that antibodies can be humanized (Jones et al., 1986), chimerized, or deimmunized. An antibody may also comprise a mutated Fc portion, such that the mutant Fc does not activate complement. The antibodies to be used in the present disclosure may be any of these. It is preferable to use humanized antibodies when the recipient of the allograft is a human.

Administration and Formulations

Administration of the inhibitor of complement activity is performed according to methods known to those of skill in the art. These inhibitors are administered preferably before the time of allograft transplantation or at the time of transplantation with administration continuing in a chronic fashion. These inhibitors can additionally be administered during a rejection episode in the event such an episode does occur.

The present disclosure also provides uses of a drug that inhibits complement activity and an immunosuppressive agent in the manufacture of a medicament or medicament package. Such medicament or medicament package is useful in prolonging allograft survival in a recipient, in particular, chronic survival of the allograft. In preferred embodiments, the

Samsung Bioepis Exhibit No. 1002
Page 10702

medicament or medicament package is formulated and prepared such that it is suitable for chronic administration to the recipient of the allograft, for example, stable formulations are employed. In certain embodiments, the medicament or medicament package is formulated and prepared such that it is suitable for concurrent administration of the drug that inhibits complement activity and the immunosuppressive drug to the recipient of the allograft. In certain embodiments, the medicament or medicament package is formulated and prepared such that it is suitable for sequential (in either order) administration of the drug that inhibits complement activity and the immunosuppressive drug to the recipient of the allograft.

A pharmaceutical package of the present disclosure may comprise a drug that inhibits complement activity and at least one immunosuppressive agent. The pharmaceutical package may further comprise a label for chronic administration. The pharmaceutical package may also comprise a label for self-administration by a patient, for example, a recipient of a transplant graft, or instructions for a caretaker of a recipient of a transplant graft. In certain embodiments, the drug and the agent in the pharmaceutical package are in a formulation or separate formulations that are suitable for chronic administration and/or self-administration.

The present disclosure also provides lyophilized formulations and formulations suitable for injection. Certain embodiments provide a lyophilized antibody formulation comprising an antibody that inhibits complement activity and a lyoprotectant. In preferred embodiments, the antibody formulation is suitable for chronic administration, for example, the antibody formulation stable. Alternative embodiments provide an injection system comprising a syringe; the syringe comprises a cartridge containing an antibody that inhibits complement activity and is in a formulation suitable for injection.

An antibody employed in various embodiments of the present disclosure preferably inhibits the formation of terminal complement or C5a. In certain embodiments, antibody inhibits formation of terminal complement or C5a is a whole antibody or an antibody fragment. The whole antibody or antibody fragment may be a human, humanized, chimerized or deimmunized antibody or antibody fragment. In certain embodiments, the whole antibody or antibody fragment may inhibit cleavage of complement C5. In certain embodiments, the antibody fragment is a Fab, an F(ab')2, an Fv, a domain antibody, or a single-chain antibody. In preferred embodiments, the antibody fragment is pexelizumab. In alternative preferred embodiments, the whole antibody is eculizumab.

Samsung Bioepis Exhibit No. 1002
Page 10703

In certain embodiments, a drug, such as an antibody, that inhibits complement activity is present in unit dosage form, which can be particularly suitable for self-administration. Similarly, an immunosuppressive agent of the present disclosure may also be present in unit dosage form. A formulated product of the present disclosure can be included within a container, typically, for example, a vial, cartridge, prefilled syringe or disposable pen. A doser such as the doser device described in U.S. Patent 6,302,855 may also be used, for example, with an injection system of the present disclosure.

A "stable" formulation is one in which the drug (e.g., an antibody) or agent therein essentially retains its physical and chemical stability and integrity upon storage. Various analytical techniques for measuring protein stability are available in the art and are reviewed in Peptide and Protein Drug Delivery, 247-301, Vincent Lee Ed., Marcel Dekker, Inc., New York, N.Y., Pubs. (1991) and Jones, A. Adv. Drug Delivery Rev. 10: 29-90 (1993). Stability can be measured at a selected temperature for a selected time period. For example, the extent of aggregation following lyophilization and storage can be used as an indicator of protein stability. For example, a "stable" formulation may be one wherein less than about 10% and preferably less than about 5% of the protein is present as an aggregate in the formulation. In other embodiments, any increase in aggregate formation following lyophilization and storage of the lyophilized formulation can be determined. For example, a "stable" lyophilized formulation may be one wherein the increase in aggregate in the lyophilized formulation is less than about 5% and preferably less than about 3%, when the lyophilized formulation is stored at 2-8 °C for at least one year. In other embodiments, stability of the protein formulation may be measured using a biological activity assay.

A "reconstituted" formulation is one which has been prepared by dissolving a lyophilized protein formulation in a diluent such that the protein is dispersed in the reconstituted formulation. The reconstituted formulation in suitable for administration (e.g. parenteral administration) to a patient to be treated with the protein of interest and, in certain embodiments of the invention, may be one which is suitable for subcutaneous administration.

An isotonic reconstituted formulation is preferable in certain embodiments. By "isotonic" is meant that the formulation of interest has essentially the same osmotic pressure as human blood. Isotonic formulations will generally have an osmotic pressure from about 250 to 350 mOsm. Isotonicity can be measured using a vapor pressure or ice-freezing type osmometer, for example.

Samsung Bioepis Exhibit No. 1002
Page 10704

A "lyoprotectant" is a molecule which, when combined with a drug (e.g., antibody) of interest, significantly prevents or reduces chemical and/or physical instability of the drug (e.g., antibody) upon lyophilization and subsequent storage. Exemplary lyoprotectants include sugars such as sucrose or trehalose; an amino acid such as monosodium glutamate or histidine; a methylamine such as betaine; a lyotropic salt such as magnesium sulfate; a polyol such as trihydric or higher sugar alcohols, e.g. glycerin, erythritol, glycerol, arabitol, xylitol, sorbitol, and mannitol; propylene glycol; polyethylene glycol; Pluronics; and combinations thereof. The preferred lyoprotectant is a non-reducing sugar, such as trehalose or sucrose.

The lyoprotectant is added to the pre-lyophilized formulation in a "lyoprotecting amount" which means that, following lyophilization of the drug (e.g., antibody) in the presence of the lyoprotecting amount of the lyoprotectant, the drug (e.g., antibody) essentially retains its physical and chemical stability and integrity upon lyophilization and storage.

The "diluent" of interest herein is one which is pharmaceutically acceptable (safe and non-toxic for administration to a human) and is useful for the preparation of a reconstituted formulation. Exemplary diluents include sterile water, bacteriostatic water for injection (BWFI), a pH buffered solution (e.g. phosphate-buffered saline), sterile saline solution, Ringer's solution or dextrose solution.

A "preservative" is a compound which can be added to the diluent to essentially reduce bacterial action in the reconstituted formulation, thus facilitating the production of a multi-use reconstituted formulation, for example. Examples of potential preservatives include octadecyldimethylbenzyl ammonium chloride, hexamethonium chloride, benzalkonium chloride (a mixture of alkylbenzyldimethylammonium chlorides in which the alkyl groups are long-chain compounds), and benzethonium chloride. Other types of preservatives include aromatic alcohols such as phenol, butyl and benzyl alcohol, alkyl parabens such as methyl or propyl parahen, catechol, resorcinol, cyclohexanol, 3-pentanol, and m-cresol.

A "bulking agent" is a compound which adds mass to the lyophilized mixture and contributes to the physical structure of the lyophilized cake (e.g. facilitates the production of an essentially uniform lyophilized cake which maintains an open pore structure). Exemplary bulking agents include mannitol, glycine, polyethylene glycol and xorbitol.

Accordingly, a stable lyophilized antibody formulation can be prepared using a lyoprotectant (preferably a sugar such as sucrose or trehalose), which lyophilized formulation

Samsung Bioepis Exhibit No. 1002
Page 10705

can be reconstituted to generate a stable reconstituted formulation having an antibody concentration which is significantly higher (e.g. from about 2-40 times higher, preferably 3-10 times higher and most preferably 3-6 times higher) than the antibody concentration in the pre-lyophilized formulation. Such high protein concentrations in the reconstituted formulation are considered to be particularly useful where the formulation is intended for subcutaneous administration. Despite the very high protein concentration in the reconstituted formulation, the reconstituted formulation can be stable (i.e. fails to display significant or unacceptable levels of chemical or physical instability of the protein) at 2-8 °C. for at least about 30 days. See U.S. Patent 6,821,515. In certain embodiments, the reconstituted formulation is isotonic.

When reconstituted with a diluent comprising a preservative (such as bacteriostatic water for injection, BWFI), the reconstituted formulation may be used as a multi-use formulation. Such a formulation is useful, for example, where a subject patient requires frequent administrations of the drug or antibody and/or agent to treat a chronic medical condition. The advantage of a multi-use formulation is that it facilitates ease of use for the patient, reduces waste by allowing complete use of vial contents, and results in a significant cost savings for the manufacturer since several doses are packaged in a single vial (lower filling and shipping costs).

The present disclosure also provides a method for preparing a formulation comprising the steps of: (a) lyophilizing a mixture of an antibody and a lyoprotectant; and (b) reconstituting the lyophilized mixture of step (a) in a diluent such that the reconstituted formulation is isotonic and stable.

An article of manufacture is also provided herein which comprises: (a) a container which holds a lyophilized mixture of an antibody and a lyoprotectant; and (b) instructions for reconstituting the lyophilized mixture with a diluent to a desirable antibody concentration in the reconstituted formulation. The article of manufacture may further comprise a second container which holds a diluent (e.g. bacteriostatic water for injection (BWFI) comprising an aromatic alcohol).

An injection system of the present disclosure may employ a medication delivery pen as described in U.S. Patent 5,308,341. Medication delivery pens have been developed to facilitate the self-administration of medication. A medication of the present disclosure can be a drug that inhibits complement activity, for example an antibody specific to complement C5,

Samsung Bioepis Exhibit No. 1002
Page 10706

and/or an immunosuppressive agent. One medication delivery pen includes a vial holder into which a vial of insulin or other medication may be received. The vial holder is an elongate generally tubular structure with proximal and distal ends. The distal end of the vial holder includes mounting means for engaging a double-ended needle cannula. The proximal end also includes mounting means for engaging a pen body which includes a driver and dose setting apparatus. A disposable medication containing vial for use with the prior art vial holder includes a distal end having a pierceable elastomeric septum that can be pierced by one end of a double-ended needle cannula. The proximal end of this vial includes a stopper slidably disposed in fluid tight engagement with the cylindrical wall of the vial. This medication delivery pen is used by inserting the vial of medication into the vial holder. A pen body then is connected to the proximal end of the vial holder. The pen body includes a dose setting apparatus for designating a dose of medication to be delivery by the pen and a driving apparatus for urging the stopper of the vial distally for a distance corresponding to the selected dose.

The user of the pen mounts a double-ended needle cannula to the distal end of the vial holder such that the proximal point of the needle cannula pierces the septum on the vial. The patient then selects a dose and operates the pen to urge the stopper distally to deliver the selected dose. The dose selecting apparatus returns to zero upon injection of the selected dose. The patient then removes and discards the needle cannula, and keeps the prior art medication delivery pen in a convenient location for the next required medication administration. The medication in the vial will become exhausted after several such administrations of medication. The patient then separates the vial holder from the pen body. The empty vial may then be removed and discarded. A new vial can be inserted into the vial holder, and the vial holder and pen body can be reassembled and used as explained above.

Accordingly, a medication delivery pen generally has a drive mechanism for accurate dosing and ease of use. A dosage mechanism such as a rotatable knob allows the user to accurately adjust the amount of medication that will be injected by the pen from a prepackaged vial of medication. To inject the dose of medication, the user inserts the needle under the skin and depresses the knob once as far as it will depress. The pen may be an entirely mechanical device or it may be combined with electronic circuitry to accurately set and/or indicate the dosage of medication that is injected into the user. See U.S. Patent 6,192,891.

Samsung Bioepis Exhibit No. 1002
Page 10707

The present disclosure also presents controlled-release or extended-release formulations suitable for chronic and/or self-administration of a medication.

The various formulations can be administered to a patient in need of treatment (e.g., a recipient of an allograft) with the medication (e.g., an antibody of the present disclosure and at least one immunosuppressive agent) by intravenous administration as a bolus or by continuous infusion over a period of time, by intramuscular, intraperitoneal, intracerobrospinal, subcutaneous, intra-articular, intrasynovial, intrathecal, oral, topical, or inhalation routes.

In certain embodiments, a formulation is administered to the patient by subcutaneous (i.e. beneath the skin) administration. For such purposes, the formulation may be injected using a syringe. However, other devices for administration of the formulation are available such as injection devices (e.g. the Inject-ease® and Genject® devices); injector pens (such as the GenPen®); needleless devices (e.g. MediJector® and BioJector®); and subcutaneous patch delivery systems.

The present methods and uses are described with reference to the following Examples, which are offered by way of illustration and are not intended to limit the disclosure in any manner. Standard techniques well known in the art or the techniques specifically described below are utilized. The following abbreviations are used herein: ABMR, antibody-mediated rejection; ACHR, accelerated humoral rejection; ACR, acute cellular rejection; AVR, acute vascular rejection; CsA, cyclosporin; CyP, cyclophosphamide; HAR, hyperacute rejection; MCP-1, monocyte chemotactic protein 1; MST, mean survival time; POD, postoperative day.

Example 1

Methods

Animals and Immunosuppressive Drugs Male adult C3H (H-2^k) mice and BALB/c (H-2^d) mice (Jackson Labs, Bar Harbor, Maine) weighing 25-30 g were chosen as donors and recipients, respectively. In the groups receiving immunosuppression, the recipients were injected with CsA (15 mg/kg/day, s.c., daily from day 0 to endpoint rejection or until day 100), or with CyP (40 mg/kg/day, i.v., on day 0 and 1), or with anti-C5 mAb (clone BB5.1, Alexion Pharmaceuticals Inc., 40 mg/kg/day, i.p., day 0–2, followed by twice a week, day 0-60). Animals were housed under conventional conditions at the Animal Care Facility,

Samsung Bioepis Exhibit No. 1002
Page 10708

University of Western Ontario, and were cared for in accordance with the guidelines established by the Canadian Council on Animal Care. Olfert et al., 1993.

Skin Presensitization Full-thickness skin grafts taken from C3H donors were cut into square pieces of 1×1 cm^2 and transplanted onto the back of the BALB/c recipients' thorax one week prior to heart transplantation from the same donors. Rejection was defined as complete necrosis of the skin grafts.

Abdominal and Cervical Cardiac Transplantation Seven days after skin presensitization, C3H mouse hearts were transplanted into the abdomen of presensitized BALB/c recipients by anastomosing the donor aorta and recipient aorta, and the donor pulmonary artery and recipient inferior vena cava. In the groups with re-transplantation, second heart grafts harvested from either naive C3H mice or long-term surviving presensitized BALB/c recipients were transplanted into the cervical area of the recipients carrying a long-term surviving first abdominal heart graft by anastomosing the donor aorta and recipient carotid artery, and the donor pulmonary artery and recipient external jugular vein (end-to-side). The heart grafts were monitored daily until rejection unless otherwise indicated and rejection was defined as complete cessation of pulsation.

Experimental Groups Presensitized recipients were randomly assigned to eight groups, each consisting of eight animals: Group 1, mice with no treatment; Group 2, mice treated with CsA; Group 3, mice treated with CyP; Group 4, mice treated with CsA plus CyP; Group 5, mice treated with anti-C5 mAb; Group 6, mice treated with anti-C5 mAb plus CsA; Group 7, mice treated with anti-C5 mAb plus CyP; Group 8, mice treated with anti-C5 mAb in combination of CsA and CyP. When cardiac impulses were no longer palpable or at POD100, the grafts were removed for routine histology, immunohistochemistry and western blot analysis, serum samples were collected for flow cytometric analysis and complement hemolytic assay. Five additional animals were placed and sacrificed in groups 6 and 8 on POD3 (MST for groups 1-5, 7) to allow for comparisons at a uniform time point. Serum samples were also collected on POD 11, 21, 28 and 60 in Group 8 for detecting the sequential changes of anti-donor antibody levels and complement activity. In addition, when triple therapy treated presensitized recipients carried a first heart graft for 100 days, they were re-transplanted with a second heart. A naive C3H heart or a 100-day surviving C3H heart from another presensitized BALB/c recipient was used as the second heart. Eight animals were included in each re-transplant group.

Samsung Bioepis Exhibit No. 1002
Page 10709

Graft Histology Tissue samples were fixed in 10% buffered formaldehyde. Specimens were then embedded in paraffin, and sectioned for H&E staining. The microscopic sections were examined in a blinded fashion for severity of rejection by a pathologist. Criteria for graft rejection included the presence of vasculitis, thrombosis, hemorrhage and lymphocyte infiltration. These changes were scored as: 0, no change; 1, minimum change; 2, mild change; 3, moderate change; or 4, marked change.

Immunohistochemistry Four micrometer sections were cut from tissue samples embedded in Tissue-Tek O.C.T gel (Optimum Cutting Temperature, Skura Finetek, Torrance, CA) mounted on gelatin-coated glass microscope slides and stained by a standard indirect avidin-biotin immunoperoxidase staining method using an Elite Vectastain ABC kit (Vector Laboratories Inc., Burlingame, CA). Specimens were stained for $CD4^+$ and $CD8^+$ cells with biotin-conjugated rat anti-mouse CD4 mAb (clone YTS 191.1.2, Cedarlane Laboratories Ltd., Hornby, Ontario, Canada) and biotin-conjugated rat anti-mouse CD8 mAb (clone 53-6.7, Pharmingen, Franklin Lakes, NJ), respectively. Intragraft monocyte/macrophage infiltration was detected by staining with biotin-conjugated rat anti-mouse Mac-1 mAb (Cedarlane Laboratories Ltd., Hornby, Ontario, Canada). Mouse IgG and IgM deposition in grafts was detected using biotin-conjugated goat anti-mouse-IgG and goat anti-mouse-IgM (Cedarlane). For identification of complement deposition, sections were serially incubated with goat anti-C3 or anti-C5 polyclonal Abs (Quidel, San Diego, CA), biotinylated rabbit anti-goat IgG (Vector Laboratories), and HRP-conjugated-streptavidin (Zymed Laboratories, South San Francisco, CA). Slides were washed with phosphate-buffered saline between steps, and examined under light microscopy. Negative controls were performed by omitting the primary antibodies. The immunostaining was scored in five high-power fields of each section, and five independent experiments were performed. The sections of immunoperoxidase staining were graded from 0 to 4+ according to the staining intensity: 0, negative; 1+, equivocal; 2+, weak staining; 3+, moderate staining; and 4+, very intensive staining.

Flow Cytometry The circulating anti-donor specific IgG and IgM antibodies were evaluated in the recipient serum by FACScan flow cytometry (Becton Dickinson, Mountain View, CA). Glotz et al., (1993); Tyan et al. (1994). Briefly, C3H mouse splenocytes were isolated and incubated at 37 °C for 30 minutes with serum from naive control and experimental groups. To stain for total IgG, IgG1, IgG2a, IgG2b and IgM, the cells were washed and incubated with FITC-conjugated goat antibody specific for the Fc portion of mouse IgG or with

Samsung Bioepis Exhibit No. 1002
Page 10710

phycoerythrin-conjugated goat antibody specific for the μ-chain of mouse IgM (Jackson ImmunoResearch Laboratories, West Grove, PA), or with FITC-conjugated goat anti-mouse IgG1 (CALTAG Laboratories, Burlingame, CA), or with FITC-conjugated goat anti-mouse IgG2a (CALTAG), or with FITC-conjugated goat anti-mouse IgG2b (CALTAG). After 1 hour of staining at 4 °C, the cells were washed with PBS, resuspended at 5×10^6/mL, and analyzed by flow cytometry for mean channel fluorescence intensity, which represents the antibody-binding reactivity.

Complement Hemolytic Assay The purified anti-C5 mAb was serially diluted twofold (175-0.1 μg/ml) in GVB^{2+} buffer (gelatin Veronal-buffered saline: 0.1% gelatin, 141 mM NaCl, 0.5 mM $MgCl_2$, 0.15 mM $CaCl_2$, and 1.8 mM sodium barbital) and added in triplicate (50 μl/well) to a 96-well plate. BALB/c mouse serum was diluted to 40% v/v with GVB^{2+} buffer and added (50 μl/ml) to the rows of the same 96-well plate such that the final concentration of BALB/c mouse serum in each well was 20%. The plate was then incubated at room temperature for approximately 30 min while chicken erythrocytes were prepared. Chicken erythrocytes were washed 5×1 ml with GVB^{2+} buffer and resuspended to a final concentration of 5×10^7/ml in GVB^{2+}. Four milliliters of the chicken erythrocytes were sensitized by adding anti-chicken RBC polyclonal antibody (Intercell Technologies, Hopewell, NJ, 0.1% v/v) and the cells were incubated at 4 °C for 15 min with frequent vortexing. The cells were then washed 2×1 ml with GVB^{2+} and resuspended to a final volume of 2.4 ml in GVB^{2+}. The chicken erythrocytes (30 μl/well, 2.5×10^6 cells) were added to the plate containing serum and anti-C5 mAb as described above, mixed well, and incubated at 37 °C for 30 min. The plate was then centrifuged at 1000×g for 2 min, and 85 μl of the supernatant was transferred to a new 96-well microtiter plate. The plate was read at OD 415 nm using a microplate reader and the percentage of hemolysis was determined using this formula:

$$\%\ \text{hemolysis} = 100 \times \frac{(\text{OD sample}) - (\text{OD } GVB^{2+} \text{ control})}{(\text{OD 100\% lysed control}) - (\text{OD } GVB^{2+} \text{ control})}$$

with 100% lysed control obtained by the addition of 100 μl GVB^{2+} containing 0.1% NP-40 to the 30 μg/ml of chicken erythrocytes as prepared above.

Samsung Bioepis Exhibit No. 1002
Page 10711

Western Blot Analysis Sonication of frozen heart samples was performed in RIPA lysis buffer (Santa Cruz Biotechnology, Inc.) at 4 °C for 1 minute at 10-second intervals, followed by microcentrifugation at 13,000 rpm for 10 minutes at 4 °C. Clarified supernatants were immediately quantitated in triplicate for protein content using Detergent-compatible protein assay kit (BIO-RAD). Heart lysates (10μg protein/well) were separated on NuPAGE, 4-12% gradient Bis-Tris gels and MES buffer system (Invitrogen) and transferred to polyvinylidene difluoride (PVDF) membrane (0.45 μm pore size; Invitrogen) using a semi-dry transfer apparatus (BIO-RAD). Membranes were cut appropriately at the correct molecular weights to allow the development of the blots with two different primary antibodies per blot such that each blot was exposed to a test antibody and an internal control antibody to insure equal sample loading. The test primary antibodies including anti-Bcl-2 (N-19) rabbit polyclonal sera (Santa Cruz Biotechnology, Inc.) and anti-Bcl-XS/L (M-125) rabbit polyclonal sera (Santa Cruz Biotechnology, Inc.) were used to detect intragraft expression of Bcl-2 and Bcl-xl proteins. Anti-calsequestrin rabbit polyclonal sera (Calbiochem) were used as internal control primary antibody (Kobayashi et al., 1999). Detection of primary antibody binding was performed as previously described (Arp et al., 1996) by exposing washed incubated blots to a polyclonal goat anti-rabbit IgG fraction conjugated to horseradish peroxidase (HRP; Roche Laboratories) and then appropriately developed by exposure to enhance chemiluminescence for HRP-conjugated antibodies (Roche Laboratories).

Statistical Analysis The data were reported as the mean ± SD. Allograft survival among experimental groups was compared using the rank-log test. Histological and immunohistological findings were analyzed using the Mann-Whitney U test. Flow cytometric data and western blot data were analyzed using one-way ANOVA. Differences with p values less than 0.05 were considered significant.

Example 2

Presensitization with C3H donor skin graft induces antibody-mediated ACHR in heart allografts of BALB/c recipients.

To develop a suitable small animal model that mimics presensitized patients in the clinic and to study ABMR, a novel, fully MHC-mismatched mouse ABMR model has been developed through presensitization of mouse recipients. In this model, BALB/c recipients were presensitized with C3H donor skin grafts one week prior to heart transplantation from the same donor. Seven days after donor skin presensitization, serum level of anti-donor IgG,

Samsung Bioepis Exhibit No. 1002
Page 10712

but not IgM antibody was markedly elevated and reached to a peak level in the presensitized BALB/c recipients (Figure 1A). Heart transplantation from same donor was then performed in these highly sensitized recipients. Without immunosuppression, C3H heart grafts were rapidly rejected in 3.1 ± 0.4 days by ACHR, characterized by severe thrombosis, hemorrhage and infarction (Figure 1B-a). In contrast, same heart grafts in unsensitized BALB/c recipients (with mean survival time, MST of 8.2 ± 0.8 days) show the normal histology on post-operative day (POD) 3 (Figure 1B-b). When compared to unsensitized BALB/c recipients at the same day, heart grafts in presensitized animals revealed massive IgG antibody and complement (C3 and C5) deposition, but minimal $CD4^+$ and $CD8^+$ cell infiltration (Table 1). Furthermore, circulating anti-donor IgG levels in presensitized recipients were significantly higher than those of unsensitized same recipients receiving a heart graft on POD3 ($P< 0.01$, Figure 1C). However, anti-donor IgM remained at very low levels both in circulation (Figure 1C) and in heart grafts (Table 1) and it showed no significant difference between unsensitized and presensitized recipients. In addition, normal levels of complement hemolytic activity were shown in both presensitized and unsensitized heart recipients without treatment (Figure 1D). These data indicate that this is an ideal transplant model to study ABMR in presensitized recipients in which complement plays an important role in the pathogenesis.

Table 1.

Comparison of immunohistological changes of C3H heart allografts in unsensitized and presensitized BALB/c recipients on POD3

Groups	Unsensitized	Presensitized
IgG	1+	4+
IgM	1+	1+
C3	2+	3+
C5	2+	3+
CD4	0	1+
CD8	0	1+

Samsung Bioepis Exhibit No. 1002
Page 10713

Grades for immunoperoxidase staining: 0, negative; 1+, equivocal; 2+, weak; 3+, moderate; 4+, intense.

Anti-C5 mAb in combination with CsA and CyP prevents ABMR and achieves indefinite heart allograft survival in presensitized mouse recipients.

Complement has been shown to play an important role in ABMR. However, the inhibitory effect of functionally blocking terminal complement cascade at the C5 level in highly sensitized recipients is unknown. In the study presented herein, the presensitized model was used to study the efficacy of anti-C5 mAb either alone or combined with CsA and /or CyP in prevention of ABMR. As presented in Figure 2A, treatment with either CsA or CyP or the two drugs in combination did not prevent ABMR and grafts were rejected in 3.0 ± 0.0 days, 3.3 ± 0.5 days and 3.5 ± 0.6 days, respectively with typical pathological features of ACHR including intravascular thrombosis and interstitial hemorrhage (Figure 2B-b, c, d), which were indistinguishable from heart grafts in untreated presensitized BALB/c recipients (Figure 2B-a). Anti-C5 monotherapy or combined with CyP was not able to improve graft survival and heart grafts were rejected by ACHR (Figure 2B-e, f) in 3.5 ± 0.6 days and 3.2 ± 0.4 days, respectively (Figure 2A). Although the combination therapy of anti-C5 mAb and CsA, the protocol capable of inducing long-term heart allograft survival in unsensitized animals, marginally prolonged graft survival in this presensitized model, heart grafts were also rejected by severe humoral rejection with vasculitis, thrombosis, hemorrhage and minimal cell infiltration (Figure 2B-g) in 11.9 ± 1.8 days (Figure 2A). In contrast, triple therapy of anti-C5 mAb in combination of CsA and CyP achieved indefinite heart graft survival over 100 days (Figure 2A) in presensitized animals ($P<0.01$ vs. the animals without treatment or treated with either monotherapy or two drugs in combination) with no evidence of rejection (Figure 2B-h). In this presensitized mouse model, as shown in Table 2, only minor intragraft $CD4^+$ and $CD8^+$ cell infiltration was observed in the recipients that rejected their heart grafts within 3 days. However, the number of these T cells was slightly increased if heart grafts survived longer in anti-C5 mAb plus CsA-treated recipients at the time of rejection (POD11) and in triple therapy-treated recipients at early stages of graft survival (e.g. POD11). Furthermore, with continuous treatment of CsA in the triple therapy group, $CD4^+$ and $CD8^+$ cell infiltration was inhibited in long-term surviving heart grafts on POD60 and 100. In addition, moderate intragraft Mac-1^+ cell infiltration, including monocytes and macrophages, was found in untreated and CsA-, CyP- or CsA plus CyP-treated animals,

Samsung Bioepis Exhibit No. 1002
Page 10714

while the infiltration of these cells was significantly reduced in anti-C5 mAb treated animals (Table 2). These results indicate that functionally blocking anti-C5 mAb enables the use and efficacy of conventional immunosuppressive agents, thereby preventing ABMR and achieving indefinite heart graft survival in presensitized recipients.

Table 2.

Grades for immunoperoxidase staining of heart allografts

in presensitized mouse recipients at necropsy

Groups	Date for sample collection (POD)	C3	C5	**CD4**	CD8	Mac-1	IgG	IgM
Untreated	3	3+	3+	1+	1+	3+	4+	1+
CsA	3	3+	3+	1+	1+	3+	4+	1+
CyP	3	3+	3+	1+	1+	3+	3+	1+
CsA+CyP	3	3+	3+	1+	1+	3+	3+	1+
Anti-C5mAb	3	3+	0	1+	1+	2+	4+	1+
Anti-C5mAb+CsA	11	3+	0	2+	2+	2+	4+	1+
Anti-C5mAb+CyP	3	3+	0	1+	1+	2+	3+	1+
Anti-C5mAb+CsA+CyP	3	3+	0	1+	1+	2+	3+	1+
Anti-C5mAb+CsA+CyP	11	3+	0	2+	2+	1+	3+	1+
Anti-C5mAb+CsA+CyP	60	3+	0	1+	1+	0	2+	1+
Anti-C5mAb+CsA+CyP	100	3+	2+	0	0	0	2+	1+

Grades: 0, negative; 1+, equivocal; 2+, weak; 3+, moderate; 4+, intense.

Anti-C5 mAb completely inhibits total complement hemolytic activity and local C5 deposition in presensitized recipients receiving a heart allograft.

Anti-C5 mAb was previously shown to block the cleavage of complement protein C5 into the proinflammatory molecules C5a and C5b-9 (Kroshus et al., 1995), and to completely and consistently block terminal complement activity in mice (Wang et al., 1999). In the current study, terminal complement activity was measured by assessing the ability of

Samsung Bioepis Exhibit No. 1002
Page 10715

recipient mouse sera to lyse antibody presensitized chicken erythrocytes and was compared at the same time-point (POD3). Treatment of mice with either CsA or CyP or the two drugs in combination had no effect on terminal complement activity, while treatment with anti-C5 mAb either alone or combined with CsA or/and CyP completely inhibited this activity (Figure 3; $P<0.01$, vs. naive and untreated animals, as well as CsA-, CyP-, or CsA plus CyP-treated animals). In addition, sera obtained from anti-C5 mAb treated animals at several earlier time points showed similarly diminished hemolytic activity, suggesting that serum terminal complement was inhibited throughout the treatment period. Furthermore, local C5 deposition in heart grafts was completely prevented in the anti-C5 mAb treated presensitized recipients, but not in untreated, or CsA-, CyP- and CsA plus CyP-treated presensitized animals (Table 2). As predicted, treatment with anti-C5 mAb did not prevent C3 deposition in the grafts (Table 2). These results suggest anti-C5 therapy completely blocks total complement activity after cardiac allografting in highly sensitized recipients.

Long-term surviving heart grafts in presensitized animals are resistant to humoral injury in the presence of low level of anti-donor antibodies and complement- a situation of accommodation.

To further investigate the role of anti-C5 mAb in humoral rejection, anti-donor alloantibody levels were measured in recipient sera by flow cytometry and intragraft antibody deposition by using immunostaining techniques in different groups. Figure 4A shows that on POD3 untreated presensitized BALB/c recipients had high levels of circulating anti-donor IgG antibodies. When presensitized recipients receiving either monotherapy or two drugs in combination, CsA and/or CyP partially down-regulated circulating anti-donor IgG levels, while treatment with anti-C5 mAb either alone or combined with CsA or CyP did not further affect anti-donor antibody levels at the same day. In contrast, with triple therapy of anti-C5 mAb, CsA and CyP, a high level of circulating anti-donor IgG was gradually downregulated and reached a low level on POD60, thereafter remaining at this level until day 100 (Figure 4B). Similar to levels of circulating antibodies in the different treatment groups, Table 2 shows that strong deposition of anti-mouse IgG was present in the rapidly rejected heart grafts of presensitized animals with no treatment or treated with monotherapy or two drugs in combination therapy. Interestingly, with triple therapy, IgG antibody deposition was gradually attenuated to a mild level in the long-term surviving heart grafts on POD 100 (Figure 4C-a, Table 2). In this model, IgM remained at very low levels in either circulation (Figure 4A, B) or transplanted heart grafts (Figure 4C-b, Table 2) in presensitized recipients

Samsung Bioepis Exhibit No. 1002
Page 10716

with or without treatment. In addition, treatment with anti-C5 mAb eliminated complement activity to an undetectable level until day 60, followed by a progressive recovery to predepletion levels on POD 100 after discontinuation of anti-C5 therapy in presensitized mouse recipients receiving triple therapy (Figure 4D). Furthermore, intragraft C5 deposition was also detected in 100-day surviving presensitized animals (Table 2). These data demonstrate that ongoing transplant accommodation occurs in triple therapy treated presensitized recipients despite the presence of anti-graft antibodies and complement activation.

Anti-C5 mAb in combination with CsA and CyP reduces the IgG1/IgG2a ratio and leads to a shift in IgG subclass to IgG2b in recipients with accommodated grafts.

To determine whether anti-C5 mAb-based triple therapy would induce a shift in IgG subclass, which may be associated with accommodation, serum levels of anti-donor IgG subclasses of IgG1, IgG2a and IgG2b were compared between untreated recipients and the recipients with accommodated heart graft. Sera from untreated recipients contained predominant IgG1 isotype, indicated by a high ratio of IgG1/IgG2a (Figure 5A). In contrast, a significant reduction in the ratio of IgG1/IgG2a was observed in the recipients carrying accommodated grafts (Figure 5A, $P<0.01$). Furthermore, presensitized recipients with the accommodated heart grafts displayed an increased level of anti-donor IgG2b as compared to the same recipients with rejected grafts (Figure 5B, $P<0.01$). In addition, the pattern of IgG isotypes in the recipients treated with either monotherapy or two drugs in combination is indistinguishable from that of untreated animals. These data indicate that anti-donor IgG1 isotype may be associated with graft rejection, while production of anti-donor IgG2b subclass may function as a protective antibody and plays an important role in the induction of accommodation.

Anti-C5 mAb in combination with CsA and CyP induces intragraft Bcl-2 and Bcl-xl expression in highly sensitized mouse recipients.

To determine whether a causal relationship exists between intragraft expression of protective proteins and graft resistance to humoral injury in this model, western blot analysis was employed to detect proteins of interest in heart graft tissues from highly sensitized mouse recipients. Long-term surviving heart grafts were found to express high levels of Bcl-2 and Bcl-xl proteins on POD100, and these proteins were detected as early as 12 days after heart transplantation in highly sensitized recipients receiving anti-C5 mAb-based triple therapy

Samsung Bioepis Exhibit No. 1002
Page 10717

(Figure 6). In contrast, there were no Bcl-2 and Bcl-xl proteins expressed on heart grafts of untreated animals (Figure 6) or animals treated with either monotherapy or two drugs in combination therapy. This result suggests that graft resistance to humoral injury in indefinite surviving animals is associated with the protection provided by Bcl-2 and Bcl-xl proteins in this presensitized model.

Presensitized recipients with an accommodating first heart graft accept a second accommodated heart graft but reject a second naive heart graft from the same donors.

The ability of accommodated grafts to resist rejection has not been tested directly under pathophysiological conditions where naive grafts undergo rejection following allotransplantation. In this model, to determine whether presensitized recipients with an accommodating first heart graft will accept a second accommodated graft but reject a second naive graft, we performed re-transplantation scenarios. After the accommodated C3H heart grafts have survived to the 100-day point, the time at which low levels of alloantibodies were detected (Figure 4B) and complement activity has returned to pretreatment levels (Figure 4D), in presensitized BALB/c recipient treated with anti-C5 mAb-based triple therapy, these recipients received a second heart graft. Specifically, either a naive (Figure 7A) or a 100-day accommodated C3H heart (Figure 7B) from another presensitized BALB/c recipient was transplanted into the neck of the presensitized recipients carrying an accommodating first C3H heart. These recipients rejected a second naive heart at 6.6 ± 1.1 days (Figure 8A) with severe AVR (Figure 8B-a) while the first heart continued to survive. In contrast, when the accommodated hearts that had been already surviving for 100 days in different presensitized mice were used as second grafts, these grafts were accepted by the presensitized recipients carrying an accommodating first heart graft (Figure 8A). There was no sign of rejection in those accommodated second heart grafts 90 days after second transplantation (Figure 8B-b). These data indicate that accommodated grafts become resistant to the effects of anti-donor antibodies and complement that normally mediate allograft rejection in these presensitized recipients. Furthermore, the fact that the host of the accommodated graft rejected a new graft suggests that accommodation involves changes to the graft.

Presensitized recipients being treated with CsA reject accommodated heart grafts.

Another re-transplantation was performed to determine whether accommodation in this presensitized model would be caused by the changes in the grafts and/or the recipients. Specifically, after C3H heart grafts have been accommodated in presensitized BALB/c mice

Samsung Bioepis Exhibit No. 1002
Page 10718

for 100 days, the accommodated heart graft will then be re-transplanted into a second presensitized BALB/c recipient being treated with CsA alone (Figure 7C), a therapy that can prevent cellular rejection but cannot prevent accelerated humoral rejection of a fresh C3H heart in presensitized recipients. The accommodated C3H heart grafts were rapidly rejected in CsA treated presensitized BALB/c recipients. After re-transplantation, the pathology in accommodated heart grafts was changed from normal (Figure 9A) to severe ACHR with massive interstitial hemorrhage but few cell infiltrates (Figure 9B). In addition, high levels of anti-donor IgG and normal levels of complement hemolytic activity in these recipients receiving an accommodated C3H heart were similar to those of CsA treated presensitized recipients receiving a naive C3H heart. This result further indicates that accommodation induced by anti-C5 mAb-based triple therapy can originate from mechanisms involving changes not only to the graft, but also to the recipient.

Example 3

Acute Vascular Rejection in a Heart Transplantation Model

Experiments were performed to determine whether inclusion of an inhibitor of formation of terminal complement would attenuate acute vascular rejection and whether the use of such an inhibitor in conjunction with an immunosuppressant would achieve long-term allograft survival. In this set of experiments an anti-C5 monoclonal antibody was used in conjunction with cyclosporin. The model used was an allograft heterotopic heart transplant from C3H mice into BALB/c mice. This model is a stringent acute vascular rejection model with the C3H and BALB/c mice being strongly MHC mismatched. The transplantations and other methods were performed as described in Wang et al. (2003).

Heterotopic Cardiac Transplantation

Intra-abdominal heterotopic cardiac transplantation was performed as previously described by Wang et al. (2003). Briefly, a median sternotomy was performed on the donor, and the heart graft was slowly perfused in situ with 1.0 ml of cold heparinized Ringer's lactate solution through the inferior vena cava and aorta before the superior vena cava and pulmonary veins were ligated and divided. The ascending aorta and pulmonary artery were transected, and the graft was removed from the donor. The graft was then revascularized with end-to-side anastomoses between the donor's pulmonary artery and the recipient's inferior vena cava as well as the donor's aorta and the recipient's abdominal aorta using 11-0 nylon suture. The beating of the grafted heart was monitored daily by direct abdominal palpation.

Samsung Bioepis Exhibit No. 1002
Page 10719

The degree of pulsation was scored as: A, beating strongly; B, noticeable decline in the intensity of pulsation; or C, complete cessation of cardiac impulses. When cardiac impulses were no longer palpable, the graft was removed for routine histology. In certain instances, mice in which the graft was still functioning were sacrificed to perform histology.

Results

Mice (male 8-12 week old mice weighing 25 – 30 g) were split into six experimental groups with six to eight mice per group. Transplant occurred on day 0. Histological changes were checked at the endpoint (the endpoint being graft failure) or in some cases a mouse was sacrificed prior to graft failure. The dosage of BB5.1 which was administered (40 mg/kg body weight three times per week) was known from prior studies to completely inhibit terminal complement activity.

Group 1' (control) - mice were administered 0.75 mL of saline intraperitoneally on days -1, 0, 1 and 2. Subsequently these mice were treated with 0.75 mL of saline intraperitoneally three times per week (Monday, Wednesday, Friday) until the endpoint.

Group 2' (cyclosporin A alone) - mice were administered 15 mg/kg body weight of cyclosporin A subcutaneously on a daily basis beginning at day 0 (day of transplant) until the endpoint.

Group 3' (anti-complement antibody alone) - mice were administered the anti-mouse C5 antibody BB5.1 (Frei et al., 1987) at 40 mg/kg body weight intraperitoneally on days -1, 0, 1 and 2 followed by 40 mg/kg body weight administered three times per week (Monday, Wednesday, Friday) until the endpoint.

Group 4' (anti-complement antibody until day 14 post-transplant plus cyclosporin A) - mice were administered the anti-mouse C5 antibody BB5.1 at 40 mg/kg body weight intravenously on days -1 through day 14 and were also administered cyclosporin A at 15 mg/kg of body weight on a daily basis beginning at day 0 until the endpoint. Note that this differs from the other groups in that the BB5.1 was administered intravenously and on a daily basis.

Group 5' (anti-complement antibody until day 28 post-transplant plus cyclosporin A) - mice were administered the anti-mouse C5 antibody BB5.1 at 40 mg/kg body weight intraperitoneally on days -1, 0, 1 and 2 followed by 40 mg/kg body weight administered three times per week (Monday, Wednesday, Friday) until day 28 and were also administered

Samsung Bioepis Exhibit No. 1002
Page 10720

cyclosporin A at 15 mg/kg of body weight on a daily basis beginning at day 0 until the endpoint.

Group 6' (anti-complement antibody chronically until 100 days plus cyclosporin) - mice were administered the anti-mouse C5 antibody BB5.1 at 40 mg/kg body weight intraperitoneally on days -1, 0, 1 and 2 followed by 40 mg/kg body weight administered three times per week (Monday, Wednesday, Friday) until 100 days and were also administered cyclosporin A at 15 mg/kg of body weight on a daily basis beginning at day 0 until 100 days.

The results of this experiment are shown in Tables 3 and 4. Table 3 shows the survival time for the grafts. Table 4 sets forth the histological scores.

Table 3

Allograft Survival

Group (Treatment)	Individual Survival (days)	Mean Survival Time (days)
1'. Saline	8, 8, 8, 8, 8, 9	8.3 ± 0.5
2'. Cyclosporin A	14, 15, 15, 16, 16, 16, 17	15.5 ± 1.1
3'. BB5.1	7, 8, 8, 8, 8, 9	8.0 ± 0.6
4'. BB5.1 until day 14 + cyclosporin A	35, 38, 43, 45, 46, 47	42.3 ± 4.8
5'. BB5.1 until day 28 + cyclosporin A	77, 80, 80, 81, 82	80 ±1.9
6'. BB5.1 until day 100 + cyclosporin A	>100 days (7 mice; one sacrificed for histology)	> 100 days

Samsung Bioepis Exhibit No. 1002
Page 10721

Table 4

Median Scores of Histological Changes of Heart Allografts at Necropsy

Groups	Vasc*	Infarc	Lymph	Throm	Hemo	Fibrin	PMN
1'. Saline (endpoint)	3.0	3.0	1.0	4.0	3.0	3.0	3.0
2'. Cyclosporin A (endpoint)	2.0	1.0	2.0	3.0	2.0	2.0	3.0
3'. BB5.1 (endpoint)	2.0	1.0	2.0	2.0	1.0	0.0	0.0
4'. BB5.1 until day 14 + cyclosporin A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
5'. BB5.1 28 days + Cyclosporin A (post-operative day 8)	0.0	0.0	0.0	0.0	0.0	0.0	0.0
5'. BB5.1 28 days + Cyclosporin A (endpoint)	0.0	0.0	1.0	1.0	2.0	1.0	0.0
6'. BB5.1 until day 100 + Cyclosporin A (post-operative day 100)	0.0	0.0	0.0	0.0	0.0	0.0	0.0

Median scores: 0 - normal; 1- minimum change; 2 - mild change; 3 - moderate change; 4 - marked change. N/A - not available.

*Vasc - vasculitis; Infar - infarction; Lymph - lymphocyte infiltration; Throm - thrombosis; Hemo - hemorrhage; Fibrin - fibrin deposition; PMN - polymorphonuclear cell infiltrate

The results indicate the synergistic effects of using a complement inhibiting drug in addition to an immunosuppressant. In untreated mice the grafts were rejected in about 8 davs. Use of the immunosuppressant cyclosporin A alone on a daily, chronic basis resulted

Samsung Bioepis Exhibit No. 1002
Page 10722

in an increase in graft survival until approximately 15 days post-transplant. The use of the anti-C5 antibody BB5.1 to inhibit formation of terminal complement had no effect on its own, graft rejection occurring at 8 days post-transplant as in the control group (Group 1'). The combination of BB5.1 through day 28 post-transplant plus cyclosporin A showed a synergistic effect with graft survival being extended until approximately day 80. A more surprising result is that of Group 5' in which BB5.1 and cyclosporin A were each administered chronically post-transplant. In this case the graft survival was for more than 100 days (as much data as presently available). Additionally, the histological results shown in Table 4 indicate that the administration of both BB5.1 and cyclosporin A protected the graft from changes much better than either BB5.1 or cyclosporin A alone, and that the chronic administration of BB5.1 and cyclosporin A protected the graft to such an extent that even at 100 days post-transplant there were no histological changes seen in the engrafted hearts. A survival time of 100 days in these models is considered to be the gold standard. A survival of 100 days in the model is believed to indicate that there will be an indefinite survival of the allograft. When BB5.1 administration was stopped after 28 days, the grafts were protected but they did begin to show some minimal to mild histological changes by about day 80 which was the time at which graft failure occurred.

The Group 4' mice were treated differently in that they were administered BB5.1 on a daily basis by an intravenous administration. These animals became ill, showing weight loss and urine retention and were sacrificed at a time at which the grafted hearts were still beating although their function had declined. This was the first group of mice studied and it is unknown why these ill effects were seen. These ill effects were not seen when the BB5.1 was administered intraperitoneally with a schedule of three times per week. As seen below in Example 4, daily administration of BB5.1 via an intraperitoneal route did not cause ill effects. Also, intravenous administration was not necessarily the cause of the illness in these animals. Intravenous administration of eculizumab (a human equivalent antibody to BB5.1 in that it binds to human C5) has been successfully administered intravenously without ill effects to humans in a study of PNH (Hillmen et al., 2004). Complement inhibitors may be administered by other routes in addition to intravenous and intraperitoneal, with all such routes being well known by those skilled in the art.

Example 4

Samsung Bioepis Exhibit No. 1002
Page 10723

Accelerated Rejection in a Presensitized Heart Transplantation Model

A second set of experiments similar to those of Example 3 was performed but the recipient mouse was presensitized to the donor organ. In these experiments, the presensitization was brought about by prior transplantation of a skin graft. In general, presensitization can occur not only as a result of having received an earlier allograft, but can also be caused by having received multiple blood transfusions or in women who have been pregnant. Besides such presensitization methods, allografts with an ABO mismatch will be rapidly attacked and rejected because of preformed antibodies to the ABO antigens unless steps are taken to prevent such an attack.

Some mice in these studies were administered cyclophosphamide in addition to BB5.1 and/or cyclosporin A. For these experiments BALB/c recipient mice were presensitized with C3H skin grafts one week prior to heart transplantation from the same donor (using the method of Pruitt and Bollinger, 1991). This model is designed to mimic presensitized transplantation in humans, especially in relation to accelerated humoral rejection. Recipient mice were split into eight groups of six to eight mice each. The treatments were as follow.

Group 1" (control) - mice (male 8-12 week old mice weighing 25 – 30 g) were administered 0.75 mL saline intraperitoneally on a daily basis beginning at day -1 and continuing until the endpoint (graft rejection).

Group 2" (cyclosporin A alone) - mice were administered cyclosporin A subcutaneously at a dose of 15 mg/kg body weight beginning on day 0 (day of transplant) until the endpoint.

Group 3" (BB5.1 alone) - mice were administered the anti-mouse complement monoclonal antibody BB5.1 at a dose of 40 mg/kg body weight delivered intraperitoneally on a daily basis beginning at day -1 and continuing until the endpoint.

Group 4" (cyclophosphamide alone) - mice were administered cyclophosphamide intravenously at a dose of 40 mg/kg body weight on each of days 0 and 1.

Group 5" (BB5.1 plus cyclosporin A) - mice were administered BB5.1 intraperitoneally at a dose of 40 mg/kg body weight on a daily basis beginning at day -1 and continuing until the endpoint. These mice were additionally administered cyclosporin A subcutaneously at a dose of 15 mg/kg body weight on a daily basis from day 0 until the endpoint.

Samsung Bioepis Exhibit No. 1002
Page 10724

Group 6" (BB5.1 plus cyclophosphamide) - mice were administered BB5.1 intraperitoneally at a dose of 40 mg/kg body weight on a daily basis beginning at day -1 and continuing until the endpoint. These mice were additionally administered cyclophosphamide intravenously at a dose of 40 mg/kg body weight on each of days 0 and 1.

Group 7" (cyclosporin A plus cyclophosphamide) - mice were administered cyclosporin A subcutaneously at a dose of 15 mg/kg body weight on a daily basis from day 0 until the endpoint. These mice were additionally administered cyclophosphamide intravenously at a dose of 40 mg/kg body weight on each of days 0 and 1.

Group 8" (BB5.1 plus cyclosporin A plus cyclophosphamide) - mice were administered BB5.1 intraperitoneally at a dose of 40 mg/kg body weight on a daily basis beginning at day -1 and continuing until 100 days. These mice were also administered cyclosporin A subcutaneously at a dose of 15 mg/kg body weight on a daily basis from day 0 until 100 days. These mice were additionally administered cyclophosphamide intravenously at a dose of 40 mg/kg body weight on each of days 0 and 1. Two mice in this group were sacrificed at day 60 for histological studies (no rejection had yet occurred) and the four remaining mice still had not rejected their grafts by day 100.

Additionally a control group of mice which was not presensitized and received only the saline treatment as for Group 1" was tested.

The results of these experiments are shown in Tables 5 and 6. Table 5 lists survival times for the grafts and Table 6 summarizes the histological results.

Samsung Bioepis Exhibit No. 1002
Page 10725

Table 5

Allograft Survival

Groups (Treatment)	Individual survival (days)	Mean survival time (days)
No presensitization	8, 8, 8, 8, 8, 9	8.3 ± 0.5*
1". One skin presensitization	3, 3, 3, 3, 3, 3, 3, 4	3.1 ± 0.4
2". Cyclosporin A	3, 3, 3, 3	3.0 ± 0.0
3". BB5.1	3, 3, 4, 4	3.5 ± 0.6
4". Cyclophosphamide	3, 3, 3, 4	3.3 ± 0.5
5". BB5.1 + Cyclosporin A	10, 10, 11, 11, 12, 12, 14, 15	11.9 ± 1.8**
6". BB5.1 + Cyclophosphamide	3, 3, 3, 3, 3, 4	3.2 ± 0.4
7". Cyclosporin A + Cyclophosphamide	3, 3, 3, 4, 4, 4	3.5 ± 0.6
8". BB5.1 + Cyclosporin A + Cyclophosphamide	> 100 days (4 mice)	> 100***

*P < 0.01 group 1" vs. no presensitization

**P < 0.01 group 5" vs. groups 1"-4" and 6"-7".

***P<0.01 group 8" vs. groups 1"-7".

Samsung Bioepis Exhibit No. 1002
Page 10726

Table 6

Median Scores of Histological Changes of Heart Allografts at Necropsy

Groups	Vasc*	Infar	Lymph	Throm	Hemo	Fibrin	PMN
No presensitization (endpoint)	3.0	3.0	1.0	4.0	3.0	3.0	3.0
1". One skin presensitization (endpoint)	0.0	4.0	1.0	4.0	3.0	0.0	0.0
2". Cyclosporin A (endpoint)	0.0	4.0	0.0	3.0	3.0	N/A	N/A
3". BB5.1 (endpoint)	2.0	2.0	2.0	2.0	3.0	N/A	N/A
4". Cyclophosphamide (endpoint)	2.0	4.0	0.0	3.0	2.0	N/A	N/A
5". BB5.1 + Cyclosporin A (post-operative day 3)	0.0	1.0	1.0	0.0	0.0	0.0	0.0
5". BB5.1 + Cyclosporin A (endpoint)	2.0	2.0	2.0	2.0	2.0	0.0	0.0
6". BB5.1 + Cyclophosphamide (endpoint)	1.0	3.0	0.0	3.0	2.0	N/A	N/A
7". Cyclosporin A + Cyclophosphamide (endpoint)	0.0	1.0	1.0	2.0	3.0	N/A	N/A
8". BB5.1 + Cyclosporin A + Cyclophosphamide (post-operative day 3)	0.0	0.0	1.0	0.0	0.0	N/A	N/A
8. BB5.1 + Cyclosporin A + Cyclophosphamide (post-operative day 12)	0.0	0.0	1.0	0.0	0.0	N/A	N/A
8". BB5.1 + Cyclosporin A + Cyclophosphamide (post-	0.0	0.0	1.0	0.0	0.0	N/A	N/A

Samsung Bioepis Exhibit No. 1002
Page 10727

operative day 60)							
8". BB5.1 + Cyclosporin A + Cyclophosphamide (post-operative day 100)	N/A	N/A	N/A	N/A	N/A	N/A	N/A

Median scores: 0 - normal; 1- minimum change; 2 - mild change; 3 - moderate change; 4 - marked change. N/A - not available.

*Vasc - vasculitis; Infar - infarction; Lymph - lymphocyte infiltration; Throm - thrombosis; Hemo - hemorrhage; Fibrin - fibrin deposition; PMN - polymorphonuclear cell infiltrate

The results shown in Table 5 indicate a difference between the presensitized mouse model and the nonpresensitized mouse model as used in Example 3. The results indicate that in the absence of presensitization, grafts are rejected in approximately 8 days in the absence of treatment with any drugs. Presensitizing the animals causes a more rapid rejection, the rejection of the graft in the presensitized animals being in approximately 3 days in the absence of any drug treatment. Treatment with either BB5.1, cyclosporin A or cyclophosphamide had no effect upon graft survival, with the grafts being rejected in approximately 3-4 days in each of these groups of animals. The combination of BB5.1 and cyclosporin A showed some effect with rejection occurring about day 12. The combination of BB5.1 and cyclophosphamide had no protective effect with rejection occurring about day 3. Similarly the combination of cyclosporin A and cyclophosphamide had essentially no protective effect with rejection occurring at 3-4 days. Very surprisingly, the combination of all three drugs (chronic administration of BB5.1 and cyclosporin plus administration of cyclophosphamide at the time of transplant) showed a highly synergistic effect with all of the mice surviving for more than 100 days. Again, a survival of 100 days in this model is considered to be the gold standard and assumes an indefinite survival.

These results as well as the histological results as shown in Table 6 indicate that the combination of chronic treatment with a complement inhibitor and an immunosuppressant such as cyclosporin A in treating a presensitized mouse results in some attenuation of accelerated rejection. Treatment of these animals additionally with cyclophosphamide at the time of transplant and on the first day after transplant results in a much greater time of survival, no rejection having been seen by at least day 100.

Samsung Bioepis Exhibit No. 1002
Page 10728

It will be appreciated that the methods and compositions of the instant disclosure can be incorporated in the form of a variety of embodiments, only a few of which are disclosed herein. It will be apparent to the artisan that other embodiments exist and do not depart from the spirit of the disclosure. Thus, the described embodiments are illustrative and should not be construed as restrictive.

Samsung Bioepis Exhibit No. 1002
Page 10729

LIST OF REFERENCES

The publications and other materials used herein to illuminate the background of the disclosure, and in particular, cases to provide additional details respecting the practice, are incorporated herein by reference in their entirety, and for convenience, are referenced by author and date in the text and respectively grouped in the following List of References.

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The contents of all references cited herein are incorporated by reference in their entirety.

CLAIMS

1. A method to prolong survival of an MHC mismatched allograft in a recipient mammal, said method comprising administering to said mammal a) a drug which inhibits complement activity and b) at least one immunosuppressive drug, wherein said drug which inhibits complement activity is administered chronically.

2. The method of claim 1 wherein said mammal is a human.

3. The method of claim 2 wherein said MHC mismatched allograft is an HLA mismatched allograft.

4. The method of claim 1 wherein said drug which inhibits complement activity inhibits the formation of terminal complement or C5a.

5. The method of claim 4 wherein said drug which inhibits formation of terminal complement or C5a is a whole antibody or an antibody fragment.

6. The method of claim 5 wherein said whole antibody or antibody fragment is a human, humanized, chimerized or deimmunized antibody or antibody fragment.

7. The method of claim 5 wherein said whole antibody or antibody fragment inhibits cleavage of complement C5.

8. The method of claim 5 wherein said antibody fragment is selected from the group consisting of an Fab, an $F(ab')_2$, an Fv, a domain antibody, and a single-chain antibody.

9. The method of claim 5 wherein said antibody fragment is pexelizumab.

10. The method of claim 5 wherein said whole antibody is eculizumab.

11. The method claim 10 wherein said eculizumab is administered once every 2 weeks.

12. The method of claim 1 wherein said inhibitor of complement activity is selected from the group consisting of a i) soluble complement receptor, ii) CD59, iii) CD55, iv) CD46, and v) an antibody to C5, C6, C7, C8, or C9.

13. The method of claim 1 wherein said immunosuppressive drug inhibits T-cell activity or B-cell activity.

Samsung Bioepis Exhibit No. 1002
Page 10734

14. The method of claim 1 wherein said immunosuppressive drug inhibits T-cell activity and B-cell activity.

15. The method of claim 1 wherein said immunosuppressive drug is selected from the group consisting of cyclosporin A, tacrolimus, sirolimus, OKT3, a corticosteroid, daclizumab, basiliximab, azathioprene, mycophenolate mofetil, methotrexate, 6-mercaptopurine, anti-T cell antibodies, cyclophosphamide, leflunamide, brequinar, ATG, ALG, 15-deoxyspergualin, and bredinin.

16. The method of claim 1 wherein more than one immunosuppressive drug is administered.

17. The method of claim 1 wherein said method comprises administering i) a drug which inhibits complement activity and ii) cyclosporin A.

18. The method of claim 17 wherein said drug which inhibits complement activity is an antibody which inhibits cleavage of complement C5.

19. The method of claim 1 wherein said allograft is selected from the group consisting of i) heart, ii) kidney, iii) lung, iv) pancreas, v) liver, vi) vascular tissue, vii) eye, viii) cornea, ix) lens, x) skin, xi) bone marrow, xii) muscle, xiii) connective tissue, xiv) gastrointestinal tissue, xv) nervous tissue, xvi) bone, xvii) stem cells, xviii) islets, xix) cartilage, xx) hepatocytes, and xxi) hematopoietic cells.

20. The method of claim 1 wherein said allograft survives for a time at least 20% longer than would occur if said method were to be performed without said drug which inhibits complement activity.

21. The method of claim 1 wherein said allograft survives for a time at least 40% longer than would occur if said method were to be performed without said drug which inhibits complement activity.

22. The method of claim 1 wherein said allograft survives for the remaining life-time of said mammal.

23. The method of claim 2 wherein said allograft survives for at least six months.

24. The method of claim 2 wherein said allograft survives for at least one year.

25. The method of claim 2 wherein said allograft survives for at least five years.

Samsung Bioepis Exhibit No. 1002
Page 10735

26. The method of claim 2 wherein said allograft survives for the remaining life-time of said human.

27. The method of claim 1 wherein said drug which inhibits complement activity is administered chronically for at least 14 days.

28. The method of claim 1 wherein said drug which inhibits complement activity is administered chronically for at least 28 days.

29. The method of claim 1 wherein said drug which inhibits complement activity is administered chronically for at least 3 months.

30. The method of claim 1 wherein said drug which inhibits complement activity is administered chronically for at least 6 months.

31. The method of claim 1 wherein said drug which inhibits complement activity is administered chronically for at least 1 year.

32. The method of claim 1 wherein said drug which inhibits complement activity is administered chronically for at least 5 years.

33. The method of claim 1 wherein said drug which inhibits complement activity is administered chronically for the remaining life-time of said mammal.

34. The method of claim 1 wherein at least one immunosuppressive drug is administered chronically for the remaining life-time of said mammal.

35. The method of claim 34 wherein at least cyclosporin A is administered chronically for the remaining life-time of said mammal.

36. A method to prolong survival of an allograft in a recipient mammal presensitized to said allograft, said method comprising administering to said mammal a) a drug which inhibits complement activity and b) at least one immunosuppressive drug, wherein said drug which inhibits complement activity is administered chronically.

37. The method of claim 36 wherein said mammal is a human.

38. The method of claim 36 wherein said drug which inhibits complement activity inhibits the formation of terminal complement or C5a.

Samsung Bioepis Exhibit No. 1002
Page 10736

39. The method of claim 38 wherein said drug that inhibits formation of terminal complement or C5a is a whole antibody or an antibody fragment.

40. The method of claim 39 wherein said whole antibody or antibody fragment is a human, humanized, chimerized or deimmunized antibody or antibody fragment.

41. The method of claim 39 wherein said whole antibody or antibody fragment inhibits cleavage of complement C5.

42. The method of claim 39 wherein said antibody fragment is selected from the group consisting of an Fab, an $F(ab')_2$, an Fv, a domain antibody, and a single-chain antibody.

43. The method of claim 39 wherein said antibody fragment is pexelizumab.

44. The method of claim 39 wherein said whole antibody is eculizumab.

45. The method claim 44 wherein said eculizumab is administered once every 2 weeks.

46. The method of claim 36 wherein said inhibitor of complement activity is selected from the group consisting of a i) soluble complement receptor, ii) CD59, iii) CD55, iv) CD46, and v) an antibody to C5, C6, C7, C8, or C9.

47. The method of claim 36 wherein said immunosuppressive drug inhibits T-cell activity or B-cell activity.

48. The method of claim 36 wherein said immunosuppressive drug inhibits T-cell activity and B-cell activity.

49. The method of claim 36 wherein said immunosuppressive drug is selected from the group consisting of cyclosporin A, tacrolimus, sirolimus, OKT3, a corticosteroid, daclizumab, basiliximab, azathioprene, mycophenolate mofetil, methotrexate, 6-mercaptopurine, anti-T cell antibodies, cyclophosphamide, leflunamide, brequinar, ATG, ALG, 15-deoxyspergualin, and bredinin.

50. The method of claim 36 wherein more than one immunosuppressive drug is administered.

51. The method of claim 36 wherein said method comprises administering i) a drug which inhibits complement activity and ii) cyclosporin A.

Samsung Bioepis Exhibit No. 1002
Page 10737

52. The method of claim 51 wherein said method comprises administering i) a drug which inhibits complement activity, ii) cyclosporin A, and iii) cyclophosphamide.

53. The method of claim 51 wherein said drug which inhibits complement activity is an antibody which inhibits cleavage of complement C5.

54. The method of claim 36 wherein said allograft is selected from the group consisting of i) heart, ii) kidney, iii) lung, iv) pancreas, v) liver, vi) vascular tissue, vii) eye, viii) cornea, ix) lens, x) skin, xi) bone marrow, xii) muscle, xiii) connective tissue, xiv) gastrointestinal tissue, xv) nervous tissue, xvi) bone, xvii) stem cells, xviii) islets, xix) cartilage, xx) hepatocytes, and xxi) hematopoietic cells.

55. The method of claim 36 wherein said allograft survives for a time at least 20% longer than would occur if said method were to be performed without said drug which inhibits complement activity.

56. The method of claim 36 wherein said allograft survives for a time at least 40% longer than would occur if said method were to be performed without said drug which inhibits complement activity.

57. The method of claim 36 wherein said allograft survives for the remaining life-time of said mammal.

58. The method of claim 37 wherein said allograft survives for at least six months.

59. The method of claim 37 wherein said allograft survives for at least one year.

60. The method of claim 37 wherein said allograft survives for at least five years.

61. The method of claim 37 wherein said allograft survives for the remaining life-time of said human.

62. The method of claim 36 wherein said drug which inhibits complement activity is administered chronically for at least 14 days.

63. The method of claim 36 wherein said drug which inhibits complement activity is administered chronically for at least 28 days.

64. The method of claim 36 wherein said drug which inhibits complement activity is administered chronically for at least 3 months.

Samsung Bioepis Exhibit No. 1002
Page 10738

65. The method of claim 36 wherein said drug which inhibits complement activity is administered chronically for at least 6 months.

66. The method of claim 36 wherein said drug which inhibits complement activity is administered chronically for at least 1 year.

67. The method of claim 36 wherein said drug which inhibits complement activity is administered chronically for at least 5 years.

68. The method of claim 36 wherein said drug which inhibits complement activity is administered chronically for the remaining life-time of said mammal.

69. The method of claim 36 wherein at least one immunosuppressive drug is administered chronically for the remaining life-time of said mammal.

70. The method of claim 69 wherein at least cyclosporin A is administered chronically for the remaining life-time of said mammal.

71. A method to prolong survival of an allograft in a recipient mammal which is an ABO mismatch to said allograft, said method comprising administering to said mammal a) a drug which inhibits complement activity and b) at least one immunosuppressive drug, wherein said drug which inhibits complement activity is administered chronically.

72. The method of claim 71 wherein said mammal is a human.

73. The method of claim 71 wherein said drug which inhibits complement activity inhibits the formation of terminal complement or C5a.

74. The method of claim 73 wherein said drug which inhibits formation of terminal complement or C5a is a whole antibody or an antibody fragment.

75. The method of claim 74 wherein said whole antibody or antibody fragment is a human, humanized, chimerized or deimmunized antibody or antibody fragment.

76. The method of claim 74 wherein said whole antibody or antibody fragment inhibits cleavage of complement C5.

77. The method of claim 74 wherein said antibody fragment is selected from the group consisting of an Fab, an $F(ab')_2$, an Fv, a domain antibody, and a single-chain antibody.

Samsung Bioepis Exhibit No. 1002
Page 10739

78. The method of claim 74 wherein said antibody fragment is pexelizumab.

79. The method of claim 74 wherein said whole antibody is eculizumab.

80. The method claim 79 wherein said eculizumab is administered once every 2 weeks.

81. The method of claim 71 wherein said inhibitor of complement activity is selected from the group consisting of a i) soluble complement receptor, ii) CD59, iii) CD55, iv) CD46, and v) an antibody to C5, C6, C7, C8, or C9.

82. The method of claim 71 wherein said immunosuppressive drug inhibits T-cell activity or B-cell activity.

83. The method of claim 71 wherein said immunosuppressive drug inhibits T-cell activity and B-cell activity.

84. The method of claim 71 wherein said immunosuppressive drug is selected from the group consisting of cyclosporin A, tacrolimus, sirolimus, OKT3, a corticosteroid, daclizumab, basiliximab, azathioprene, mycophenolate mofetil, methotrexate, 6-mercaptopurine, anti-T cell antibodies, cyclophosphamide, leflunamide, brequinar, ATG, ALG, 15-deoxyspergualin, and bredinin.

85. The method of claim 71 wherein more than one immunosuppressive drug is administered.

86. The method of claim 71 wherein said method comprises administering i) a drug which inhibits complement activity and ii) cyclosporin A.

87. The method of claim 86 wherein said method comprises administering i) a drug which inhibits complement activity, ii) cyclosporin A, and iii) cyclophosphamide.

88. The method of claim 86 wherein said drug that inhibits complement activity is an antibody that inhibits cleavage of complement C5.

89. The method of claim 71 wherein said allograft is selected from the group consisting of i) heart, ii) kidney, iii) lung, iv) pancreas, v) liver, vi) vascular tissue, vii) eye, viii) cornea, ix) lens, x) skin, xi) bone marrow, xii) muscle, xiii) connective tissue, xiv) gastrointestinal tissue, xv) nervous tissue, xvi) bone, xvii) stem cells, xviii) islets, xix) cartilage, xx) hepatocytes, and xxi) hematopoietic cells.

Samsung Bioepis Exhibit No. 1002
Page 10740

90. The method of claim 71 wherein said allograft survives for a time at least 20% longer than would occur if said method were to be performed without said drug that inhibits complement activity.

91. The method of claim 71 wherein said allograft survives for a time at least 40% longer than would occur if said method were to be performed without said drug that inhibits complement activity.

92. The method of claim 71 wherein said allograft survives for the remaining life-time of said mammal.

93. The method of claim 72 wherein said allograft survives for at least six months.

94. The method of claim 72 wherein said allograft survives for at least one year.

95. The method of claim 72 wherein said allograft survives for at least five years.

96. The method of claim 72 wherein said allograft survives for the remaining life-time of said human.

97. The method of claim 71 wherein said drug which inhibits complement activity is administered chronically for at least 14 days.

98. The method of claim 71 wherein said drug which inhibits complement activity is administered chronically for at least 28 days.

99. The method of claim 71 wherein said drug which inhibits complement activity is administered chronically for at least 3 months.

100. The method of claim 71 wherein said drug which inhibits complement activity is administered chronically for at least 6 months.

101. The method of claim 71 wherein said drug which inhibits complement activity is administered chronically for at least 1 year.

102. The method of claim 71 wherein said drug which inhibits complement activity is administered chronically for at least 5 years.

103. The method of claim 71 wherein said drug which inhibits complement activity is administered chronically for the remaining life-time of said mammal.

Samsung Bioepis Exhibit No. 1002
Page 10741

104. The method of claim 71 wherein at least one immunosuppressive drug is administered chronically for the remaining life-time of said mammal.

105. The method of claim 104 wherein at least cyclosporin A is administered chronically for the remaining life-time of said mammal.

106. Use of a drug that inhibits complement activity and an immunosuppressive drug in the manufacture of a medicament or medicament package for prolong survival of an allograft in a mammal.

107. The use of claim 106, wherein more than one immunosuppressive drug is included in said medicament or medicament package.

108. The use of claim 106, wherein said drug that inhibits complement activity and said immunosuppressive drug are in a formulation suitable for concurrent administration to said mammal.

109. The use of claim 106, wherein said drug that inhibits complement activity and said immunosuppressive drug are in a formulation or formulations suitable for sequential administration to said mammal.

110. The use of claim 106, wherein said drug that inhibits complement activity is in a formulation suitable for chronic administration to said mammal.

111. The use of claim 106, wherein said immunosuppressive drug is in a formulation suitable for chronic administration to said mammal.

112. A method to prolong survival of allograft in a recipient mammal, comprising preparing an allograft from a first allograft accommodated by a first recipient mammal, wherein said first recipient mammal, after receiving said first allograft, has been treated with a drug that inhibits complement activity and at least one immunosuppressive agent.

113. An allograft that has prolonged survival in a recipient mammal, wherein said allograft is prepared from a first recipient mammal and was transplanted to the first recipient mammal that has been treated with a drug that inhibits complement activity and at least one immunosuppressive agent.

Samsung Bioepis Exhibit No. 1002
Page 10742

114. A pharmaceutical package comprising a drug that inhibits complement activity and at least one immunosuppressive agent, wherein said drug and said agent are formulated for chronic administration.

115. The pharmaceutical package of claim 114, wherein said drug is an antibody in a lyophilized formulation comprising the antibody and a lyoprotectant.

116. The pharmaceutical package of claim 114, wherein said agent is in a lyophilized formulation comprising the agent and a lyoprotectant.

117. The pharmaceutical package of claim 114, wherein said drug and said agent are in the same lyophilized formulation comprising said drug, said agent, and a lyoprotectant.

118. The pharmaceutical package of claim 114, wherein said drug is in an injection system comprising a syringe that comprises a cartridge, wherein said cartridge contains said drug in a formulation suitable for injection.

119. The pharmaceutical package of claim 114, wherein said agent is in an injection system comprising a syringe that comprises a cartridge, wherein said cartridge contains said agent in a formulation suitable for injection.

120. The pharmaceutical package of claim 114, wherein said drug and said agent are in an injection system comprising a syringe that comprises a cartridge, wherein said cartridge contains said drug and said agent in a formulation suitable for injection.

121. The pharmaceutical package of claim 114, wherein said drug is present in unit dosage form.

122. The pharmaceutical package of claim 114, wherein said agent is present in unit dosage form.

123. A lyophilized antibody formulation comprising an antibody that inhibits complement activity and a lyoprotectant, wherein said antibody formulation is suitable for chronic administration.

124. The lyophilized antibody formulation of claim 123, wherein the antibody inhibits the formation of terminal complement or C5a.

Samsung Bioepis Exhibit No. 1002
Page 10743

125. The lyophilized antibody formulation of claim 123, wherein the antibody is a whole antibody or an antibody fragment.

126. The lyophilized antibody formulation of claim 125, wherein the antibody wherein said whole antibody or antibody fragment is a human, humanized, chimerized or deimmunized antibody or antibody fragment.

127. The lyophilized antibody formulation of claim 125, wherein said whole antibody or antibody fragment inhibits cleavage of complement C5.

128. The lyophilized antibody formulation of claim 125, wherein said antibody fragment is selected from the group consisting of an Fab, an $F(ab')_2$, an Fv, a domain antibody, and a single-chain antibody.

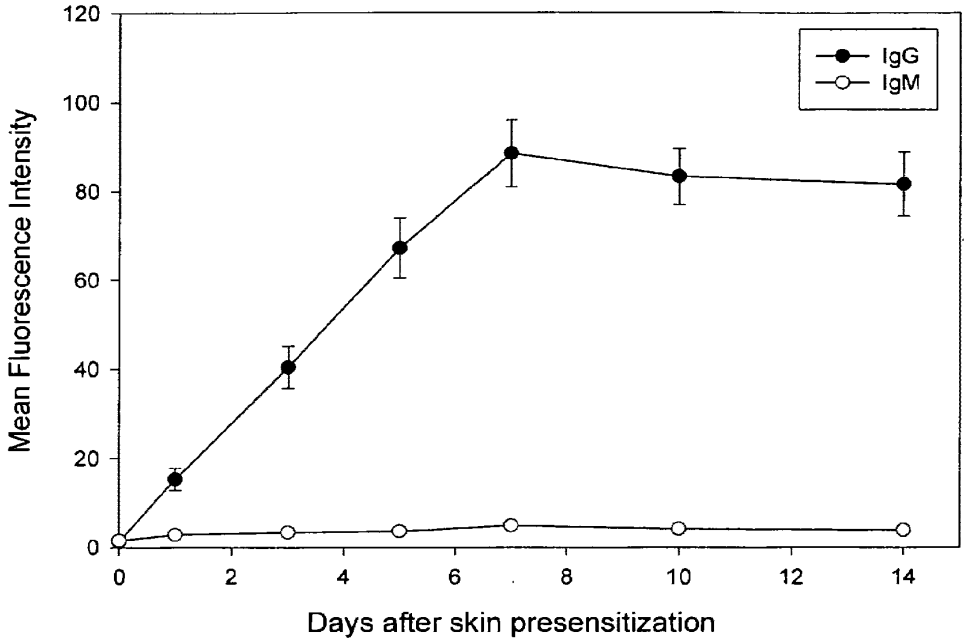
129. The lyophilized antibody formulation of claim 125, wherein said antibody fragment is pexelizumab.

130. The lyophilized antibody formulation of claim 125, wherein said whole antibody is eculizumab.

131. An injection system comprising a syringe, wherein said syringe comprises a cartridge containing an antibody that inhibits complement activity and is formulated suitable for injection.

Samsung Bioepis Exhibit No. 1002
Page 10744

A



B

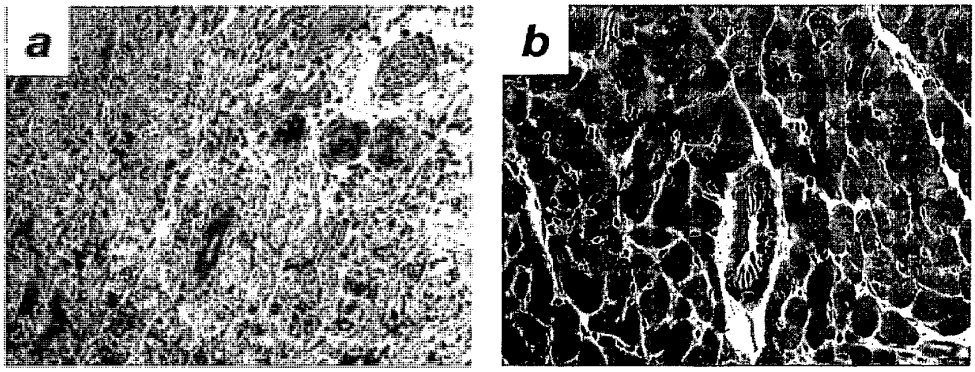


Figure 1A, B

Samsung Bioepis Exhibit No. 1002
Page 10745

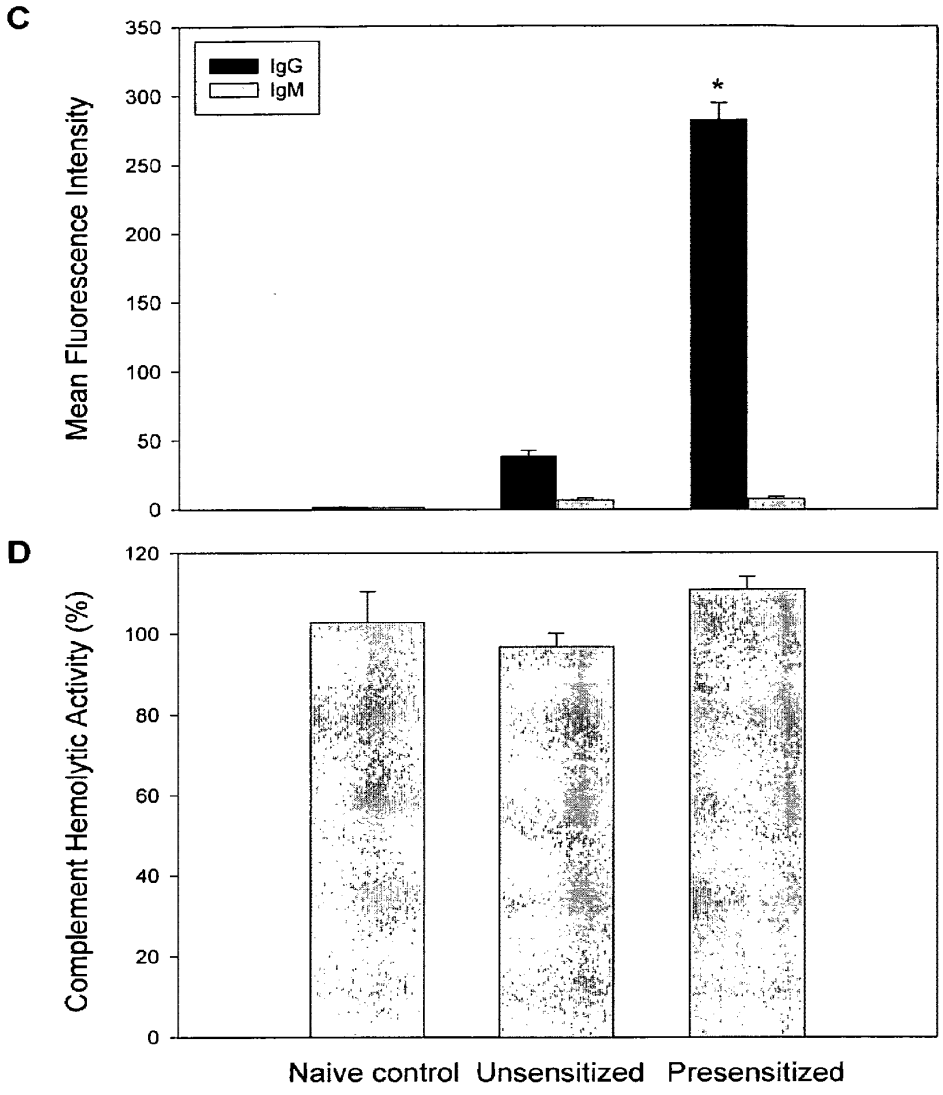


Figure 1C, D

Samsung Bioepis Exhibit No. 1002
Page 10746

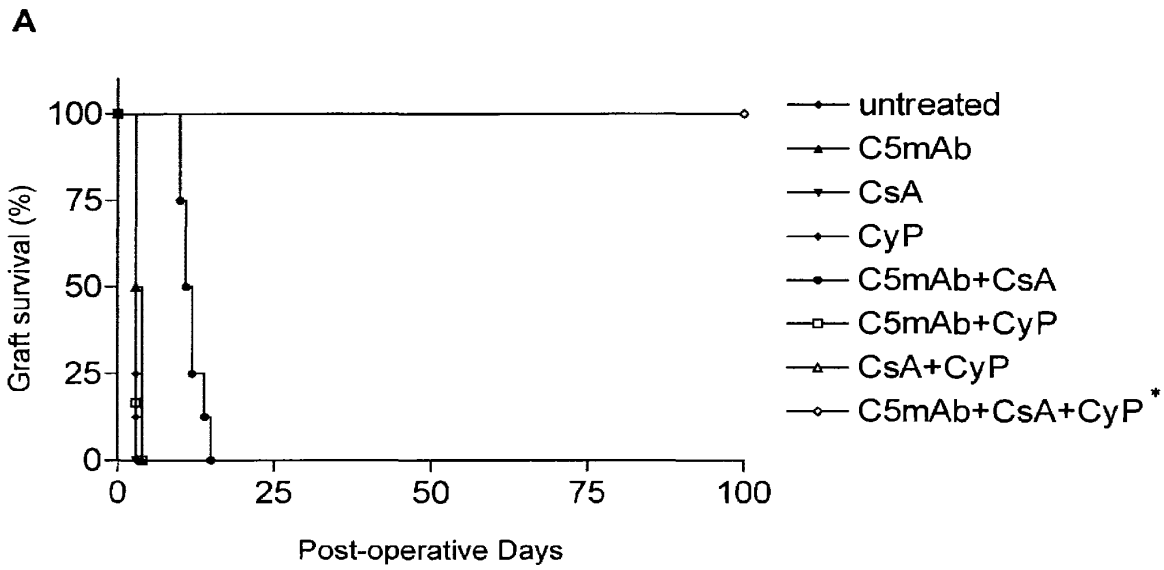


Figure 2A

Samsung Bioepis Exhibit No. 1002
Page 10747

B

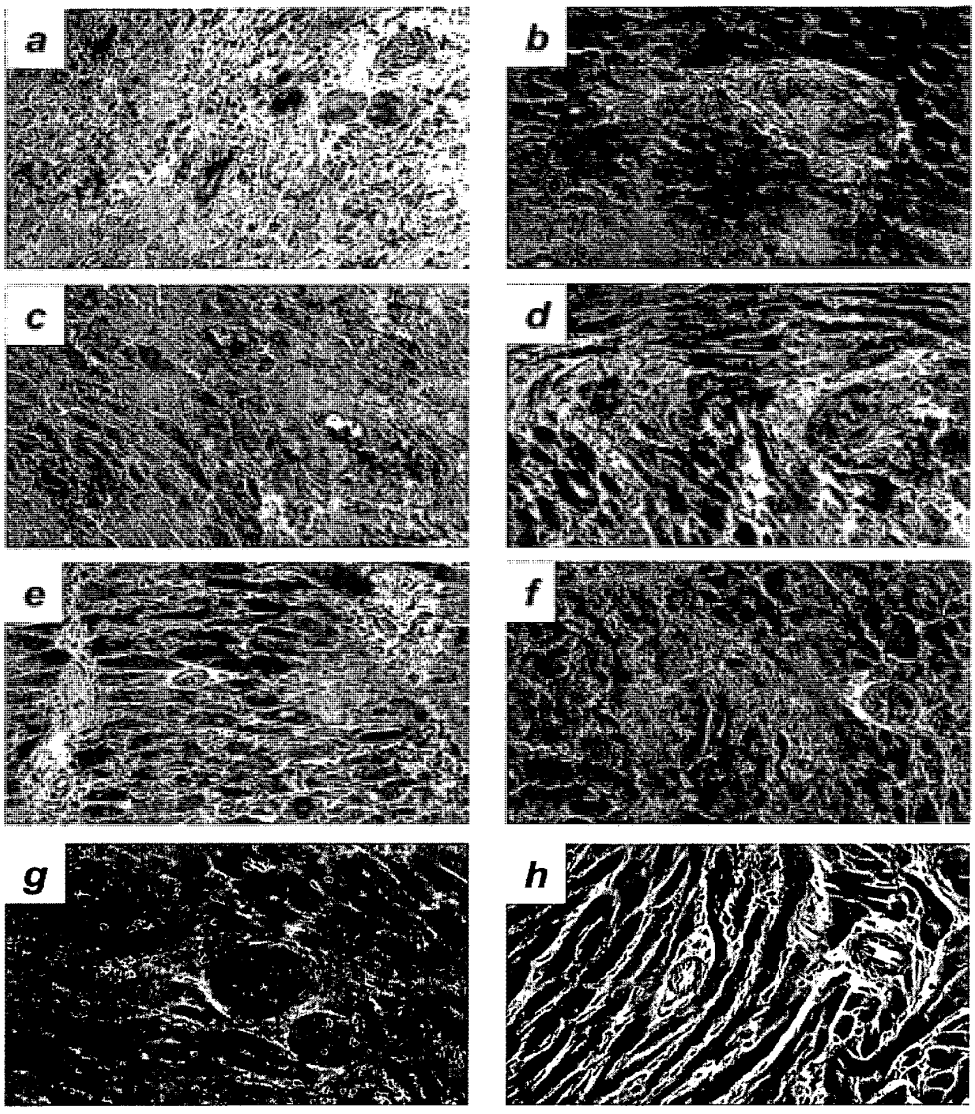


Figure 2B

Samsung Bioepis Exhibit No. 1002
Page 10748

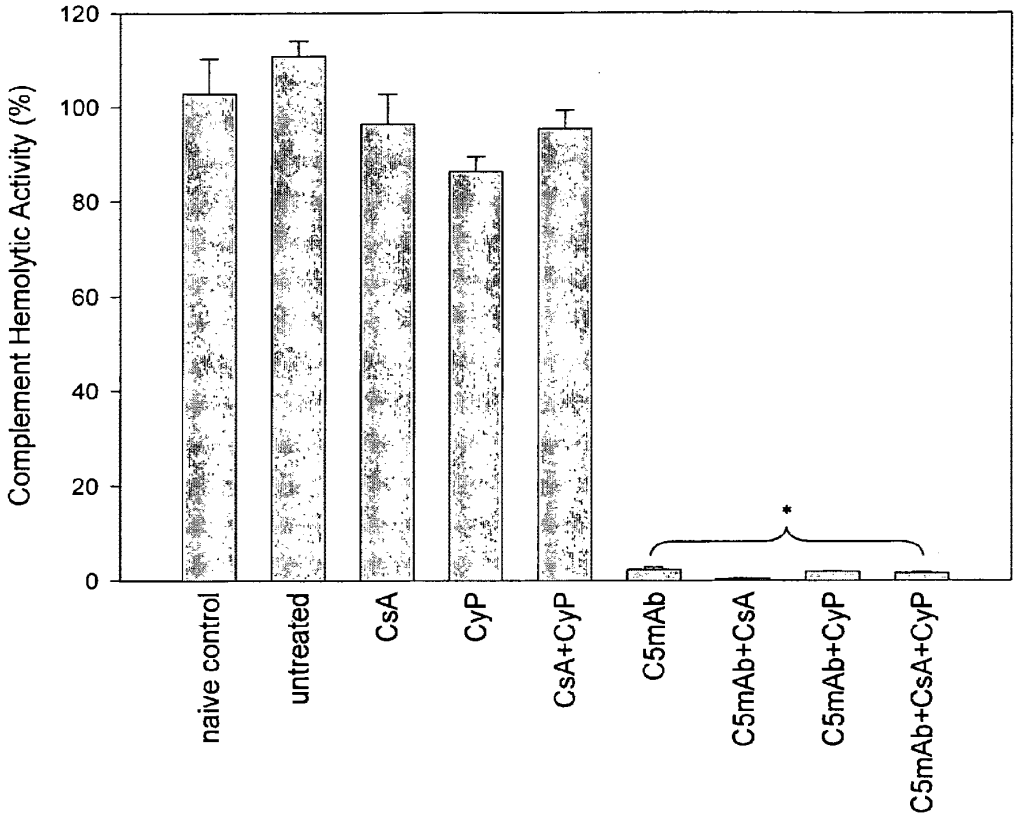


Figure 3

Samsung Bioepis Exhibit No. 1002
Page 10749

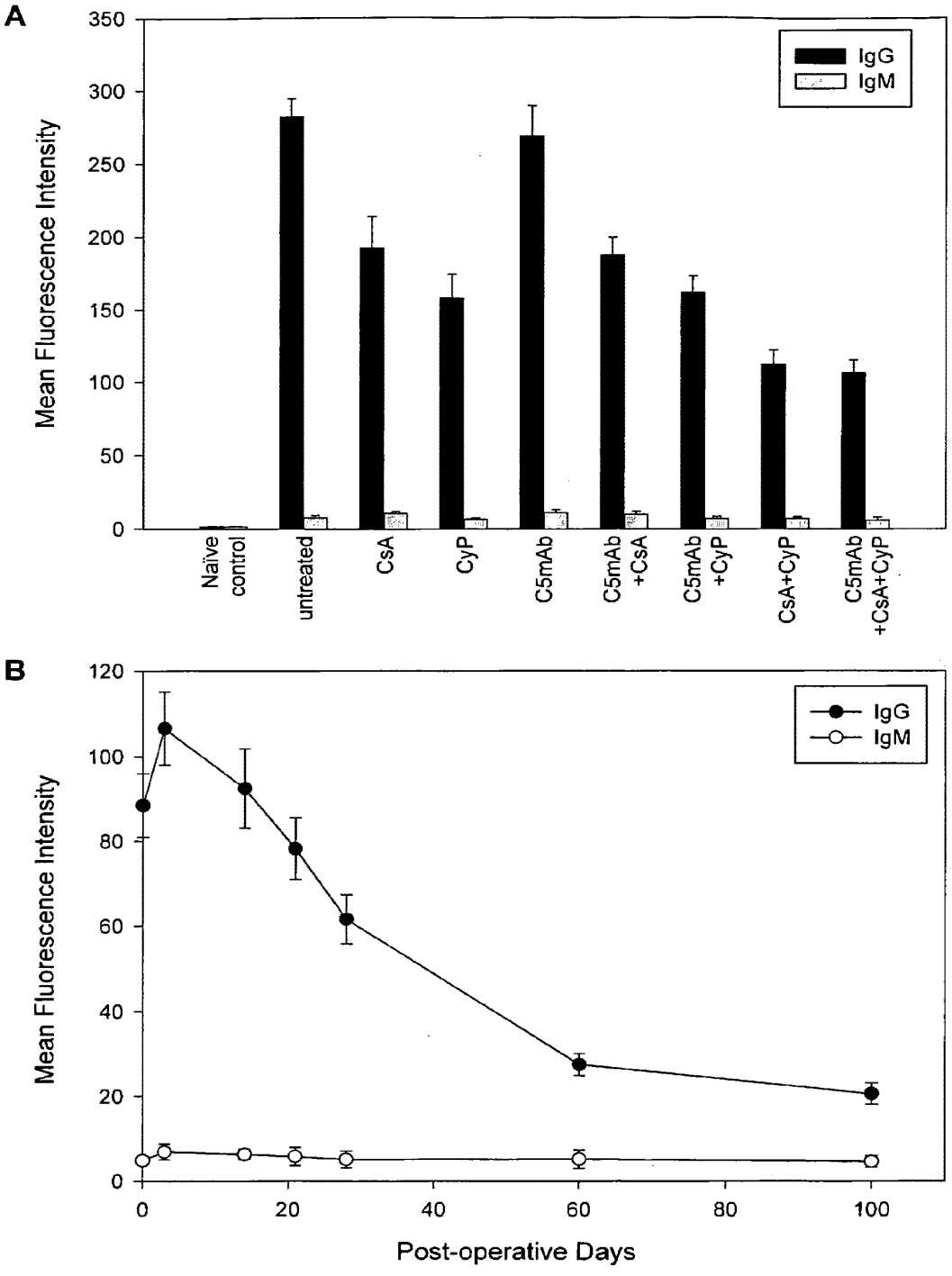
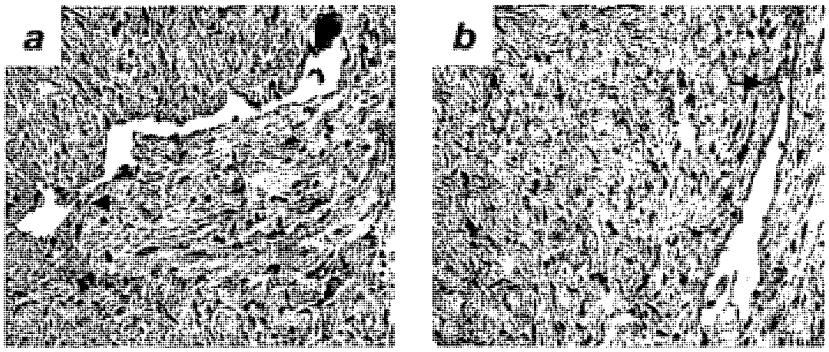


Figure 4A, B

Samsung Bioepis Exhibit No. 1002
Page 10750

C



D

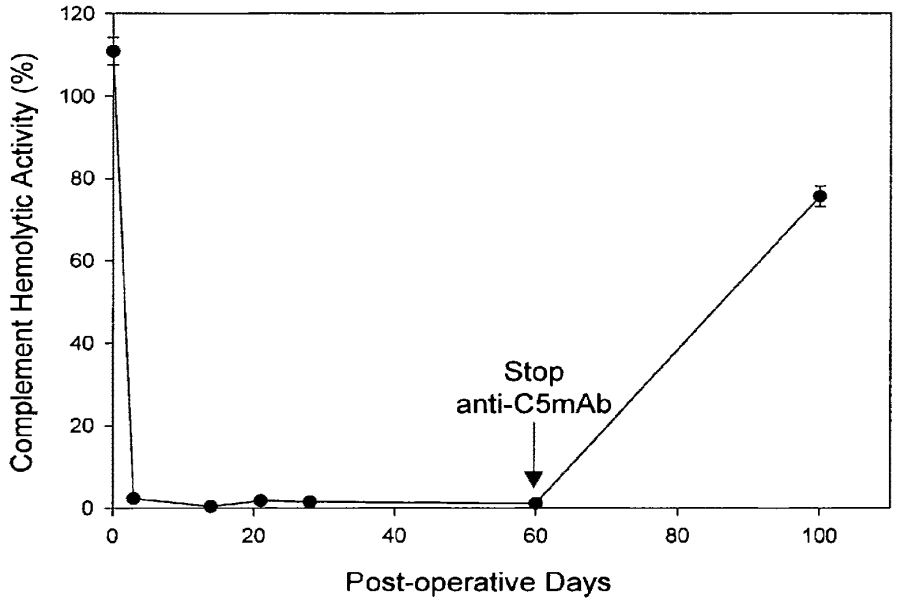


Figure 4C, D

Samsung Bioepis Exhibit No. 1002
Page 10751

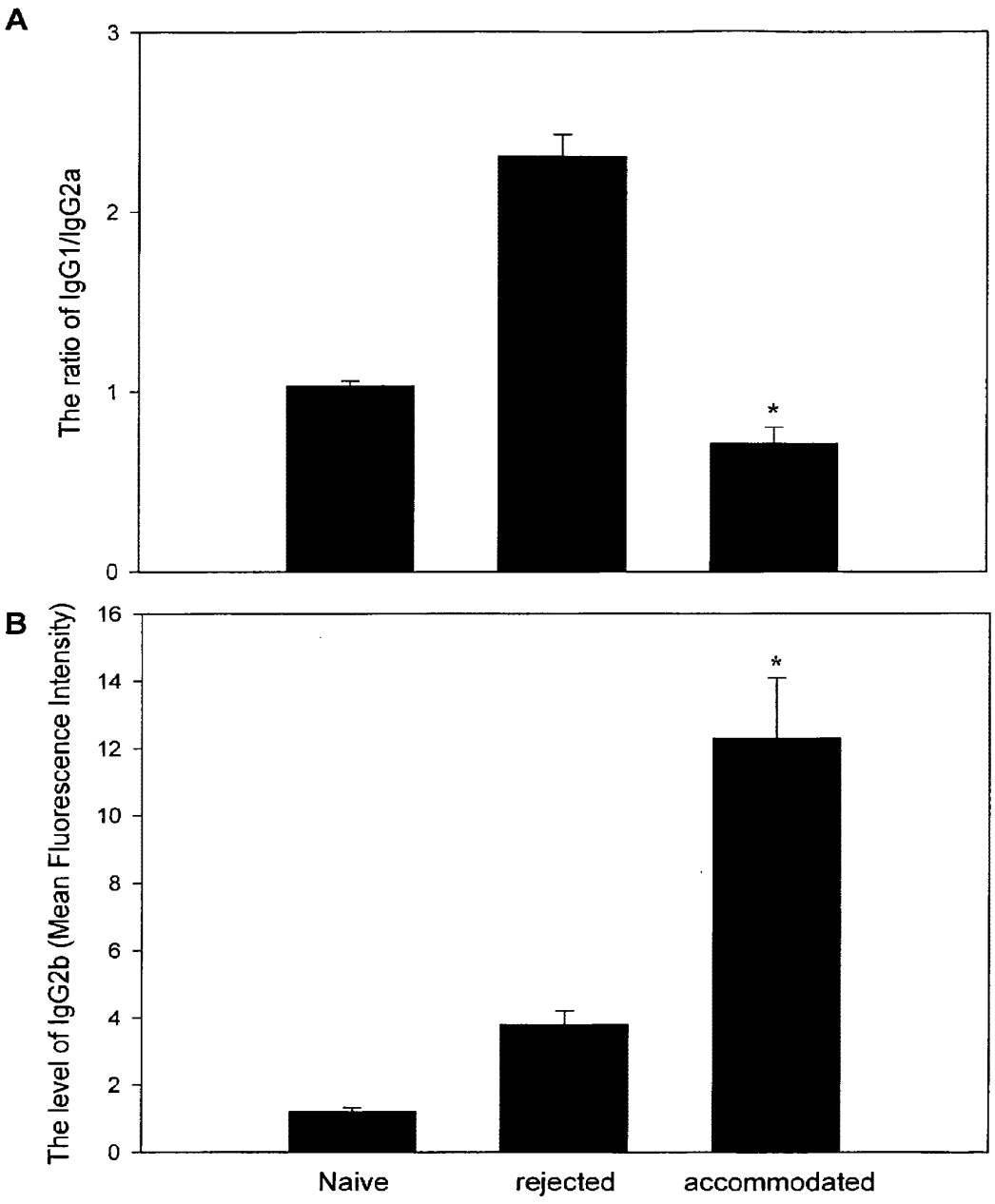


Figure 5A, B

Samsung Bioepis Exhibit No. 1002
Page 10752

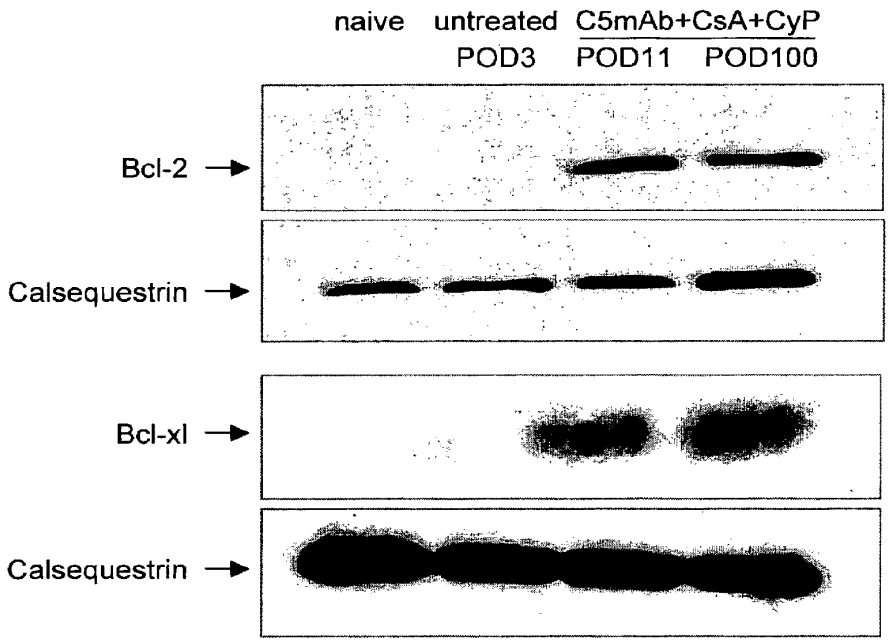


Figure 6

Samsung Bioepis Exhibit No. 1002
Page 10753

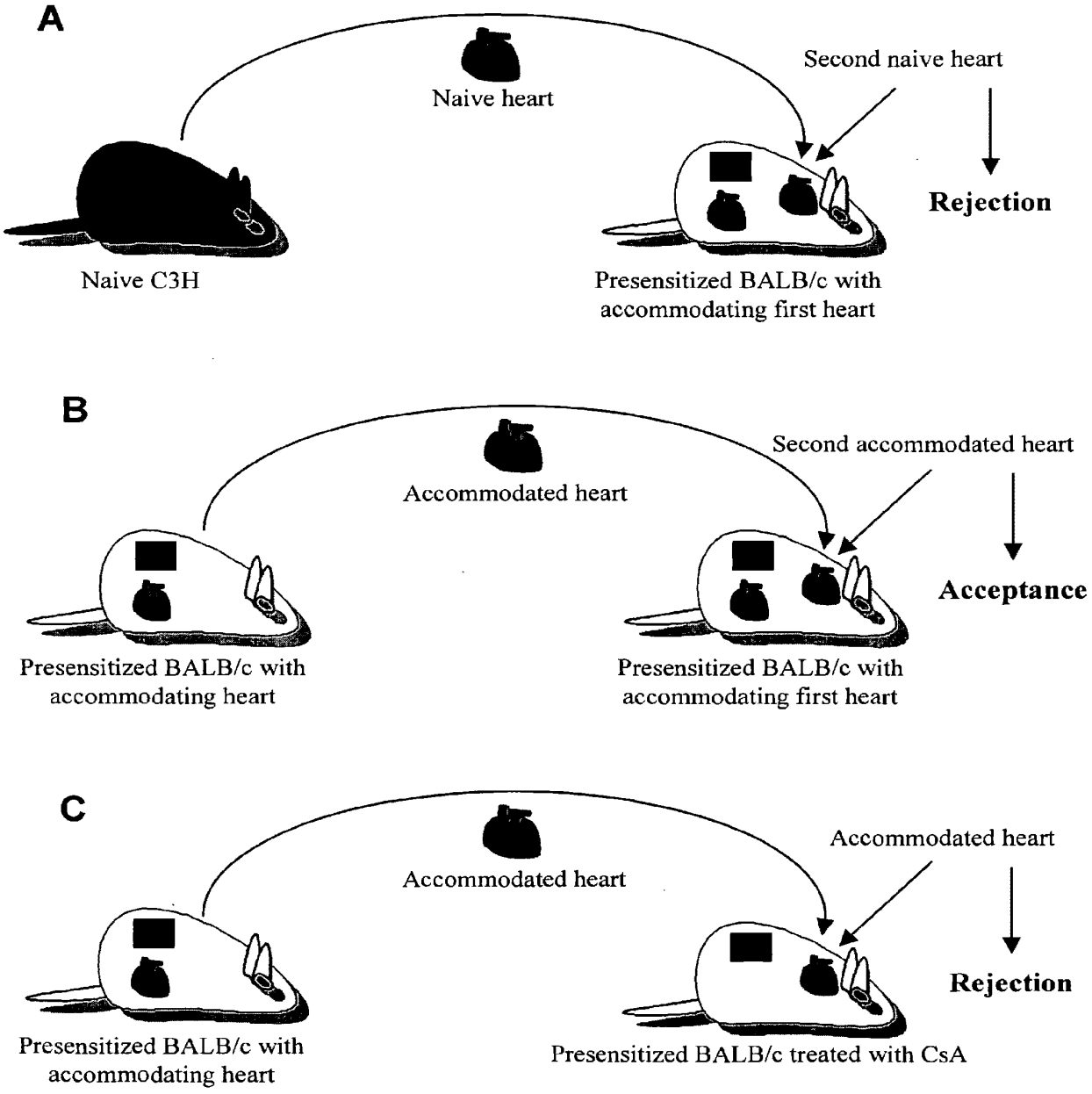


Figure 7

Samsung Bioepis Exhibit No. 1002
Page 10754

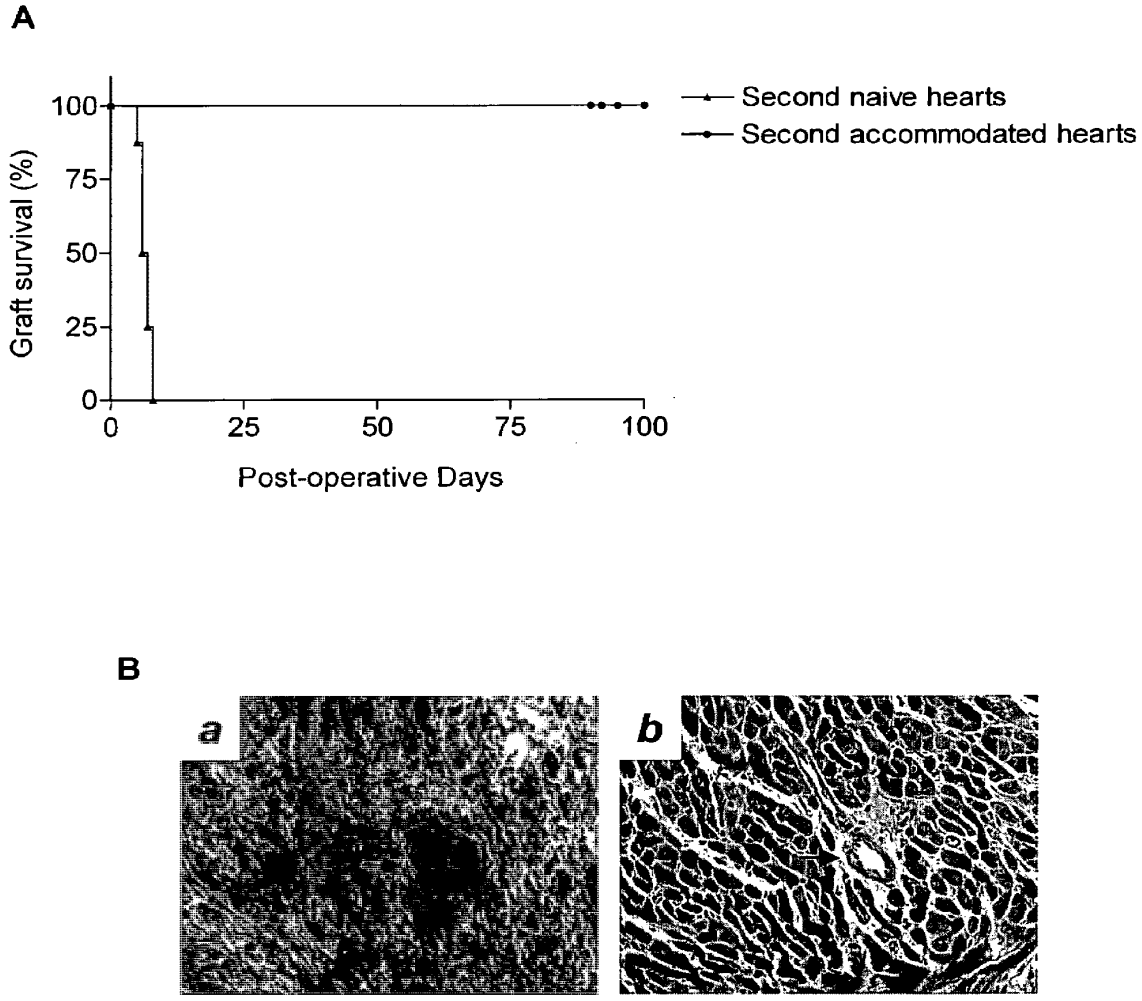


Figure 8

Samsung Bioepis Exhibit No. 1002
Page 10755

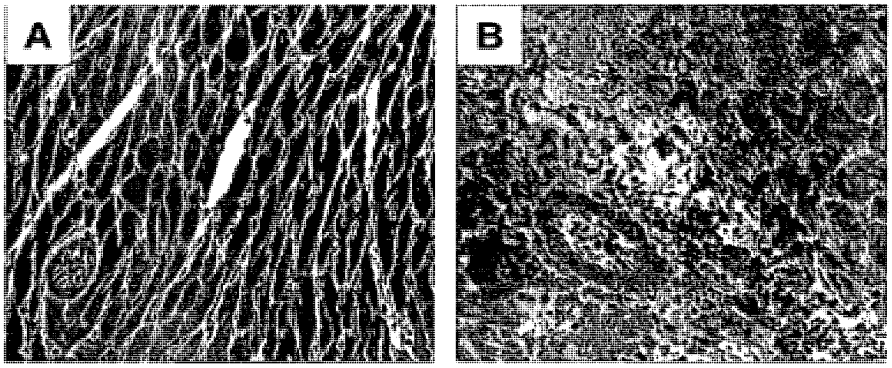


Figure 9

Samsung Bioepis Exhibit No. 1002
Page 10756

ClinicalTrials.gov archive
A service of the U.S. National Institutes of Health — Developed by the National Library of Medicine

← History of this study ↑ Current version of this study

View of NCT00098280 on 2005_06_23

ClinicalTrials Identifier: NCT00098280
Updated: 2005_06_23

Descriptive Information

Brief title Eculizumab to Treat Paroxysmal Nocturnal Hemoglobinuria

Official title A Hemoglobin Stabilization and Transfusion Reduction Efficacy and Safety Clinical Investigation, Randomized, Multi-Center, Double-Blind, Placebo-Controlled, Using Eculizumab in Paroxysmal Nocturnal Hemoglobinuria Patients

Brief summary

This study will examine the safety and effectiveness of the experimental drug eculizumab in treating patients with paroxysmal nocturnal hemoglobinuria (PNH), a rare disorder of red blood cells that leads to premature destruction of the cells and resulting anemia. Patients may be at high risk of blood clots and may develop bone marrow failure or aplastic anemia, with low white blood cell and platelet counts. Eculizumab is a monoclonal antibody that may help improve the survival of red blood cells.

Patients 18 years of age and older with PNH who require blood transfusions for anemia and have received at least four transfusions in the 12 months preceding evaluation for this study may be eligible to enroll. Candidates are screened with a medical history, physical examination, and check of vital signs.

Participants have an electrocardiogram (EKG) and blood and urine tests, and are vaccinated against Neisseria meningitides, a common bacteria that can cause a disabling or fatal type of meningitis. They then enter an observation phase of the study, with monthly visits during which they complete a questionnaire; update their health status, transfusion record, and medication use; have their vital signs checked and PNH symptoms evaluated; have blood and urine tests; and receive a transfusion, if necessary. These visits continue for up to 3 months until patients receive a "qualifying" transfusion; that is, a transfusion given as a consequence of a certain hemoglobin level with symptoms or a different level without symptoms.

Patients are then randomly assigned to receive either eculizumab or a placebo (salt solution with no active ingredient). Both study medications are given intravenously (through a vein) over 30 minutes once a week for five doses and then once every 2 weeks for another 11 doses. At each treatment visit (study weeks 0-24), patients update their health status, transfusion records, and medication use; have their vital signs checked; and provide a blood sample. At various visits, they also complete a questionnaire, provide a urine sample and have an EKG. At the last treatment visit (week 26 or the final visit for patients who end their participation before visit 18) patients have a complete physical examination in addition to the procedures listed above.

Detailed description

Paroxysmal nocturnal hemoglobinuria (PNH) is an acquired clonal disorder of the hematopoietic stem cell characterized by intravascular hemolysis, hemoglobinuria,

anemia, and thrombosis. The clinical features of PNH result from the lack of one or more of the GPI-linked proteins that serve to protect cells from autologous complement mediated attack. Two such proteins, CD55 (decay accelerating factor) and CD59 (reactive lysis inhibitor) have been shown to be absent from PNH erythrocytes and platelets as well as other cell types.

Evidence strongly suggests that lack of the terminal complement inhibitor CD59 is responsible for the sensitivity of PNH erythrocytes and platelets to the effects of autologous complement. Since the pathogenesis of PNH is due to the inability of PNH red cells and platelets to inhibit the activation of terminal complement, it is logical to hypothesize that a terminal complement inhibitor could effectively stop the intravascular hemolysis, obviate or lessen the need for transfusions, and possibly decrease the propensity of life threatening thrombosis. Eculizumab is a humanized monoclonal antibody that like CD59 inhibits terminal complement.

This study is a randomized, double-blind, placebo controlled, multi-center study of eculizumab or placebo administered intravenously to approximately 75 PNH patients. The study is designed to evaluate the safety of eculizumab in transfusion dependent patients with paroxysmal nocturnal hemoglobinuria (PNH) and to determine if the administration of this terminal complement inhibitor could provide a safe and effective substitute for CD59 function.

Phase	III
Study type	Interventional
Condition	Hemoglobinuria, Paroxysmal
Intervention	Drug: Eculizumab
Reference	Citation: Hillmen P, et al. Natural history of paroxysmal nocturnal hemoglobinuria. N Engl J Med. 1995 Nov 9;333(19):1253-8. MEDLINE: 7566002
Reference	Citation: Tabbara IA. Hemolytic anemias. Diagnosis and management. Med Clin North Am. 1992 May;76(3):649-68. Review. MEDLINE: 1578962
Reference	Citation: Rosse WF. Phosphatidylinositol-linked proteins and paroxysmal nocturnal hemoglobinuria. Blood. 1990 Apr 15;75(8):1595-601. Review. No abstract available. MEDLINE: 2183885
URL	http://clinicalstudies.info.nih.gov/detail/A_2005-H-0048.html
See also	Detailed Web Page

Recruitment Information

Status	Recruiting
Start date	2004-12-02

Criteria

INCLUSION CRITERIA - Screening Period:

Individuals at least 18 years of age;

Patients must have required at least 4 episodes of transfusions in the 12 months prior to Visit 1 for anemia or anemia-related symptoms;

Presence of a GPI deficient red blood cell clone (type II cells) by flow cytometry of greater than or equal to 10%;

Samsung Bioepis Exhibit No. 1002
Page 10758

Patients taking erythropoietin must be on a stable dose for 26 weeks prior to visit 1 and the dose must be expected to remain stable during the Observation Period and the Treatment Phase;

Patients taking immunosuppressants must be on a stable dose for at least 26 weeks prior to Visit 1 and the dose must be expected to remain stable during the Observation period and the Treatment Phase;

Patients taking corticosteroids must be on a stable dose for at least 4 weeks prior to Visit 1. The dose level may be decreased during the study as clinically appropriate. If the corticosteroids need to be increased, they may not be increased above the dose reported at Visit 1;

Patients are allowed to take coumadin, but must be at a stable international normalized ratio (INR) level for 4 weeks prior to Visit 1 and are expected to maintain a stable INR level during the Observation Period and the Treatment Phase;

Patients taking iron supplements or folic acid must be on a stable dose for 4 weeks prior to Visit 3 and be expected to remain stable during Observation Period and the Treatment Phase;

Patients are allowed to take low molecular weight heparin, but must be on a stable dose for 4 weeks prior to Visit 1 and the dose must be expected to remain stable during Observation period and the Treatment Phase;

Patient must be willing and able to give written informed consent;

Patients must be vaccinated against N. meningitidis at Visit 1 or at least 14 days prior to Visit 3;

Patient must avoid conception during the trial using a method that is most appropriate for their physical state and culture.

INCLUSION CRITERIA - Observation Period:

Documented LDH level greater than or equal to 1.5 x upper limit of normal (ULN) either at Visit 1 or during the Observation Period;

Patients who have received one PRBC transfusion during the Observation Period at a hemoglobin value of less than or equal to 9 gm/dL with symptoms or at a hemoglobin value of less than or equal to 7 gm/dL without symptoms, and also within 1.5 gm/dL of the mean hemoglobin pre-transfusion value for the previous 12 months. This transfusion should be in accordance with that patient's individual transfusion hemoglobin algorithm, and occur within 48 hours of the hemoglobin sample that precipitated the transfusion;

Platelet count greater than or equal to 100,000/mm(3) either at Visit 1 or during the Observation Period.

EXCLUSION CRITERIA:

Patients whose mean hemoglobin levels prior to transfusion over the previous 12 months is greater than 10.5 gm/dL;

Absolute Neutrophil count less than or equal to 500/microL;

Samsung Bioepis Exhibit No. 1002
Page 10759

Presence or suspicion of active bacterial infection, in the opinion of the Investigator, at Visit 3 or recurrent bacterial infections;

Known or suspected hereditary complement deficiency;

Participation in any other investigational drug trial or exposure to other investigational agent, device, or procedure within 30 days prior to Visit 1;

Pregnant, breast-feeding, or intending to conceive during the course of the study, including the Post-treatment Phase;

History of meningococcal disease;

History of bone marrow transplantation;

Any condition that, in the opinion of the Investigator, could increase the patient's risk by participating in the study or confound the outcome of the study.

Gender	Both
Healthy volunteers	Yes
Expected enrollment	75

Administrative Data

Secondary ID	05-H-0048
Sponsor	National Heart, Lung and Blood Institute (NHLBI)

Samsung Bioepis Exhibit No. 1002
Page 10760

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
15/260,888	09/09/2016	Leonard BELL	AXJ-114BUSCN3	2558

133485 7590 05/11/2017

Nelson Mullins Riley & Scarborough LLP/Alexion
One Post Office Square
30th Floor
Boston, MA 02109-2127

EXAMINER	
ROGERS, JAMES L	

ART UNIT	PAPER NUMBER
1644	

NOTIFICATION DATE	DELIVERY MODE
05/11/2017	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

ipboston.docketing@nelsonmullins.com
chris.schlauch@nelsonmullins.com
ipqualityassuranceboston@nelsonmullins.com

Applicant-Initiated Interview Summary	Application No.	Applicant(s)	
	15/260,888	BELL ET AL.	
	Examiner	Art Unit	
	JAMES ROGERS	1644	

All participants (applicant, applicant's representative, PTO personnel):

(1) *JAMES ROGERS*.

(2) *DANIEL KOLKER, SPE*.

(3)*JILL SLOPER*.

(4)*JANE REMILLARD*.

Date of Interview: *01 May 2017*.

Type: ☐ Telephonic ☐ Video Conference
☒ Personal [copy given to: ☐ applicant ☐ applicant's representative]

Exhibit shown or demonstration conducted: ☒ Yes ☐ No.
If Yes, brief description: *TABLES RE: Listing of Clinical Trials*.

Issues Discussed ☐101 ☐112 ☒102 ☒103 ☐Others
(For each of the checked box(es) above, please describe below the issue and detailed description of the discussion)

Claim(s) discussed: *1*.

Identification of prior art discussed: _____.

Substance of Interview
(For each issue discussed, provide a detailed description and indicate if agreement was reached. Some topics may include: identification or clarification of a reference or a portion thereof, claim interpretation, proposed amendments, arguments of any applied references etc...)

In addition to the above named participants, Phil Gambel was present for the USPTO and Tara Rahemba, Todd Spalding, and Darrel Fontenot from Alexion were also present. All were present in-person except James Rogers, who joined by video conference.
A follow up to the interview was conducted on 5/5/2017. All of the same participants were present except for Phil Gambel.

The applicant and examiners discussed the Rule 37 CFR 1.105 Request for Additional Information contained in the last office action, and applicant's proposed response. The examiners stated that a rule 132 declaration would be helpful to place all of the documents into context.

The examiners also noted that while no 35 USC 102(a) is on record, the "known or used by others" provisions of 102(a) require public knowledge or use. Thus, if the examiners determine that there is no 102(b) use after consideration of applicant's proposed response, there will also be no 102(a) use.

Applicant recordation instructions: The formal written reply to the last Office action must include the substance of the interview. (See MPEP section 713.04). If a reply to the last Office action has already been filed, applicant is given a non-extendable period of the longer of one month or thirty days from this interview date, or the mailing date of this interview summary form, whichever is later, to file a statement of the substance of the interview

Examiner recordation instructions: Examiners must summarize the substance of any interview of record. A complete and proper recordation of the substance of an interview should include the items listed in MPEP 713.04 for complete and proper recordation including the identification of the general thrust of each argument or issue discussed, a general indication of any other pertinent matters discussed regarding patentability and the general results or outcome of the interview, to include an indication as to whether or not agreement was reached on the issues raised.

☐ Attachment

/JAMES ROGERS/ Examiner, Art Unit 1644	/DANIEL E. KOLKER/ Supervisory Patent Examiner, Art Unit 1644

Summary of Record of Interview Requirements

Manual of Patent Examining Procedure (MPEP), Section 713.04, Substance of Interview Must be Made of Record
A complete written statement as to the substance of any face-to-face, video conference, or telephone interview with regard to an application must be made of record in the application whether or not an agreement with the examiner was reached at the interview.

Title 37 Code of Federal Regulations (CFR) § 1.133 Interviews
Paragraph (b)

In every instance where reconsideration is requested in view of an interview with an examiner, a complete written statement of the reasons presented at the interview as warranting favorable action must be filed by the applicant. An interview does not remove the necessity for reply to Office action as specified in §§ 1.111, 1.135. (35 U.S.C. 132)

37 CFR §1.2 Business to be transacted in writing.
All business with the Patent or Trademark Office should be transacted in writing. The personal attendance of applicants or their attorneys or agents at the Patent and Trademark Office is unnecessary. The action of the Patent and Trademark Office will be based exclusively on the written record in the Office. No attention will be paid to any alleged oral promise, stipulation, or understanding in relation to which there is disagreement or doubt.

The action of the Patent and Trademark Office cannot be based exclusively on the written record in the Office if that record is itself incomplete through the failure to record the substance of interviews.

It is the responsibility of the applicant or the attorney or agent to make the substance of an interview of record in the application file, unless the examiner indicates he or she will do so. It is the examiner's responsibility to see that such a record is made and to correct material inaccuracies which bear directly on the question of patentability.

Examiners must complete an Interview Summary Form for each interview held where a matter of substance has been discussed during the interview by checking the appropriate boxes and filling in the blanks. Discussions regarding only procedural matters, directed solely to restriction requirements for which interview recordation is otherwise provided for in Section 812.01 of the Manual of Patent Examining Procedure, or pointing out typographical errors or unreadable script in Office actions or the like, are excluded from the interview recordation procedures below. Where the substance of an interview is completely recorded in an Examiners Amendment, no separate Interview Summary Record is required.

The Interview Summary Form shall be given an appropriate Paper No., placed in the right hand portion of the file, and listed on the "Contents" section of the file wrapper. In a personal interview, a duplicate of the Form is given to the applicant (or attorney or agent) at the conclusion of the interview. In the case of a telephone or video-conference interview, the copy is mailed to the applicant's correspondence address either with or prior to the next official communication. If additional correspondence from the examiner is not likely before an allowance or if other circumstances dictate, the Form should be mailed promptly after the interview rather than with the next official communication.

The Form provides for recordation of the following information:
- Application Number (Series Code and Serial Number)
- Name of applicant
- Name of examiner
- Date of interview
- Type of interview (telephonic, video-conference, or personal)
- Name of participant(s) (applicant, attorney or agent, examiner, other PTO personnel, etc.)
- An indication whether or not an exhibit was shown or a demonstration conducted
- An identification of the specific prior art discussed
- An indication whether an agreement was reached and if so, a description of the general nature of the agreement (may be by attachment of a copy of amendments or claims agreed as being allowable). Note: Agreement as to allowability is tentative and does not restrict further action by the examiner to the contrary.
- The signature of the examiner who conducted the interview (if Form is not an attachment to a signed Office action)

It is desirable that the examiner orally remind the applicant of his or her obligation to record the substance of the interview of each case. It should be noted, however, that the Interview Summary Form will not normally be considered a complete and proper recordation of the interview unless it includes, or is supplemented by the applicant or the examiner to include, all of the applicable items required below concerning the substance of the interview.

A complete and proper recordation of the substance of any interview should include at least the following applicable items:
1) A brief description of the nature of any exhibit shown or any demonstration conducted,
2) an identification of the claims discussed,
3) an identification of the specific prior art discussed,
4) an identification of the principal proposed amendments of a substantive nature discussed, unless these are already described on the Interview Summary Form completed by the Examiner,
5) a brief identification of the general thrust of the principal arguments presented to the examiner,
   (The identification of arguments need not be lengthy or elaborate. A verbatim or highly detailed description of the arguments is not required. The identification of the arguments is sufficient if the general nature or thrust of the principal arguments made to the examiner can be understood in the context of the application file. Of course, the applicant may desire to emphasize and fully describe those arguments which he or she feels were or might be persuasive to the examiner.)
6) a general indication of any other pertinent matters discussed, and
7) if appropriate, the general results or outcome of the interview unless already described in the Interview Summary Form completed by the examiner.

Examiners are expected to carefully review the applicant's record of the substance of an interview. If the record is not complete and accurate, the examiner will give the applicant an extendable one month time period to correct the record.

Examiner to Check for Accuracy

If the claims are allowable for other reasons of record, the examiner should send a letter setting forth the examiner's version of the statement attributed to him or her. If the record is complete and accurate, the examiner should place the indication, "Interview Record OK" on the paper recording the substance of the interview along with the date and the examiner's initials.

Samsung Bioepis Exhibit No. 1002
Page 10763

I hereby certify that this paper (along with any paper referred to as being attached or enclosed) is being transmitted via the Office electronic filing system in accordance with 37 CFR § 1.6(a)(4).

Dated: June 13, 2017
Electronic Signature for Jill Gorny Sloper, Esq.: /Jill Gorny Sloper, Esq./

Docket No.: AXJ-114BUSCN3
(PATENT)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of:
Leonard Bell *et al.*

Application No.: 15/260,888 Confirmation No.: 2558

Filed: September 9, 2016 Art Unit: 1644

For: TREATMENT OF PAROXYSMAL NOCTURNAL HEMOGLOBINURIA PATIENTS BY AN INHIBITOR OF COMPLEMENT

Examiner: J. L. Rogers

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

SUPPLEMENTAL INFORMATION DISCLOSURE STATEMENT (SIDS)

Dear Sir:

In compliance with 37 C.F.R. § 1.56, 1.97 and 1.98, the attention of the Patent and Trademark Office is hereby directed to the document listed on the attached PTO/SB/08. In accordance with 37 C.F.R. § 1.98(a)(2)(i)-(iv), Applicant has not included copies of U.S. patent publication.

It is respectfully requested that the document listed on the PTO/SB/08 be expressly considered by the Examiner during the prosecution of this application, and that the document be made of record therein and appear among the "References Cited" on any patent to issue therefrom.

Samsung Bioepis Exhibit No. 1002
Page 10764

Applicant provides herewith copies of Office Actions from Applications previously made of record:

Office Actions (copies enclosed)				
Examiner's Initials	Serial No.:	Date Mailed from USPTO	Examiner	Docket No.
	15/284,015	04-11-2017	J. Rogers	AXJ-114BUSCN4
	15/284,015	11-01-2016	J. Rogers	AXJ-114BUSCN4
	15/148,839	06-07-2017	J. Rogers	AXJ-114BUSCN2
	15/148,839	04-04-2017	J. Rogers	AXJ-114BUSCN2

The Examiner is requested to review the file histories of these applications, including cited references, Office Actions, Responses, etc., and is asked to contact Applicant's Attorney if the Examiner would like the Applicant to supply copies of any or all of the information included in these applications. If Applicant's Attorney is not contacted by the Examiner with such a request, then it will be concluded that the Examiner has reviewed or will review the file content of these applications.

Applicant respectfully requests that the Examiner initial the blank columns next to the cited Office Actions, to indicate that the information has been considered by the Examiner. Alternatively, Applicant requests that the Examiner insert the phrase, "All references considered except where lined through," on each page of the Information Disclosure Statement, along with the Examiner's initials.

The filing of this Information Disclosure Statement is not to be interpreted as a representation that the cited document is material, that an exhaustive search has been conducted, or that no other relevant information exists. Nor shall the citation of the document herein be construed *per se* as a representation that such document is prior art. Moreover, Applicant understands the Examiner will make an independent evaluation of the cited document.

This Information Disclosure Statement is filed after the mailing date of a first Office Action on the merits, but before the mailing date of any of a Final Action under 37 C.F.R.§ 1.113, a Notice

of Allowance under 37 C.F.R. § 1.311 or an action that otherwise closes prosecution in this application (37 C.F.R. § 1.97(c)).

Please charge our Deposit Account No. 12-0080 in the amount of $180.00 covering the fee set forth in 37 C.F.R. § 1.17(p). The Director is hereby authorized to charge any deficiency in the fees filed, asserted to be filed or which should have been filed herewith to our Deposit Account No. 12-0080, under Order No. AXJ-114BUSCN3.

Dated: June 13, 2017

Respectfully submitted,

Electronic signature: /Jill Gorny Sloper, Esq./
Jill Gorny Sloper, Esq.
Registration No.: 60,760
NELSON MULLINS RILEY & SCARBOROUGH LLP
One Post Office Square
Boston, Massachusetts 02109-2127
(617) 217-4630
(617) 742-4214 (Fax)
Attorney/Agent For Applicant

PTO/SB/08a (03-15)
Approved for use through 07/31/2016. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it contains a valid OMB control number.

INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Not for submission under 37 CFR 1.99)

Application Number	15260888
Filing Date	2016-09-09
First Named Inventor	Leonard BELL
Art Unit	1644
Examiner Name	J. L. Rogers
Attorney Docket Number	AXJ-114BUSCN3

U.S.PATENTS Remove

Examiner Initial*	Cite No	Patent Number	Kind Code[1]	Issue Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear
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Examiner Initial*	Cite No	Publication Number	Kind Code[1]	Publication Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear
	1	20170015741	A1	2017-01-19	Leonard BELL	

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Examiner Initial*	Cite No	Foreign Document Number[3]	Country Code[2] i	Kind Code[4]	Publication Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear	T[5]
	1							

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NON-PATENT LITERATURE DOCUMENTS Remove

Examiner Initials*	Cite No	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc), date, pages(s), volume-issue number(s), publisher, city and/or country where published.	T[5]

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
	Application Number	15260888
	Filing Date	2016-09-09
	First Named Inventor	Leonard BELL
	Art Unit	1644
	Examiner Name	J. L. Rogers
	Attorney Docket Number	AXJ-114BUSCN3

	1		

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EXAMINER SIGNATURE

Examiner Signature		Date Considered	

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through a citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

[1] See Kind Codes of USPTO Patent Documents at www.USPTO.GOV or MPEP 901.04. [2] Enter office that issued the document, by the two-letter code (WIPO Standard ST.3). [3] For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. [4] Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16 if possible. [5] Applicant is to place a check mark here if English language translation is attached.

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
	Application Number	15260888
	Filing Date	2016-09-09
	First Named Inventor	Leonard BELL
	Art Unit	1644
	Examiner Name	J. L. Rogers
	Attorney Docket Number	AXJ-114BUSCN3

CERTIFICATION STATEMENT

Please see 37 CFR 1.97 and 1.98 to make the appropriate selection(s):

That each item of information contained in the information disclosure statement was first cited in any communication from a foreign patent office in a counterpart foreign application not more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(1).

OR

☐ That no item of information contained in the information disclosure statement was cited in a communication from a foreign patent office in a counterpart foreign application, and, to the knowledge of the person signing the certification after making reasonable inquiry, no item of information contained in the information disclosure statement was known to any individual designated in 37 CFR 1.56(c) more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(2).

See attached certification statement.

☒ The fee set forth in 37 CFR 1.17 (p) has been submitted herewith.

☒ A certification statement is not submitted herewith.

SIGNATURE

A signature of the applicant or representative is required in accordance with CFR 1.33, 10.18. Please see CFR 1.4(d) for the form of the signature.

Signature	/Jill Gorny Sloper, Esq./	Date (YYYY-MM-DD)	2017-06-13
Name/Print	Jill Gorny Sloper, Esq.	Registration Number	60,760

This collection of information is required by 37 CFR 1.97 and 1.98. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 1 hour to complete, including gathering, preparing and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

Privacy Act Statement

The Privacy Act of 1974 (P.L. 93-579) requires that you be given certain information in connection with your submission of the attached form related to a patent application or patent. Accordingly, pursuant to the requirements of the Act, please be advised that: (1) the general authority for the collection of this information is 35 U.S.C. 2(b)(2); (2) furnishing of the information solicited is voluntary; and (3) the principal purpose for which the information is used by the U.S. Patent and Trademark Office is to process and/or examine your submission related to a patent application or patent. If you do not furnish the requested information, the U.S. Patent and Trademark Office may not be able to process and/or examine your submission, which may result in termination of proceedings or abandonment of the application or expiration of the patent.

The information provided by you in this form will be subject to the following routine uses:

1. The information on this form will be treated confidentially to the extent allowed under the Freedom of Information Act (5 U.S.C. 552) and the Privacy Act (5 U.S.C. 552a). Records from this system of records may be disclosed to the Department of Justice to determine whether the Freedom of Information Act requires disclosure of these record s.

2. A record from this system of records may be disclosed, as a routine use, in the course of presenting evidence to a court, magistrate, or administrative tribunal, including disclosures to opposing counsel in the course of settlement negotiations.

3. A record in this system of records may be disclosed, as a routine use, to a Member of Congress submitting a request involving an individual, to whom the record pertains, when the individual has requested assistance from the Member with respect to the subject matter of the record.

4. A record in this system of records may be disclosed, as a routine use, to a contractor of the Agency having need for the information in order to perform a contract. Recipients of information shall be required to comply with the requirements of the Privacy Act of 1974, as amended, pursuant to 5 U.S.C. 552a(m).

5. A record related to an International Application filed under the Patent Cooperation Treaty in this system of records may be disclosed, as a routine use, to the International Bureau of the World Intellectual Property Organization, pursuant to the Patent Cooperation Treaty.

6. A record in this system of records may be disclosed, as a routine use, to another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c)).

7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (i.e., GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.

8. A record from this system of records may be disclosed, as a routine use, to the public after either publication of the application pursuant to 35 U.S.C. 122(b) or issuance of a patent pursuant to 35 U.S.C. 151. Further, a record may be disclosed, subject to the limitations of 37 CFR 1.14, as a routine use, to the public if the record was filed in an application which became abandoned or in which the proceedings were terminated and which application is referenced by either a published application, an application open to public inspections or an issued patent.

9. A record from this system of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.

Electronic Patent Application Fee Transmittal

Application Number:	15260888
Filing Date:	09-Sep-2016
Title of Invention:	TREATMENT OF PAROXYSMAL NOCTURNAL HEMOGLOBINURIA PATIENTS BY AN INHIBITOR OF COMPLEMENT
First Named Inventor/Applicant Name:	Leonard BELL
Filer:	Jill R. Gorny Sloper/Anita Costa
Attorney Docket Number:	AXJ-114BUSCN3

Filed as Large Entity

Filing Fees for Utility under 35 USC 111(a)

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Basic Filing:				
Pages:				
Claims:				
Miscellaneous-Filing:				
Petition:				
Patent-Appeals-and-Interference:				
Post-Allowance-and-Post-Issuance:				
Extension-of-Time:				

Samsung Bioepis Exhibit No. 1002
Page 10771

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Miscellaneous:				
Submission- Information Disclosure Stmt	1806	1	180	180
		Total in USD ($)		**180**

Samsung Bioepis Exhibit No. 1002
Page 10772

Electronic Acknowledgement Receipt

EFS ID:	29476501
Application Number:	15260888
International Application Number:	
Confirmation Number:	2558
Title of Invention:	TREATMENT OF PAROXYSMAL NOCTURNAL HEMOGLOBINURIA PATIENTS BY AN INHIBITOR OF COMPLEMENT
First Named Inventor/Applicant Name:	Leonard BELL
Customer Number:	133485
Filer:	Jill R. Gorny Sloper/Danielle Gamache
Filer Authorized By:	Jill R. Gorny Sloper
Attorney Docket Number:	AXJ-114BUSCN3
Receipt Date:	13-JUN-2017
Filing Date:	09-SEP-2016
Time Stamp:	17:42:41
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	no

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Information Disclosure Statement (IDS) Form (SB08)	IDSTRANS.pdf	29075 07a258fdb5618973ece4ec5c9bafd536d905cd20	no	3

Warnings:

Samsung Bioepis Exhibit No. 1002
Page 10773

Information:					
This is not an USPTO supplied IDS fillable form					
2	Other Reference-Patent/App/Search documents	15148839.pdf	1283152 4a25e8cac05a74d368ecb24df8b848247d44656b	no	22
Warnings:					
Information:					
3	Other Reference-Patent/App/Search documents	15284015.pdf	833952 89bd33145425f7db20114be5364e3bae63a465d5	no	17
Warnings:					
Information:					
4	Information Disclosure Statement (IDS) Form (SB08)	SB08.pdf	1072692 bc1f71ac4c98cbec244977b995b1a055a21c9990	no	4
Warnings:					
Information:					
5	Fee Worksheet (SB06)	fee-info.pdf	30872 fc5d396415088b3f2e3f90e4d6bfa36cd7c54445	no	2
Warnings:					
Information:					
		Total Files Size (in bytes):	3249743		

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111

If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371

If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office

If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

Samsung Bioepis Exhibit No. 1002
Page 10774

I hereby certify that this paper (along with any paper referred to as being attached or enclosed) is being transmitted via the Office electronic filing system in accordance with 37 CFR § 1.6(a)(4).

Dated: June 13, 2017
Electronic Signature for Jill Gorny Sloper, Esq.: /Jill Gorny Sloper, Esq./

Docket No.: AXJ-114BUSCN3
(PATENT)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of:
Leonard Bell *et al.*

Application No.: 15/260,888 Confirmation No.: 2558

Filed: September 9, 2016 Art Unit: 1644

For: TREATMENT OF PAROXYSMAL NOCTURNAL HEMOGLOBINURIA PATIENTS BY AN INHIBITOR OF COMPLEMENT

Examiner: J. L. Rogers

MS Amendment
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

AMENDMENT IN RESPONSE TO NON-FINAL OFFICE ACTION UNDER 37 C.F.R. § 1.111

Dear Sir:

In response to the Office Action dated April 11, 2017 (Paper No. 20170227), please amend the above-identified U.S. patent application as follows:

A Listing of the Claims begins on page 2 of this paper.

Remarks/Arguments begin on page 4 of this paper.

Samsung Bioepis Exhibit No. 1002
Page 10775

LISTING OF THE CLAIMS

1. **(Original)** A method of treating a patient suffering from paroxysmal nocturnal hemoglobinuria (PNH) comprising administering to the patient a pharmaceutical composition comprising an antibody that binds C5, wherein the antibody comprises a heavy chain consisting of SEQ ID NO: 2 and a light chain consisting of SEQ ID NO: 4.

2. **(Original)** The method of claim 1, wherein the pharmaceutical composition is administered by intravenous infusion.

3. **(Original)** The method of claim 1, wherein the antibody is administered to the patient at a dosage level of between 5 mg per kg and 50 mg per kg per patient per treatment.

4. **(Original)** The method of claim 1, wherein the pharmaceutical composition is in a single unit dosage form.

5. **(Original)** The method of claim 4, wherein the single unit dosage form is a 300 mg single unit dosage form.

6. **(Original)** The method of claim 1, wherein the pharmaceutical composition comprises a 300 mg single-use formulation of 30 ml of a 10 mg/ml sterile, preservative free solution.

7. **(Original)** The method of claim 1, wherein the patient is anemic.

8. **(Original)** The method of claim 1, wherein the patient is dosed as follows: 600 mg of the antibody via intravenous infusion every 7±1 days for 4 doses; followed by 900 mg of the antibody via intravenous infusion 7±1 days later; followed by a maintenance dose of 900 mg of the antibody via intravenous infusion every 14±2 days.

9. **(Original)** The method of claim 1, wherein administration of the antibody results in an immediate and sustained decrease in mean levels of lactate dehydrogenase (LDH).

10. **(Original)** The method of claim 9, wherein the immediate decrease occurs within one week of administration of the antibody.

REMARKS

Claims 1-10 are pending.

Interview Summary

Applicants thank the Examiner and his Supervisor for the interview held on May 1, 2017 and follow-up discussion on May 5, 2017, during which the outstanding rejections and related Rule 37 C.F.R. § 1.105 Request for Additional Information in the above-referenced application were discussed. The substance of the interview and follow-up discussion is reflected in the following remarks.

Moreover, as confirmed in the Interview Summary dated May 11, 2017, if the Examiners determine after consideration of the present response and accompanying Declaration (submitted for related Application No. 15/148,839) that there was no 35 U.S.C. § 102(b) "public use" of the claimed invention, then there also was no 35 U.S.C. § 102(a) "knowledge or use" of the claimed invention.

Information Disclosure Statement

Applicants submit herewith a Supplemental Information Disclosure Statement to make of record additional information for the Examiner's consideration.

Rejection of Claims 1-2 and 7-10 Under 35 U.S.C. § 102(b)

The Examiner has rejected claims 1-2 and 7-10 as allegedly being anticipated by Hillmen *et al.* (*N. Engl. J. Med.* 2004; 350; 552-9), as evidenced by Applicants' specification as filed at page 44 and Thomas *et al.* (*Molecular Immunology*, 33 (17/18), pp. 1389-1401, 1996). The Examiner relies on Hillmen *et al.* for teaching a method for treating a human patient that suffers from PNH by administering to the patient an effective amount of eculizumab. The Examiner relies on Applicants' specification at page 44 for disclosing that SEQ ID NOs: 2 and 4 constitute the heavy and light chains of eculizumab. The Examiner relies on Thomas *et al.* for teaching the humanized h5G1.1 antibody, which retains the affinity and blocking functions of its murine counterpart.

The Examiner acknowledges that none of the cited references specifically teaches that eculizumab comprises heavy and light chains consisting of the amino acid sequences set forth in SEQ ID NO:2 and SEQ ID NO:4, respectively. However, the Examiner is of the opinion that, absent evidence to the contrary, these heavy and light chain sequences are "inherent properties" of eculizumab.

Applicants respectfully traverse the rejection. As explained in the Office Action on pages 4-5, the premise of the Examiner's inherency rejection is that eculizumab (and thus, its full length sequence) "was effectively in the public domain", as evidenced by Exhibit A (studies 41-60 from clinicaltrials.gov), Exhibit B (clinicaltrials.gov from 6/23/2005 for NCT00098280), Exhibit C (printout for NCT00005571), Exhibit D (Kaplan 2002), Exhibit E (Appel *et al.* 2006), Exhibit F (Wang, US20050271660), Exhibit G (Rother, WO 2005/110481), and Exhibit H (Rother, US 2009/0028850). However, this is incorrect. Neither eculizumab nor its complete sequence, including the sequence of its unique, non-naturally occurring, protein-engineered heavy chain, was in the public domain prior to the March 15, 2007 effective filing date of the present application, as discussed in detail below. Accordingly, the presently claimed method of treating a patient suffering from paroxysmal nocturnal hemoglobinuria (PNH) comprising administering to the patient a pharmaceutical composition comprising eculizumab (and the specific sequences thereof) was also not in the public domain prior to that time.

A. Exhibits A-C: Clinical Trials

With respect to the clinical trials cited by the Examiner in Appendices A-C, these clinical trials did not constitute "public use" of eculizumab under pre-AIA 35 U.S.C. § 102(b), as they were controlled, restricted, and subject to strict confidentiality obligations. As discussed below in response to the Request for Additional Information under 37 C.F.R. § 1.105, Applicants provide a copy of the (1) Amendment and Response and (2) Declaration Pursuant to 37 C.F.R. § 1.132 by Dr. Laural Boone that were submitted in related U.S. Patent Application No: 15/148,839 ("the '839 application") on May 12, 2017. Specifically, as discussed in the enclosed Declaration Pursuant to 37 C.F.R. § 1.132 by Dr. Laural Boone, the cited clinical trials using eculizumab were strictly controlled and governed by clinical trial protocols which included explicit confidentiality

requirements. The Federal Circuit has clearly held that clinical trials performed under such confidentiality and restrictions do not constitute "public use" within the meaning of 35 U.S.C. § 102(b). In *Dey, L.P. v. Sunovion Pharmaceuticals, Inc.* (No. 2012-1428, Fed. Cir. May 20, 2013) the Federal Circuit considered whether a clinical trial constitutes an invalidating "public use" under 35 U.S.C. § 102(b). Sunovion, the accused infringer, asserted that its own clinical trial was an invalidating public use against Dey's patents, because they involved the accused formulation and took place before Dey's 102(b) critical date. The Federal Circuit concluded that the trial was not an invalidating public use of the study medication based on the following factors: the nature of the activity that occurred in public; the public access to and knowledge of the public use; and whether there was any confidentiality obligation imposed on persons who observed the use (citing *Bernhardt, L.L.C. v. Collezione Europa USA, Inc.*, 386 F.3d 1371, 1379 (Fed. Cir. 2004)). Applying this standard, the Federal Circuit reversed the district court's grant of summary judgment to Sunovion because the clinical trial's restrictions, instructions, and records requirements supported a conclusion ***that the trial was sufficiently controlled and restricted and therefore, not an invalidating public use***. In addition, the Court noted that the ***investigators (i.e., "the most knowledgeable persons involved in the study") were under express confidentiality restrictions, and neither the patients nor the doctors were aware of the claimed particulars of Sunovion's formulation*** (page 10 of *Dey*). Specifically, "while it is true that participants were permitted to discuss the study with their doctors, ***they were not in a position to reveal the composition…because they were unaware of the specifics of the inventive formulations***" (page 10 of *Dey*). As argued by Dey and agreed by the Court, "***if members of the public are not informed of, and cannot readily discern, the claimed features of the invention in the allegedly invalidating prior art, the public has not been put in possession of those features***."

Similar to the facts in *Dey*, the trials cited in Exhibits A-C on page 4 of the Office Action were tightly controlled, restricted and governed by express confidentiality provisions, as discussed in detail in the enclosed Declaration Pursuant to 37 C.F.R. § 1.132 by Dr. Laural Boone. Moreover, similar to the facts in *Dey*, the clinical trial protocols did not contain the specifics of the claimed invention or allow the participants to readily discern the features of the presently claimed invention, including the sequence of the antibody being administered, *i.e.*, eculizumab. Thus, in accordance

Samsung Bioepis Exhibit No. 1002
Page 10780

with *Dey*, the cited clinical trials did not constitute "public use" of eculizumab under pre-AIA 35 U.S.C. § 102(b).

B. Exhibits D-H: Publications

With respect to the publications cited in Exhibit D (Kaplan 2002), Exhibit E (Appel *et al.* 2006), Exhibit F (Wang, US20050271660), Exhibit G (Rother, WO 2005/110481), and Exhibit H (Rother, US 2009/0028850), the Examiner is of the opinion that these publications demonstrate that "eculizumab was effectively in the public domain" prior to the effective filing date of the present application. In support of this assertion, the Examiner cites *In re Antor Media Corp* (CAFC, 2012) for the proposition that "the subject matter disclosed in a reference, whether it is a ***patent claim***, ***other parts of a patent***, or non-patent literature, is presumed to be enabling absent evidence to the contrary (emphasis added)."

Applicants respectfully disagree with the Examiner's position. From the outset, as noted by the Court in *In re Antor Media Corp*, the question of enablement only arises if the cited reference in fact teaches each and every element of the claimed invention (page 9 of *In re Antor Media Corp*). In the present case, none of the publications cited in Exhibits D-H teach the complete structure of eculizumab, as presently claimed, including its complete sequence with a unique, non-naturally occurring, protein-engineered heavy chain. Nor do these references enable the presently claimed full biochemical structure of eculizumab, for the reasons discussed above. Exhibit D (Kaplan 2002) describes clinical studies that used eculizumab. Exhibit E (Appel *et al.* 2006) merely discloses that eculizumab is a humanized monoclonal antibody that prevents the activation of complement component C5. Exhibit F (Wang, US20050271660) discloses antibody formulations suitable for nebulization using murine antibodies in the examples. Exhibit G (Rother, WO 2005/110481) and Exhibit H (Rother, US 2009/0028850, which was not published until after March 16, 2007) disclose the use of eculizumab for treating PNH patients, as well as the use of the mouse anti-C5 antibody BB5.1 in prolonging the survival of an allograft. Importantly, none of the cited references teach the sequence of eculizumab, let alone its unique, non-naturally occurring, protein-engineered full heavy chain (including the CH1-hinge-CH2-CH3 regions).

As discussed above, to anticipate a claimed invention, a reference must provide an enabling disclosure of the desired subject matter. Specifically, pursuant to M.P.E.P § 2121.1, "***mere naming or description of the subject matter is insufficient,*** if it cannot be produced without undue experimentation. *Elan Pharm., Inc. v. Mayo Found. For Med. Educ. & Research,* 346 F.3d 1051, 1054, 68 USPQ2d 1373, 1376 (Fed. Cir. 2003) (emphasis added)." Further, a "reference contains an 'enabling disclosure' if the public was in possession of the claimed invention before the date of invention." Such "***possession is effected if one of ordinary skill in the art could have combined the publication's description of the invention with his [or her] own knowledge to make the claimed invention***. *In re Donohue,* 766 F.2d 531, 226 USPQ 619 (Fed. Cir. 1985) (emphasis added)."

It is clear that the public was not in possession of the claimed sequences of eculizumab prior to the effective filing date of the present application by virtue of the cited publications, because the ***mere naming of eculizumab is insufficient to enable*** the claimed sequences and ***one of ordinary skill in the art could <u>not</u> have readily determined the sequences based on the limited disclosure in the publications and his or her own general knowledge***.

C. <u>Conclusion</u>

In sum, <u>none</u> of the cited references teach or enable the complete sequence of eculizumab, as presently claimed. Moreover, eculizumab was not in "public use" under 35 U.S.C. § 102(b) prior to the March 15, 2007 effective filing date of the present application, at least because the clinical trials cited by the Examiner were tightly controlled, restricted, governed by confidentiality obligations, and conducted according to protocols that did not disclose the claimed features of the invention (see *Dey, L.P. v. Sunovion Pharmaceuticals, Inc.*). Accordingly, it is clear that the public was not in possession of the claimed sequences of eculizumab prior to the effective filing date of the present application, and for at least this reason, the Examiner is respectfully requested to reconsider and withdraw the rejection.

<u>Rejection Under 35 U.S.C. § 103</u>

Claims 1-10 are rejected under 35 U.S.C. § 103 as being unpatentable over Hillmen *et al.* (*N. Engl. J. Med.* 2004; 350:552-9), in view of Thomas *et al.* (Molecular Immunology, 33(17/18), pp.

1389-1401, 1996) and Evans *et al.* (US 6,355,245) and further in view of Wang (US 2005/0271660).

Applicants respectfully traverse the rejection. As discussed above, neither eculizumab nor its complete sequence were available to the public or in "public use" prior to the March 15, 2007 effective filing date of the present application. Therefore, the Examiner's underlying premise supporting the present obviousness rejection (*i.e.*, that eculizumab was publicly known or used prior to March 15, 2007) is factually incorrect. Moreover, none of Hillmen *et al.*, Thomas *et al.*, Evans *et al.* or Wang teach or suggest the complete sequence of eculizumab. Thus, the Examiner has failed to establish a prima facie case of obviousness.

Accordingly, for at the least the above-discussed reasons, the pending claims are patentable and the Examiner is respectfully requested to reconsider and withdraw this rejection.

Obviousness-Type Double Patenting

The Examiner has rejected claims 1-10 on the ground of non-statutory obviousness-type double patenting as being unpatentable over:

1. Claims 1-19 of US Patent No: 9,494,601 in view of Hillmen *et al.*, Thomas *et al.*, Evans *et al.*, and Wang;
2. Claims 1-17 of US Patent No: 9,409,980 in view of Hillmen *et al.*, Thomas *et al.*, Evans *et al.*, and Wang;
3. Claims 1-14 of US Patent No: 9,556,263 in view of Hillmen *et al.*, Thomas *et al.*, Evans *et al.*, and Wang.

While in no way acquiescing to the rejection, Applicants respectfully submit herewith a terminal disclaimer over US Patent No: 9,494,601, US Patent No: 9,409,980, and US Patent No: 9,556,263, thereby obviating the rejection. Accordingly, Applicants respectfully request that the Examiner reconsider and withdraw the rejection.

Response to Request for Additional Information Under 37 C.F.R. § 1.105

In response to the Examiner's specific inquiries and request for additional information under 37 C.F.R. § 1.105 (Rule 105 Request), Applicants provide a copy of the (1) Amendment and Response and (2) Declaration Pursuant to 37 C.F.R. § 1.132 by Dr. Laural Boone that were submitted in related U.S. Patent Application No: 15/148,839 ("the '839 application") on May 12, 2017.

The interrogatories set forth in the Rule 105 Request for the present case consist of a subset of the interrogatories set forth in the Rule 105 Request issued in the '839 application (as part of the Office Action dated April 4, 2017 ("'839 Office Action"))). Specifically, the interrogatories and corresponding Exhibits in the present case are identical to those raised in the '839 application, except that Exhibits C and F from the '839 Office Action (and the corresponding interrogatories) were not included in the Rule 105 Request for the present case.

Accordingly, in response to the Rule 105 Interrogatories (A-E) for the present case, Applicants refer the Examiner to Applicants' response to the identical Interrogatories (i.e., A, B, D, E and G) for the '839 application, provided in the enclosed Amendment and Response and Declaration submitted in the '839 application dated May 12, 2017.

CONCLUSION

If a telephone conversation with Applicants' attorney would help expedite the prosecution of the above-identified application, the Examiner is urged to call Applicants' attorney at (617) 217-4630. The Director is hereby authorized to charge any deficiency in the fees filed, asserted to be filed or which should have been filed herewith (or with any paper hereafter filed in this application by this firm) to our Deposit Account No. 12-0080, under Order No. AXJ-114BUSCN3.

Dated: June 13, 2017

Respectfully submitted,

Electronic signature: /Jill Gorny Sloper, Esq./
Jill Gorny Sloper, Esq.
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One Post Office Square
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Attorney/Agent For Applicants

Copy of Amendment and Response and

Declaration Pursuant to 37 C.F.R. § 1.132 by Dr. Laural Boone,

Filed on May 12, 2017 in U.S. Patent Application No: 15/148,839

Samsung Bioepis Exhibit No. 1002
Page 10786

I hereby certify that this paper (along with any paper referred to as being attached or enclosed) is being transmitted via the Office electronic filing system in accordance with 37 CFR § 1.6(a)(4).

Dated: May 12, 2017
Electronic Signature for Jill Gorny Sloper, Esq.: /Jill Gorny Sloper, Esq./

Docket No.: AXJ-114BUSCN2
(PATENT)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of:
Leonard Bell *et al.*

Application No.: 15/148,839 Confirmation No.: 3159

Filed: May 6, 2016 Art Unit: 1644

For: TREATMENT OF PAROXYSMAL NOCTURNAL HEMOGLOBINURIA PATIENTS BY AN INHIBITOR OF COMPLEMENT

Examiner: J. L. Rogers

MS Amendment
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

RESPONSE TO NON-FINAL OFFICE ACTION UNDER 37 C.F.R. § 1.111

Dear Sir:

In response to the Office Action dated April 4, 2017 (Paper No. 20170227), please amend the above-identified U.S. patent application as follows:

A Listing of the Claims begins on page 2 of this paper.

Remarks/Arguments begin on page 3 of this paper.

Samsung Bioepis Exhibit No. 1002
Page 10787

LISTING OF THE CLAIMS

1. **(Previously Presented)** A pharmaceutical composition for use in treating a patient afflicted with paroxysmal nocturnal hemoglobinuria (PNH), wherein the composition is a sterile, preservative free, 300 mg single-use dosage form comprising 30 ml of a 10 mg/ml antibody solution, wherein the antibody comprises a heavy chain consisting of SEQ ID NO: 2 and a light chain consisting of SEQ ID NO: 4.

2. **(Previously Presented)** A pharmaceutical composition comprising an anti-C5 antibody, wherein the anti-C5 antibody comprises a heavy chain consisting of SEQ ID NO: 2 and a light chain consisting of SEQ ID NO: 4.

3. **(Previously Presented)** The pharmaceutical composition of claim 2, wherein the pharmaceutical composition is a sterile, preservative free 300 mg single-use dosage form comprising 30 ml of a 10 mg/ml anti-C5 antibody solution.

Samsung Bioepis Exhibit No. 1002
Page 10788

REMARKS

Claims 1-3 are pending.

Interview Summary

Applicants thank the Examiner and his Supervisor for the interview held on May 1, 2017 and follow-up discussion on May 5, 2017, during which the outstanding rejections and related Rule 37 C.F.R. § 1.105 Request for Additional Information in the above-referenced application were discussed. The substance of the interview and follow-up discussion is reflected in the following remarks.

Moreover, as confirmed in the Interview Summary dated May 11, 2017, if the Examiners determine after consideration of the present response and accompanying Declaration that there was no 35 U.S.C. § 102(b) "public use" of the claimed invention, then there also was no 35 U.S.C. § 102(a) "knowledge or use" of the claimed invention.

Information Disclosure Statement

Applicants acknowledge with appreciation that the Information Disclosure Statements filed on May 6, 2016 and February 15, 2017 have been considered by the Examiner. Additionally, Applicants submit herewith a further Supplemental Information Disclosure Statement to make of record additional information for the Examiner's consideration.

Rejection of Claim 2 Under 35 U.S.C. § 102(b)

The Examiner has rejected claim 2 as allegedly being anticipated by the following references, which the Examiner has characterized as follows:

Cited Reference	Examiner's Characterization
Hillmen *et al.* (*N. Engl. J. Med.* 2004; 350; 552-9), as evidenced by Applicant's specification as filed at page 44 and Thomas *et al.* (*Molecular Immunology*, 33 (17/18), pp. 1389-1401, 1996)	Hillmen *et al.* teaches a method for treating a human patient that suffers from PNH by administering to the patient an effective amount of eculizumab. Applicant's specification at page 44 discloses that SEQ ID NOs: 2 and 4 constitute the heavy and light chains of eculizumab. Thomas *et al.* teach the humanized h5G1.1 antibody, which retains the affinity and blocking functions of its murine counterpart.

Samsung Bioepis Exhibit No. 1002
Page 10789

Appel *et al*. (*Kidney International*, 70, S45-S50, 2006)	Appel *et al*. teaches that eculizumab is a humanized monoclonal antibody that prevents the activation of complement component C5.
Wang (US2005/0271660)	Wang teaches that eculizumab inhibits activity of the complement system.

The Examiner acknowledges that none of the cited references specifically teaches that eculizumab comprises heavy and light chains consisting of the amino acid sequences set forth SEQ ID NO:2 and SEQ ID NO:4, respectively. However, the Examiner is of the opinion that, absent evidence to the contrary, these heavy and light chain sequences are "inherent properties" of eculizumab.

Applicants respectfully traverse the rejection. As explained in the April 4, 2017 Office Action on pages 3-4, the premise of the Examiner's inherency rejection is that eculizumab (and thus, its full length sequence) "was effectively in the public domain", as evidenced by Exhibit A (studies 41-60 from clinicaltrials.gov), Exhibit B (printout for NCT00005571), Exhibit C (clinicaltrials.gov from 6/23/2005 for NCT00098280), Exhibit D (Kaplan 2002), Exhibit E (Appel *et al.* 2006), Exhibit F (Wang, US20050271660), Exhibit G (Rother, WO 2005/110481), and Exhibit H (Rother, US 2009/0028850). However, this is incorrect. Neither eculizumab nor its complete sequence, including the sequence of its unique, non-naturally occurring, protein-engineered heavy chain, was in the public domain prior to the March 15, 2007 effective filing date of the present application, as discussed in detail below. Accordingly, the presently claimed pharmaceutical composition comprising eculizumab (and the specific sequences thereof) was also not in the public domain prior to that time.

A. Exhibits A-C: Clinical Trials

With respect to the clinical trials cited by the Examiner in Appendices A-C, these clinical trials did not constitute "public use" of eculizumab under pre-AIA 35 U.S.C. § 102(b), as they were controlled, restricted, and subject to strict confidentiality obligations. Specifically, as discussed in the enclosed Declaration Pursuant to 37 C.F.R. § 1.132 by Dr. Laural Boone, the cited clinical trials using eculizumab were strictly controlled and governed by clinical trial protocols which included explicit confidentiality requirements. The Federal Circuit has clearly held that clinical trials performed under such confidentiality and restrictions do not constitute

"public use" within the meaning of 35 U.S.C. § 102(b). In *Dey, L.P. v. Sunovion Pharmaceuticals, Inc.* (No. 2012-1428, Fed. Cir. May 20, 2013) the Federal Circuit considered whether a clinical trial constitutes an invalidating "public use" under 35 U.S.C. § 102(b). Sunovion, the accused infringer, asserted that its own clinical trial was an invalidating public use against Dey's patents, because they involved the accused formulation and took place before Dey's 102(b) critical date. The Federal Circuit concluded that the trial was not an invalidating public use of the study medication based on the following factors: the nature of the activity that occurred in public; the public access to and knowledge of the public use; and whether there was any confidentiality obligation imposed on persons who observed the use (citing *Bernhardt, L.L.C. v. Collezione Europa USA, Inc.*, 386 F.3d 1371, 1379 (Fed. Cir. 2004)). Applying this standard, the Federal Circuit reversed the district court's grant of summary judgment to Sunovion because the clinical trial's restrictions, instructions, and records requirements supported a conclusion ***that the trial was sufficiently controlled and restricted and therefore, not an invalidating public use***. In addition, the Court noted that the ***investigators (i.e., "the most knowledgeable persons involved in the study") were under express confidentiality restrictions, and neither the patients nor the doctors were aware of the claimed particulars of Sunovion's formulation*** (page 10 of *Dey*). Specifically, "while it is true that participants were permitted to discuss the study with their doctors, ***they were not in a position to reveal the composition…because they were unaware of the specifics of the inventive formulations***" (page 10 of *Dey*). As argued by Dey and agreed by the Court, "***if members of the public are not informed of, and cannot readily discern, the claimed features of the invention in the allegedly invalidating prior art, the public has not been put in possession of those features***."

Similar to the facts in *Dey*, the trials cited in Exhibits A-C on page 3 of the Office Action were tightly controlled, restricted and governed by express confidentiality provisions, as discussed in detail in the enclosed Declaration Pursuant to 37 C.F.R. § 1.132 by Dr. Laural Boone. Moreover, similar to the facts in *Dey*, the clinical trial protocols did not contain the specifics of the claimed invention or allow the participants to readily discern the features of the presently claimed invention, including the sequence of the antibody being administered, *i.e.*, eculizumab. Thus, in accordance with *Dey*, the cited clinical trials did not constitute "public use" of eculizumab under pre-AIA 35 U.S.C. § 102(b).

B. Exhibits D-H: Publications

With respect to the publications cited in Exhibit D (Kaplan 2002), Exhibit E (Appel *et al.* 2006), Exhibit F (Wang, US20050271660), Exhibit G (Rother, WO 2005/110481), and Exhibit H (Rother, US 2009/0028850), the Examiner is of the opinion that these publications demonstrate that "eculizumab was effectively in the public domain" prior to the effective filing date of the present application. In support of this assertion, the Examiner cites *In re Antor Media Corp* (CAFC, 2012) for the proposition that "the subject matter disclosed in a reference, whether it is a ***patent claim***, ***other parts of a patent***, or non-patent literature, is presumed to be enabling absent evidence to the contrary (emphasis added)."

Applicants respectfully disagree with the Examiner's position. From the outset, as noted by the Court in *In re Antor Media Corp*, the question of enablement only arises if the cited reference in fact teaches each and every element of the claimed invention (page 9 of *In re Antor Media Corp*). In the present case, none of the publications cited in Exhibits D-H teach the complete structure of eculizumab, as presently claimed, including its complete sequence with a unique, non-naturally occurring, protein-engineered heavy chain. Nor do these references enable the presently claimed full biochemical structure of eculizumab, for the reasons discussed above. Exhibit D (Kaplan 2002) describes clinical studies that used eculizumab. Exhibit E (Appel *et al.* 2006) merely discloses that eculizumab is a humanized monoclonal antibody that prevents the activation of complement component C5. Exhibit F (Wang, US20050271660) discloses antibody formulations suitable for nebulization using murine antibodies in the examples. Exhibit G (Rother, WO 2005/110481) and Exhibit H (Rother, US 2009/0028850, which was not published until after March 16, 2007) disclose the use of eculizumab for treating PNH patients, as well as the use of the mouse anti-C5 antibody BB5.1 in prolonging the survival of an allograft. Importantly, none of the cited references teach the sequence of eculizumab, let alone its unique, non-naturally occurring, protein-engineered full heavy chain (including the CH1-hinge-CH2-CH3 regions).

As discussed above, to anticipate a claimed invention, a reference must provide an enabling disclosure of the desired subject matter. Specifically, pursuant to M.P.E.P § 2121.1, "***mere naming or description of the subject matter is insufficient,*** if it cannot be produced without undue experimentation. *Elan Pharm., Inc. v. Mayo Found. For Med. Educ. & Research,*

346 F.3d 1051, 1054, 68 USPQ2d 1373, 1376 (Fed. Cir. 2003) (emphasis added)." Further, a "reference contains an 'enabling disclosure' if the public was in possession of the claimed invention before the date of invention." Such "***possession is effected if one of ordinary skill in the art could have combined the publication's description of the invention with his [or her] own knowledge to make the claimed invention***. *In re Donohue,* 766 F.2d 531, 226 USPQ 619 (Fed. Cir. 1985) (emphasis added)."

It is clear that the public was not in possession of the claimed sequences of eculizumab prior to the effective filing date of the present application by virtue of the cited publications, because the ***mere naming of eculizumab is insufficient to enable*** the claimed sequences and ***one of ordinary skill in the art could not have readily determined the sequences based on the limited disclosure in the publications and his or her own general knowledge***.

C. Conclusion

In sum, none of the cited references teach or enable the complete sequence of eculizumab, as presently claimed. Moreover, eculizumab was not in "public use" under 35 U.S.C. § 102(b) prior to the March 15, 2007 effective filing date of the present application, at least because the clinical trials cited by the Examiner were tightly controlled, restricted, governed by confidentiality obligations, and conducted according to protocols that did not disclose the claimed features of the invention (see *Dey, L.P. v. Sunovion Pharmaceuticals, Inc.*). Accordingly, it is clear that the public was not in possession of the claimed sequences of eculizumab prior to the effective filing date of the present application, and the Examiner is respectfully requested to reconsider and withdraw the rejection.

Rejection of Claims 1-3 Under 35 U.S.C. § 103(a)

Claims 1-3 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Hillmen *et al.* (*N. Engl. J. Med.* 2004; 350; 552-9), in view of Evans *et al.* (US 6,355,245) and Wang (2005/0271660), and as evidenced by the parent specification (US Patent Application No.: 13/426,973). The Examiner asserts that Applicants' argument that the complete structure of eculizumab was not disclosed in the art or available to the public is unpersuasive because "the preponderance of evidence indicates that the antibody was in public use" and this public

availability was "sufficient to have placed one of skill in the art in possession of applicant's currently claimed sequences of eculizumab."

Applicants respectfully traverse the rejection. As discussed above, neither eculizumab nor its complete sequence were available to the public or in "public use" prior to the March 15, 2007 effective filing date of the present application. Therefore, the Examiner's underlying premise supporting the present obviousness rejection (*i.e.*, that eculizumab was in "public use") is factually incorrect. Moreover, as acknowledged by the Examiner on page 7 of the Office Action, none of Hillmen *et al.*, Evans *et al.* or Wang teach or suggest the complete sequence of eculizumab. Clearly, the Examiner has failed even to establish a prima facie case of obviousness.

Accordingly, for at the least the above-discussed reasons, the pending claims are patentable and the Examiner is respectfully requested to reconsider and withdraw this rejection.

Obviousness-Type Double Patenting

The Examiner has rejected claims 1-3 on the ground of non-statutory obviousness-type double patenting as being unpatentable over:

1. Claims 1-9 of US Patent No: 9,494,601 in view of Hillmen *et al.*, Evans *et al.*, and Wang;
2. Claims 1-18 of US Patent No: 8,999,340 in view of Hillmen *et al.*, Evans *et al.*, and Wang;
3. Claims 1-17 of US Patent No: 9,409,980 in view of Hillmen *et al.*, Evans *et al.*, and Wang;
4. Claims 3-14 of US Patent No: 9,556,263 in view of Hillmen *et al.*, Evans *et al.*, and Wang;
5. Claims 1-22 of US Patent No: 9,352,035 in view of Hillmen *et al.*, Evans *et al.*, and Wang;
6. Claims 1-14 of US Patent No: 9,415,102 in view of Hillmen *et al.*, Evans *et al.*, and Wang;
7. Claims 1-17 of US Patent No: 9,409,980 in view of Hillmen *et al.*, Evans *et al.*, and Wang;
8. Claims 1-4 of US Patent No: 9,447,176 in view of Hillmen *et al.*, Evans *et al.*, and Wang;

9. Claims 1-5, 7, 9-16 of US Patent No: 9,388,235 in view of Hillmen *et al.*, Evans *et al.*, and Wang;
10. Claims 15-17 and 58-59 of US Patent Application No: 11/127,438 in view of Hillmen *et al.*, Evans *et al.*, and Wang;
11. Claims 1-4 of US Patent Application No: 15/243,386 in view of Hillmen *et al.*, Evans *et al.*, and Wang;
12. Claims 1-4 of US Patent Application No: 15/243,290 in view of Hillmen *et al.*, Evans *et al.*, and Wang;
13. Claims 94 and 97-98 of US Patent Application No: 15/282,464 in view of Hillmen *et al.*, Evans *et al.*, and Wang; and
14. Claims 129-138 of US Patent Application No: 15/148,491 in view of Hillmen *et al.*, Evans *et al.*, and Wang.

While in no way acquiescing to the rejection, Applicants respectfully submit herewith a terminal disclaimer over US Patent No: 9,494,601, US Patent No: 8,999,340**,** US Patent No: 9,409,980,US Patent No: 9,556,263, US Patent No: 9,352,035, US Patent No: 9,415,102, US Patent No: 9,447,176, US Patent No: 9,388,235, US Patent Application No: 15/243,290, US Patent Application No: 15/282,464, and US Patent Application No: 15/148,491.

With respect to US Patent Application No: 15/243,386, Applicants note that this application lapsed on April 20, 2017 for failure to respond to the Office Action dated October 19, 2016. Accordingly, the rejection relating to the '386 application has been rendered moot.

Finally, with respect to US Patent Application No: 11/127,438, while the Examiner acknowledges that "the conflicting claims are not identical", the Examiner asserts that "they are not patentably distinct from each other because both the current application and the '438 claim [application] claim eculizumab." Applicants respectfully traverse this rejection.

The pending claims are drawn to pharmaceutical compositions comprising *eculizumab as defined by the complete heavy and light chain sequences of the antibody*. In contrast, claims 15-17 and 58-59 of the '438 application are drawn to an *aerosol composition* comprising h5G1.1, which is useful for the treatment of asthma. Importantly, the claims of the '438 application fail to recite any part of the sequence of eculizumab, let alone the complete heavy and light chain sequences. Nor does the specification of the '438 application teach, enable or in any way render

obvious the complete structure of eculizumab, as presently claimed. Moreover, as discussed above and in the attached Declaration, neither eculizumab nor its complete sequence were available to the public or in "public use" prior to the March 15, 2007 effective filing date of the present application. Accordingly, the mere naming of h5G1.1 in the claims of the '438 application does not render the present claims anticipated by or obvious over those of the '438 application.

A "nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s)" (see MPEP § 804). In view of the above, it is clear that the pending claims of the present '839 application and the pending claims of the '438 application are ***patentably distinct***. Accordingly, Applicants respectfully request that the Examiner reconsider and withdraw the rejection.

Response to Request for Additional Information Under 37 C.F.R. § 1.105

In response to the Examiner's specific inquiries and request for additional information under 37 C.F.R. § 1.105, Applicants provide the following factual information, as well as the enclosed Declaration Pursuant to 37 C.F.R. § 1.132 by Dr. Laural Boone.

(1) Interrogatories A–F

As attested in the enclosed Declaration, Exhibits A through F cited by the Examiner on pages 7-9 of the Office Action reference 17 different clinical studies using eculizumab that occurred prior to March 16, 2007. Of the 17 studies, 4 are referred to as "extension" studies, which are studies that are appended to a clinical study to prolong the treatment and/or monitoring period of the same patients that participated in the initial study.

Of these 17 clinical studies, one that is described in both Exhibits D and F and entitled, "A Randomized, Third-Party-Blind, Placebo-Controlled, Pilot Study of the Effect of h5G1.1-mAb in Patients with Bullous Pemphigoid," only enrolled one patient, and that one patient was randomized to receive placebo. Thus, no patient received eculizumab in the course of this study and the study was terminated.

For the remaining 16 clinical studies identified in Exhibits A through F, the below table includes: the full name of each study (and extension study thereof, if applicable, identified by an "E" or an "X" in the study number), the study number(s), the Exhibit(s) cited by the Examiner on pages 7-8 of the Office Action that each study was described in, and whether the study (including any extension study thereof) included a confidentiality provision (as described in further detail below).

Study Name[1]	**Study Number**	**Exhibit(s)**	**Explicit Confidentiality Provision**
An Open-Label Study of the Effect of Eculizumab (h5G1.1-mAb) on Patients with Transfusion Dependent, Hemolytic, Paroxysmal Nocturnal Hemoglobinuria	C02-001	F	Yes
Extension Study of Eculizumab in Patients with Transfusion Dependent, Haemolytic, Paroxysmal Nocturnal Haemoglobinuria Who Previously Participated in Study C02-001	E02-001		
An Open-Label Extension Study of Eculizumab in Patients with Transfusion Dependent, Haemolytic, Paroxysmal Nocturnal Hemoglobinuria Who Previously Participated in Study E02-001	X03-001		
A Hemoglobin Stabilization and Transfusion Reduction Efficacy and Safety Clinical Investigation, Randomized, Multi-Center, Double-Blind, Placebo-Controlled, Using Eculizumab in Paroxysmal Nocturnal Hemoglobinuria Patients (TRIUMPH)	C04-001	A[2], F	Yes
Safety in Hemolytic PNH Patients Treated with Eculizumab: A Multi-Center Open-Label Research Design Study (SHEPHERD)	C04-002	A, C, F	Yes

[1] Although some of these studies may not have occurred in the United States and thus are not available to give rise to public use under 35 U.S.C. § 102(b), all of the trials have been in included in this table (regardless of where they occurred).

[2] Of the studies referenced in Exhibit A, studies 41-43, 45-46, 52-54, 56-58 and 60 are all indicated as having been "received" or "started" *after* March 16, 2007, *i.e.*, the date eculizumab was first approved for commercial marketing and sale. Thus, only studies identified as numbers 44, 47-51, 55 and 59 in Exhibit A are included in this table.

Study Name[1]	Study Number	Exhibit(s)	Explicit Confidentiality Provision
A Phase III, Open-Label, Extension Study of Eculizumab in Patients with Transfusion Dependent, Hemolytic Paroxysmal Nocturnal Hemoglobinuria (PNH) Who Have Participated in the TRIUMPH (C04-001), SHEPHERD (C04-002) or X03-001 Studies	E05-001	A, F	Yes
A Randomized, Double-Blind, Placebo-Controlled Pilot Study of the Effect of h5G1.1-mAb on Dermatomyositis Patients	C99-006	B, D[3], F	Yes
Phase I Study of h5G1.1-mAb in Patients with Rheumatoid Arthritis	C97-001	F	Yes
A Phase II Randomized, Double-Blind, Placebo-Controlled Study of the Effect of h5G1.1-mAb on Rheumatoid Arthritis Patients Receiving Methotrexate	C99-001	D, F	Yes
A Phase IIB Randomized, Double-Blind, Placebo-Controlled Study of the Effect of h5G1.1-mAb on Rheumatoid Arthritis (RA) Patients with Active Disease Despite Receiving Methotrexate or Leflunomide	C01-004	D, F	Yes
A Phase II Randomized, Double-Blind, Placebo-Controlled Study of the Effect of h5G1.1-mAb on the Reduction of Proteinuria in Patients with Idiopathic Membranous Glomerulopathy An Open Label Study of the Long-Term Safety of h5G1.1-mAb on the Reduction of Proteinuria in Patients with Idiopathic Membranous Glomerulopathy	C99-004 E99-004	D, E, F	Yes
Phase I Study of h5G1.1-mAb in Patients with Systemic Lupus Erythematosus	C97-002	D, F	Yes
A Randomized, Double-Blind, Placebo-Controlled Pilot Study of the Effect of h5G1.1-mAb on Psoriatic Patients	C99-007	D, F	Yes
The Paroxysmal Nocturnal Hemoglobinuria Early Access Treatment Protocol (EMBRACE)	C06-002	F	Yes
PNH Registry	M07-001	A, F	Yes

[3] Item 445382 referenced in the Examiner's question regarding the Kaplan reference (Exhibit D) does not refer to an actual study. However, to address any potential questions the Examiner has with respect to Exhibit D, the Kaplan reference has been reviewed in its entirety and the clinical studies described therein that used eculizumab have been included.

(i) The Antibody Sequences Used in the Clinical Studies

As attested in the enclosed Declaration, the antibody (eculizumab) used in each of the studies included in the above table contained the heavy and light chain sequences of SEQ ID NOs: 2 and 4. However, the protocols used to conduct those studies did not inform either doctors or patients of the sequences.

(ii, iii) Confidentiality Provisions in the Clinical Studies

As indicated in the table above and discussed in the enclosed Declaration, in the course of conducting each of the clinical trials listed, participating physicians and others involved in the study were required to maintain Alexion's confidential and/or proprietary information in strict confidence. For example, these individuals were required to maintain the confidentiality of the clinical trial protocols themselves, as each protocol was marked "Confidential". These individuals were also bound by explicit confidentiality provisions in the protocol. As attested to in the attached Declaration of Dr. Boone, the following language from the protocol for study number C04-001, which refers to the Phase III TRIUMPH study, provides a representative example of the confidentiality requirements set forth directly within these clinical study protocols:

> "THE INVESTIGATOR AND ALL EMPLOYEES AND COWORKERS INVOLVED WITH THIS STUDY SHALL NOT DISCLOSE OR USE FOR ANY PURPOSE, OTHER THAN PERFORMANCE OF THE STUDY, ANY DATA, RECORDS OR OTHER UNPUBLISHED, CONFIDENTIAL INFORMATION DISCLOSED TO THOSE INDIVIDUALS FOR THE PURPOSE OF THE STUDY. PRIOR WRITTEN AGREEMENT FROM THE SPONSOR OR ITS DESIGNEE MUST BE OBTAINED FOR THE DISCLOSURE OF ANY SAID CONFIDENTIAL INFORMATION TO OTHER PARTIES."

As another representative example, Dr. Boone cites the protocol for the study in dermatomyositis (study number C02-002), which stated:

> "THIS CONFIDENTIAL INFORMATION ABOUT AN INVESTIGATIONAL DRUG IS PROVIDED FOR THE EXCLUSIVE USE OF INVESTIGATORS

> OF THIS DRUG AND IS SUBJECT TO RECALL AT ANY TIME. THE INFORMATION IN THIS DOCUMENT MAY NOT BE DISCLOSED UNLESS SUCH DISCLOSURE IS REQUIRED BY FEDERAL OR STATE LAW OR REGULATIONS SUBJECT TO THE FOREGOING. THIS INFORMATION MAY BE DISCLOSED ONLY TO THOSE PERSONS INVOLVED IN THE STUDY WHO HAVE A NEED TO KNOW WITH THE OBLIGATION NOT TO FURTHER DISSEMINATE THIS INFORMATION. THESE RESTRICTIONS ON DISCLOSURE WILL APPLY EQUALLY TO ALL FUTURE ORAL OR WRITTEN INFORMATION SUPPLIED TO YOU BY ALEXION, WHICH IS DESIGNATED AS 'PRIVILEGED' OR 'CONFIDENTIAL'."

As Dr. Boone explains, all confidentiality provisions in the protocols for the studies listed in the table above were substantively identical to these representative confidentiality provisions from studies C04-001 and C02-002.

In addition, Dr. Boone attests that each clinical trial protocol required strict control over the physical drug product (eculizumab). For example, the clinical trial protocol for the TRIUMPH study described the secure storage and inventory and disposal requirements of each participating physician and study site as shown below:

> "Eculizumab must be stored in a secure, limited-access storage area. . . .
>
> Test Article Accountability…When a drug shipment is received at the site, the pharmacist at each site shall verify the contents, sign the packing invoice provided with the shipment, and maintain the original copy for review by the study monitor. The duplicate copy should be kept in the pharmacy binder.
>
> Each shipment of investigational drug supplies will contain an accountability log to assist the pharmacist in maintaining current and accurate inventory records covering receipt, dispensing, and disposition of the investigational product. During the study, the following information must be noted in the accountability log: the identification number(s), initials of patient(s) who is dispensed investigational product, the date(s) that the investigational product is prepared and dispensed, and the initials of the pharmacist or designee who prepared the investigational product. Empty vials and vials with residual materials should be kept for inspection by the study monitor.
>
> The study monitor will examine the inventory records during study conduct. Additionally, the inventory records must be readily available and may be subject

> to regulatory authorities or an independent auditor's inspection at any time. At the completion of the study, to satisfy regulatory requirements regarding drug accountability, all remaining investigational product inventory will be reconciled and retained or destroyed according to applicable local, state, and federal regulations."

Dr. Boone also explains that all of the protocols for the studies listed in the above table included similar (if not identical) drug storage and accountability provisions, except for the PNH Registry protocol (the last entry in the table above). The PNH Registry was not a study in which eculizumab was administered to any patients; rather, it was a "non-interventional study designed to collect post-marketing pharmacovigilance and effectiveness data on patients treated with Soliris® (eculizumab)" and to "collect information on the progression of disease in the Soliris treated and untreated PNH patient population." Accordingly, the protocol for the PNH Registry did not contain drug storage or accountability provisions. The PNH Registry protocol did, however, include strict confidentiality provisions as indicated in the table above, *e.g.*, requiring all physicians to "agree to maintain the confidentiality of all information received or developed in connection with [the] protocol."

(iv) Physicians Acting at Alexion's Direction

As discussed in the enclosed Declaration, to participate in each clinical trial listed in the table above, each physician had to sign the protocol for the trial, committing to adhere to the respective clinical trial protocol's provisions. For example, the TRIUMPH study protocol, just prior to the physician's signature line, stated:

> "I agree to conduct the study as outlined in the protocol entitled: *"TRIUMPH*: A Hemoglobin Stabilization and Transfusion Reduction Efficacy and Safety Clinical Investigation, Randomized, Multi-Center, Double-Blind, Placebo-Controlled, Using Eculizumab in Paroxysmal Nocturnal Hemoglobinuria Patients" and in accordance with the guidelines and all applicable government regulations. I have read and understand all sections of the protocol including Section 11, Administrative Considerations."

As Dr. Boone states, all of the other protocols similarly required each physician (or investigator) to agree to conduct the study in accordance with the protocol.

(2) Interrogatory G

As attested in the enclosed Declaration, the antibody having the heavy chain described by SEQ ID NO:2 and the light chain described by SEQ ID NO:4 was first approved for commercial marketing and sale on March 16, 2007.

CONCLUSION

In view of the above amendment, arguments, and accompanying Declaration, Applicants believe the pending application is in condition for allowance. If a telephone conversation with Applicants' attorney would help expedite the prosecution of the above-identified application, the Examiner is urged to call Applicants' attorney at (617) 217-4630.

Applicants believe no fee is required with this submission. However, should any additional fee be due, the Director is hereby authorized to charge any deficiency in the fees filed, asserted to be filed or which should have been filed herewith (or with any paper hereafter filed in this application by this firm) to our Deposit Account No. 12-0080, under Order No. AXJ-114BUSCN2.

Dated: May 12, 2017

Respectfully submitted,

Electronic signature: /Jill Gorny Sloper, Esq./
Jill Gorny Sloper, Esq.
Registration No.: 60,760
NELSON MULLINS RILEY & SCARBOROUGH LLP
One Post Office Square
Boston, Massachusetts 02109-2127
(617) 217-4630
(617) 217-4699 (Fax)
Attorney/Agent For Applicant

I hereby certify that this paper (along with any paper referred to as being attached or enclosed) is being transmitted via the Office electronic filing system in accordance with 37 CFR § 1.6(a)(4).

Dated: May 12, 2017
Electronic Signature for Jill Gorny Sloper, Esq.: /Jill Gorny Sloper, Esq./

Docket No.: AXJ-114BUSCN2
(PATENT)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of:
Leonard Bell *et al.*

Application No.: 15/148,839

Confirmation No.: 3159

Filed: May 6, 2016

Art Unit: 1644

For: TREATMENT OF PAROXYSMAL NOCTURNAL HEMOGLOBINURIA PATIENTS BY AN INHIBITOR OF COMPLEMENT

Examiner: J. L. Rogers

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

DECLARATION PURSUANT TO 37 C.F.R. § 1.132 BY DR. LAURAL BOONE

I, Laural S. Boone, J.D., Ph.D., declare the following:

1. I am presently a Senior Director and Patent Counsel at Alexion Pharmaceuticals, Inc., (hereafter, "Alexion") which is located in New Haven, Connecticut. I have been employed in this capacity at Alexion for three years to date. Alexion is the Assignee of the above-referenced patent application. I received a B.A. in Chemistry from Barnard College, a M.S. and Ph.D. in Organic Chemistry from the University of Chicago, and a J.D. from the George Washington University Law School. I also completed a Postdoctoral Fellowship in Cellular and Molecular Biophysics at Rockefeller University. I am registered to practice as a patent attorney before the United States Patent & Trademark Office.

Samsung Bioepis Exhibit No. 1002
Page 10803

2. I have reviewed the Examiner's request for additional information under 37 C.F.R. § 1.105 and provide the following statements.

3. I have reviewed Exhibits A through F cited by the Examiner on pages 7-8 of the April 4, 2017 Office Action, including each of the 37 documents listed in Exhibit F. These exhibits and the documents listed therein reference 17 different clinical studies using eculizumab that occurred prior to March 16, 2007. Of the 17 studies, 4 are referred to as "extension" studies, which are studies that are appended to a clinical study to prolong the treatment and/or monitoring period of the same patients that participated in the initial study.

4. Of these 17 clinical studies, one that is described in both Exhibits D and F, is entitled "A Randomized, Third-Party-Blind, Placebo-Controlled, Pilot Study of the Effect of h5G1.1-mAb in Patients with Bullous Pemphigoid." Based on my review of communications between Alexion employees and physicians participating in this study, I have determined that only one patient was enrolled in this study, and that the one patient was randomized to receive placebo. Thus, no patient received eculizumab in the course of this study, and the study was terminated.

5. For the remaining 16 clinical studies identified in Exhibits A through F, I have reviewed each of the clinical trial protocols and the following information from the protocols is shown in the table below: the full name of each study (and extension study thereof, if applicable, identified by an "E" or an "X" in the study number), the study number(s), the Exhibit(s) cited by the Examiner on pages 7-8 of the Office Action that each study was described in, and whether the study (including any extension study thereof) included a confidentiality provision (as described in further detail below).

Study Name[1]	Study Number	Exhibit(s)	Explicit Confidentiality Provision
An Open-Label Study of the Effect of Eculizumab (h5G1.1-mAb) on Patients with Transfusion Dependent, Hemolytic, Paroxysmal Nocturnal Hemoglobinuria Extension Study of Eculizumab in Patients with Transfusion Dependent, Haemolytic, Paroxysmal Nocturnal Haemoglobinuria Who Previously Participated in Study C02-001 An Open-Label Extension Study of Eculizumab in Patients with Transfusion Dependent, Haemolytic, Paroxysmal Nocturnal Hemoglobinuria Who Previously Participated in Study E02-001	C02-001 E02-001 X03-001	F	Yes
A Hemoglobin Stabilization and Transfusion Reduction Efficacy and Safety Clinical Investigation, Randomized, Multi-Center, Double-Blind, Placebo-Controlled, Using Eculizumab in Paroxysmal Nocturnal Hemoglobinuria Patients (TRIUMPH)	C04-001	A[2], F	Yes
Safety in Hemolytic PNH Patients Treated with Eculizumab: A Multi-Center Open-Label Research Design Study (SHEPHERD)	C04-002	A, C, F	Yes
A Phase III, Open-Label, Extension Study of Eculizumab in Patients with Transfusion Dependent, Hemolytic Paroxysmal Nocturnal Hemoglobinuria (PNH) Who Have Participated in the TRIUMPH (C04-001), SHEPHERD (C04-002) or X03-001 Studies	E05-001	A, F	Yes
A Randomized, Double-Blind, Placebo-Controlled Pilot Study of the Effect of h5G1.1-mAb on Dermatomyositis Patients	C99-006	B, D[3], F	Yes

[1] Although some of these studies may not have occurred in the United States and thus are not available to give rise to public use under 35 U.S.C. § 102(b), all of the trials are included in this table (regardless of where they occurred).

[2] Of the studies referenced in Exhibit A, studies 41-43, 45-46, 52-54, 56-58 and 60 are all indicated as having been "received" or "started" *after* March 16, 2007, *i.e.*, the date eculizumab was first approved for commercial marketing and sale. Thus, only studies started before the marketing approval, identified as numbers 44, 47-51, 55, and 59 in Exhibit A, are included in this table.

[3] Item 445382 referenced in the Examiner's question regarding the Kaplan reference (Exhibit D) does not refer to an actual study. However, to address any potential questions the Examiner has with respect to

Study Name[1]	Study Number	Exhibit(s)	Explicit Confidentiality Provision
Phase I Study of h5G1.1-mAb in Patients with Rheumatoid Arthritis	C97-001	F	Yes
A Phase II Randomized, Double-Blind, Placebo-Controlled Study of the Effect of h5G1.1-mAb on Rheumatoid Arthritis Patients Receiving Methotrexate	C99-001	D, F	Yes
A Phase IIB Randomized, Double-Blind, Placebo-Controlled Study of the Effect of h5G1.1-mAb on Rheumatoid Arthritis (RA) Patients with Active Disease Despite Receiving Methotrexate or Leflunomide	C01-004	D, F	Yes
A Phase II Randomized, Double-Blind, Placebo-Controlled Study of the Effect of h5G1.1-mAb on the Reduction of Proteinuria in Patients with Idiopathic Membranous Glomerulopathy An Open Label Study of the Long-Term Safety of h5G1.1-mAb on the Reduction of Proteinuria in Patients with Idiopathic Membranous Glomerulopathy	C99-004 E99-004	D, E, F	Yes
Phase I Study of h5G1.1-mAb in Patients with Systemic Lupus Erythematosus	C97-002	D, F	Yes
A Randomized, Double-Blind, Placebo-Controlled Pilot Study of the Effect of h5G1.1-mAb on Psoriatic Patients	C99-007	D, F	Yes
The Paroxysmal Nocturnal Hemoglobinuria Early Access Treatment Protocol (EMBRACE)	C06-002	F	Yes
PNH Registry	M07-001	A, F	Yes

Exhibit D, I reviewed the Kaplan reference in its entirety, and the clinical studies described therein that used eculizumab are also included in this table.

6. I have reviewed an alignment of the sequence of eculizumab that is listed in the Biologic License Application for Soliris®(eculizumab) ("BLA") with the heavy and light chain sequences of SEQ ID NOs: 2 and 4 of the parent of the pending application, PCT/US2007/006606 (published as WO 2007/106585). I have concluded that the antibody (eculizumab) used in each of the studies included in the above table contained the heavy and light chain sequences of SEQ ID NOs: 2 and 4. However, the protocols used to conduct those studies did not inform either doctors or patients of the sequences.

7. As indicated in the table above, in the course of conducting each of the clinical trials listed, participating physicians and other participants in the study were required to maintain Alexion's confidential and/or proprietary information in strict confidence. For example, these individuals were required to maintain the confidentiality of the clinical trial protocols themselves, as each protocol was marked "Confidential." These individuals were also bound by explicit confidentiality provisions in the protocol. The following language from the protocol for study number C04-001, which refers to the Phase III TRIUMPH study, provides a representative example of the confidentiality requirements set forth directly within these clinical study protocols (emphasis added):

> "THE INVESTIGATOR AND ALL EMPLOYEES AND COWORKERS INVOLVED WITH THIS STUDY SHALL NOT DISCLOSE OR USE FOR ANY PURPOSE, OTHER THAN PERFORMANCE OF THE STUDY, ANY DATA, RECORDS OR OTHER UNPUBLISHED, CONFIDENTIAL INFORMATION DISCLOSED TO THOSE INDIVIDUALS FOR THE PURPOSE OF THE STUDY. PRIOR WRITTEN AGREEMENT FROM THE SPONSOR OR ITS DESIGNEE MUST BE OBTAINED FOR THE DISCLOSURE OF ANY SAID CONFIDENTIAL INFORMATION TO OTHER PARTIES."

8. As another representative example, the protocol for the study in dermatomyositis (study number C02-002) stated:

Samsung Bioepis Exhibit No. 1002
Page 10807

> "THIS CONFIDENTIAL INFORMATION ABOUT AN INVESTIGATIONAL DRUG IS PROVIDED FOR THE EXCLUSIVE USE OF INVESTIGATORS OF THIS DRUG AND IS SUBJECT TO RECALL AT ANY TIME. THE INFORMATION IN THIS DOCUMENT MAY NOT BE DISCLOSED UNLESS SUCH DISCLOSURE IS REQUIRED BY FEDERAL OR STATE LAW OR REGULATIONS SUBJECT TO THE FOREGOING. THIS INFORMATION MAY BE DISCLOSED ONLY TO THOSE PERSONS INVOLVED IN THE STUDY WHO HAVE A NEED TO KNOW WITH THE OBLIGATION NOT TO FURTHER DISSEMINATE THIS INFORMATION. THESE RESTRICTIONS ON DISCLOSURE WILL APPLY EQUALLY TO ALL FUTURE ORAL OR WRITTEN INFORMATION SUPPLIED TO YOU BY ALEXION, WHICH IS DESIGNATED AS 'PRIVILEGED' OR 'CONFIDENTIAL'."

9. All confidentiality provisions in the protocols for the studies listed in the table above were substantively identical to these representative confidentiality provisions from studies C04-001 and C02-002.

10. In addition, each clinical trial protocol that I reviewed also required strict control over the physical drug product (eculizumab). For example, the clinical trial protocol for the TRIUMPH study described the secure storage and inventory and disposal requirements of each participating physician and study site as shown below:

> "Eculizumab must be stored in a secure, limited-access storage area. . . .
>
> Test Article Accountability…When a drug shipment is received at the site, the pharmacist at each site shall verify the contents, sign the packing invoice provided with the shipment, and maintain the original copy for review by the study monitor. The duplicate copy should be kept in the pharmacy binder.
>
> Each shipment of investigational drug supplies will contain an accountability log to assist the pharmacist in maintaining current and accurate inventory records covering receipt, dispensing, and disposition of the investigational product. During the study, the following information must be noted in the accountability log: the identification number(s), initials of patient(s) who is dispensed investigational product, the date(s) that the investigational product is prepared and dispensed, and the initials of the pharmacist or designee who prepared the investigational product. Empty vials and vials with residual materials should be kept for inspection by the study monitor.

> The study monitor will examine the inventory records during study conduct. Additionally, the inventory records must be readily available and may be subject to regulatory authorities or an independent auditor's inspection at any time. At the completion of the study, to satisfy regulatory requirements regarding drug accountability, all remaining investigational product inventory will be reconciled and retained or destroyed according to applicable local, state, and federal regulations."

11. All of the protocols that I reviewed for the studies listed in the above table included similar (if not identical) drug storage and accountability provisions, except for the PNH Registry protocol (the last entry in the table above). The PNH Registry was not a study in which eculizumab was administered to any patients, but was a registry for all participating patients with PNH either treated or untreated. More particularly, it was a "non-interventional study designed to collect post-marketing pharmacovigilance and effectiveness data on patients treated with Soliris® (eculizumab)" and to "collect information on the progression of disease in the Soliris treated and untreated PNH patient population." Accordingly, the protocol for the PNH Registry did not contain drug storage or accountability provisions. The PNH Registry protocol did, however, include strict confidentiality provisions as indicated in the table above, *e.g.*, requiring all physicians to "agree to maintain the confidentiality of all information received or developed in connection with [the] protocol."

12. To participate in each clinical trial listed in the table above, each physician had to sign the protocol for the trial, committing to adhere to the respective clinical trial protocol's provisions. For example, the TRIUMPH study protocol, just prior to the physician's signature line, states:

> "I agree to conduct the study as outlined in the protocol entitled: *"TRIUMPH*: A Hemoglobin Stabilization and Transfusion Reduction Efficacy and Safety Clinical Investigation, Randomized, Multi-Center, Double-Blind, Placebo-Controlled, Using Eculizumab in Paroxysmal Nocturnal Hemoglobinuria Patients" and in accordance with the guidelines and all applicable government regulations. I have read and understand all sections of the protocol including Section 11, Administrative Considerations."

13. All of the other protocols that I reviewed similarly required each physician (or investigator) to agree to conduct the study in accordance with the protocol.

14. In response to the Examiner's Request (G), based on the BLA approval letter that I reviewed from the Food and Drug Administration Department of Health & Human Services to Alexion regarding eculizumab, the antibody having the heavy chain described by SEQ ID NO: 2 and the light chain described by SEQ ID NO: 4 was first approved for commercial marketing and sale on March 16, 2007.

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or of any patent issued thereon.

Laural S. Boone, J.D., Ph.D. 11 MAY 2017
Date

Samsung Bioepis Exhibit No. 1002
Page 10810

PTO/AIA/96 (08-12)
Approved for use through 01/31/2013. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number.

STATEMENT UNDER 37 CFR 3.73(c)

Applicant/Patent Owner: Alexion Pharmaceuticals, Inc.

Application No./Patent No.: 15/260,888 Filed/Issue Date: September 9, 2016

Titled: TREATMENT OF PAROXYSMAL NOCTURNAL HEMOGLOBINURIA PATIENTS BY AN INHIBITOR OF COMPLEMENT

Alexion Pharmaceuticals, Inc. (Name of Assignee) , a Corporation (Type of Assignee, e.g., corporation, partnership, university, government agency, etc.)

states that, for the patent application/patent identified above, it is (choose **one** of options 1, 2, 3 or 4 below):

1. [X] The assignee of the entire right, title, and interest.

2. [ ] An assignee of less than the entire right, title, and interest (check applicable box):

   [ ] The extent (by percentage) of its ownership interest is _____ %). Additional Statement(s) by the owners holding the balance of the interest must be submitted to account for 100% of the ownership interest.

   [ ] There are unspecified percentages of ownership. The other parties, including inventors, who together own the entire right, title and interest are:

   Additional Statement(s) by the owner(s) holding the balance of the interest must be submitted to account for the entire right, title, and interest.

3. [ ] The assignee of an undivided interest in the entirety (a complete assignment from one of the joint inventors was made). The other parties, including inventors, who together own the entire right, title, and interest are:

   Additional Statement(s) by the owner(s) holding the balance of the interest must be submitted to account for the entire right, title, and interest.

4. [ ] The recipient, via a court proceeding or the like (*e.g.*, bankruptcy, probate), of an undivided interest in the entirety (a complete transfer of ownership interest was made). The certified document(s) showing the transfer is attached.

The interest identified in option 1, 2 or 3 above (not option 4) is evidenced by either (choose **one** of options A or B below):

A. [ ] An assignment from the inventor(s) of the patent application/patent identified above. The assignment was recorded in the United States Patent and Trademark Office at Reel _____, Frame _____, or for which a copy thereof is attached.

B. [X] A chain of title from the inventor(s), of the patent application/patent identified above, to the current assignee as follows:

1. From: Leonard Bell To: Alexion Pharmaceuticals, Inc.
   The document was recorded in the United States Patent and Trademark Office at
   Reel 039718, Frame 0748, or for which a copy thereof is attached.

2. From: Russell P. Rother To: Alexion Pharmaceuticals, Inc.
   The document was recorded in the United States Patent and Trademark Office at
   Reel 039718, Frame 0748, or for which a copy thereof is attached.

PTO/AIA/96 (08-12)
Approved for use through 01/31/2013. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number.

STATEMENT UNDER 37 CFR 3.73(c)

3. From: Mark J. Evans To: Alexion Pharmaceuticals, Inc.
The document was recorded in the United States Patent and Trademark Office at
Reel 041065 , Frame 0336 , or for which a copy thereof is attached.

4. From: _____ To: _____
The document was recorded in the United States Patent and Trademark Office at
Reel _____ , Frame _____ , or for which a copy thereof is attached.

5. From: _____ To: _____
The document was recorded in the United States Patent and Trademark Office at
Reel _____ , Frame _____ , or for which a copy thereof is attached.

6. From: _____ To: _____
The document was recorded in the United States Patent and Trademark Office at
Reel _____ , Frame _____ , or for which a copy thereof is attached.

☐ Additional documents in the chain of title are listed on a supplemental sheet(s).

☒ As required by 37 CFR 3.73(c)(1)(i), the documentary evidence of the chain of title from the original owner to the assignee was, or concurrently is being, submitted for recordation pursuant to 37 CFR 3.11.

[NOTE: A separate copy (i.e., a true copy of the original assignment document(s)) must be submitted to Assignment Division in accordance with 37 CFR Part 3, to record the assignment in the records of the USPTO. See MPEP 302.08]

The undersigned (whose title is supplied below) is authorized to act on behalf of the assignee.

Signature | Date: June 13 2017

Todd Spalding
Printed or Typed Name

Vice President, Head of Intellectual Property
Title or Registration Number

Samsung Bioepis Exhibit No. 1002
Page 10812

PTO/SB/17 (03-13)
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U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
Under the Paperwork Reduction Act of 1995 no persons are required to respond to a collection of information unless it displays a valid OMB control number

FEE TRANSMITTAL

		Complete if known	
		Application Number	15/260,888-Conf. #2558
		Filing Date	September 9, 2016
☐	Applicant asserts small entity status. See 37 CFR 1.27.	First Named Inventor	Leonard BELL
☐	Applicant certifies micro entity status. See 37 CFR 1.29. Form PTO/SB/15A or B or equivalent must either be enclosed or have been submitted previously.	Examiner Name	J. L. Rogers
		Art Unit	1644
TOTAL AMOUNT OF PAYMENT	($) 340.00	Practitioner Docket No.	AXJ-114BUSCN3

METHOD OF PAYMENT (check all that apply)

☐ Check ☐ Credit Card ☐ Money Order ☐ None ☐ Other (please identify): _____

☒ Deposit Account Deposit Account Number: 12-0080 Deposit Account Name: Nelson Mullins Riley & Scarborough LLP

For the above-identified deposit account, the Director is hereby authorized to (check all that apply):

☒ Charge fee(s) indicated below ☐ Charge fee(s) indicated below, **except for the filing fee**

☒ Charge any additional fee(s) or underpayment of fee(s) under 37 CFR 1.16 and 1.17 ☒ Credit any overpayment of fee(s)

WARNING: Information on this form may become public. Credit card information should not be included on this form. Provide credit card information and authorization on PTO-2038.

FEE CALCULATION

1. BASIC FILING, SEARCH, AND EXAMINATION FEES (U = undiscounted fee; S = small entity fee; M = micro entity fee)

	FILING FEES			SEARCH FEES			EXAMINATION FEES			
Application Type	**U ($)**	**S ($)**	**M ($)**	**U ($)**	**S ($)**	**M ($)**	**U ($)**	**S ($)**	**M ($)**	**Fees Paid ($)**
Utility	280	140*	70	600	300	150	720	360	180	
Design	180	90	45	120	60	30	460	230	115	
Plant	180	90	45	380	190	95	580	290	145	
Reissue	280	140	70	600	300	150	2,160	1,080	540	
Provisional	260	130	65	0	0	0	0	0	0	

* The $140 small entity status filing fee for a utility application is further reduced to $70 for a small entity status applicant who files the application via EFS-Web.

2. EXCESS CLAIM FEES

Fee Description	**Undiscounted Fee ($)**	**Small Entity Fee ($)**	**Micro Entity Fee ($)**
Each claim over 20 (including Reissues)	80	40	20
Each independent claim over 3 (including Reissues)	420	210	105
Multiple dependent claims	780	390	195

Total Claims	**Extra Claims**	**Fee ($)**	**Fee Paid ($)**	**Multiple Dependent Claims**	
				Fee ($)	**Fee Paid ($)**
_____ - 20 or HP =	_____ x	_____ =	_____	_____	_____

HP = highest number of total claims paid for, if greater than 20.

Indep. Claims	**Extra Claims**	**Fee ($)**	**Fee Paid ($)**
_____ - 3 or HP =	_____ x	_____ =	_____

HP = highest number of independent claims paid for, if greater than 3.

3. APPLICATION SIZE FEE

If the specification and drawings exceed 100 sheets of paper (excluding electronically filed sequence or computer listings under 37 CFR 1.52(e)), the application size fee due is $400 ($200 for small entity) ($100 for micro entity) for each additional 50 sheets or fraction thereof. See 35 U.S.C. 41(a)(1)(G) and 37 CFR 1.16(s).

Total Sheets	**Extra Sheets**	**Number of each additional 50 or fraction thereof**	**Fee ($)**	**Fee Paid ($)**
_____ - 100 =	_____ /50 =	_____ (round **up** to a whole number) x	_____ =	_____

4. OTHER FEE(S)

	Fees Paid ($)
Non-English specification, $130 fee (no small or micro entity discount)	
Non-electronic filing fee under 37 CFR 1.16(t) for a utility application, $400 fee ($200 small or micro entity)	
Other (e.g., late filing surcharge): 1806 Submission of an Information Disclosure Statement	180.00
1814 Statutory disclaimer, including terminal ...	160.00

SUBMITTED BY

Signature	/Jill Gorny Sloper, Esq./	Registration No. (Attorney/Agent)	60,760	Telephone	(617) 217-4630
Name (Print/Type)	Jill Gorny Sloper, Esq.			Date	June 13, 2017

I hereby certify that this paper (along with any paper referred to as being attached or enclosed) is being transmitted via the Office electronic filing system in accordance with 37 CFR § 1.6(a)(4).

Dated: June 13, 2017 Electronic Signature for Jill Gorny Sloper, Esq.: /Jill Gorny Sloper, Esq./

Samsung Bioepis Exhibit No. 1002
Page 10813

Electronic Acknowledgement Receipt

EFS ID:	29486469
Application Number:	15260888
International Application Number:	
Confirmation Number:	2558
Title of Invention:	TREATMENT OF PAROXYSMAL NOCTURNAL HEMOGLOBINURIA PATIENTS BY AN INHIBITOR OF COMPLEMENT
First Named Inventor/Applicant Name:	Leonard BELL
Customer Number:	133485
Filer:	Jill R. Gorny Sloper/Carolyn Blake
Filer Authorized By:	Jill R. Gorny Sloper
Attorney Docket Number:	AXJ-114BUSCN3
Receipt Date:	13-JUN-2017
Filing Date:	09-SEP-2016
Time Stamp:	18:03:22
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	no

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Fee Worksheet (SB06)	AXJ-114BUSCN3_Fee-Transmittal.pdf	32380 a705aa76c4bfd5fc446a29c660c6daebb4bb7cb6	no	1

Warnings:

Samsung Bioepis Exhibit No. 1002
Page 10814

Information:	
Total Files Size (in bytes):	32380

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111
If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.
National Stage of an International Application under 35 U.S.C. 371
If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.
New International Application Filed with the USPTO as a Receiving Office
If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

Samsung Bioepis Exhibit No. 1002
Page 10815

PTO/AIA/26 (04-14)
Approved for use through 07/31/2016. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number.

TERMINAL DISCLAIMER TO OBVIATE A DOUBLE PATENTING REJECTION OVER A "PRIOR" PATENT	Docket Number (Optional) AXJ-114BUSCN3

In re Application of: Leonard BELL *et al.*

Application No.: 15/260,888-Conf. #2558

Filed: September 9, 2016

For: TREATMENT OF PAROXYSMAL NOCTURNAL HEMOGLOBINURIA PATIENTS BY AN INHIBITOR OF COMPLEMENT

The applicant, Alexion Pharmaceuticals, Inc., owner of 100 percent interest in the instant application hereby disclaims, except as provided below, the terminal part of the statutory term of any patent granted on the instant application which would extend beyond the expiration date of the full statutory term of **prior patent** No. (see attached) as the term of said **prior patent** is presently shortened by any terminal disclaimer. The applicant hereby agrees that any patent so granted on the instant application shall be enforceable only for and during such period that it and the **prior patent** are commonly owned. This agreement runs with any patent granted on the instant application and is binding upon the grantee, its successors or assigns.

In making the above disclaimer, the applicant does not disclaim the terminal part of the term of any patent granted on the instant application that would extend to the expiration date of the full statutory term of the **prior patent**, "as the term of said **prior patent** is presently shortened by any terminal disclaimer," in the event that said **prior patent** later:

expires for failure to pay a maintenance fee;
is held unenforceable;
is found invalid by a court of competent jurisdiction;
is statutorily disclaimed in whole or terminally disclaimed under 37 CFR 1.321;
has all claims canceled by a reexamination certificate;
is reissued; or
is in any manner terminated prior to the expiration of its full statutory term as presently shortened by any terminal disclaimer.

Check either box 1 or 2 below, if appropriate.

1. [X] The undersigned is the applicant. If the applicant is an assignee, the undersigned is authorized to act on behalf of the assignee.

I hereby acknowledge that any willful false statements made are punishable under 18 U.S.C. 1001 by fine or imprisonment of not more than five (5) years, or both.

2. [ ] The undersigned is an attorney or agent of record. Reg. No. _____



Signature

June 13, 2017
Date

Todd Spalding
Typed or printed name

Vice President, Head of Intellectual Property
Title

Telephone Number

[X] Terminal disclaimer fee under 37 CFR 1.20(d) included.

WARNING: Information on this form may become public. Credit card information should not be included on this form. Provide credit card information and authorization on PTO-2038.

Samsung Bioepis Exhibit No. 1002
Page 10816

SUPPLEMENTAL SHEET FOR TERMINAL DISCLAIMER TO OBVIATE A DOUBLE PATENTING REJECTION OVER A "PRIOR" PATENT	Docket Number (Optional) AXJ-114BUSCN3

Prior patent Nos. applicable to this terminal disclaimer (referenced on first page):

9,494,601
9,409,980
9,556,263

Samsung Bioepis Exhibit No. 1002
Page 10817

Electronic Patent Application Fee Transmittal

Application Number:	15260888
Filing Date:	09-Sep-2016
Title of Invention:	TREATMENT OF PAROXYSMAL NOCTURNAL HEMOGLOBINURIA PATIENTS BY AN INHIBITOR OF COMPLEMENT
First Named Inventor/Applicant Name:	Leonard BELL
Filer:	Jill R. Gorny Sloper/Danielle Gamache
Attorney Docket Number:	AXJ-114BUSCN3

Filed as Large Entity

Filing Fees for Utility under 35 USC 111(a)

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Basic Filing:				
Pages:				
Claims:				
Miscellaneous-Filing:				
Petition:				
Patent-Appeals-and-Interference:				
Post-Allowance-and-Post-Issuance:				
Extension-of-Time:				

Samsung Bioepis Exhibit No. 1002
Page 10818

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Miscellaneous:				
STATUTORY OR TERMINAL DISCLAIMER	1814	1	160	160
		Total in USD ($)		**160**

Samsung Bioepis Exhibit No. 1002
Page 10819

Electronic Acknowledgement Receipt

EFS ID:	29483167
Application Number:	15260888
International Application Number:	
Confirmation Number:	2558
Title of Invention:	TREATMENT OF PAROXYSMAL NOCTURNAL HEMOGLOBINURIA PATIENTS BY AN INHIBITOR OF COMPLEMENT
First Named Inventor/Applicant Name:	Leonard BELL
Customer Number:	133485
Filer:	Jill R. Gorny Sloper/Danielle Gamache
Filer Authorized By:	Jill R. Gorny Sloper
Attorney Docket Number:	AXJ-114BUSCN3
Receipt Date:	13-JUN-2017
Filing Date:	09-SEP-2016
Time Stamp:	17:44:51
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	no

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1		AXJ_114BUSCN3_Response_with_Courtesy_Copies.pdf	1529515 dce35b66ec3c6770fde24956732afed602d950d1	yes	36

Samsung Bioepis Exhibit No. 1002
Page 10820

	Multipart Description/PDF files in .zip description				
	Document Description	**Start**	**End**		
	Amendment/Req. Reconsideration-After Non-Final Reject	1	1		
	Claims	2	3		
	Applicant Arguments/Remarks Made in an Amendment	4	36		
Warnings:					
Information:					
2	Assignee showing of ownership per 37 CFR 3.73	AXJ_114BUSCN3_Assignee_Ownership.pdf	122490 3d5728d5117028f3f3568ffa8e9a7423ceef2032	no	2
Warnings:					
Information:					
3	Terminal Disclaimer Filed	AXJ_114_BUSCN3_TD_over_patents.pdf	90254 b5f80a5c43307896d868432efe5ad6f450a45456	no	2
Warnings:					
Information:					
4	Fee Worksheet (SB06)	fee-info.pdf	30674 1e5fad1b5ec487268a349b04ea43a908bff8f33f	no	2
Warnings:					
Information:					
		Total Files Size (in bytes):	1772933		

Samsung Bioepis Exhibit No. 1002
Page 10821

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111

If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371

If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office

If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

Samsung Bioepis Exhibit No. 1002
Page 10822

Application Number	Application/Control No.	Applicant(s)/Patent under Reexamination	
	15/260,888	BELL ET AL.	

Document Code - DISQ	Internal Document – DO NOT MAIL

TERMINAL DISCLAIMER	☒ APPROVED	☐ DISAPPROVED
Date Filed : 13 June, 2017	This patent is subject to a Terminal Disclaimer	

Approved/Disapproved by:

PAMELA YOUNG

Technology Center: PLRC

Telephone: _____

U.S. Patent and Trademark Office

Samsung Bioepis Exhibit No. 1002
Page 10823

PTO/SB/06 (09-11)
Approved for use through 1/31/2014. OMB 0651-0032
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number.

PATENT APPLICATION FEE DETERMINATION RECORD Substitute for Form PTO-875	Application or Docket Number 15/260,888	Filing Date 09/09/2016	☐ To be Mailed

ENTITY: ☒ LARGE ☐ SMALL ☐ MICRO

APPLICATION AS FILED – PART I

	(Column 1)	(Column 2)		
FOR	NUMBER FILED	NUMBER EXTRA	RATE ($)	FEE ($)
☐ BASIC FEE (37 CFR 1.16(a), (b), or (c))	N/A	N/A	N/A	
☐ SEARCH FEE (37 CFR 1.16(k), (i), or (m))	N/A	N/A	N/A	
☐ EXAMINATION FEE (37 CFR 1.16(o), (p), or (q))	N/A	N/A	N/A	
TOTAL CLAIMS (37 CFR 1.16(i))	minus 20 =	*	X $ =	
INDEPENDENT CLAIMS (37 CFR 1.16(h))	minus 3 =	*	X $ =	
☐ APPLICATION SIZE FEE (37 CFR 1.16(s))	If the specification and drawings exceed 100 sheets of paper, the application size fee due is $310 ($155 for small entity) for each additional 50 sheets or fraction thereof. See 35 U.S.C. 41(a)(1)(G) and 37 CFR 1.16(s).			
☐ MULTIPLE DEPENDENT CLAIM PRESENT (37 CFR 1.16(j))				
* If the difference in column 1 is less than zero, enter "0" in column 2.			TOTAL	

APPLICATION AS AMENDED – PART II

		(Column 1)		(Column 2)	(Column 3)		
AMENDMENT	06/13/2017	CLAIMS REMAINING AFTER AMENDMENT		HIGHEST NUMBER PREVIOUSLY PAID FOR	PRESENT EXTRA	RATE ($)	ADDITIONAL FEE ($)
	Total (37 CFR 1.16(i))	* 10	Minus	** 20	= 0	X $80 =	0
	Independent (37 CFR 1.16(h))	* 1	Minus	***3	= 0	X $420 =	0
	☐ Application Size Fee (37 CFR 1.16(s))						
	☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))						
						TOTAL ADD'L FEE	**0**

		(Column 1)		(Column 2)	(Column 3)		
AMENDMENT		CLAIMS REMAINING AFTER AMENDMENT		HIGHEST NUMBER PREVIOUSLY PAID FOR	PRESENT EXTRA	RATE ($)	ADDITIONAL FEE ($)
	Total (37 CFR 1.16(i))	*	Minus	**	=	X $ =	
	Independent (37 CFR 1.16(h))	*	Minus	***	=	X $ =	
	☐ Application Size Fee (37 CFR 1.16(s))						
	☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))						
						TOTAL ADD'L FEE	

* If the entry in column 1 is less than the entry in column 2, write "0" in column 3.
** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 20, enter "20".
*** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 3, enter "3".
The "Highest Number Previously Paid For" (Total or Independent) is the highest number found in the appropriate box in column 1.

LIE
TONI HAKIM

This collection of information is required by 37 CFR 1.16. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 12 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**
If you need assistance in completing the form, call 1-800-PTO-9199 and select option 2.

Samsung Bioepis Exhibit No. 1002
Page 10824

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

NOTICE OF ALLOWANCE AND FEE(S) DUE

133485 7590 06/28/2017

Nelson Mullins Riley & Scarborough LLP/Alexion
One Post Office Square
30th Floor
Boston, MA 02109-2127

EXAMINER
ROGERS, JAMES L

ART UNIT	PAPER NUMBER
1644	

DATE MAILED: 06/28/2017

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
15/260,888	09/09/2016	Leonard BELL	AXJ-114BUSCN3	2558

TITLE OF INVENTION: TREATMENT OF PAROXYSMAL NOCTURNAL HEMOGLOBINURIA PATIENTS BY AN INHIBITOR OF COMPLEMENT

APPLN. TYPE	ENTITY STATUS	ISSUE FEE DUE	PUBLICATION FEE DUE	PREV. PAID ISSUE FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	UNDISCOUNTED	$960	$0	$0	$960	09/28/2017

THE APPLICATION IDENTIFIED ABOVE HAS BEEN EXAMINED AND IS ALLOWED FOR ISSUANCE AS A PATENT. PROSECUTION ON THE MERITS IS CLOSED. THIS NOTICE OF ALLOWANCE IS NOT A GRANT OF PATENT RIGHTS. THIS APPLICATION IS SUBJECT TO WITHDRAWAL FROM ISSUE AT THE INITIATIVE OF THE OFFICE OR UPON PETITION BY THE APPLICANT. SEE 37 CFR 1.313 AND MPEP 1308.

THE ISSUE FEE AND PUBLICATION FEE (IF REQUIRED) MUST BE PAID WITHIN THREE MONTHS FROM THE MAILING DATE OF THIS NOTICE OR THIS APPLICATION SHALL BE REGARDED AS ABANDONED. THIS STATUTORY PERIOD CANNOT BE EXTENDED. SEE 35 U.S.C. 151. THE ISSUE FEE DUE INDICATED ABOVE DOES NOT REFLECT A CREDIT FOR ANY PREVIOUSLY PAID ISSUE FEE IN THIS APPLICATION. IF AN ISSUE FEE HAS PREVIOUSLY BEEN PAID IN THIS APPLICATION (AS SHOWN ABOVE), THE RETURN OF PART B OF THIS FORM WILL BE CONSIDERED A REQUEST TO REAPPLY THE PREVIOUSLY PAID ISSUE FEE TOWARD THE ISSUE FEE NOW DUE.

HOW TO REPLY TO THIS NOTICE:

I. Review the ENTITY STATUS shown above. If the ENTITY STATUS is shown as SMALL or MICRO, verify whether entitlement to that entity status still applies.

If the ENTITY STATUS is the same as shown above, pay the TOTAL FEE(S) DUE shown above.

If the ENTITY STATUS is changed from that shown above, on PART B - FEE(S) TRANSMITTAL, complete section number 5 titled "Change in Entity Status (from status indicated above)".

For purposes of this notice, small entity fees are 1/2 the amount of undiscounted fees, and micro entity fees are 1/2 the amount of small entity fees.

II. PART B - FEE(S) TRANSMITTAL, or its equivalent, must be completed and returned to the United States Patent and Trademark Office (USPTO) with your ISSUE FEE and PUBLICATION FEE (if required). If you are charging the fee(s) to your deposit account, section "4b" of Part B - Fee(s) Transmittal should be completed and an extra copy of the form should be submitted. If an equivalent of Part B is filed, a request to reapply a previously paid issue fee must be clearly made, and delays in processing may occur due to the difficulty in recognizing the paper as an equivalent of Part B.

III. All communications regarding this application must give the application number. Please direct all communications prior to issuance to Mail Stop ISSUE FEE unless advised to the contrary.

IMPORTANT REMINDER: Utility patents issuing on applications filed on or after Dec. 12, 1980 may require payment of maintenance fees. It is patentee's responsibility to ensure timely payment of maintenance fees when due.

PART B - FEE(S) TRANSMITTAL

Complete and send this form, together with applicable fee(s), to: Mail **Mail Stop ISSUE FEE**
Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450
or Fax (571)-273-2885

INSTRUCTIONS: This form should be used for transmitting the ISSUE FEE and PUBLICATION FEE (if required). Blocks 1 through 5 should be completed where appropriate. All further correspondence including the Patent, advance orders and notification of maintenance fees will be mailed to the current correspondence address as indicated unless corrected below or directed otherwise in Block 1, by (a) specifying a new correspondence address; and/or (b) indicating a separate "FEE ADDRESS" for maintenance fee notifications.

CURRENT CORRESPONDENCE ADDRESS (Note: Use Block 1 for any change of address)

133485 7590 06/28/2017
Nelson Mullins Riley & Scarborough LLP/Alexion
One Post Office Square
30th Floor
Boston, MA 02109-2127

Note: A certificate of mailing can only be used for domestic mailings of the Fee(s) Transmittal. This certificate cannot be used for any other accompanying papers. Each additional paper, such as an assignment or formal drawing, must have its own certificate of mailing or transmission.

Certificate of Mailing or Transmission
I hereby certify that this Fee(s) Transmittal is being deposited with the United States Postal Service with sufficient postage for first class mail in an envelope addressed to the Mail Stop ISSUE FEE address above, or being facsimile transmitted to the USPTO (571) 273-2885, on the date indicated below.

(Depositor's name)
(Signature)
(Date)

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
15/260,888	09/09/2016	Leonard BELL	AXJ-114BUSCN3	2558

TITLE OF INVENTION: TREATMENT OF PAROXYSMAL NOCTURNAL HEMOGLOBINURIA PATIENTS BY AN INHIBITOR OF COMPLEMENT

APPLN. TYPE	ENTITY STATUS	ISSUE FEE DUE	PUBLICATION FEE DUE	PREV. PAID ISSUE FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	UNDISCOUNTED	$960	$0	$0	$960	09/28/2017

EXAMINER	ART UNIT	CLASS-SUBCLASS
ROGERS, JAMES L	1644	424-133100

1. Change of correspondence address or indication of "Fee Address" (37 CFR 1.363).
- ❑ Change of correspondence address (or Change of Correspondence Address form PTO/SB/122) attached.
- ❑ "Fee Address" indication (or "Fee Address" Indication form PTO/SB/47; Rev 03-02 or more recent) attached. **Use of a Customer Number is required.**

2. For printing on the patent front page, list
(1) The names of up to 3 registered patent attorneys or agents OR, alternatively,
(2) The name of a single firm (having as a member a registered attorney or agent) and the names of up to 2 registered patent attorneys or agents. If no name is listed, no name will be printed.
1 _____
2 _____
3 _____

3. ASSIGNEE NAME AND RESIDENCE DATA TO BE PRINTED ON THE PATENT (print or type)

PLEASE NOTE: Unless an assignee is identified below, no assignee data will appear on the patent. If an assignee is identified below, the document has been filed for recordation as set forth in 37 CFR 3.11. Completion of this form is NOT a substitute for filing an assignment.

(A) NAME OF ASSIGNEE (B) RESIDENCE: (CITY and STATE OR COUNTRY)

Please check the appropriate assignee category or categories (will not be printed on the patent) : ❑ Individual ❑ Corporation or other private group entity ❑ Government

4a. The following fee(s) are submitted:
- ❑ Issue Fee
- ❑ Publication Fee (No small entity discount permitted)
- ❑ Advance Order - # of Copies _____

4b. Payment of Fee(s): **(Please first reapply any previously paid issue fee shown above)**
- ❑ A check is enclosed.
- ❑ Payment by credit card. Form PTO-2038 is attached.
- ❑ The director is hereby authorized to charge the required fee(s), any deficiency, or credits any overpayment, to Deposit Account Number _____ (enclose an extra copy of this form).

5. **Change in Entity Status** (from status indicated above)
- ❑ Applicant certifying micro entity status. See 37 CFR 1.29
  NOTE: Absent a valid certification of Micro Entity Status (see forms PTO/SB/15A and 15B), issue fee payment in the micro entity amount will not be accepted at the risk of application abandonment.
- ❑ Applicant asserting small entity status. See 37 CFR 1.27
  NOTE: If the application was previously under micro entity status, checking this box will be taken to be a notification of loss of entitlement to micro entity status.
- ❑ Applicant changing to regular undiscounted fee status.
  NOTE: Checking this box will be taken to be a notification of loss of entitlement to small or micro entity status, as applicable.

NOTE: This form must be signed in accordance with 37 CFR 1.31 and 1.33. See 37 CFR 1.4 for signature requirements and certifications.

Authorized Signature _____ Date _____

Typed or printed name _____ Registration No. _____

PTOL-85 Part B (10-13) Approved for use through 10/31/2013. OMB 0651-0033 U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

786

Samsung Bioepis Exhibit No. 1002
Page 10826

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
15/260,888	09/09/2016	Leonard BELL	AXJ-114BUSCN3	2558

133485 7590 06/28/2017

Nelson Mullins Riley & Scarborough LLP/Alexion
One Post Office Square
30th Floor
Boston, MA 02109-2127

EXAMINER	
ROGERS, JAMES L	
ART UNIT	PAPER NUMBER
1644	

DATE MAILED: 06/28/2017

Determination of Patent Term Adjustment under 35 U.S.C. 154 (b)
(Applications filed on or after May 29, 2000)

The Office has discontinued providing a Patent Term Adjustment (PTA) calculation with the Notice of Allowance.

Section 1(h)(2) of the AIA Technical Corrections Act amended 35 U.S.C. 154(b)(3)(B)(i) to eliminate the requirement that the Office provide a patent term adjustment determination with the notice of allowance. See Revisions to Patent Term Adjustment, 78 Fed. Reg. 19416, 19417 (Apr. 1, 2013). Therefore, the Office is no longer providing an initial patent term adjustment determination with the notice of allowance. The Office will continue to provide a patent term adjustment determination with the Issue Notification Letter that is mailed to applicant approximately three weeks prior to the issue date of the patent, and will include the patent term adjustment on the patent. Any request for reconsideration of the patent term adjustment determination (or reinstatement of patent term adjustment) should follow the process outlined in 37 CFR 1.705.

Any questions regarding the Patent Term Extension or Adjustment determination should be directed to the Office of Patent Legal Administration at (571)-272-7702. Questions relating to issue and publication fee payments should be directed to the Customer Service Center of the Office of Patent Publication at 1-(888)-786-0101 or (571)-272-4200.

OMB Clearance and PRA Burden Statement for PTOL-85 Part B

The Paperwork Reduction Act (PRA) of 1995 requires Federal agencies to obtain Office of Management and Budget approval before requesting most types of information from the public. When OMB approves an agency request to collect information from the public, OMB (i) provides a valid OMB Control Number and expiration date for the agency to display on the instrument that will be used to collect the information and (ii) requires the agency to inform the public about the OMB Control Number's legal significance in accordance with 5 CFR 1320.5(b).

The information collected by PTOL-85 Part B is required by 37 CFR 1.311. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 12 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, Virginia 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, Virginia 22313-1450. Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number.

Privacy Act Statement

The Privacy Act of 1974 (P.L. 93-579) requires that you be given certain information in connection with your submission of the attached form related to a patent application or patent. Accordingly, pursuant to the requirements of the Act, please be advised that: (1) the general authority for the collection of this information is 35 U.S.C. 2(b)(2); (2) furnishing of the information solicited is voluntary; and (3) the principal purpose for which the information is used by the U.S. Patent and Trademark Office is to process and/or examine your submission related to a patent application or patent. If you do not furnish the requested information, the U.S. Patent and Trademark Office may not be able to process and/or examine your submission, which may result in termination of proceedings or abandonment of the application or expiration of the patent.

The information provided by you in this form will be subject to the following routine uses:

1. The information on this form will be treated confidentially to the extent allowed under the Freedom of Information Act (5 U.S.C. 552) and the Privacy Act (5 U.S.C 552a). Records from this system of records may be disclosed to the Department of Justice to determine whether disclosure of these records is required by the Freedom of Information Act.
2. A record from this system of records may be disclosed, as a routine use, in the course of presenting evidence to a court, magistrate, or administrative tribunal, including disclosures to opposing counsel in the course of settlement negotiations.
3. A record in this system of records may be disclosed, as a routine use, to a Member of Congress submitting a request involving an individual, to whom the record pertains, when the individual has requested assistance from the Member with respect to the subject matter of the record.
4. A record in this system of records may be disclosed, as a routine use, to a contractor of the Agency having need for the information in order to perform a contract. Recipients of information shall be required to comply with the requirements of the Privacy Act of 1974, as amended, pursuant to 5 U.S.C. 552a(m).
5. A record related to an International Application filed under the Patent Cooperation Treaty in this system of records may be disclosed, as a routine use, to the International Bureau of the World Intellectual Property Organization, pursuant to the Patent Cooperation Treaty.
6. A record in this system of records may be disclosed, as a routine use, to another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c)).
7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (i.e., GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.
8. A record from this system of records may be disclosed, as a routine use, to the public after either publication of the application pursuant to 35 U.S.C. 122(b) or issuance of a patent pursuant to 35 U.S.C. 151. Further, a record may be disclosed, subject to the limitations of 37 CFR 1.14, as a routine use, to the public if the record was filed in an application which became abandoned or in which the proceedings were terminated and which application is referenced by either a published application, an application open to public inspection or an issued patent.
9. A record from this system of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.

Samsung Bioepis Exhibit No. 1002
Page 10828

Notice of Allowability	Application No. 15/260,888	Applicant(s) BELL ET AL.	
	Examiner JAMES ROGERS	Art Unit 1644	AIA (First Inventor to File) Status No

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address--

All claims being allowable, PROSECUTION ON THE MERITS IS (OR REMAINS) CLOSED in this application. If not included herewith (or previously mailed), a Notice of Allowance (PTOL-85) or other appropriate communication will be mailed in due course. **THIS NOTICE OF ALLOWABILITY IS NOT A GRANT OF PATENT RIGHTS.** This application is subject to withdrawal from issue at the initiative of the Office or upon petition by the applicant. See 37 CFR 1.313 and MPEP 1308.

1. ☒ This communication is responsive to *6/13/2017*.
   ☐ A declaration(s)/affidavit(s) under **37 CFR 1.130(b)** was/were filed on_____.
2. ☐ An election was made by the applicant in response to a restriction requirement set forth during the interview on _____; the restriction requirement and election have been incorporated into this action.
3. ☒ The allowed claim(s) is/are *1-10*. As a result of the allowed claim(s), you may be eligible to benefit from the **Patent Prosecution Highway** program at a participating intellectual property office for the corresponding application. For more information, please see http://www.uspto.gov/patents/init_events/pph/index.jsp or send an inquiry to PPHfeedback@uspto.gov.
4. ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

   Certified copies:

   a) ☐ All b) ☐ Some *c) ☐ None of the:
   1. ☐ Certified copies of the priority documents have been received.
   2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
   3. ☐ Copies of the certified copies of the priority documents have been received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

   * Certified copies not received: _____.

Applicant has THREE MONTHS FROM THE "MAILING DATE" of this communication to file a reply complying with the requirements noted below. Failure to timely comply will result in ABANDONMENT of this application.
THIS THREE-MONTH PERIOD IS NOT EXTENDABLE.

5. ☐ CORRECTED DRAWINGS (as "replacement sheets") must be submitted.
   ☐ including changes required by the attached Examiner's Amendment / Comment or in the Office action of Paper No./Mail Date _____.

   Identifying indicia such as the application number (see 37 CFR 1.84(c)) should be written on the drawings in the front (not the back) of each sheet. Replacement sheet(s) should be labeled as such in the header according to 37 CFR 1.121(d).
6. ☐ DEPOSIT OF and/or INFORMATION about the deposit of BIOLOGICAL MATERIAL must be submitted. Note the attached Examiner's comment regarding REQUIREMENT FOR THE DEPOSIT OF BIOLOGICAL MATERIAL.

Attachment(s)

1. ☐ Notice of References Cited (PTO-892)
2. ☒ Information Disclosure Statements (PTO/SB/08), Paper No./Mail Date _____
3. ☐ Examiner's Comment Regarding Requirement for Deposit of Biological Material
4. ☐ Interview Summary (PTO-413), Paper No./Mail Date _____ .
5. ☒ Examiner's Amendment/Comment
6. ☒ Examiner's Statement of Reasons for Allowance
7. ☐ Other _____.

/JAMES ROGERS/ Examiner, Art Unit 1644	/DANIEL E. KOLKER/ Supervisory Patent Examiner, Art Unit 1644

Samsung Bioepis Exhibit No. 1002
Page 10829

DETAILED ACTION

1. The present application is being examined under the pre-AIA first to invent provisions.

2. Applicant's Amendment/Response, filed 6/13/2017, is acknowledged.

3. Applicant's IDSs, filed 6/13/2017, are acknowledged and have been considered.

REASONS FOR ALLOWANCE

4. The following is an Examiner's Statement of Reasons for Allowance:

The claims are drawn to a method of treating a patient suffering from paroxysmal nocturnal hemoglobinuria (PNH) by administering to the patient an antibody that binds C5, wherein the antibody comprises a heavy chain consisting of SEQ ID NO: 2 and a light chain consisting of SEQ ID NO: 4.

Applicant's arguments in the Response of 6/13/2017 to the outstanding Non-final OA of 4/11/2017 which included rejections under 35 USC 102, 35 USC 103 and double patenting rejections as well as a Request for Additional Information Under 37 CFR 1.105 in conjunction with the Declaration Pursuant to 37 CFR 1.132 by Dr. Laural Boone, dated May 11, 2017 (previously submitted in a related case 15/148,839), is persuasive to overcome all of the rejections for the following reasons:

(a) None of the applied references in the rejections recite using an antibody which comprises a heavy chain consisting of SEQ ID NO: 2 and a light chain consisting of SEQ ID NO: 4 as currently recited and one of skill in the art would not have been easily guided to making antibodies with these recited sequences.

(b) Applicant's Response to the Request for Additional Information is considered sufficient and persuasive to conclude that each of the clinical trials conducted by applicant referenced in the Request did not constitute "public use" under 35 USC 102(b) of the claimed invention as they were not accessible to the public. As applicant notes in the response, factors which are used to determine if an invention is accessible to the public are set out by the Federal Circuit in *Dey, L.P. v. Sunovion Pharmaceuticals, Inc.*, (No. 2012-1428, Fed. Cir. May 20, 2013). The factual circumstances cited by applicant considered by the examiner as being most persuasive to negate any determination that the referenced clinical trials constituted "public use" is the use by applicant of confidentiality provisions and the fact that neither doctors nor patients had any knowledge of the currently claimed sequences of the antibody used in the studies. Other factual evidence presented by applicant includes the declaration by Laural S. Boone that strict control over the eculizumab drug was exercised for each clinical trial referenced (see p. 6 of the Declaration).

(c) The Double Patenting rejections have been overcome in light of applicant's approved TDs of 6/13/2017 over the '601, '980 and '263 patents.

Accordingly, claims 1-10, are deemed allowable.

5. Any comments considered necessary by applicant must be submitted no later than the payment of the issue fee and, to avoid processing delays, should preferably accompany the issue fee. Such submissions should be clearly labeled "Comments on Statement of Reasons for Allowance."

6. Any inquiry concerning this communication or earlier communications from the examiner should be directed to James Rogers whose telephone number is (571) 270-5374. The examiner can normally be reached Monday through Friday from 8:00 am to 5:30 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, **Daniel E. Kolker** can be reached on (571) 272-3181. The fax number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

June 21, 2017

/JAMES ROGERS/
Examiner, Art Unit 1644

/DANIEL E. KOLKER/

Supervisory Patent Examiner, Art Unit 1644

Samsung Bioepis Exhibit No. 1002
Page 10831

Doc code: IDS
Doc description: Information Disclosure Statement (IDS) Filed

PTO/SB/08a (03-15)
Approved for use through 07/31/2016. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it contains a valid OMB control number.

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (**Not for submission under 37 CFR 1.99**)		
	Application Number	15260888
	Filing Date	2016-09-09
	First Named Inventor	Leonard BELL
	Art Unit	1644
	Examiner Name	J. L. Rogers
	Attorney Docket Number	AXJ-114BUSCN3

U.S.PATENTS Remove

Examiner Initial*	Cite No	Patent Number	Kind Code[1]	Issue Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear
	1					

If you wish to add additional U.S. Patent citation information please click the Add button. Add

U.S.PATENT APPLICATION PUBLICATIONS Remove

Examiner Initial*	Cite No	Publication Number	Kind Code[1]	Publication Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear
	1	20170015741	A1	2017-01-19	Leonard BELL	

If you wish to add additional U.S. Published Application citation information please click the Add button. Add

FOREIGN PATENT DOCUMENTS Remove

Examiner Initial*	Cite No	Foreign Document Number[3]	Country Code[2] i	Kind Code[4]	Publication Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear	T[5]
	1							

If you wish to add additional Foreign Patent Document citation information please click the Add button Add

NON-PATENT LITERATURE DOCUMENTS Remove

Examiner Initials*	Cite No	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc), date, pages(s), volume-issue number(s), publisher, city and/or country where published.	T[5]

EFS Web 2.1.17

792

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /J.L.R/

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
	Application Number	15260888
	Filing Date	2016-09-09
	First Named Inventor	Leonard BELL
	Art Unit	1644
	Examiner Name	J. L. Rogers
	Attorney Docket Number	AXJ-114BUSCN3

	1		

If you wish to add additional non-patent literature document citation information please click the Add button Add

EXAMINER SIGNATURE

Examiner Signature	/JAMES L ROGERS/	Date Considered	06/21/2017

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through a citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

[1] See Kind Codes of USPTO Patent Documents at www.USPTO.GOV or MPEP 901.04. [2] Enter office that issued the document, by the two-letter code (WIPO Standard ST.3). [3] For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. [4] Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16 if possible. [5] Applicant is to place a check mark here if English language translation is attached.

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /J.L.R/

Samsung Bioepis Exhibit No. 1002
Page 10833

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
	Application Number	15260888
	Filing Date	2016-09-09
	First Named Inventor	Leonard BELL
	Art Unit	1644
	Examiner Name	J. L. Rogers
	Attorney Docket Number	AXJ-114BUSCN3

CERTIFICATION STATEMENT

Please see 37 CFR 1.97 and 1.98 to make the appropriate selection(s):

That each item of information contained in the information disclosure statement was first cited in any communication from a foreign patent office in a counterpart foreign application not more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(1).

OR

☐ That no item of information contained in the information disclosure statement was cited in a communication from a foreign patent office in a counterpart foreign application, and, to the knowledge of the person signing the certification after making reasonable inquiry, no item of information contained in the information disclosure statement was known to any individual designated in 37 CFR 1.56(c) more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(2).

See attached certification statement.

☒ The fee set forth in 37 CFR 1.17 (p) has been submitted herewith.

☒ A certification statement is not submitted herewith.

SIGNATURE

A signature of the applicant or representative is required in accordance with CFR 1.33, 10.18. Please see CFR 1.4(d) for the form of the signature.

Signature	/Jill Gorny Sloper, Esq./	Date (YYYY-MM-DD)	2017-06-13
Name/Print	Jill Gorny Sloper, Esq.	Registration Number	60,760

This collection of information is required by 37 CFR 1.97 and 1.98. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 1 hour to complete, including gathering, preparing and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

794

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /J.L.R/

Privacy Act Statement

The Privacy Act of 1974 (P.L. 93-579) requires that you be given certain information in connection with your submission of the attached form related to a patent application or patent. Accordingly, pursuant to the requirements of the Act, please be advised that: (1) the general authority for the collection of this information is 35 U.S.C. 2(b)(2); (2) furnishing of the information solicited is voluntary; and (3) the principal purpose for which the information is used by the U.S. Patent and Trademark Office is to process and/or examine your submission related to a patent application or patent. If you do not furnish the requested information, the U.S. Patent and Trademark Office may not be able to process and/or examine your submission, which may result in termination of proceedings or abandonment of the application or expiration of the patent.

The information provided by you in this form will be subject to the following routine uses:

1. The information on this form will be treated confidentially to the extent allowed under the Freedom of Information Act (5 U.S.C. 552) and the Privacy Act (5 U.S.C. 552a). Records from this system of records may be disclosed to the Department of Justice to determine whether the Freedom of Information Act requires disclosure of these record s.

2. A record from this system of records may be disclosed, as a routine use, in the course of presenting evidence to a court, magistrate, or administrative tribunal, including disclosures to opposing counsel in the course of settlement negotiations.

3. A record in this system of records may be disclosed, as a routine use, to a Member of Congress submitting a request involving an individual, to whom the record pertains, when the individual has requested assistance from the Member with respect to the subject matter of the record.

4. A record in this system of records may be disclosed, as a routine use, to a contractor of the Agency having need for the information in order to perform a contract. Recipients of information shall be required to comply with the requirements of the Privacy Act of 1974, as amended, pursuant to 5 U.S.C. 552a(m).

5. A record related to an International Application filed under the Patent Cooperation Treaty in this system of records may be disclosed, as a routine use, to the International Bureau of the World Intellectual Property Organization, pursuant to the Patent Cooperation Treaty.

6. A record in this system of records may be disclosed, as a routine use, to another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c)).

7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (i.e., GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.

8. A record from this system of records may be disclosed, as a routine use, to the public after either publication of the application pursuant to 35 U.S.C. 122(b) or issuance of a patent pursuant to 35 U.S.C. 151. Further, a record may be disclosed, subject to the limitations of 37 CFR 1.14, as a routine use, to the public if the record was filed in an application which became abandoned or in which the proceedings were terminated and which application is referenced by either a published application, an application open to public inspections or an issued patent.

9. A record from this system of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /J.L.R/

Samsung Bioepis Exhibit No. 1002
Page 10835

I hereby certify that this paper (along with any paper referred to as being attached or enclosed) is being transmitted via the Office electronic filing system in accordance with 37 CFR § 1.6(a)(4).

Dated: June 13, 2017
Electronic Signature for Jill Gorny Sloper, Esq.: /Jill Gorny Sloper, Esq./

Docket No.: AXJ-114BUSCN3
(PATENT)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of:
Leonard Bell *et al.*

Application No.: 15/260,888 Confirmation No.: 2558

Filed: September 9, 2016 Art Unit: 1644

For: TREATMENT OF PAROXYSMAL NOCTURNAL HEMOGLOBINURIA PATIENTS BY AN INHIBITOR OF COMPLEMENT

Examiner: J. L. Rogers

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

SUPPLEMENTAL INFORMATION DISCLOSURE STATEMENT (SIDS)

Dear Sir:

In compliance with 37 C.F.R. § 1.56, 1.97 and 1.98, the attention of the Patent and Trademark Office is hereby directed to the document listed on the attached PTO/SB/08. In accordance with 37 C.F.R. § 1.98(a)(2)(i)-(iv), Applicant has not included copies of U.S. patent publication.

It is respectfully requested that the document listed on the PTO/SB/08 be expressly considered by the Examiner during the prosecution of this application, and that the document be made of record therein and appear among the "References Cited" on any patent to issue therefrom.

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /J.L.R/

Samsung Bioepis Exhibit No. 1002
Page 10836

Applicant provides herewith copies of Office Actions from Applications previously made of record:

Office Actions (copies enclosed)				
Examiner's Initials	Serial No.:	Date Mailed from USPTO	Examiner	Docket No.
	15/284,015	04-11-2017	J. Rogers	AXJ-114BUSCN4
	15/284,015	11-01-2016	J. Rogers	AXJ-114BUSCN4
	15/148,839	06-07-2017	J. Rogers	AXJ-114BUSCN2
	15/148,839	04-04-2017	J. Rogers	AXJ-114BUSCN2

/JAMES L ROGERS/ 06/21/2017

The Examiner is requested to review the file histories of these applications, including cited references, Office Actions, Responses, etc., and is asked to contact Applicant's Attorney if the Examiner would like the Applicant to supply copies of any or all of the information included in these applications. If Applicant's Attorney is not contacted by the Examiner with such a request, then it will be concluded that the Examiner has reviewed or will review the file content of these applications.

Applicant respectfully requests that the Examiner initial the blank columns next to the cited Office Actions, to indicate that the information has been considered by the Examiner. Alternatively, Applicant requests that the Examiner insert the phrase, "All references considered except where lined through," on each page of the Information Disclosure Statement, along with the Examiner's initials.

The filing of this Information Disclosure Statement is not to be interpreted as a representation that the cited document is material, that an exhaustive search has been conducted, or that no other relevant information exists. Nor shall the citation of the document herein be construed *per se* as a representation that such document is prior art. Moreover, Applicant understands the Examiner will make an independent evaluation of the cited document.

This Information Disclosure Statement is filed after the mailing date of a first Office Action on the merits, but before the mailing date of any of a Final Action under 37 C.F.R.§ 1.113, a Notice

797

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /J.L.R/

Samsung Bioepis Exhibit No. 1002
Page 10837

of Allowance under 37 C.F.R. § 1.311 or an action that otherwise closes prosecution in this application (37 C.F.R. § 1.97(c)).

Please charge our Deposit Account No. 12-0080 in the amount of $180.00 covering the fee set forth in 37 C.F.R. § 1.17(p). The Director is hereby authorized to charge any deficiency in the fees filed, asserted to be filed or which should have been filed herewith to our Deposit Account No. 12-0080, under Order No. AXJ-114BUSCN3.

Dated: June 13, 2017

Respectfully submitted,

Electronic signature: /Jill Gorny Sloper, Esq./
Jill Gorny Sloper, Esq.
Registration No.: 60,760
NELSON MULLINS RILEY & SCARBOROUGH LLP
One Post Office Square
Boston, Massachusetts 02109-2127
(617) 217-4630
(617) 742-4214 (Fax)
Attorney/Agent For Applicant

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /J.L.R/

Search Notes	Application/Control No.	Applicant(s)/Patent Under Reexamination
	15260888	BELL ET AL.
	Examiner	Art Unit
	JAMES ROGERS	1644

CPC- SEARCHED		
Symbol	Date	Examiner

CPC COMBINATION SETS - SEARCHED		
Symbol	Date	Examiner

US CLASSIFICATION SEARCHED			
Class	Subclass	Date	Examiner

SEARCH NOTES		
Search Notes	Date	Examiner
STN: DISSABS MEETINGS BIOSCI CAPLUS MEDICINE	10/19/2016	JR
EAST: PGPUB, USPAT, JPO, EPO, INVENTOR SEARCH	10/19/2016	JR
updated	6/21/2017	JR

INTERFERENCE SEARCH			
US Class/ CPC Symbol	US Subclass / CPC Group	Date	Examiner
	USPAT, USPAD, SEQ ID NO: 2, 4	10/19/2016	JR

/JAMES ROGERS/ Examiner.Art Unit 1644	

EAST Search History

EAST Search History (Prior Art)

<This search history is empty>

EAST Search History (Interference)

Ref #	Hits	Search Query	DBs	Default Operator	Plurals	Time Stamp
L1	14	(((hemolytic near3 disease) or hemolysis or hemoglobinuria) near20 (C5 near10 antibody)).clm.	US-PGPUB; USPAT	OR	ON	2017/06/21 12:20

6/21/2017 12:21:50 PM

Issue Classification	Application/Control No.	Applicant(s)/Patent Under Reexamination
	15260888	BELL ET AL.
	Examiner	**Art Unit**
	JAMES ROGERS	1644

CPC							
Symbol						**Type**	**Version**
C07K		16	/	18		F	2013-01-01
A61K		31	/	7105		I	2013-01-01
A61K		2039	/	505		A	2013-01-01
A61K		38	/	00		A	2013-01-01
C07K		2317	/	24		A	2013-01-01
C07K		2317	/	565		A	2013-01-01
A61K		9	/	0019		I	2013-01-01
C07K		2317	/	51		A	2013-01-01
C07K		2317	/	515		A	2013-01-01
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CPC Combination Sets								
Symbol					**Type**	**Set**	**Ranking**	**Version**
			/					
			/					

/JAMES ROGERS/ Examiner.Art Unit 1644		**Total Claims Allowed:**	
(Assistant Examiner)	(Date)	10	
/DANIEL E KOLKER/ Supervisory Patent Examiner.Art Unit 1644	06/21/2017	O.G. Print Claim(s)	O.G. Print Figure
(Primary Examiner)	(Date)	1	none

U.S. Patent and Trademark Office — Part of Paper No. 20170621

Samsung Bioepis Exhibit No. 1002
Page 10841

Issue Classification	Application/Control No.	Applicant(s)/Patent Under Reexamination
	15260888	BELL ET AL.
	Examiner	**Art Unit**
	JAMES ROGERS	1644

US ORIGINAL CLASSIFICATION		INTERNATIONAL CLASSIFICATION										
CLASS	SUBCLASS	CLAIMED					NON-CLAIMED					
		A	6	1	K	39 / 00 (2006.01.01)						
CROSS REFERENCE(S)		A	6	1	K	9 / 00 (2006.0)						
		C	0	7	K	16 / 18 (2006.0)						
CLASS	SUBCLASS (ONE SUBCLASS PER BLOCK)	C	0	7	K	19 / 00 (2006.0)						

/JAMES ROGERS/ Examiner.Art Unit 1644 (Assistant Examiner)	(Date)	**Total Claims Allowed:** 10	
/DANIEL E KOLKER/ Supervisory Patent Examiner.Art Unit 1644 (Primary Examiner)	06/21/2017 (Date)	O.G. Print Claim(s) 1	O.G. Print Figure none

Issue Classification	Application/Control No.	Applicant(s)/Patent Under Reexamination
	15260888	BELL ET AL.
	Examiner	**Art Unit**
	JAMES ROGERS	1644

☒ Claims renumbered in the same order as presented by applicant ☐ CPA ☒ T.D. ☐ R.1.47

Final	Original	Final	Original	Final	Original	Final	Original	Final	Original	Final	Original	Final	Original	Final	Original

/JAMES ROGERS/ Examiner.Art Unit 1644		**Total Claims Allowed:**	
(Assistant Examiner)	(Date)	10	
/DANIEL E KOLKER/ Supervisory Patent Examiner.Art Unit 1644	06/21/2017	O.G. Print Claim(s)	O.G. Print Figure
(Primary Examiner)	(Date)	1	none

U.S. Patent and Trademark Office Part of Paper No. 20170621

Samsung Bioepis Exhibit No. 1002
Page 10843

PART B–FEE(S) TRANSMITTAL

Complete and send this form, together with the applicable fee(s), to: Mail **Mail Stop ISSUE FEE**
Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22314-1450
or Fax **(571)-273-2885**

INSTRUCTIONS: This form should be used for transmitting the ISSUE FEE and PUBLICATION FEE (if required). Blocks 1 through 5 should be completed where appropriate. All further correspondence including the Patent, advance orders and notification of maintenance fees will be mailed to the current correspondence address as indicated unless corrected below or directed otherwise in Block 1, by (a) specifying a new correspondence address; and/or (b) indicating a separate "FEE ADDRESS" for maintenance fee notifications.

CURRENT CORRESPONDENCE ADDRESS (Note Use Block 1 for any change of address)

133485 7590 06/28/2017
NELSON MULLINS RILEY & SCARBOROUGH LLP
One Post Office Square
Boston, Massachusetts 02109-2127

Note: A certificate of mailing can only be used for domestic mailings of the Fee(s) Transmittal. This certificate cannot be used for any other accompanying papers. Each additional paper, such as an assignment or formal drawing, must have its own certificate of mailing or transmission.

Certificate of Mailing or Transmission

I hereby certify that this Fee(s) Transmittal is being deposited with the United States Postal Service with sufficient postage for first class mail in an envelope addressed to the Mail Stop ISSUE FEE address above, or being facsimile transmitted to the USPTO (571) 273-2885, on the date indicated below.

(Depositor's Name)
(S-signature)
(Date)

APPLICATION NO	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO	CONFIRMATION NO
15/260,888	09/09/2016	Leonard BELL	AXJ-114BUSCN3	2558

TITLE OF INVENTION: TREATMENT OF PAROXYSMAL NOCTURNAL HEMOGLOBINURIA PATIENTS BY AN INHIBITOR OF COMPLEMENT

APPLN: TYPE	ENTITY STATUS	ISSUE FEE DUE	PUBLICATION FEE DUE	PREV. PAID ISSUE FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	UNDISCOUNTED	$960.00	$0	$0	$963.00	09/28/2017

EXAMINER	ART UNIT	CLASS-SUBCLASS
J. L. Rogers	1644	424-133100

1. Change of correspondence address or indication of "Fee Address" (37CFR 1.363).

[ ] Change of correspondence address (or Change of Correspondence Address form PTO/SB/122) attached.

[x] "Fee Address" indication (or "Fee Address" Indication form PTO/SB/47; Rev 03-02 or more recent) attached. **Use of a Customer Number is required.**

2. For printing on the patent front page, list
(1) The names of up to 3 registered patent attorneys or agents OR, alternatively,
(2) The name of a single firm (having as a member a registered attorney or agent) and the names of up to 2 registered attorney or agent. If no name is listed, no name will be printed

1. J. Darrell Fontenot, Ph.D., J.D.
2. Jane E. Remillard, Esq.
3. Jill Gorny Sloper, Esq.

3. ASSIGNEE NAME AND RESIDENCE DATA TO BE PRINTED ON THE PATENT (print or type)

PLEASE NOTE: Unless an assignee is identified below, no assignee data will appear on the patent. If an assignee is identified below, the document has been filed for recordation as set forth in 37 CFR 3.11. Completion of this form is NOT a substitute for filing an assignment.

1a. NAME OF ASSIGNEE: Alexion Pharmaceuticals, Inc.

(B) RESIDENCE: (CITY and STATE OR COUNTRY): New Haven, Connecticut

Please check the appropriate assignee categories (will not be printed on the patent): [ ] Individual [x] Corporation or other private group entity [ ] Government

4a. The following fee(s) are submitted:

[x] Issue Fee

[ ] Publication Fee (No small entity discount permitted)

[x] Advance Order - # of Copies 1

4b. Payment of Fees(s): **(Please first reapply and previously paid fee shown above)**

[ ] A check is enclosed

[ ] Payment be credit card. Form PTO-2038 is attached

[x] The director is hereby authorized to charge the required fee(s), any deficiency, or credits any overpayment, to Deposit Account Number 12-0080 (enclose an extra copy of this form)

5. Change of Entity Status (from status indicated above)

[ ] Applicant certifying micro entity status. See 37 CFR 1.29 NOTE: Absent a valid certification of Micro Entity Status (see forms PTO/SB/15A and 15B), issue fee payment in the micro entity amount will not be accepted at the risk of application abandonment.

[ ] Applicant asserting small entity status. See 37 CFR 1.27 NOTE: If the application was previously under micro entity status, checking this box will be taken to be a notification of loss of entitlement to micro entity status.

[ ] Applicant changing to regnlar undiscounted fee status. NOTE: Checking this box will be taken to be notification of loss of entitlement to small or micro entity status, as applicable.

NOTE: This form must be signed in accordance with 37 CFR 1.31 and 1.33. See 37 CFR 1.4 for signature requirements and certifications.

Authorized Signature /Jill Gorny Sloper, Esq./ Date June 28, 2017

Typed or printed name Jill Gorny Sloper, Esq. Registration No. 60,760

PTO/SB/47 (03-09)
Approved for use through 05/31/2015. OMB 0651-0016
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"FEE ADDRESS" INDICATION FORM

Address to:
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Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

- OR -

Fax to:
571-273-6500

INSTRUCTIONS: The issue fee must have been paid for application(s) listed on this form. In addition, only an address represented by a Customer Number can be established as the fee address for maintenance fee purposes (hereafter, fee address). A fee address should be established when correspondence related to maintenance fees should be mailed to a different address than the correspondence address for the application. **When to check the first box below:** If you have a Customer Number to represent the fee address. **When to check the second box below:** If you have no Customer Number representing the desired fee address, in which case a completed Request for Customer Number (PTO/SB/125) must be attached to this form. For more information on Customer Numbers, see the Manual of Patent Examining Procedure (MPEP) § 403.

For the following listed application(s), please recognize as the "Fee Address" under the provisions of 37 CFR 1.363 the address associated with:

[X] Customer Number: 127532

OR

[ ] The attached Request for Customer Number (PTO/SB/125) form.

PATENT NUMBER (if known)	APPLICATION NUMBER
	15/260,888

Completed by (check one):

[ ] Applicant/Inventor

[X] Attorney or Agent of record 60,760 (Reg. No.)

[ ] Assignee of record of the entire interest. See 37 CFR 3.71. Statement under 37 CFR 3.73(b) is enclosed. (Form PTO/SB/96)

[ ] Assignee recorded at Reel _____ Frame _____

/Jill Gorny Sloper, Esq./
Signature

Jill Gorny Sloper, Esq.
Typed or printed name

(617) 217-4630
Requester's telephone number

June 28, 2017
Date

NOTE: Signatures of all the inventors or assignees of record of the entire interest or their representative(s) are required. Submit multiple forms if more that one signature is required, see below*.

[ ] * Total of 1 forms are submitted.

I hereby certify that this paper (along with any paper referred to as being attached or enclosed) is being transmitted via the Office electronic filing system in accordance with 37 CFR § 1.6(a)(4).

Dated: June 28, 2017 Electronic Signature for Jill Gorny Sloper, Esq.: /Jill Gorny Sloper, Esq./

Electronic Patent Application Fee Transmittal

Application Number:	15260888
Filing Date:	09-Sep-2016
Title of Invention:	TREATMENT OF PAROXYSMAL NOCTURNAL HEMOGLOBINURIA PATIENTS BY AN INHIBITOR OF COMPLEMENT
First Named Inventor/Applicant Name:	Leonard BELL
Filer:	Jill R. Gorny Sloper/Danielle Gamache
Attorney Docket Number:	AXJ-114BUSCN3

Filed as Large Entity

Filing Fees for Utility under 35 USC 111(a)

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Basic Filing:				
Pages:				
Claims:				
Miscellaneous-Filing:				
Petition:				
Patent-Appeals-and-Interference:				
Post-Allowance-and-Post-Issuance:				
UTILITY APPL ISSUE FEE	1501	1	960	960

Samsung Bioepis Exhibit No. 1002
Page 10846

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Extension-of-Time:				
Miscellaneous:				
Printed copy of patent - no color	8001	1	3	3
		Total in USD ($)		**963**

Samsung Bioepis Exhibit No. 1002
Page 10847

Electronic Acknowledgement Receipt	
EFS ID:	29631671
Application Number:	15260888
International Application Number:	
Confirmation Number:	2558
Title of Invention:	TREATMENT OF PAROXYSMAL NOCTURNAL HEMOGLOBINURIA PATIENTS BY AN INHIBITOR OF COMPLEMENT
First Named Inventor/Applicant Name:	Leonard BELL
Customer Number:	133485
Filer:	Jill R. Gorny Sloper/Danielle Gamache
Filer Authorized By:	Jill R. Gorny Sloper
Attorney Docket Number:	AXJ-114BUSCN3
Receipt Date:	28-JUN-2017
Filing Date:	09-SEP-2016
Time Stamp:	15:56:37
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	yes
Payment Type	DA
Payment was successfully received in RAM	$963
RAM confirmation Number	062917INTEFSW00002943120080
Deposit Account	120080
Authorized User	Jill Sloper
The Director of the USPTO is hereby authorized to charge indicated fees and credit any overpayment as follows: 37 CFR 1.16 (National application filing, search, and examination fees) 37 CFR 1.17 (Patent application and reexamination processing fees)	

37 CFR 1.19 (Document supply fees)

37 CFR 1.20 (Post Issuance fees)

37 CFR 1.21 (Miscellaneous fees and charges)

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Issue Fee Payment (PTO-85B)	IFT.pdf	119819 8f70c5e40d18de7b524fc56bf94f3bc944a0cdbe	no	1
Warnings:					
Information:					
2	Change of Address	Change_Fee.pdf	122136 6108b391150fcc582d7289caad988d5a1613a882	no	1
Warnings:					
Information:					
3	Fee Worksheet (SB06)	fee-info.pdf	32390 fae13ec15d3262d4ffa123aef0f6ebbde6baf21d	no	2
Warnings:					
Information:					
		Total Files Size (in bytes):	274345		

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111

If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371

If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office

If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

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Page 10849

UNITED STATES PATENT AND TRADEMARK OFFICE

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Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	ISSUE DATE	PATENT NO.	ATTORNEY DOCKET NO.	CONFIRMATION NO.
15/260,888	08/08/2017	9725504	AXJ-114BUSCN3	2558

133485 7590 07/19/2017

Nelson Mullins Riley & Scarborough LLP/Alexion
One Post Office Square
30th Floor
Boston, MA 02109-2127

ISSUE NOTIFICATION

The projected patent number and issue date are specified above.

Determination of Patent Term Adjustment under 35 U.S.C. 154 (b)
(application filed on or after May 29, 2000)

The Patent Term Adjustment is 0 day(s). Any patent to issue from the above-identified application will include an indication of the adjustment on the front page.

If a Continued Prosecution Application (CPA) was filed in the above-identified application, the filing date that determines Patent Term Adjustment is the filing date of the most recent CPA.

Applicant will be able to obtain more detailed information by accessing the Patent Application Information Retrieval (PAIR) WEB site (http://pair.uspto.gov).

Any questions regarding the Patent Term Extension or Adjustment determination should be directed to the Office of Patent Legal Administration at (571)-272-7702. Questions relating to issue and publication fee payments should be directed to the Application Assistance Unit (AAU) of the Office of Data Management (ODM) at (571)-272-4200.

APPLICANT(s) (Please see PAIR WEB site http://pair.uspto.gov for additional applicants):

Leonard BELL, Woodbridge, CT;
Alexion Pharmaceuticals, Inc., New Haven, CT;
Russell P. ROTHER, Oklahoma City, OK;
Mark J. EVANS, Radnor, PA;

The United States represents the largest, most dynamic marketplace in the world and is an unparalleled location for business investment, innovation, and commercialization of new technologies. The USA offers tremendous resources and advantages for those who invest and manufacture goods here. Through SelectUSA, our nation works to encourage and facilitate business investment. To learn more about why the USA is the best country in the world to develop technology, manufacture products, and grow your business, visit SelectUSA.gov.

PTO/SB/44 (09-07)
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UNITED STATES PATENT AND TRADEMARK OFFICE
CERTIFICATE OF CORRECTION

PATENT NO.	:	9,725,504
APPLICATION NO.	:	15/260,888
ISSUE DATE	:	August 8, 2017
INVENTOR(S)	:	Leonard BELL *et al.*

It is certified that an error appears or errors appear in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

On page 2, first column, under “Other Publications”, line 25, delete “nocturnal; hemogloinuria” and insert - - nocturnal hemoglobinuria - -, therefor.

On page 3, first column, under “Other Publications”, line 38, delete “Neisseia” and insert - - Neisseria - -, therefor.

On page 3, second column, under “Other Publications”, line 33, delete “Hemoglobinuira” and insert - - Hemoglobinuria - -, therefor.

On page 3, second column, under “Other Publications”, line 37, delete “Phamaceuticals:” and insert - - Pharmaceuticals: - -, therefor.

On page 4, first column, under “Other Publications”, line 23, delete “Pharmaceuitcals” and insert - - Pharmaceuticals - -, therefor.

On page 4, first column, under “Other Publications”, line 53, delete “Endonuclial” and insert - - Endothelial - -, therefor.

On page 4, second column, under “Other Publications”, line 12, delete “EMAIHMPC” and insert - - EMA/HMPC - -, therefor.

On page 4, second column, under “Other Publications”, line 34, delete “htto:” and insert - - http: - -, therefor.

MAILING ADDRESS OF SENDER (Please do not use Customer Number below):
Jill Gorny Sloper, Esq.
NELSON MULLINS RILEY & SCARBOROUGH LLP 1
One Post Office Square
Boston, Massachusetts 02109-2127

Samsung Bioepis Exhibit No. 1002
Page 10851

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UNITED STATES PATENT AND TRADEMARK OFFICE
CERTIFICATE OF CORRECTION

PATENT NO.	:	9,725,504
APPLICATION NO.	:	15/260,888
ISSUE DATE	:	August 8, 2017
INVENTOR(S)	:	Leonard BELL *et al.*

It is certified that an error appears or errors appear in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

In column 2, line 65, delete “embodiment,” and insert - - embodiments, - -, therefor.

In column 4, line 2, delete “antibodies;” and insert - - antibodies, - -, therefor.

In column 4, line 23, delete “comprises,” and insert - - comprises - -, therefor.

In column 4, line 28, delete “the” and insert - - an - -, therefor.

In column 4, line 43, delete “No:5,” and insert - - No: 5, - -, therefor.

In column 4, line 43, delete “No:6,” and insert - - No: 6, - -, therefor.

In column 4, line 44, delete “No:7,” and insert - - No: 7, - -, therefor.

In column 4, line 47, delete “No:8,” and insert - - No: 8, - -, therefor.

In column 4, line 47, delete “No:9,” and insert - - No: 9, - -, therefor.

In column 4, line 47, delete “SEQ, ID NO:10.” and insert - - SEQ ID NO: 10. - -, therefor.

In column 4, line 65, delete “lass” and insert - - less - -, therefor.

In column 5, line 45, delete “life” and insert - - Life - -, therefor.

In column 6, line 24, delete “art,” and insert - - art. - -, therefor.

In column 6, line 25, delete “on” and insert - - or - -, therefor.

In column 6, line 35, delete “HSF S2” and insert - - HSP S2 - -, therefor.

In column 7, line 39, delete “pathway),” and insert - - pathway) - -, therefor.

MAILING ADDRESS OF SENDER (Please do not use Customer Number below):
Jill Gorny Sloper, Esq.
NELSON MULLINS RILEY & SCARBOROUGH LLP 2
One Post Office Square
Boston, Massachusetts 02109-2127

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Page 10852

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UNITED STATES PATENT AND TRADEMARK OFFICE
CERTIFICATE OF CORRECTION

PATENT NO.	:	9,725,504
APPLICATION NO.	:	15/260,888
ISSUE DATE	:	August 8, 2017
INVENTOR(S)	:	Leonard BELL *et al.*

It is certified that an error appears or errors appear in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

In column 7, line 61, delete “T,” and insert - - I, - -, therefor.

In column 7, line 65, delete “75 µg/ml,” and insert - - 75 µg/mL - -, therefor.

In column 7, line 67, delete “999 amino,” and insert - - 999 amino - -, therefor.

In column 8, line 26, delete “1975;” and insert - - 1978; - -, therefor.

In column 8, line 54, delete “al.;” and insert - - al., - -, therefor.

In column 9, line 14, delete “formation, of” and insert - - formation of - -, therefor.

In column 9, line 35, delete “as death” and insert - - as 1, death - -, therefor.

In column 10, line 31, delete “macro molecule” and insert - - macromolecule - -, therefor.

In column 10, line 42, delete “of” and insert - - or - -, therefor.

In column 11, line 42, delete “2d” and insert - - 2nd - -, therefor.

In column 12, line 7, delete “levels,” and insert - - levels - -, therefor.

In column 12, line 9, delete “BIA kit,” and insert - - EIA kit, - -, therefor.

In column 12, line 18, delete “anaphylatoxic” and insert - - anaphylatoxin - -, therefor.

In column 12, line 67, delete “fragments;” and insert - - fragments, - -, therefor.

In column 13, line 19, delete “tight” and insert - - light - -, therefor.

In column 13, line 19, delete “(CH1),” and insert - - (CH1) - -, therefor.

MAILING ADDRESS OF SENDER (Please do not use Customer Number below):
Jill Gorny Sloper, Esq.
NELSON MULLINS RILEY & SCARBOROUGH LLP 3
One Post Office Square
Boston, Massachusetts 02109-2127

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Page 10853

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UNITED STATES PATENT AND TRADEMARK OFFICE
CERTIFICATE OF CORRECTION

PATENT NO.	:	9,725,504
APPLICATION NO.	:	15/260,888
ISSUE DATE	:	August 8, 2017
INVENTOR(S)	:	Leonard BELL *et al.*

It is certified that an error appears or errors appear in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

In column 13, line 33, delete “scFV” and insert - - scFv - -, therefor.

In column 14, line 25, delete “(see, U.S.” and insert - - (see, e.g., U.S. - -, therefor.

In column 14, line 64, delete “from,” and insert - - from - -, therefor.

In column 14, line 66, delete “same/anti-human” and insert - - same anti-human - -, therefor.

In column 15, line 45, delete “&.” and insert - - & - -, therefor.

In column 16, line 47, delete “Philadelphia;” and insert - - Philadelphia, - -, therefor.

In column 17, line 62, delete “another,” and insert - - another - -, therefor.

In column 17, line 63, delete “liquid,” and insert - - liquid - -, therefor.

In column 19, line 2, after “(mg/mL)]” insert - - . - -.

In column 19, line 6, delete “antibodies,” and insert - - antibodies - -, therefor.

In column 19, line 25, delete “antibody,” and insert - - antibody - -, therefor.

In column 19, line 44, delete “syringes;” and insert - - syringes, - -, therefor.

In column 20, line 2, delete “genetically,” and insert - - genetically - -, therefor.

In column 20, lines 3-4, delete “Meningitides.” and insert - - meningitides. - -, therefor.

In column 20, line 24, delete “PBRC” and insert - - PRBC - -, therefor.

In column 20, line 31, delete “individuals” and insert - - individual's - -, therefor.

MAILING ADDRESS OF SENDER (Please do not use Customer Number below):
Jill Gorny Sloper, Esq.
NELSON MULLINS RILEY & SCARBOROUGH LLP 4
One Post Office Square
Boston, Massachusetts 02109-2127

Samsung Bioepis Exhibit No. 1002
Page 10854

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UNITED STATES PATENT AND TRADEMARK OFFICE
CERTIFICATE OF CORRECTION

PATENT NO.	:	9,725,504
APPLICATION NO.	:	15/260,888
ISSUE DATE	:	August 8, 2017
INVENTOR(S)	:	Leonard BELL *et al.*

It is certified that an error appears or errors appear in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

In column 20, line 65, delete “QoL,” and insert - - QoL - -, therefor.

In column 21, line 3, delete “baseline,” and insert - - baseline - -, therefor.

In column 21, line 59, delete “cohorts;” and insert - - cohorts: - -, therefor.

In column 21, lines 62-63, delete “myelodysplasia” and insert - - myelodysplastic - -, therefor.

In column 22, line 11, delete “Pharmacodynamics.” and insert - - Pharmacodynamics - -, therefor.

In column 22, line 49, delete “above,” and insert - - above - -, therefor.

In column 22, line 56, delete “(standard” and insert - - (±standard - -, therefor.

In column 22, line 63, delete “type II” and insert - - type III - -, therefor.

In column 23, line 19, delete “(P=0.001),” and insert - - (P<0.001), - -, therefor.

In column 23, line 28, delete “patients,” and insert - - patients - -, therefor.

In columns 23-24, in Table 1, line 17, delete “2-sidexl” and insert - - 2-sided - -, therefor.

In column 24, line 6, delete “1.2 from” and insert - - 1.2 points from - -, therefor.

In column 24, line 17, delete “(P<0:001),” and insert - - (P<0.001), - -, therefor.

In column 24, line 21, delete “improvements,” and insert - - improvements - -, therefor.

In column 25, line 29, delete “analysis” and insert - - analysis, - -, therefor.

In column 25, line 30, delete “levels” and insert - - levels, - -, therefor.

MAILING ADDRESS OF SENDER (Please do not use Customer Number below):
Jill Gorny Sloper, Esq.
NELSON MULLINS RILEY & SCARBOROUGH LLP 5
One Post Office Square
Boston, Massachusetts 02109-2127

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Page 10855

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UNITED STATES PATENT AND TRADEMARK OFFICE
CERTIFICATE OF CORRECTION

PATENT NO.	:	9,725,504
APPLICATION NO.	:	15/260,888
ISSUE DATE	:	August 8, 2017
INVENTOR(S)	:	Leonard BELL *et al.*

It is certified that an error appears or errors appear in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

In column 25, in Table 3, line 49, delete “Categery” and insert - - Category - -, therefor.

In column 26, lines 1-2, delete “(treatment” and insert - - treatment - -, therefor.

In column 26, line 62, after “treated” insert - - patients - -.

In column 28, line 10, delete “patient,” and insert - - patient - -, therefor.

In column 28, line 54, delete “gene,” and insert - - gene - -, therefor.

In column 28, line 58, delete “PIG-A gene,” and insert - - PIG-A gene. - -, therefor.

In column 29, line 61, delete “Ref Type: Abstract”.

MAILING ADDRESS OF SENDER (Please do not use Customer Number below):
Jill Gorny Sloper, Esq.
NELSON MULLINS RILEY & SCARBOROUGH LLP 6
One Post Office Square
Boston, Massachusetts 02109-2127

I hereby certify that this paper (along with any paper referred to as being attached or enclosed) is being transmitted via the Office electronic filing system in accordance with 37 CFR § 1.8(a)(4).

Dated: September 22, 2017
Electronic Signature for Jill Gorny Sloper, Esq.: /Jill Gorny Sloper, Esq./

Docket No.: AXJ-114BUSCN3
(PATENT)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Letters Patent of:
Leonard Bell *et al.*

Patent No.: 9,725,504

Issued: August 8, 2017

For: TREATMENT OF PAROXYSMAL NOCTURNAL HEMOGLOBINURIA PATIENTS BY AN INHIBITOR OF COMPLEMENT

Attention: Certificate of Correction Branch
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

REQUEST FOR CERTIFICATE OF CORRECTION
PURSUANT TO 37 C.F.R. § 1.323

Dear Sir:

Upon reviewing the above-identified patent, Patentee noted typographical errors which should be corrected.

On page 2, first column, under "Other Publications", line 25, delete "nocturnal; hemogloinuria" and insert - - nocturnal hemoglobinuria - -, therefor.

On page 3, first column, under "Other Publications", line 38, delete "Neisseia" and insert - - Neisseria - -, therefor.

On page 3, second column, under "Other Publications", line 33, delete "Hemoglobinuira" and insert - - Hemoglobinuria - -, therefor.

On page 3, second column, under "Other Publications", line 37, delete "Phamaceuticals:" and insert - - Pharmaceuticals: - -, therefor.

Samsung Bioepis Exhibit No. 1002
Page 10857

On page 4, first column, under "Other Publications", line 23, delete "Pharmaceuitcals" and insert - - Pharmaceuticals - -, therefor.

On page 4, first column, under "Other Publications", line 53, delete "Endonuclial" and insert - - Endothelial - -, therefor.

On page 4, second column, under "Other Publications", line 12, delete "EMAIHMPC" and insert - - EMA/HMPC - -, therefor.

On page 4, second column, under "Other Publications", line 34, delete "htto:" and insert - - http: - -, therefor.

In the Specification:

In column 2, line 65, delete "embodiment," and insert - - embodiments, - -, therefor.

In column 4, line 2, delete "antibodies;" and insert - - antibodies, - -, therefor.

In column 4, line 23, delete "comprises," and insert - - comprises - -, therefor.

In column 4, line 28, delete "the" and insert - - an - -, therefor.

In column 4, line 43, delete "No:5," and insert - - No: 5, - -, therefor.

In column 4, line 43, delete "No:6," and insert - - No: 6, - -, therefor.

In column 4, line 44, delete "No:7," and insert - - No: 7, - -, therefor.

In column 4, line 47, delete "No:8," and insert - - No: 8, - -, therefor.

In column 4, line 47, delete "No:9," and insert - - No: 9, - -, therefor.

In column 4, line 47, delete "SEQ, ID NO:10." and insert - - SEQ ID NO: 10. - -, therefor.

In column 4, line 65, delete "lass" and insert - - less - -, therefor.

In column 5, line 45, delete "life" and insert - - Life - -, therefor.

In column 6, line 24, delete "art," and insert - - art. - -, therefor.

In column 6, line 25, delete "on" and insert - - or - -, therefor.

In column 6, line 35, delete "HSF S2" and insert - - HSP S2 - -, therefor.

In column 7, line 39, delete "pathway)," and insert - - pathway) - -, therefor.

In column 7, line 61, delete "T," and insert - - I, - -, therefor.

In column 7, line 65, delete "75 μg/ml," and insert - - 75 μg/mL - -, therefor.

In column 7, line 67, delete "999 amino," and insert - - 999 amino - -, therefor.

In column 8, line 26, delete "1975;" and insert - - 1978; - -, therefor.

In column 8, line 54, delete "al.;" and insert - - al., - -, therefor.

In column 9, line 14, delete "formation, of" and insert - - formation of - -, therefor.

In column 9, line 35, delete "as death" and insert - - as 1, death - -, therefor.

In column 10, line 31, delete "macro molecule" and insert - - macromolecule - -, therefor.

In column 10, line 42, delete "of" and insert - - or - -, therefor.

In column 11, line 42, delete "2d" and insert - - 2nd - -, therefor.

In column 12, line 7, delete "levels," and insert - - levels - -, therefor.

In column 12, line 9, delete "BIA kit," and insert - - EIA kit, - -, therefor.

In column 12, line 18, delete "anaphylatoxic" and insert - - anaphylatoxin - -, therefor.

In column 12, line 67, delete "fragments;" and insert - - fragments, - -, therefor.

In column 13, line 19, delete "tight" and insert - - light - -, therefor.

In column 13, line 19, delete "(CH1)," and insert - - (CH1) - -, therefor.

In column 13, line 33, delete "scFV" and insert - - scFv - -, therefor.

In column 14, line 25, delete "(see, U.S." and insert - - (see, e.g., U.S. - -, therefor.

In column 14, line 64, delete "from," and insert - - from - -, therefor.

In column 14, line 66, delete "same/anti-human" and insert - - same anti-human - -, therefor.

In column 15, line 45, delete "&." and insert - - & - -, therefor.

In column 16, line 47, delete "Philadelphia;" and insert - - Philadelphia, - -, therefor.

In column 17, line 62, delete "another," and insert - - another - -, therefor.

In column 17, line 63, delete "liquid," and insert - - liquid - -, therefor.

In column 19, line 2, after "(mg/mL)]" insert - - . - -.

In column 19, line 6, delete "antibodies," and insert - - antibodies - -, therefor.

In column 19, line 25, delete "antibody," and insert - - antibody - -, therefor.

In column 19, line 44, delete "syringes;" and insert - - syringes, - -, therefor.

In column 20, line 2, delete "genetically," and insert - - genetically - -, therefor.

In column 20, lines 3-4, delete "Meningitides." and insert - - meningitides. - -, therefor.

In column 20, line 24, delete "PBRC" and insert - - PRBC - -, therefor.

In column 20, line 31, delete "individuals" and insert - - individual's - -, therefor.

In column 20, line 65, delete "QoL," and insert - - QoL - -, therefor.

In column 21, line 3, delete "baseline," and insert - - baseline - -, therefor.

In column 21, line 59, delete "cohorts;" and insert - - cohorts: - -, therefor.

In column 21, lines 62-63, delete "myelodysplasia" and insert - - myelodysplastic - -, therefor.

In column 22, line 11, delete "Pharmacodynamics." and insert - - Pharmacodynamics - -, therefor.

In column 22, line 49, delete "above," and insert - - above - -, therefor.

In column 22, line 56, delete "(standard" and insert - - (±standard - -, therefor.

In column 22, line 63, delete "type II" and insert - - type III - -, therefor.

In column 23, line 19, delete "(P=0.001)," and insert - - (P<0.001), - -, therefor.

In column 23, line 28, delete "patients," and insert - - patients - -, therefor.

In columns 23-24, in Table 1, line 17, delete "2-sidexl" and insert - - 2-sided - -, therefor.

In column 24, line 6, delete "1.2 from" and insert - - 1.2 points from - -, therefor.

In column 24, line 17, delete "(P<0:001)," and insert - - (P<0.001), - -, therefor.

In column 24, line 21, delete "improvements," and insert - - improvements - -, therefor.

In column 25, line 29, delete "analysis" and insert - - analysis, - -, therefor.

In column 25, line 30, delete "levels" and insert - - levels, - -, therefor.

In column 25, in Table 3, line 49, delete "Categery" and insert - - Category - -, therefor.

In column 26, lines 1-2, delete "(treatment" and insert - - treatment - -, therefor.

In column 26, line 62, after "treated" insert - - patients - -.

In column 28, line 10, delete "patient," and insert - - patient - -, therefor.

In column 28, line 54, delete "gene," and insert - - gene - -, therefor.

In column 28, line 58, delete "PIG-A gene," and insert - - PIG-A gene. - -, therefor.

In column 29, line 61, delete "Ref Type: Abstract".

The errors now sought to be corrected are typographical errors the correction of which does not involve new matter or require reexamination.

Transmitted herewith is a proposed Certificate of Correction effecting such amendment. Patentee respectfully solicits the granting of the requested Certificate of Correction.

Please charge our Deposit Account No. 12-0080 in the amount of $100.00 covering the fee set forth in 37 C.F.R. § 1.20(a). The Director is hereby authorized to charge any deficiency in the fees filed, asserted to be filed or which should have been filed herewith (or with any paper hereafter filed in this application by this firm) to our Deposit Account No. 12-0080, under Order No. AXJ-114BUSCN3.

Dated: September 22, 2017

Respectfully submitted,

Electronic signature: /Jill Gorny Sloper, Esq./
Jill Gorny Sloper, Esq.
Registration No.: 60,760
NELSON MULLINS RILEY & SCARBOROUGH LLP
One Post Office Square
Boston, Massachusetts 02109-2127
(617) 217-4630
(617) 217-4699 (Fax)
Attorney/Agent For Applicant

Electronic Patent Application Fee Transmittal

Application Number:	15260888
Filing Date:	09-Sep-2016
Title of Invention:	TREATMENT OF PAROXYSMAL NOCTURNAL HEMOGLOBINURIA PATIENTS BY AN INHIBITOR OF COMPLEMENT
First Named Inventor/Applicant Name:	Leonard BELL
Filer:	Jill R. Gorny Sloper/Danielle Gamache
Attorney Docket Number:	AXJ-114BUSCN3

Filed as Large Entity

Filing Fees for Utility under 35 USC 111(a)

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Basic Filing:				
Pages:				
Claims:				
Miscellaneous-Filing:				
Petition:				
Patent-Appeals-and-Interference:				
Post-Allowance-and-Post-Issuance:				
Certificate of correction	1811	1	100	100

Samsung Bioepis Exhibit No. 1002
Page 10862

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Extension-of-Time:				
Miscellaneous:				
			Total in USD ($)	**100**

Samsung Bioepis Exhibit No. 1002
Page 10863

Electronic Acknowledgement Receipt	
EFS ID:	30439063
Application Number:	15260888
International Application Number:	
Confirmation Number:	2558
Title of Invention:	TREATMENT OF PAROXYSMAL NOCTURNAL HEMOGLOBINURIA PATIENTS BY AN INHIBITOR OF COMPLEMENT
First Named Inventor/Applicant Name:	Leonard BELL
Customer Number:	133485
Filer:	Jill R. Gorny Sloper/Danielle Gamache
Filer Authorized By:	Jill R. Gorny Sloper
Attorney Docket Number:	AXJ-114BUSCN3
Receipt Date:	22-SEP-2017
Filing Date:	09-SEP-2016
Time Stamp:	15:43:24
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	yes
Payment Type	DA
Payment was successfully received in RAM	$100
RAM confirmation Number	092517INTEFSW00003040120080
Deposit Account	
Authorized User	
The Director of the USPTO is hereby authorized to charge indicated fees and credit any overpayment as follows:	

Samsung Bioepis Exhibit No. 1002
Page 10864

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Request for Certificate of Correction	AXJ_114BUSCN3_Proposed_CoC.pdf	159699 86d6f17d18c99d8cdc9bd61b1db43cfc672d5424	no	6
Warnings:					
Information:					
2	Request for Certificate of Correction	AXJ_114BUSCN3_Request_CoC.pdf	215684 d48617e65c9d06b72b1855f0576432398c09d5eb	no	5
Warnings:					
Information:					
3	Fee Worksheet (SB06)	fee-info.pdf	30618 87ec0de752cf049bca51190b4a41dafcc099c964	no	2
Warnings:					
Information:					
		Total Files Size (in bytes):	406001		

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111

If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371

If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office

If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

Samsung Bioepis Exhibit No. 1002
Page 10865

UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

PATENT NO. : 9,725,504 B2
APPLICATION NO. : 15/260888
DATED : August 8, 2017
INVENTOR(S) : Leonard Bell et al.

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

On the Title Page

On page 2, first column, item (56) under "Other Publications", Line 25, delete "nocturnal; hemogloinuria" and insert -- nocturnal hemoglobinuria --, therefor.

On page 3, first column, item (56) under "Other Publications", Line 38, delete "Neisseia" and insert -- Neisseria --, therefor.

On page 3, second column, item (56) under "Other Publications", Line 33, delete "Hemoglobinuira" and insert -- Hemoglobinuria --, therefor.

On page 3, second column, item (56) under "Other Publications", Line 37, delete "Phamaceuticals:" and insert -- Pharmaceuticals: --, therefor.

On page 4, first column, item (56) under "Other Publications", Line 23, delete "Pharmaceuitcals" and insert -- Pharmaceuticals --, therefor.

On page 4, first column, item (56) under "Other Publications", Line 53, delete "Endonuclial" and insert -- Endothelial --, therefor.

On page 4, second column, item (56) under "Other Publications", Line 12, delete "EMAIHMPC" and insert -- EMA/HMPC --, therefor.

On page 4, second column, item (56) under "Other Publications", Line 34, delete "htto:" and insert -- http: --, therefor.

In the Specification

In Column 2, Line 65, delete "embodiment," and insert -- embodiments, --, therefor.

Signed and Sealed this
Thirty-first Day of October, 2017

Joseph Matal

Joseph Matal
Performing the Functions and Duties of the
Under Secretary of Commerce for Intellectual Property and
Director of the United States Patent and Trademark Office

Samsung Bioepis Exhibit No. 1002
Page 10866

In Column 4, Line 2, delete "antibodies;" and insert -- antibodies, --, therefor.

In Column 4, Line 23, delete "comprises," and insert -- comprises --, therefor.

In Column 4, Line 28, delete "the" and insert -- an --, therefor.

In Column 4, Line 43, delete "No:5," and insert -- No: 5, --, therefor.

In Column 4, Line 43, delete "No:6," and insert -- No: 6, --, therefor.

In Column 4, Line 44, delete "No:7," and insert -- No: 7, --, therefor.

In Column 4, Line 47, delete "No:8," and insert -- No: 8, --, therefor.

In Column 4, Line 47, delete "No:9," and insert -- No: 9, --, therefor.

In Column 4, Line 47, delete "SEQ, ID NO:10." and insert -- SEQ ID NO: 10. --, therefor.

In Column 4, Line 65, delete "lass" and insert -- less --, therefor.

In Column 5, Line 45, delete "life" and insert -- Life --, therefor.

In Column 6, Line 24, delete "art," and insert -- art. --, therefor.

In Column 6, Line 25, delete "on" and insert -- or --, therefor.

In Column 6, Line 35, delete "HSF S2" and insert -- HSP S2 --, therefor.

In Column 7, Line 39, delete "pathway)," and insert -- pathway) --, therefor.

In Column 7, Line 61, delete "T," and insert -- I, --, therefor.

In Column 7, Line 65, delete "75 μg/ml," and insert -- 75 μg/mL --, therefor.

In Column 7, Line 67, delete "999 amino," and insert -- 999 amino --, therefor.

In Column 8, Line 26, delete "1975;" and insert -- 1978; --, therefor.

In Column 8, Line 54, delete "al.;" and insert -- al., --, therefor.

In Column 9, Line 14, delete "formation, of" and insert -- formation of --, therefor.

In Column 9, Line 35, delete "as death" and insert -- as 1, death --, therefor.

In Column 10, Line 31, delete "macro molecule" and insert -- macromolecule --, therefor.

Samsung Bioepis Exhibit No. 1002
Page 10867

In Column 10, Line 42, delete "of" and insert -- or --, therefor.

In Column 11, Line 42, delete "2d" and insert -- 2nd --, therefor.

In Column 12, Line 7, delete "levels," and insert -- levels --, therefor.

In Column 12, Line 9, delete "BIA kit," and insert -- EIA kit, --, therefor.

In Column 12, Line 18, delete "anaphylatoxic" and insert -- anaphylatoxin --, therefor.

In Column 12, Line 67, delete "fragments;" and insert -- fragments, --, therefor.

In Column 13, Line 19, delete "tight" and insert -- light --, therefor.

In Column 13, Line 19, delete "(CH1)," and insert -- (CH1) --, therefor.

In Column 13, Line 33, delete "scFV" and insert -- scFv --, therefor.

In Column 14, Line 25, delete "(see, U.S." and insert -- (see, e.g., U.S. --, therefor.

In Column 14, Line 64, delete "from," and insert -- from --, therefor.

In Column 14, Line 66, delete "same/anti-human" and insert -- same anti-human --, therefor.

In Column 15, Line 45, delete "&." and insert -- & --, therefor.

In Column 16, Line 47, delete "Philadelphia;" and insert -- Philadelphia, --, therefor.

In Column 17, Line 62, delete "another," and insert -- another --, therefor.

In Column 17, Line 63, delete "liquid," and insert -- liquid --, therefor.

In Column 19, Line 2, after "(mg/mL)]" insert -- . --.

In Column 19, Line 6, delete "antibodies," and insert -- antibodies --, therefor.

In Column 19, Line 25, delete "antibody," and insert -- antibody --, therefor.

In Column 19, Line 44, delete "syringes;" and insert -- syringes, --, therefor.

In Column 20, Line 2, delete "genetically," and insert -- genetically --, therefor.

In Column 20, Lines 3-4, delete "Meningitides." and insert -- meningitides. --, therefor.

In Column 20, Line 24, delete "PBRC" and insert -- PRBC --, therefor.

In Column 20, Line 31, delete "individuals" and insert -- individual's --, therefor.

In Column 20, Line 65, delete "QoL," and insert -- QoL --, therefor.

In Column 21, Line 3, delete "baseline," and insert -- baseline --, therefor.

In Column 21, Line 59, delete "cohorts;" and insert -- cohorts: --, therefor.

In Column 21, Lines 62-63, delete "myelodysplasia" and insert -- myelodysplastic --, therefor.

In Column 22, Line 11, delete "Pharmacodynamics." and insert -- Pharmacodynamics --, therefor.

In Column 22, Line 49, delete "above," and insert -- above --, therefor.

In Column 22, Line 56, delete "(standard" and insert -- (±standard --, therefor.

In Column 22, Line 63, delete "type II" and insert -- type III --, therefor.

In Column 23, Line 19, delete "(P=0.001)," and insert -- (P<0.001), --, therefor.

In Column 23, Line 28, delete "patients," and insert -- patients --, therefor.

In Columns 23-24, in Table 1, Line 17, delete "2-sidexl" and insert -- 2-sided --, therefor.

In Column 24, Line 6, delete "1.2 from" and insert -- 1.2 points from --, therefor.

In Column 24, Line 17, delete "(P<0:001)," and insert -- (P<0.001), --, therefor.

In Column 24, Line 21, delete "improvements," and insert -- improvements --, therefor.

In Column 25, Line 29, delete "analysis" and insert -- analysis, --, therefor.

In Column 25, Line 30, delete "levels" and insert -- levels, --, therefor.

In Column 25, in Table 3, Line 49, delete "Categery" and insert -- Category --, therefor.

In Column 26, Lines 1-2, delete "(treatment" and insert -- treatment --, therefor.

In Column 26, Line 62, after "treated" insert -- patients --.

In Column 28, Line 10, delete "patient," and insert -- patient --, therefor.

In Column 28, Line 54, delete "gene," and insert -- gene --, therefor.

In Column 28, Line 58, delete "PIG-A gene," and insert -- PIG-A gene. --, therefor.

In Column 29, Line 61, delete "Ref Type: Abstract".

Samsung Bioepis Exhibit No. 1002
Page 10870

I hereby certify that this paper (along with any paper referred to as being attached or enclosed) is being transmitted via the Office electronic filing system in accordance with 37 C.F.R. § 1.6(a)(4).

Dated: May 15, 2018
Electronic Signature for Jill Gorny Sloper, Esq.: /Jill Gorny Sloper, Esq./

Docket No.: AXJ-114BUSCN3
(PATENT)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Letters Patent of:
Leonard Bell *et al.*

Patent No.: 9,725,504

Issued: August 8, 2017

For: TREATMENT OF PAROXYSMAL NOCTURNAL HEMOGLOBINURIA PATIENTS BY AN INHIBITOR OF COMPLEMENT

Attention: Certificate of Correction Branch
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

REQUEST FOR CERTIFICATE OF CORRECTION
PURSUANT TO 37 C.F.R. § 1.322

Dear Sir:

Upon reviewing the above-identified patent, Patentee noted a typographical error which should be corrected.

In the Sequence Listing:

At column 30, line number 31, delete

"SDGSFFLYSRLTVDKSRWQEGNVFSCSVMHEALHNHYTQKSLSLSGK" and insert

- - SDGSFFLYSRLTVDKSRWQEGNVFSCSVMHEALHNHYTQKSLSLSLGK - -, therefor.

The error was not in the application as filed by applicant; accordingly, no fee is required.

Samsung Bioepis Exhibit No. 1002
Page 10871

Transmitted herewith is a proposed Certificate of Correction effecting such amendment. Patentee respectfully solicits the granting of the requested Certificate of Correction.

Dated: May 15, 2018

Respectfully submitted,

Electronic signature: /Jill Gorny Sloper, Esq./
Jill Gorny Sloper, Esq.
Registration No.: 60,760
NELSON MULLINS RILEY & SCARBOROUGH LLP
One Post Office Square
Boston, Massachusetts 02109-2127
(617) 217-4630
(617) 217-4699 (Fax)
Attorney/Agent For Patentee

PTO/SB/44 (09-07)
Approved for use through 01/31/2020. OMB 0651-0033
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number.
(Also Form PTO-1050)

UNITED STATES PATENT AND TRADEMARK OFFICE
CERTIFICATE OF CORRECTION

PATENT NO. : 9,725,504

APPLICATION NO. : 15/260,888

ISSUE DATE : August 8, 2017

INVENTOR(S) : Leonard BELL *et al.*

It is certified that an error appears or errors appear in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

At column 30, line number 31, delete

"SDGSFFLYSRLTVDKSRWQEGNVFSCSVMHEALHNHYTQKSLSLSGK" and insert

- - SDGSFFLYSRLTVDKSRWQEGNVFSCSVMHEALHNHYTQKSLSLSLGK - -, therefor.

I hereby certify that this paper (along with any paper referred to as being attached or enclosed) is being transmitted via the Office electronic filing system in accordance with 37 C.F.R. § 1.6(a)(4).

Dated: May 15, 2018 Electronic Signature for Jill Gorny Sloper, Esq.: /Jill Gorny Sloper, Esq./

MAILING ADDRESS OF SENDER (Please do not use Customer Number below):
Jill Gorny Sloper, Esq.
NELSON MULLINS RILEY & SCARBOROUGH LLP 1
One Post Office Square
Boston, Massachusetts 02109-2127

Electronic Acknowledgement Receipt

EFS ID:	32620104
Application Number:	15260888
International Application Number:	
Confirmation Number:	2558
Title of Invention:	TREATMENT OF PAROXYSMAL NOCTURNAL HEMOGLOBINURIA PATIENTS BY AN INHIBITOR OF COMPLEMENT
First Named Inventor/Applicant Name:	Leonard BELL
Customer Number:	133485
Filer:	Jill R. Gorny Sloper/Carolyn Blake
Filer Authorized By:	Jill R. Gorny Sloper
Attorney Docket Number:	AXJ-114BUSCN3
Receipt Date:	15-MAY-2018
Filing Date:	09-SEP-2016
Time Stamp:	16:18:01
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	no

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Request for Certificate of Correction	AXJ-114BUSCN3_Request-for-COC.pdf	26979 34eb55bdf3b42d60f5022dd06f8d06feb7e0f821	no	2

Warnings:

Samsung Bioepis Exhibit No. 1002
Page 10874

Information:					
2	Request for Certificate of Correction	AXJ-114BUSCN3_COC.pdf	24642 3a1025a0965069ded81ef2b1eab2ed03f535c2be	no	1
Warnings:					
Information:					
			Total Files Size (in bytes):	51621	

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111

If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371

If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office

If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

Samsung Bioepis Exhibit No. 1002
Page 10875

UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

PATENT NO.	: 9,725,504 B2
APPLICATION NO.	: 15/260888
DATED	: August 8, 2017
INVENTOR(S)	: Leonard Bell et al.

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

In the Specification

At Column 30, Line number 31, delete
"SDGSFFLYSRLTVDKSRWQEGNVFSCSVMHEALHNHYTQKSLSLSGK" and insert
-- SDGSFFLYSRLTVDKSRWQEGNVFSCSVMHEALHNHYTQKSLSLSLGK --, therefor.

Signed and Sealed this
Twelfth Day of June, 2018

Andrei Iancu
Director of the United States Patent and Trademark Office

Samsung Bioepis Exhibit No. 1002
Page 10876

I hereby certify that this paper (along with any paper referred to as being attached or enclosed) is being transmitted via the Office electronic filing system in accordance with 37 CFR § 1.6(a)(4).

Dated: October 3, 2016
Electronic Signature for Jill Gorny Sloper, Esq.: /Jill Gorny Sloper, Esq./

Docket No.: AXJ-114BUSCN4
(PATENT)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of:
Leonard Bell *et al.*

Application No.: Not Yet Assigned

Confirmation No.: N/A

Filed: Concurrently Herewith

Art Unit: N/A

For: TREATMENT OF PAROXYSMAL NOCTURNAL HEMOGLOBINURIA PATIENTS BY AN INHIBITOR OF COMPLEMENT

Examiner: Not Yet Assigned

MS Amendment
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

FIRST PRELIMINARY AMENDMENT UNDER 37 C.F.R. § 1.115

Dear Sir:

Prior to examination on the merits, please amend the above-identified U.S. patent application as follows:

Amendments to the Specification begin on page 2 of this paper.

Remarks/Arguments begin on page 3 of this paper.

AMENDMENTS TO THE SPECIFICATION

Please insert the following paragraphs after the title:

CROSS REFERENCE TO RELATED APPLICATIONS

This application is a continuation of U.S. Patent Application No. 15/260,888, filed September 9, 2016, which is a continuation of U.S. Patent Application No. 15/148,839, filed May 6, 2016, which is a continuation of U.S. Patent Application No. 13/426,973, filed March 22, 2012, which is a continuation of U.S. Patent Application No. 12/225,040, filed on May 13, 2009, which is a 35 U.S.C. 371 national stage filing of International Application No. PCT/US2007/006606, filed March 15, 2007. The contents of the aforementioned applications are hereby incorporated by reference in their entireties.

SEQUENCE LISTING

The instant application contains a Sequence Listing which has been submitted electronically in ASCII format and is hereby incorporated by reference in its entirety. Said ASCII copy, created on October 3, 2016, is named AXJ_114BUSCN4_Seq_Listing.txt and is 10,521 bytes in size.

REMARKS

Amendments to the Specification

Applicant has amended the specification at page 1 to update the related applications and Sequence Listing sections. *No new matter has been added.*

CONCLUSION

If a telephone conversation with Applicant's Attorney would expedite the prosecution of the above-identified application, the Examiner is urged to call the undersigned at (617) 217-4630.

The Director is hereby authorized to charge any deficiency in the fees filed, asserted to be filed or which should have been filed herewith (or with any paper hereafter filed in this application by this firm) to our Deposit Account No. 12-0080, under Order No. AXJ-114BUSCN4.

Dated: October 3, 2016

Respectfully submitted,

Electronic signature: /Jill Gorny Sloper, Esq./
Jill Gorny Sloper, Esq.
Registration No.: 60,760
NELSON MULLINS RILEY & SCARBOROUGH LLP
One Post Office Square
Boston, Massachusetts 02109-2127
(617) 217-4630
(617) 742-4214 (Fax)
Attorney/Agent For Applicant

Doc Code: PA..
Document Description: Power of Attorney

PTO/AIA/82A (07-13)
Approved for use through 11/30/2014. OMB 0651-0051
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
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TRANSMITTAL FOR POWER OF ATTORNEY TO ONE OR MORE REGISTERED PRACTITIONERS

NOTE: This form is to be submitted with the Power of Attorney by Applicant form (PTO/AIA/82B) to identify the application to which the Power of Attorney is directed, in accordance with 37 CFR 1.5, unless the application number and filing date are identified in the Power of Attorney by Applicant form. If neither form PTO/AIA/82A nor form PTO/AIA82B identifies the application to which the Power of Attorney is directed, the Power of Attorney will not be recognized in the application.

Application Number	Not Yet Assigned
Filing Date	Concurrently Herewith
First Named Inventor	Leonard BELL
Title	TREATMENT OF PAROXYSMAL NOCTURNAL HEMOGLOBINURIA PATIENTS BY AN INHIBITOR OF COMPLEMENT
Art Unit	N/A
Examiner Name	Not Yet Assigned
Attorney Docket Number	AXJ-114BUSCN4

SIGNATURE of Applicant or Patent Practitioner

Signature		Date (Optional)	October 3, 2016
Name	Jill Gorny Sloper, Esq.	Registration Number	60,760
Title (if Applicant is a juristic entity)			
Applicant Name (if Applicant is a juristic entity)			

NOTE: This form must be signed in accordance with 37 CFR 1.33. See 37 CFR 1.4(d) for signature requirements and certifications. If more than one applicant, use multiple forms.

☐ *Total of 1 forms are submitted.

Samsung Bioepis Exhibit No. 1002
Page 10880

Doc Code: PA..
Document Description: Power of Attorney

PTO/AIA/82B (07-13)
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U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
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POWER OF ATTORNEY BY APPLICANT

I hereby revoke all previous powers of attorney given in the application identified in either the attached transmittal letter or the boxes below.

Application Number	Filing Date

(Note: The boxes above may be left blank if information is provided on form PTO/AIA/82A.)

[X] I hereby appoint the Patent Practitioner(s) associated with the following Customer Number as my/our attorney(s) or agent(s), and to transact all business in the United States Patent and Trademark Office connected therewith for the application referenced in the attached transmittal letter (form PTO/AIA/82A) or identified above: 133485

OR

[ ] I hereby appoint Practitioner(s) named in the attached list (form PTO/AIA/82C) as my/our attorney(s) or agent(s), and to transact all business in the United States Patent and Trademark Office connected therewith for the patent application referenced in the attached transmittal letter (form PTO/AIA/82A) or identified above. (Note: Complete form PTO/AIA/82C.)

Please recognize or change the correspondence address for the application identified in the attached transmittal letter or the boxes above to:

[X] The address associated with the above-mentioned Customer Number

OR

[ ] The address associated with Customer Number:

OR

Firm or Individual Name	Jane E. Remillard, Esq. NELSON MULLINS RILEY & SCARBOROUGH LLP				
Address	One Post Office Square				
City	Boston	State	MA	Zip	02109-2127
Country	US				
Telephone	(800) 237-2000	Email	IPBoston.Docketing@nelsonmullins.com		

I am the Applicant (if the Applicant is a juristic entity, list the Applicant name in the box):

Alexion Pharmaceuticals, Inc.

[ ] Inventor or Joint Inventor (title not required below)

[ ] Legal Representative of a Deceased or Legally Incapacitated Inventor (title not required below)

[X] Assignee or Person to Whom the Inventor is Under an Obligation to Assign (provide signer's title if applicant is a juristic entity)

[ ] Person Who Otherwise Shows Sufficient Proprietary Interest (e.g., a petition under 37 CFR 1.46(b)(2) was granted in the application or is concurrently being filed with this document) (provide signer's title if applicant is a juristic entity)

SIGNATURE of Applicant for Patent

The undersigned (whose title is supplied below) is authorized to act on behalf of the applicant (e.g., where the applicant is a juristic entity).

Signature		Date (Optional)	07/20/15
Name	Todd Spalding		
Title	Vice President, Head of Intellectual Property		

NOTE: Signature - This form must be signed by the applicant in accordance with 37 CFR 1.33. See 37 CFR 1.4 for signature requirements and certifications. If more than one applicant, use multiple forms.

[ ] Total of 1 forms are submitted.

Samsung Bioepis Exhibit No. 1002
Page 10881

Doc Code: TRACK1.REQ
Document Description: TrackOne Request

PTO/AIA/424 (04-14)

CERTIFICATION AND REQUEST FOR PRIORITIZED EXAMINATION UNDER 37 CFR 1.102(e) (Page 1 of 1)

First Named Inventor:	Leonard BELL	Nonprovisional Application Number (if known):	Not Yet Assigned
Title of Invention:	TREATMENT OF PAROXYSMAL NOCTURNAL HEMOGLOBINURIA PATIENTS BY AN INHIBITOR OF COMPLEMENT		

APPLICANT HEREBY CERTIFIES THE FOLLOWING AND REQUESTS PRIORITIZED EXAMINATION FOR THE ABOVE-IDENTIFIED APPLICATION.

1. The processing fee set forth in 37 CFR 1.17(i)(1) and the prioritized examination fee set forth in 37 CFR 1.17(c) have been filed with the request. The publication fee requirement is met because that fee, set forth in 37 CFR 1.18(d), is currently $0. The basic filing fee, search fee, and examination fee are filed with the request or have been already been paid. I understand that any required excess claims fees or application size fee must be paid for the application.
2. I understand that the application may not contain, or be amended to contain, more than four independent claims, more than thirty total claims, or any multiple dependent claims, and that any request for an extension of time will cause an outstanding Track I request to be dismissed.
3. The applicable box is checked below:

I. [x] **Original Application (Track One) - Prioritized Examination under § 1.102(e)(1)**

i. (a) The application is an original nonprovisional utility application filed under 35 U.S.C. 111(a). This certification and request is being filed with the utility application via EFS-Web.

---OR---

(b) The application is an original nonprovisional plant application filed under 35 U.S.C. 111(a). This certification and request is being filed with the plant application in paper.

ii. An executed inventor's oath or declaration under 37 CFR 1.63 or 37 CFR 1.64 for each inventor, **or** the application data sheet meeting the conditions specified in 37 CFR 1.53(f)(3)(i) is filed with the application.

II. [ ] **Request for Continued Examination - Prioritized Examination under § 1.102(e)(2)**

i. A request for continued examination has been filed with, or prior to, this form.
ii. If the application is a utility application, this certification and request is being filed via EFS-Web.
iii. The application is an original nonprovisional utility application filed under 35 U.S.C. 111(a), or is a national stage entry under 35 U.S.C. 371.
iv. This certification and request is being filed prior to the mailing of a first Office action responsive to the request for continued examination.
v. No prior request for continued examination has been granted prioritized examination status under 37 CFR 1.102(e)(2).

Signature	/Jill Gorny Sloper, Esq./	Date	October 3, 2016
Name (Print/Typed)	Jill Gorny Sloper, Esq.	Practitioner Registration Number	60,760

***Note**: This form must be signed in accordance with 37 CFR 1.33. See 37 CFR 1.4(d) for signature requirements and certifications. Submit multiple forms if more than one signature is required.**

[ ] *Total of 1 forms are submitted.

I hereby certify that this paper (along with any paper referred to as being attached or enclosed) is being transmitted via the Office electronic filing system in accordance with 37 CFR § 1.6(a)(4).

Dated: October 3, 2016 Electronic Signature for Jill Gorny Sloper, Esq.: /Jill Gorny Sloper, Esq./

I hereby certify that this paper (along with any paper referred to as being attached or enclosed) is being transmitted via the Office electronic filing system in accordance with 37 CFR § 1.6(a)(4).

Dated: October 3, 2016
Electronic Signature for Jill Gorny Sloper, Esq.: /Jill Gorny Sloper, Esq./

Docket No.: AXJ-114BUSCN4
(PATENT)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of:
Leonard Bell *et al.*

Application No.: Not Yet Assigned

Confirmation No.: N/A

Filed: Concurrently Herewith

Art Unit: N/A

For: TREATMENT OF PAROXYSMAL NOCTURNAL HEMOGLOBINURIA PATIENTS BY AN INHIBITOR OF COMPLEMENT

Examiner: Not Yet Assigned

MS Sequence
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

STATEMENT PURSUANT TO 37 CFR 1.821

Dear Sir:

Submitted herewith in connection with the above-referenced patent application and in full compliance with 37 C.F.R. §§1.821-1.825 is a computer readable copy and paper copy of the Sequence Listing (filed together as a .txt file via the United States Patent Office's Electronic Filing System).

I hereby state that I have reviewed the paper copy of the Sequence Listing, as required by 37 CFR 1.821(c), and have reviewed the computer readable form of the Sequence Listing, as required by 37 CFR 1.821(e), and that the content of the paper and computer readable copies for the above-referenced Patent application are the same as required by 37 CFR 1.821(f) (note that these documents are submitted as one electronic file). No new matter has been added to the Sequence Listing.

Dated: October 3, 2016

Respectfully submitted,

Electronic signature: /Jill Gorny Sloper, Esq./
Jill Gorny Sloper, Esq.
Registration No.: 60,760
NELSON MULLINS RILEY &
SCARBOROUGH LLP
One Post Office Square
Boston, Massachusetts 02109-2127
(617) 217-4630 (617) 742-4214 (Fax)
Attorney/Agent For Applicant

Electronic Patent Application Fee Transmittal	
Application Number:	
Filing Date:	
Title of Invention:	TREATMENT OF PAROXYSMAL NOCTURNAL HEMOGLOBINURIA PATIENTS BY AN INHIBITOR OF COMPLEMENT
First Named Inventor/Applicant Name:	Leonard BELL
Filer:	Jill R. Gorny Sloper/Danielle Gamache
Attorney Docket Number:	AXJ-114BUSCN4
Filed as Large Entity	
Filing Fees for Track I Prioritized Examination - Nonprovisional Application under 35 USC 111(a)	

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Basic Filing:				
UTILITY APPLICATION FILING	1011	1	280	280
UTILITY SEARCH FEE	1111	1	600	600
UTILITY EXAMINATION FEE	1311	1	720	720
REQUEST FOR PRIORITIZED EXAMINATION	1817	1	4000	4000
Pages:				
Claims:				
Miscellaneous-Filing:				
PROCESSING FEE, EXCEPT PROV. APPLS.	1830	1	140	140

Samsung Bioepis Exhibit No. 1002
Page 10885

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Petition:				
Patent-Appeals-and-Interference:				
Post-Allowance-and-Post-Issuance:				
Extension-of-Time:				
Miscellaneous:				
		Total in USD ($)		**5740**

Samsung Bioepis Exhibit No. 1002
Page 10886

Electronic Acknowledgement Receipt	
EFS ID:	27101965
Application Number:	15284015
International Application Number:	
Confirmation Number:	1040
Title of Invention:	TREATMENT OF PAROXYSMAL NOCTURNAL HEMOGLOBINURIA PATIENTS BY AN INHIBITOR OF COMPLEMENT
First Named Inventor/Applicant Name:	Leonard BELL
Customer Number:	133485
Filer:	Jill R. Gorny Sloper/Danielle Gamache
Filer Authorized By:	Jill R. Gorny Sloper
Attorney Docket Number:	AXJ-114BUSCN4
Receipt Date:	03-OCT-2016
Filing Date:	
Time Stamp:	16:35:27
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	yes
Payment Type	Deposit Account
Payment was successfully received in RAM	$5740
RAM confirmation Number	3332
Deposit Account	120080
Authorized User	Sloper, Jill
The Director of the USPTO is hereby authorized to charge indicated fees and credit any overpayment as follows: Charge any Additional Fees required under 37 CFR 1.16 (National application filing, search, and examination fees) Charge any Additional Fees required under 37 CFR 1.17 (Patent application and reexamination processing fees)	

Charge any Additional Fees required under 37 CFR 1.19 (Document supply fees)

Charge any Additional Fees required under 37 CFR 1.20 (Post Issuance fees)

Charge any Additional Fees required under 37 CFR 1.21 (Miscellaneous fees and charges)

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Application Data Sheet	AXJ_114BUSCN4_ADS.pdf	62554 813825cad0311f184ed43a2539b39f5240be7406	no	9
Warnings:					
Information:					
This is not an USPTO supplied ADS fillable form					
2		AXJ_114BUSCN4_TrackOne_Application.pdf	4036291 bc02db50bdf8792883de5c53da357658ad833524	yes	47

Multipart Description/PDF files in .zip description

Document Description	Start	End
Specification	1	45
Claims	46	46
Abstract	47	47

Warnings:					
Information:					
3	Oath or Declaration filed	AXJ_114BUSCN4_Decs.pdf	2438655 5e1ce7fcc54d3f93e5974a59266d536b0a6df6e7	no	3
Warnings:					
Information:					
4	Drawings-other than black and white line drawings	AXJ_114BUSCN4_Figures.pdf	992294 caa9e479035fc3dc18bcb50b1866a5f70001b9b2	no	4
Warnings:					
Information:					

Samsung Bioepis Exhibit No. 1002
Page 10888

5		AXJ_114BUSCN4_PrelimAmdt.pdf	134875 3706040f3e2fc71e9662b33cd59c3b0eb1498cd9	yes	3
	Multipart Description/PDF files in .zip description				
	Document Description		**Start**	**End**	
	Preliminary Amendment		1	1	
	Specification		2	2	
	Applicant Arguments/Remarks Made in an Amendment		3	3	
Warnings:					
Information:					
6	Power of Attorney	AXJ_114BUSCN4_POA_82A_82B.pdf	209729 8130c9ebc326b7144751ffb539541b6d6986ff9e	no	2
Warnings:					
Information:					
7	TrackOne Request	AXJ_114BUSCN4_TrackOne_Req.pdf	109341 9a736cf4e667a878b3ab6a046ffcad4cd61bff86	no	1
Warnings:					
Information:					
8	CRF Statement Paper and CRF are the same	AXJ_114BUSCN4_Statement_re_SL.pdf	110679 4ae6be39b981e8c29867fcfc16312cb2501ea781	no	2
Warnings:					
Information:					
9	Sequence Listing (Text File)	AXJ_114BUSCN4_Seq_Listing.txt	10521	no	-
Warnings:					
Information:					
10	Fee Worksheet (SB06)	fee-info.pdf	38381 21acae1b06a90c5e730184c781c25827bb94d437	no	2
Warnings:					

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Page 10889

Information:	
Total Files Size (in bytes):	8143320

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111
If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371
If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office
If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

Samsung Bioepis Exhibit No. 1002
Page 10890

PTO/AIA/14 (11-15)
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U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it contains a valid OMB control number.

Application Data Sheet 37 CFR 1.76	Attorney Docket Number	AXJ-114BUSCN4
	Application Number	
Title of Invention	TREATMENT OF PAROXYSMAL NOCTURNAL HEMOGLOBINURIA PATIENTS BY AN INHIBITOR OF COMPLEMENT	

The application data sheet is part of the provisional or nonprovisional application for which it is being submitted. The following form contains the bibliographic data arranged in a format specified by the United States Patent and Trademark Office as outlined in 37 CFR 1.76.
This document may be completed electronically and submitted to the Office in electronic format using the Electronic Filing System (EFS) or the document may be printed and included in a paper filed application.

Secrecy Order 37 CFR 5.2:

☐ Portions or all of the application associated with this Application Data Sheet may fall under a Secrecy Order pursuant to 37 CFR 5.2 (Paper filers only. Applications that fall under Secrecy Order may not be filed electronically.)

Inventor Information:

Inventor 1 Remove

Legal Name

Prefix	Given Name	Middle Name	Family Name	Suffix
	Leonard		BELL	

Residence Information (Select One) ◉ US Residency ○ Non US Residency ○ Active US Military Service

City	Woodbridge	State/Province	CT	Country of Residence	US

Mailing Address of Inventor:

Address 1	59 Tumblebrook Road		
Address 2			
City	Woodbridge	State/Province	CT
Postal Code	06525	Country	US

Inventor 2 Remove

Legal Name

Prefix	Given Name	Middle Name	Family Name	Suffix
	Russell	P.	ROTHER	

Residence Information (Select One) ◉ US Residency ○ Non US Residency ○ Active US Military Service

City	Oklahoma City	State/Province	OK	Country of Residence	US

Mailing Address of Inventor:

Address 1	10325 Forest Meadow Drive		
Address 2			
City	Oklahoma City	State/Province	OK
Postal Code	73151	Country	US

All Inventors Must Be Listed - Additional Inventor Information blocks may be generated within this form by selecting the **Add** button. Add

Correspondence Information:

Enter either Customer Number or complete the Correspondence Information section below.
For further information see 37 CFR 1.33(a).

PTO/AIA/14 (11-15)
Approved for use through 04/30/2017. OMB 0651-0032
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
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Application Data Sheet 37 CFR 1.76	Attorney Docket Number	AXJ-114BUSCN4
	Application Number	
Title of Invention	TREATMENT OF PAROXYSMAL NOCTURNAL HEMOGLOBINURIA PATIENTS BY AN INHIBITOR OF COMPLEMENT	

☐ **An Address is being provided for the correspondence Information of this application.**			
Customer Number	133485		
Email Address	IPBoston.Docketing@nelsonmullins.com	Add Email	Remove Email

Application Information:

Title of the Invention	TREATMENT OF PAROXYSMAL NOCTURNAL HEMOGLOBINURIA PATIENTS BY AN INHIBITOR OF COMPLEMENT		
Attorney Docket Number	AXJ-114BUSCN4	**Small Entity Status Claimed**	☐
Application Type	Nonprovisional		
Subject Matter	Utility		
Total Number of Drawing Sheets (if any)	4	**Suggested Figure for Publication (if any)**	

Filing By Reference:

Only complete this section when filing an application by reference under 35 U.S.C. 111(c) and 37 CFR 1.57(a). Do not complete this section if application papers including a specification and any drawings are being filed. Any domestic benefit or foreign priority information must be provided in the appropriate section(s) below (i.e., "Domestic Benefit/National Stage Information" and "Foreign Priority Information").

For the purposes of a filing date under 37 CFR 1.53(b), the description and any drawings of the present application are replaced by this reference to the previously filed application, subject to conditions and requirements of 37 CFR 1.57(a).

Application number of the previously filed application	Filing date (YYYY-MM-DD)	Intellectual Property Authority or Country

Publication Information:

☐ Request Early Publication (Fee required at time of Request 37 CFR 1.219)

☐ **Request Not to Publish.** I hereby request that the attached application not be published under 35 U.S.C. 122(b) and certify that the invention disclosed in the attached application **has not and will not** be the subject of an application filed in another country, or under a multilateral international agreement, that requires publication at eighteen months after filing.

Representative Information:

Representative information should be provided for all practitioners having a power of attorney in the application. Providing this information in the Application Data Sheet does not constitute a power of attorney in the application (see 37 CFR 1.32).
Either enter Customer Number or complete the Representative Name section below. If both sections are completed the customer Number will be used for the Representative Information during processing.

Please Select One:	◉ Customer Number	○ US Patent Practitioner	○ Limited Recognition (37 CFR 11.9)
Customer Number	133485		

Application Data Sheet 37 CFR 1.76	Attorney Docket Number	AXJ-114BUSCN4
	Application Number	
Title of Invention	TREATMENT OF PAROXYSMAL NOCTURNAL HEMOGLOBINURIA PATIENTS BY AN INHIBITOR OF COMPLEMENT	

Domestic Benefit/National Stage Information:

This section allows for the applicant to either claim benefit under 35 U.S.C. 119(e), 120, 121, 365(c), or 386(c) or indicate National Stage entry from a PCT application. Providing benefit claim information in the Application Data Sheet constitutes the specific reference required by 35 U.S.C. 119(e) or 120, and 37 CFR 1.78.
When referring to the current application, please leave the "Application Number" field blank.

Prior Application Status	Pending		Remove
Application Number	Continuity Type	Prior Application Number	Filing or 371(c) Date (YYYY-MM-DD)
	Continuation of	15/260888	2016-09-09
Prior Application Status	Pending		Remove
Application Number	Continuity Type	Prior Application Number	Filing or 371(c) Date (YYYY-MM-DD)
15/260888	Continuation of	15/148839	2016-05-06
Prior Application Status	Pending		Remove
Application Number	Continuity Type	Prior Application Number	Filing or 371(c) Date (YYYY-MM-DD)
15/148839	Continuation of	13/426973	2012-03-22
Prior Application Status	Pending		Remove
Application Number	Continuity Type	Prior Application Number	Filing or 371(c) Date (YYYY-MM-DD)
13/426973	Continuation of	12/225040	2009-05-13
Prior Application Status			Remove
Application Number	Continuity Type	Prior Application Number	Filing or 371(c) Date (YYYY-MM-DD)
12/225040	a 371 of international	PCT/US2007/006606	2007-03-15

Additional Domestic Benefit/National Stage Data may be generated within this form by selecting the **Add** button.

Foreign Priority Information:

This section allows for the applicant to claim priority to a foreign application. Providing this information in the application data sheet constitutes the claim for priority as required by 35 U.S.C. 119(b) and 37 CFR 1.55. When priority is claimed to a foreign application that is eligible for retrieval under the priority document exchange program (PDX)[i] the information will be used by the Office to automatically attempt retrieval pursuant to 37 CFR 1.55(i)(1) and (2). Under the PDX program, applicant bears the ultimate responsibility for ensuring that a copy of the foreign application is received by the Office from the participating foreign intellectual property office, or a certified copy of the foreign priority application is filed, within the time period specified in 37 CFR 1.55(g)(1).

PTO/AIA/14 (11-15)
Approved for use through 04/30/2017. OMB 0651-0032
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it contains a valid OMB control number.

Application Data Sheet 37 CFR 1.76	Attorney Docket Number	AXJ-114BUSCN4
	Application Number	
Title of Invention	TREATMENT OF PAROXYSMAL NOCTURNAL HEMOGLOBINURIA PATIENTS BY AN INHIBITOR OF COMPLEMENT	

			Remove
Application Number	Country[i]	Filing Date (YYYY-MM-DD)	Access Code[i] (if applicable)

Additional Foreign Priority Data may be generated within this form by selecting the **Add** button.

Statement under 37 CFR 1.55 or 1.78 for AIA (First Inventor to File) Transition Applications

☐ This application (1) claims priority to or the benefit of an application filed before March 16, 2013 and (2) also contains, or contained at any time, a claim to a claimed invention that has an effective filing date on or after March 16, 2013.
NOTE: By providing this statement under 37 CFR 1.55 or 1.78, this application, with a filing date on or after March 16, 2013, will be examined under the first inventor to file provisions of the AIA.

Application Data Sheet 37 CFR 1.76	Attorney Docket Number	AXJ-114BUSCN4
	Application Number	
Title of Invention	TREATMENT OF PAROXYSMAL NOCTURNAL HEMOGLOBINURIA PATIENTS BY AN INHIBITOR OF COMPLEMENT	

Authorization or Opt-Out of Authorization to Permit Access:

When this Application Data Sheet is properly signed and filed with the application, applicant has provided written authority to permit a participating foreign intellectual property (IP) office access to the instant application-as-filed (see paragraph A in subsection 1 below) and the European Patent Office (EPO) access to any search results from the instant application (see paragraph B in subsection 1 below).

Should applicant choose not to provide an authorization identified in subsection 1 below, applicant **must opt-out** of the authorization by checking the corresponding box A or B or both in subsection 2 below.

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The applicant is reminded that the EPO's Rule 141(1) EPC (European Patent Convention) requires applicants to submit a copy of search results from the instant application without delay in a European patent application that claims priority to the instant application.

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Application Data Sheet 37 CFR 1.76	Attorney Docket Number	AXJ-114BUSCN4
	Application Number	
Title of Invention	TREATMENT OF PAROXYSMAL NOCTURNAL HEMOGLOBINURIA PATIENTS BY AN INHIBITOR OF COMPLEMENT	

Applicant Information:

Providing assignment information in this section does not substitute for compliance with any requirement of part 3 of Title 37 of CFR to have an assignment recorded by the Office.

Applicant 1

If the applicant is the inventor (or the remaining joint inventor or inventors under 37 CFR 1.45), this section should not be completed. The information to be provided in this section is the name and address of the legal representative who is the applicant under 37 CFR 1.43; or the name and address of the assignee, person to whom the inventor is under an obligation to assign the invention, or person who otherwise shows sufficient proprietary interest in the matter who is the applicant under 37 CFR 1.46. If the applicant is an applicant under 37 CFR 1.46 (assignee, person to whom the inventor is obligated to assign, or person who otherwise shows sufficient proprietary interest) together with one or more joint inventors, then the joint inventor or inventors who are also the applicant should be identified in this section.

Clear

◉ Assignee	○ Legal Representative under 35 U.S.C. 117	○ Joint Inventor
○ Person to whom the inventor is obligated to assign.	○ Person who shows sufficient proprietary interest	

If applicant is the legal representative, indicate the authority to file the patent application, the inventor is:

Name of the Deceased or Legally Incapacitated Inventor:

If the Applicant is an Organization check here. ☒

Organization Name	Alexion Pharmaceuticals, Inc.

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Phone Number		Fax Number	
Email Address			

Additional Applicant Data may be generated within this form by selecting the Add button.

Assignee Information including Non-Applicant Assignee Information:

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Assignee 1

Complete this section if assignee information, including non-applicant assignee information, is desired to be included on the patent application publication. An assignee-applicant identified in the "Applicant Information" section will appear on the patent application publication as an applicant. For an assignee-applicant, complete this section only if identification as an assignee is also desired on the patent application publication.

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Address 1			
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Signature:

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This Application Data Sheet **must** be signed by a patent practitioner if one or more of the applicants is a **juristic entity** (e.g., corporation or association). If the applicant is two or more joint inventors, this form must be signed by a patent practitioner, **all** joint inventors who are the applicant, or one or more joint inventor-applicants who have been given power of attorney (e.g., see USPTO Form PTO/AIA/81) on behalf of **all** joint inventor-applicants.

See 37 CFR 1.4(d) for the manner of making signatures and certifications.

Signature	/Jill Gorny Sloper, Esq./			Date (YYYY-MM-DD)	2016-10-03
First Name	Jill Gorny	Last Name	Sloper	Registration Number	60,760

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Application Data Sheet 37 CFR 1.76	Attorney Docket Number	AXJ-114BUSCN4
	Application Number	
Title of Invention	TREATMENT OF PAROXYSMAL NOCTURNAL HEMOGLOBINURIA PATIENTS BY AN INHIBITOR OF COMPLEMENT	

This collection of information is required by 37 CFR 1.76. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 23 minutes to complete, including gathering, preparing, and submitting the completed application data sheet form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

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8. A record from this system of records may be disclosed, as a routine use, to the public after either publication of the application pursuant to 35 U.S.C. 122(b) or issuance of a patent pursuant to 35 U.S.C. 151. Further, a record may be disclosed, subject to the limitations of 37 CFR 1.14, as a routine use, to the public if the record was filed in an application which became abandoned or in which the proceedings were terminated and which application is referenced by either a published application, an application open to public inspections or an issued patent.

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TREATMENT OF PAROXYSMAL NOCTURNAL HEMOGLOBINURIA PATIENTS BY AN INHIBITOR OF COMPLEMENT

BACKGROUND

Paroxysmal nocturnal hemoglobinuria (PNH) is an acquired hematologic disease that results from clonal expansion of hematopoietic stem cells with somatic mutations in the X-linked gene called PIG-A.[1,2] Mutations in PIG-A lead to an early block in the synthesis of glycosylphosphatidylinositol (GPI)-anchors, which are required to tether many proteins to the cell surface. Consequently, PNH blood cells have a partial (type II) or complete (type III) deficiency of GPI-anchored proteins.

Intravascular hemolysis is a prominent feature of PNH and a direct result of the absence of the GPI-anchored complement regulatory protein CD59.[3,4] Under normal circumstances, CD59 blocks the formation of the terminal complement complex (also called the membrane attack complex) on the cell surface, thereby preventing erythrocyte lysis and platelet activation.[5-8] Excessive or persistent intravascular hemolysis in PNH patients not only results in anemia (normal ranges of hemoglobin are 14-18 g/dL for men and 12-16 g/dL for women, and persons with lower levels are considered to be anemic), but also hemoglobinuria and clinical sequelae related to the release of the erythrocyte contents into the circulation: fatigue, thrombosis, abdominal pain, dysphagia, erectile dysfunction, and pulmonary hypertension.[9,10,21,22] Indeed, impaired quality of life in PNH is disproportionate to the degree of anemia. Many PNH patients depend on blood transfusions to maintain adequate erythrocyte hemoglobin levels. There have been no therapies that effectively reduce intravascular hemolysis and improve the associated clinical morbidities in PNH.

Eculizumab is a humanized monoclonal antibody directed against the terminal complement protein C5.[11] In a preliminary, 12-week, open-label clinical study in 11 PNH patients, eculizumab was shown to reduce intravascular hemolysis and transfusion requirements.[12] However, this unblinded study involved a small number of patients with no control arm and without protocol-driven transfusion standards.

Samsung Bioepis Exhibit No. 1002
Page 10900

SUMMARY

The present pivotal, phase III study, Transfusion Reduction Efficacy and Safety Clinical Investigation, Randomized, Multi-Center, Double-Blind, Placebo-Controlled, Using Eculizumab in Paroxysmal Nocturnal Hemoglobinuria (TRIUMPH), evaluated the effect of eculizumab on the stabilization of hemoglobin levels and transfusion requirements during 6 months of treatment in a cohort of 87 transfusion-dependent PNH patients. Measures of intravascular hemolysis and quality of life were also assessed. This is the first placebo controlled study of a PNH patient population to control hemolysis and to differentiate between the effects due to hemolysis and the effects due to anemia.

It has been surprisingly discovered that certain aspects of quality of life were unexpectedly improved by the treatment of PNH patients with eculizumab. Furthermore, these improvements in the quality of life were independent of transfusion. The improved aspects include, e.g., global health status, physical functioning, emotional functioning, cognitive functioning, role functioning, social functioning, fatigue, pain, dyspnea, appetite loss and insomnia. Improvement was also seen in nausea and vomiting, diarrhea, constipation, and financial difficulties but did not reach the level of statistical significance. Because the treated patients remained anemic throughout their treatment, it was unexpected that all of these improvements would have been seen because they were previously thought to be a result of the patient being anemic. Although not wishing to be bound by any theory, it appears that some of the symptoms are likely due, at least in part, to hemolysis and release of hemoglobin into the bloodstream and do not result solely from the patient being anemic. The treatment with eculizumab decreases the amount of lysis thereby limiting hemoglobin release into the bloodstream, thereby apparently resulting in the improvements seen in the treated patients' quality of life. The results presented herein indicate that any treatment that decreases hemolysis in a patient will result in an improvement in the quality of life of said patient.

In certain aspects, the application provides a method to improve at least one aspect of the quality of life of a patient suffering from paroxysmal nocturnal hemoglobinuria, said method comprising administering to said patient in need thereof a compound which inhibits complement or inhibits formation of C5b-9.

In certain aspects, the application provides a method to improve at least one aspect of the quality of life of a patient suffering from paroxysmal nocturnal hemoglobinuria, said method comprising administering to said patient in need thereof a compound which inhibits

Samsung Bioepis Exhibit No. 1002
Page 10901

intravascular hemolysis. In certain embodiments, said method results in a greater than 30% reduction in LDH in said patient.

In certain aspects, the application provides a method to improve at least one aspect of the quality of life of an anemic patient whose anemia results at least in part from hemolysis, said method comprising administering to said patient in need thereof a compound which inhibits intravascular hemolysis, wherein said patient remains anemic. In certain embodiments, said method results in a greater than 30% reduction in LDH in said patient.

In certain aspects, the application provides a method of prolonging the health-adjusted life expectancy of a patient comprising administering to said patient in need thereof a compound which inhibits formation of C5b-9. In certain embodiments, said patient is anemic. In certain embodiments, said patient remains anemic following treatment. In certain embodiments, said patient has a hemoglobin level less than i) 14 g/dL if a man or ii) 12 g/dL if a woman. In certain embodiments, said patient has a hemoglobin level less than i) 13 g/dL if a man or ii) 11 g/dL if a woman. In certain embodiments, said patient has a hemoglobin level less than i) 12 g/dL if a man or ii) 10 g/dL if a woman. In certain embodiments, said patient suffers from paroxysmal nocturnal hemoglobinuria.

In certain aspects, the application provides a pharmaceutical composition comprising an antibody that binds C5 or an active antibody fragment thereof. In certain embodiments, the antibody that binds C5 or an active antibody fragment thereof is eculizumab. In certain embodiments, the antibody that binds C5 or an active antibody fragment thereof is pexelizumab. In certain embodiments, the pharmaceutical formulations of the application may be administered to a subject, particularly a subject having PNH.

In certain aspects, the application provides a method of treating a patient suffering from paroxysmal nocturnal hemoglobinuria by administering a pharmaceutical composition comprising an antibody that binds C5 or an active antibody fragment thereof. In certain embodiments, the antibody that binds C5 or an active antibody fragment thereof is eculizumab. In certain embodiments, the antibody that binds C5 or an active antibody fragment thereof is pexelizumab. In certain embodiments, the pharmaceutical formulations of the application may be administered to a subject, particularly a subject having PNH.

In certain aspects, the application provides kits comprising a pharmaceutical composition of the application. In some embodiments, the kit further comprises at least one component of a closed sterile system. Components of the closed sterile system

Samsung Bioepis Exhibit No. 1002
Page 10902

include, but are not limited to, needles, syringes, catheter based syringes, needle based injection devices, needle-less injection devices, filters, tubing, valves and cannulas. In a related embodiment, the kit comprise components for the removal of a preservative from the composition. Such components include filters, syringes, vials, containers, tubing, etc.

In certain embodiments, said quality of life is measured by a FACIT-Fatigue score. In certain embodiments, the FACIT-Fatigue score increases by at least 3 points. In certain embodiments, the FACIT-Fatigue score increases by ≥ 4 points.

In certain embodiments, said quality of life is measured by an EORTC QLQ-C30 score. In certain embodiments, said EORTC QLQ-C30 score improves by $\geq 10\%$ of the pretreatment score. In certain embodiments, said aspect of the quality of life as measured by an EORTC QLQ-C30 score is selected from the group consisting of a) global health status, b) physical functioning, c) emotional functioning, d) cognitive functioning, e) role functioning, f) social functioning, g) fatigue, h) pain, i) dyspnea, j) appetite loss, and k) insomnia. In certain embodiments, said aspect of quality of life is fatigue.

In certain embodiments, said compound is selected from the group consisting of CR1, LEX-CR1, MCP, DAF, CD59, Factor H, cobra venom factor, FUT-175, compelstatin, and K76 COOH. In certain embodiments, said compound is a steroid that suppresses complement.

In certain embodiments, said compound is selected from the group consisting of antibodies, active antibody fragments, soluble complement inhibitory compounds, proteins, soluble complement inhibitors with a lipid tail, protein fragments, peptides, small organic compounds, RNA aptamers, L-RNA aptamers, spiegelmers, antisense compounds, serine protease inhibitors, double stranded RNA, small interfering RNA, locked nucleic acid inhibitors, and peptide nucleic acid inhibitors. In certain embodiments, said compound is an antibody or an active antibody fragment. In certain embodiments, said antibody or active antibody fragment is selected from the group consisting of a) polyclonal antibodies, b) monoclonal antibodies, c) single chain antibodies, d) chimeric antibodies, e) humanized antibodies, f) Fabs, g) F(ab')s, h) $F(ab')_2$s, i) Fvs, j) diabodies, and k) human antibodies.

In certain embodiments, said antibody or an active antibody fragment thereof binds C5. In certain embodiments, said antibody or active antibody fragment blocks C5 cleavage. In certain embodiments, said antibody or active antibody fragment inhibits the formation of C5b-9. In certain embodiments, said antibody is eculizumab. In certain embodiments, said antibody or active antibody fragment is administered for at least 6

Samsung Bioepis Exhibit No. 1002
Page 10903

months. In certain embodiments, said patient has aplastic anemia or myelodysplastic syndrome.

In certain embodiments, said antibody that binds C5 or an active antibody fragment thereof is administered in a single unit dosage form. In certain embodiments, the single unit dosage form is a 300 mg unit dosage form. In certain embodiments, the single unit dosage form is lyophilized. In certain embodiments, the single unit dosage form is a sterile solution. In certain embodiments, the single unit dosage form is a preservative free formulation. In certain embodiments, the 300 mg single-use dosage form comprises 30 ml of a 10 mg/ml sterile, preservative free solution.

In certain embodiments, the antibody that binds C5 or an active antibody fragment thereof comprises an altered constant region, wherein said antibody or antigen-binding fragment exhibits decreased effector function relative to an anti-CDCP1 antibody with a native constant region. In certain embodiments, decreased effector function comprises one or more properties of the following group: a) decreased antibody-dependent cell-mediated cytotoxicity (ADCC), and b) decreased complement dependent cytotoxicity (CDC), compared to an anti-CDCP1 antibody with a native constant region. In certain embodiments, the altered constant region comprises a G2/G4 construct in place of the G1 domain.

In certain embodiments, the antibody that binds C5 or an active antibody fragment thereof comprises a heavy chain variable region and a light chain variable region, wherein the heavy chain variable region comprises one or more CDR regions having an amino acid sequence selected from the group consisting of SEQ ID NO:5, SEQ ID NO:6, or SEQ ID NO:7, and wherein the light chain variable region comprises one or more CDR regions having an amino acid sequence selected from the group consisting of SEQ ID NO:8, SEQ ID NO:9, or SEQ ID NO:10. In certain embodiments, the antibody that binds C5 or an active antibody fragment thereof comprises a heavy chain variable region and a light chain variable region, wherein the heavy chain variable region consists of SEQ ID NO: 1 and the light chain variable region consists of SEQ ID NO: 3. In certain embodiments, the pharmaceutical composition comprises eculizumab. In certain embodiments, the pharmaceutical composition comprises pexelizumab. In certain embodiments, the antibody that binds C5 or an active antibody fragment thereof comprises a heavy chain and a light chain, wherein the heavy chain consists of SEQ ID NO: 2 and the light chain consists of SEQ ID NO: 4.

Samsung Bioepis Exhibit No. 1002
Page 10904

In certain embodiments, said patient is anemic. In certain embodiments, said patient remains anemic following treatment. In certain embodiments, said patient has a hemoglobin level less than i) 14 g/dL if a man or ii) 12 g/dL if a woman. In certain embodiments, said patient has a hemoglobin level less than i) 13 g/dL if a man or ii) 11 g/dL if a woman. In certain embodiments, said patient has a hemoglobin level less than i) 12 g/dL if a man or ii) 10 g/dL if a woman.

In certain embodiments, said health-adjusted life expectancy is measured according to a unit selected from the group consisting of Years of potential life lost, Disability-free life expectancy, Health-adjusted life year, Quality adjusted life year, Healthy years equivalents, Healthy days gained, Episode-free day, Q-TWiST, Health Utilities Index, or Years of healthy life.

In certain embodiments, the health-adjusted life expectancy in a subject is prolonged by at least one day. In certain embodiments, the health-adjusted life expectancy in a subject is prolonged by at least week. In certain embodiments, the health-adjusted life expectancy in a subject is prolonged by at least one month. In certain embodiments, the health-adjusted life expectancy in a subject is prolonged by at least one year.

In certain embodiments, the pharmaceutical composition is in a single unit dosage form. In certain embodiments, the single unit dosage form is a 300 mg unit dosage form. In certain embodiments, the pharmaceutical composition is lyophilized. In certain embodiments, the pharmaceutical composition is a sterile solution. In certain embodiments, the pharmaceutical composition is a preservative free formulation. In certain embodiments, the pharmaceutical composition comprises a 300 mg single-use formulation of 30 ml of a 10 mg/ml sterile, preservative free solution. In certain embodiments, the pharmaceutical composition comprises an antibody that binds C5 or an active antibody fragment thereof.

BRIEF DESCRIPTION OF THE FIGURES

Figures 1A-B show that eculizumab treatment decreases intravasoular hemolysis and increases PNH type III erythrocytes. Figure 1A shows the degree of intravascular hemolysis in PNH patients, demonstrated by mean lactate dehydrogenase (LDH) levels. Figure 1B shows the mean proportion of PNH type III erythrocytes assessed for placebo- and eculizumab-treated patients.

Samsung Bioepis Exhibit No. 1002
Page 10905

Figure 2 shows the effect of eculizumab treatment on transfusion requirements in PNH patients. This is a Kaplan-Meier plot of time to first transfusion for eculizumab- and placebo-treated patients from baseline through week 26. The P value is from the log rank analysis.

Figure 3 shows the effect of eculizumab on fatigue assessed by the FACIT-Fatigue Instrument. Quality of Life scores were assessed using the Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-Fatigue) instrument. Values for change from baseline to 26 weeks represent least-square means. A positive change indicates an improvement and a negative change indicates deterioration in the FACIT-Fatigue measures of quality of life.

DETAILED DESCRIPTION

I. Definitions

The term "derived from" means "obtained from" or "produced by" or "descending from".

The term "genetically altered antibodies" means antibodies wherein the amino acid sequence has been varied from that of a native antibody. Because of the relevance of recombinant DNA techniques to this application, one need not be confined to the sequences of amino acids found in natural antibodies; antibodies can be redesigned to obtain desired characteristics. The possible variations are many and range from the changing of just one or a few amino acids to the complete redesign of, for example, the variable or constant region. Changes in the constant region will, in general, be made in order to improve or alter characteristics, such as complement fixation, interaction with membranes and other effector functions. Changes in the variable region will be made in order to improve the antigen binding characteristics.

The term "an antigen-binding fragment of an antibody" refers to any portion of an antibody that retains the binding utility to the antigen. An exemplary antigen-binding fragment of an antibody is the heavy chain and/or light chain CDR, or the heavy and/or light chain variable region.

The term "homologous," in the context of two nucleic acids or polypeptides refers to two or more sequences or subsequences that have at least about 85%, at least 90%, at least 95%, or higher nucleotide or amino acid residue identity, when compared and aligned for maximum correspondence, as measured using the following sequence comparison

Samsung Bioepis Exhibit No. 1002
Page 10906

method and/or by visual inspection. In certain embodiments, the "homolog" exists over a region of the sequences that is about 50 residues in length, at least about 100 residues, at least about 150 residues, or over the full length of the two sequences to be compared.

Methods of determining percent identity are known in the art. "Percent (%) sequence identity" with respect to a specified subject sequence, or a specified portion thereof, may be defined as the percentage of nucleotides or amino acids in the candidate derivative sequence identical with the nucleotides or amino acids in the subject sequence (or specified portion thereof), after aligning the sequences and introducing gaps, if necessary to achieve the maximum percent sequence identity, as generated by the program WU-BLAST-2.0a19 (Altschul et al., J. Mol. Biol. 215:403-410 (1997); http://blast.wustl.edu/blast/README.html) with search parameters set to default values. The HSP S and HSP S2 parameters are dynamic values and are established by the program itself depending upon the composition of the particular sequence and composition of the particular database against which the sequence of interest is being searched. A "% identity value" is determined by the number of matching identical nucleotides or amino acids divided by the sequence length for which the percent identity is being reported.

II. Overview

The present disclosure relates to a method of treating paroxysmal nocturnal hemoglobinuria ("PNH"), more specifically to improving certain aspects of quality of life which are impaired in PNH patients, and other hemolytic diseases in mammals. Specifically, the methods of treating hemolytic diseases, which are described herein, involve using compounds which bind to or otherwise block the generation and/or activity of one or more complement components. The present methods have been found to provide surprising results. For instance, hemolysis rapidly ceases upon administration of the compound which binds to or otherwise blocks the generation and/or activity of one or more complement components, with hemoglobinuria being significantly reduced after treatment. Also, hemolytic patients can be rendered less dependent on transfusions or transfusion-independent for extended periods (twelve months or more), well beyond the 120 day life cycle of red blood cells. In addition, type III red blood cell count can be increased dramatically in the midst of other mechanisms of red blood cell lysis (non-complement mediated and/or earlier complement component mediated e.g., Ch3). Another example of a surprising result is that symptoms resolved, indicating that NO serum levels were increased

Samsung Bioepis Exhibit No. 1002
Page 10907

enough even in the presence of other mechanisms of red blood cell lysis. These and other results reported herein are unexpected and could not be predicted from prior treatments of hemolytic diseases.

III The Complement System

The complement system, useful complement inhibitors, and use of these inhibitors to treat PNH and other patients are more fully described in PCT Patent Application PCT/US2005/003225 filed February 3, 2005 and published as International Publication Number WO 2005/074607 A2 on August 18, 2005, the contents of which are incorporated herein by reference in their entirety.

The complement system acts in conjunction with other immunological systems of the body to defend against intrusion of cellular and viral pathogens. There are at least 25 complement proteins, which are found as a complex collection of plasma proteins and membrane cofactors. The plasma proteins make up about 10% of the globulins in vertebrate serum. Complement components achieve their immune defensive functions by interacting in a series of intricate but precise enzymatic cleavage and membrane binding events. The resulting complement cascade leads to the production of products with opsonic, immunoregulatory, and lytic functions.

The complement cascade progresses via the classical pathway or the alternative pathway. These pathways share many components and, while they differ in their initial steps, they converge and share the same "terminal complement" components (C5 through C9) responsible for the activation and destruction of target cells.

The classical complement pathway is typically initiated by antibody recognition of and binding to an antigenic site on a target cell. The alternative pathway is usually antibody independent and can be initiated by certain molecules on pathogen surfaces. Both pathways converge at the point where complement component C3 is cleaved by an active protease (which is different in each pathway) to yield C3a and C3b. Other pathways activating complement attack can act later in the sequence of events leading to various aspects of complement function.

C3a is an anaphylatoxin. C3b binds to bacterial and other cells, as well as to certain viruses and immune complexes, and tags them for removal from the circulation. C3b in this role is known as opsonin. The opsonic function of C3b is considered to be the most

Samsung Bioepis Exhibit No. 1002
Page 10908

important anti-infective action of the complement system. Patients with genetic lesions that block C3b function are prone to infection by a broad variety of pathogenic organisms, while patients with lesions later in the complement cascade sequence, i.e., patients with lesions that block C5 functions, are found to be more prone only to Neisseria infection, and then only somewhat more prone (Fearon, 1983).

C3b also forms a complex with other components unique to each pathway to form classical or alternative C5 convertase, which cleaves C5 into C5a and C5b. C3 is thus regarded as the central protein in the complement reaction sequence since it is essential to both the alternative and classical pathways (Wurzner et al., 1991). This property of C3b is regulated by the serum protease Factor I, which acts on C3b to produce iC3b. While still functional as opsonin, iC3b cannot form an active C5 convertase.

C5 is a 190 kDa beta globulin found in normal serum at approximately 75 μg/mL (0.4 μM). C5 is glycosylated, with about 1.5-3 percent of its mass attributed to carbohydrate. Mature C5 is a heterodimer of a 999 amino acid 115 kDa alpha chain that is disulfide linked to a 656 amino acid 75 kDa beta chain. C5 is synthesized as a single chain precursor protein product of a single copy gene (Haviland et al., 1991). The cDNA sequence of the transcript of this gene predicts a secreted pro-C5 precursor of 1659 amino acids along with an 18 amino acid leader sequence.

The pro-C5 precursor is cleaved after amino acid 655 and 659, to yield the beta chain as an amino terminal fragment (amino acid residues +1 to 655) and the alpha chain as a carboxyl terminal fragment (amino acid residues 660 to 1658), with four amino acids deleted between the two.

C5a is cleaved from the alpha chain of C5 by either alternative or classical C5 convertase as an amino terminal fragment comprising the first 74 amino acids of the alpha chain (i.e., amino acid residues 660-733). Approximately 20 percent of the 11 kDa mass of C5a is attributed to carbohydrate. The cleavage site for convertase action is at or immediately adjacent to amino acid residue 733. A compound that would bind at or adjacent to this cleavage site would have the potential to block access of the C5 convertase enzymes to the cleavage site and thereby act as a complement inhibitor.

C5 can also be activated by means other than C5 convertase activity. Limited trypsin digestion (Minta and Man, 1977; Wetsel and Kolb, 1982) and acid treatment

Samsung Bioepis Exhibit No. 1002
Page 10909

(Yamamoto and Gewurz, 1978; Vogt et al., 1989) can also cleave C5 and produce active C5b.

C5a is another anaphylatoxin. C5b combines with C6, C7, and C8 to form the C5b-8 complex at the surface of the target cell. Upon binding of several C9 molecules, the membrane attack complex (MAC, C5b-9, terminal complement complex-TCC) is formed. When sufficient numbers of MACs insert into target cell membranes the openings they create (MAC pores) mediate rapid osmotic lysis of the target cells. Lower, non-lytic concentrations of MACs can produce other effects. In particular, membrane insertion of small numbers of the C5b-9 complexes into endothelial cells and platelets can cause deleterious cell activation. In some cases activation may precede cell lysis.

As mentioned above, C3a and C5a are anaphylatoxins. These activated complement components can trigger mast cell degranulation, which releases histamine and other mediators of inflammation, resulting in smooth muscle contraction, increased vascular permeability, leukocyte activation, and other inflammatory phenomena including cellular proliferation resulting in hypercellularity. C5a also functions as a chemotactic peptide that serves to attract pro-inflammatory granulocytes to the site of complement activation.

The beneficial effect of anti-C5 mAb has previously been reported in several experimental models including myocardial reperfusion (Vakeva et al., 1998), systemic lupus erythematosus (Wang et al., 1996) and rheumatoid arthritis (Wang et al., 1995); as well as in human clinical trials (Kirschfink, 2001) of autoimmune disease, cardiopulmonary bypass and acute myocardial infarction.

IV Measures of Quality of Life

Various measurements exist to assess quality of life and the effect of medical interventions on quality of life for example the Mini-Mental State Examination (MMSE), the Short Test of Mental Status, the European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire, the FACIT questionnaires and subscales including fatigue and anemia, the Likert Scale, and Borg Scale (Tombaugh, et al., J. Am. Geriatr. Soc. 40:922, 1992; Cummings, JAMA. 269(18):2420, 1993; Crum, et al., JAMA. 269(18):2386, 1993; Folstein, et al., J. Psychiat. Res. 12:189,1975; Kokmen, et al., Mayo Clin. Proc. 62:281, 1987; Tang-Wai, et al., Arch. Neurol. 60:1777, 2003; Tamburini, Ann.

Samsung Bioepis Exhibit No. 1002
Page 10910

Oncol. 12(Suppl. 3):S7, 2001; Webster et al., Health and Quality of Life Outcomes. 1:79, 2003, www.hqlo.com/content/1/1/79; Grant, et al., Chest. 116:1208, 1999; and www.qolid.org). Any of these measurements may be used to assess the change in quality of life due to administration of a compound which inhibits complement or inhibits formation of C5b-9.

In certain embodiments, improvement in quality of life due to administration of a compound which inhibits complement or inhibits formation of C5b-9 is measured by the Functional Assessment of Chronic Illness Therapy (FACIT) Measurement System. In certain embodiments, improvement in quality of life is measured by: a) full scales; b) stand-alone subscales; and c) symptom indices.

In certain embodiments, improvement in quality of life due to administration of a compound which inhibits complement or inhibits formation of C5b-9 is measured by a European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire. In certain embodiments, the EORTC questionnaire is the QLQ-C30.

In certain embodiments, improvement in quality of life is measured by the health-adjusted life expectancy (HALE) index as described in Wilkins, R. and Adams, OB., Am J Public Health, 73:1073-1080 (1983). Health-adjusted life expectancy is an average of the quality-adjusted life years (QALY) for a given population and can be used to evaluate the therapeutic value of a medical intervention. Quality-adjusted life years is a health index that weighs each year of life on a scale from 1 to 0 (Weinstein MC and Stason WB, N Engl J Med, 296:716-721 (1977)). Perfect health is rated as 1, death is rated as 0, and disability and pain are rated based on severity. QALY is determined by multiplying the number of years at each health status.

In certain embodiments, improvement in quality of life is measured by the following instruments: Years of potential life lost, Disability-free life expectancy, Health-adjusted life year, Quality adjusted life year, Healthy years equivalents, Healthy days gained, Episode-free day, Q-TWiST, Health Utilities Index, and Years of healthy life. These measurements account for both changes in mortality as well as changes in morbidity and disability. Any of these measurements may be used to assess the change in quality of life due to administration of a compound which inhibits complement or inhibits formation of C5b-9.

In one embodiment, the disclosed methods improve the quality of life of a patient for at least one day, at least one week, at least two weeks, at least three weeks, at least one

Samsung Bioepis Exhibit No. 1002
Page 10911

month, at least two months, at least three months, at least 6 months, at least one year, at least 18 months, at least two years, at least 30 months, or at least three years, or the duration of treatment.

In certain embodiments, the symptoms used to measure quality of life are scaled for intensity. In certain embodiments, the symptoms are scaled for frequency. In certain embodiments, the symptoms are scaled for intensity and frequency.

In certain aspects, the application provides a method for prolonging the health-adjusted life expectancy of a subject comprising administering to the subject a compound which inhibits complement or inhibits formation of C5b-9. The above measurements account for both changes in mortality as well as changes in morbidity and disability. Any of these measurements may be used to assess the change in quality-adjusted life expectancy due to administration of a compound which inhibits complement or inhibits formation of C5b-9.

In one embodiment, the disclosed methods prolong the health-adjusted life expectancy in a subject by at least one day, at least one week, at least two weeks, at least three weeks, at least one month, at least two months, at least three months, at least 6 months, at least one year, at least 18 months, at least two years, at least 30 months, or at least three years as measured by the health-adjusted life expectancy (HALE) index as described in Wilkins et al. Am J Public Health, 73:1073-1080 (1983). Health-adjusted life expectancy is an average of the quality-adjusted life years (QALY) for a given population and can be used to evaluate the therapeutic value of a medical intervention. Quality-adjusted life years is a health index that weighs each year of life on a scale from 1 to 0 (Weinstein et al., N Engl J Med, 296:716-721 (1977)). Perfect health is rated as 1, death is rated as 0, and disability and pain are rated based on severity. QALY is determined by multiplying the number of years at each health status.

V Inhibitors of the Complement Cascade

In certain embodiments, any compound which binds to or otherwise blocks the generation and/or activity of one or more complement components can be used in the present methods. In certain embodiments, a complement inhibitor may be a small molecule (up to 6,000 Da in molecular weight), a nucleic acid or nucleic acid analog, a peptidomimetic, or a macromolecule that is not a nucleic acid, a serine protease inhibitor, or a protein. These agents include, but are not limited to, small organic molecules, RNA

Samsung Bioepis Exhibit No. 1002
Page 10912

aptamers including ARC187 (which is commercially available from Archemix Corp., Cambridge, Mass.), L-RNA aptamers, Spiegelmers, antisense compounds, molecules which may be utilized in RNA interference (RNAi) such as double stranded RNA including small interfering RNA (siRNA), locked nucleic acid (LNA) inhibitors, peptide nucleic acid (PNA) inhibitors.

In certain embodiments, a complement inhibitor may be a protein or protein fragment. Proteins are known which inhibit the complement cascade, including CD59, CD55, CD46 and other inhibitors of C8 and C9 (see, e.g., U.S. Patent 6,100,443). Proteins known as complement receptors and which bind complement are also known (see, Published PCT Patent Application WO 92/10205 and U.S. Patent 6,057,131). Use of soluble forms of complement receptors, e.g., soluble CR1, can inhibit the consequences of complement activation such as neutrophil oxidative burst, complement mediated neural injury, and C3a and C5a production. In certain embodiments, a complement inhibitor may be naturally occurring or soluble forms of complement inhibitory compounds such as CR1, LEX-CR1, MCP, DAF, CD59, Factor H, cobra venom factor, FUT-175, complestatin, and K76 COOH. Those of skill in the art recognize the above as some, but not all, of the known methods of inhibiting complement and its activation.

In certain embodiments, a complement inhibitor may be an antibody capable of inhibiting complement, such as an antibody that can block the formation of MAC. For example, an antibody complement inhibitor may include an antibody that binds C5. Such anti-C5 antibodies may directly interact with C5 and/or C5b, so as to inhibit the formation of and/or physiologic function of C5b.

Suitable anti-C5 antibodies are known to those of skill in the art. Antibodies can be made to individual components of activated complement, e.g., antibodies to C7, C9, etc. (see, e.g., U.S. Patent 6,534,058; published U.S. patent application US 2003/0129187; and U.S. Patent 5,660,825). U.S. Patent 6,355,245 teaches an antibody which binds to C5 and inhibits cleavage into C5a and C5b thereby decreasing the formation not only of C5a but also the downstream complement components.

The concentration and/or physiologic activity of C5a and C5b in a body fluid can be measured by methods well known in the art. For C5a such methods include chemotaxis assays, RIAs, or ELISAs (see, for example, Ward and Zvaifler, J Clin Invest. 1971 Mar;50(3):606-16; Wurzner, et al., Complement Inflamm. 8:328-340, 1991). For C5b, hemolytic assays or assays for soluble C5b-9 as discussed herein can be used. Other assays

Samsung Bioepis Exhibit No. 1002
Page 10913

known in the art can also be used. Using assays of these or other suitable types, candidate antibodies capable of inhibiting complement such as anti-C5 antibodies, now known or subsequently identified, can be screened in order to 1) identify compounds that are useful in the practice of the application and 2) determine the appropriate dosage levels of such compounds.

An antibody capable of inhibiting complement such as an antibody that binds C5 affecting C5b is preferably used at concentrations providing substantial reduction (i.e., reduction by at least about 25% as compared to that in the absence of the antibody that binds C5) in the C5b levels present in at least one blood-derived fluid of the patient following activation of complement within the fluid. Such concentrations can be conveniently determined by measuring the cell-lysing ability (e.g., hemolytic activity) of complement present in the fluid or the levels of soluble C5b-9 present in the fluid. Accordingly, a specific concentration for an antibody that affects C5b is one that results in a substantial reduction (i.e., a reduction by at least about 25%) in the cell-lysing ability of the complement present in at least one of the patient's blood-derived fluids. Reductions of the cell-lysing ability of complement present in the patient's body fluids can be measured by methods well known in the art such as, for example, by a conventional hemolytic assay such as the hemolysis assay described by Kabat and Mayer (eds), "Experimental Immunochemistry, 2d Edition", 135-240, Springfield, IL, CC Thomas (1961), pages 135-139, or a conventional variation of that assay such as the chicken erythrocyte hemolysis method described below.

Specific antibodies capable of inhibiting complement, such as an antibody that binds C5, are relatively specific and do not block the functions of early complement components. In particular, such specific agents will not substantially impair the opsonization functions associated with complement component C3b, which functions provide a means for clearance of foreign particles and substances from the body.

C3b is generated by the cleavage of C3, which is carried out by classical and/or alternative C3 convertases and results in the generation of both C3a and C3b. Therefore, in order not to impair the opsonization functions associated with C3b, specific antibodies capable of inhibiting complement such as an antibody that binds C5 do not substantially interfere with the cleavage of complement component C3 in a body fluid of the patient (e.g., serum) into C3a and C3b. Such interference with the cleavage of C3 can be detected by measuring body fluid levels of C3a and/or C3b, which are produced in equimolar ratios

Samsung Bioepis Exhibit No. 1002
Page 10914

by the actions of the C3 convertases. Such measurements are informative because C3a and C3b levels will be reduced (compared to a matched sample without the antibody capable of inhibiting complement such as an antibody that binds C5) if cleavage is interfered with by an antibody capable of inhibiting complement such as an antibody that binds C5.

In practice, the quantitative measurement of such cleavage is generally more accurate when carried out by the measurement of body fluid C3a levels rather than of body fluid C3b levels, since C3a remains in the fluid phase whereas C3b is rapidly cleared. C3a levels in a body fluid can be measured by methods well known in the art such as, for example, by using a commercially available C3a EIA kit, e.g., that sold by Quidel Corporation, San Diego, Calif., according to the manufacturer's specifications. Particularly specific antibodies capable of inhibiting complement such as an antibody that binds C5 produce essentially no reduction in body fluid C3a levels following complement activation when tested in such assays.

Certain antibodies of the disclosure will prevent the cleavage of C5 to form C5a and C5b, thus preventing the generation of the anaphylatoxic activity associated with C5a and preventing the assembly of the membrane attack complex associated with C5b. As discussed above, in a particular embodiment, these anti-C5 antibodies will not impair the opsonization function associated with the action of C3b.

A preferred method of inhibiting complement activity is to use a monoclonal antibody which binds to complement C5 and inhibits cleavage. This decreases the formation of both C5a and C5b while at the same time allowing the formation of C3a and C3b which are beneficial to the recipient. Such antibodies which are specific to human complement are known (U.S. Patent 6,355,245). These antibodies disclosed in U.S. Patent 6,355,245 include a preferred whole antibody (now named eculizumab). A similar antibody against mouse C5 is called BB5.1 (Frei et al., Mol. Cell. Probes. 1:141-149 (1987)). Antibodies to inhibit complement activity need not be monoclonal antibodies. They can be, e.g., polyclonal antibodies. They may additionally be antibody fragments. An antibody fragment includes, but is not limited to, an Fab, F(ab'), $F(ab')_2$, single-chain antibody, and Fv. Furthermore, it is well known by those of skill in the art that antibodies can be humanized (Jones et al., Nature 321:522-5 (1986)), chimerized, or deimmunized. The antibodies to be used in the present disclosure may be any of these. It is preferable to use humanized antibodies.

Samsung Bioepis Exhibit No. 1002
Page 10915

In specific embodiments, a therapeutic agent of the disclosure comprises an antibody or antibody fragment. Antibodies and fragments thereof may be made by any conventional method, such as those methods described herein. Antibodies are found in multiple forms, e.g., IgA, IgG, IgM, etc. Additionally, antibodies can be engineered in numerous ways. They can be made as single-chain antibodies (including small modular immunopharmaceuticals or SMIPs™), Fab and $F(ab')_2$ fragments, etc. Antibodies can be humanized, chimerized, deimmunized, or fully human. Numerous publications set forth the many types of antibodies and the methods of engineering such antibodies. For example, see U.S. Patent Nos. 6,355,245; 6,180,370; 5,693,762; 6,407,213; 6,548,640; 5,565,332; 5,225,539; 6,103,889; and 5,260,203.

This invention provides fragments of anti-C5 antibodies, which may comprise a portion of an intact antibody, preferably the antigen-binding or variable region of the intact antibody. Examples of antibody fragments include Fab, Fab', $F(ab')_2$, and Fv fragments; diabodies; linear antibodies (Zapata et al., Protein Eng. 8:1057-1062 (1995)); single-chain antibody molecules; and multispecific antibodies formed from antibody fragments.

Papain digestion of antibodies produces two identical antigen-binding fragments, called "Fab" fragments, each with a single antigen-binding site, and a residual "Fc" fragment, whose name reflects its ability to crystallize readily. Pepsin treatment of an antibody yields an $F(ab')_2$ fragment that has two antigen-combining sites and is still capable of cross-linking antigen.

"Fv" refers to the minimum antibody fragment that contains a complete antigen-recognition and -binding site. This region consists of a dimer of one heavy- and one light-chain variable domain in tight, non-covalent association. It is in this configuration that the three CDRs of each variable domain interact to define an antigen-binding site on the surface of the V_H-V_L dimer. Collectively, the six CDRs confer antigen-binding specificity to the antibody. However, even a single variable domain (or half of an Fv comprising only three CDRs specific for an antigen) has the ability to recognize and bind antigen, although likely at a lower affinity than the entire binding site.

The Fab fragment also contains the constant domain of the light chain and the first constant domain (CH1) of the heavy chain. Fab' fragments differ from Fab fragments by the addition of a few residues at the carboxy terminus of the heavy chain CH1 domain including one or more cysteines from the antibody hinge region. Fab'-SH is the designation herein for Fab' in which the cysteine residue(s) of the constant domains bear a

Samsung Bioepis Exhibit No. 1002
Page 10916

free thiol group. $F(ab')_2$ antibody fragments originally were produced as pairs of Fab' fragments that have hinge cysteines between them. Other chemical couplings of antibody fragments are also known.

"Single-chain Fv" or "scFv" antibody fragments comprise the V_H and V_L domains of an antibody, wherein these domains are present in a single polypeptide chain. Preferably, the Fv polypeptide further comprises a polypeptide linker between the V_H and V_L domains that enables the scFv to form the desired structure for antigen binding. For a review of scFv see Pluckthun in The Pharmacology of Monoclonal Antibodies, vol. 113, Rosenburg and Moore, eds. (Springer-Verlag: New York, 1994), pp. 269-315.

SMIPs are a class of single-chain peptide engineered to include a target binding region, effector domain (CH2 and CH3 domains). *See, e.g.*, U.S. Patent Application Publication No. 20050238646. The target binding region may be derived from the variable region or CDRs of an antibody, e.g., an antibody that binds C5 of the application. Alternatively, the target binding region is derived from a protein that binds C5.

The term "diabodies" refers to small antibody fragments with two antigen-binding sites, which fragments comprise a heavy-chain variable domain (V_H) connected to a light-chain variable domain (V_L) in the same polypeptide chain (V_H-V_L). By using a linker that is too short to allow pairing between the two domains on the same chain, the domains are forced to pair with the complementary domains of another chain and create two antigen-binding sites. Diabodies are described more fully in, for example, EP 404,097; WO 93/11161; and Hollinger et al., Proc. Natl. Acad. Sci. USA, 90: 6444-6448 (1993).

It is well known that the binding to a molecule (or a pathogen) of antibodies with an Fc region assists in the processing and clearance of the molecule (or pathogen). The Fc portions of antibodies are recognized by specialized receptors expressed by immune effector cells. The Fc portions of IgG1 and IgG3 antibodies are recognized by Fc receptors present on the surface of phagocytic cells such as macrophages and neutrophils, which can thereby bind and engulf the molecules or pathogens coated with antibodies of these isotypes (C. A. Janeway et al., Immunobiology 5th edition, page 147, Garland Publishing (New York, 2001)).

This disclosure also provides monoclonal anti-C5 antibodies. A monoclonal antibody can be obtained from a population of substantially homogeneous antibodies, i.e., the individual antibodies comprising the population are identical except for possible naturally-occurring mutations that may be present in minor amounts. Monoclonal

Samsung Bioepis Exhibit No. 1002
Page 10917

antibodies are highly specific, being directed against a single antigenic site. Furthermore, in contrast to conventional (polyclonal) antibody preparations that typically include different antibodies directed against different determinants (epitopes), each monoclonal antibody is directed against a single determinant on the antigen. In addition to their specificity, the monoclonal antibodies are advantageous in that they are often synthesized by the hybridoma culture, uncontaminated by other immunoglobulins. Monoclonal antibodies may also be produced in transfected cells, such as CHO cells and NS0 cells. The modifier "monoclonal" indicates the character of the antibody as being obtained from a substantially homogeneous population of antibodies and does not require production of the antibody by any particular method. For example, the monoclonal antibodies to be used in accordance with the present disclosure may be made by the hybridoma method first described by Kohler et al., Nature 256:495-497 (1975), or may be made by recombinant DNA methods (*see, e.g.*, U.S. Patent Nos. 4,816,567 and 6,331,415). The "monoclonal antibodies" may also be isolated from phage antibody libraries using the techniques described in Clackson et al., Nature 352:624-628 (1991) and Marks et al., J. Mol. Biol. 222:581-597 (1991), for example.

A description of the preparation of a mouse anti-human-C5 monoclonal antibody with specific binding characteristics is presented in U.S. Patent Application Publication No. 20050226870. Wurzner et al., Complement Inflamm. 8:328-340 (1991), describe the preparation of other mouse anti-human-C5 monoclonal antibodies referred to as N19-8 and N20-9.

Other antibodies specifically contemplated are "oligoclonal" antibodies. As used herein, the term "oligoclonal" antibodies" refers to a predetermined mixture of distinct monoclonal antibodies. *See, e.g.*, PCT publication WO 95/20401; U.S. Patent Nos. 5,789,208 and 6,335,163. In one embodiment, oligoclonal antibodies consisting of a predetermined mixture of antibodies against one or more epitopes are generated in a single cell. In other embodiments, oligoclonal antibodies comprise a plurality of heavy chains capable of pairing with a common light chain to generate antibodies with multiple specificities (*e.g.*, PCT publication WO 04/009618). Oligoclonal antibodies are particularly useful when it is desired to target multiple epitopes on a single target molecule (*e.g.*, C5). In view of the assays and epitopes disclosed herein, those skilled in the art can generate or select antibodies or mixtures of antibodies that are applicable for an intended purpose and desired need.

Samsung Bioepis Exhibit No. 1002
Page 10918

In certain embodiments that include a humanized and/or chimeric antibody, one or more of the CDRs are derived from an anti-human C5 antibody. In a specific embodiment, all of the CDRs are derived from an anti-human C5 antibody. In another specific embodiment, the CDRs from more than one anti-human C5 antibody are mixed and matched in a chimeric antibody. For instance, a chimeric antibody may comprise a CDR1 from the light chain of a first anti-human C5 antibody combined with CDR2 and CDR3 from the light chain of a second anti-human C5 antibody, and the CDRs from the heavy chain may be derived from a third anti-human C5 antibody. Further, the framework regions may be derived from one of the same anti-human C5 antibodies, from one or more different antibodies, such as a human antibody, or from a humanized antibody. Human or humanized antibodies are specific for administration to human patients.

In certain embodiments, single chain antibodies, and chimeric, humanized or primatized (CDR-grafted) antibodies, as well as chimeric or CDR-grafted single chain antibodies, comprising portions derived from different species, are also encompassed by the present disclosure as antigen-binding fragments of an antibody. The various portions of these antibodies can be joined together chemically by conventional techniques, or can be prepared as a contiguous protein using genetic engineering techniques. For example, nucleic acids encoding a chimeric or humanized chain can be expressed to produce a contiguous protein. See, e.g., U.S. Pat. Nos. 4,816,567 and 6,331,415; U.S. Pat. No. 4,816,397; European Patent No. 0,120,694; WO 86/01533; European Patent No. 0,194,276 B1; U.S. Pat. No. 5,225,539; and European Patent No. 0,239,400 B1. See also, Newman et al., BioTechnology 10:1455-1460 (1992), regarding primatized antibody. See, e.g., Ladner et al., U.S. Pat. No. 4,946,778; and Bird et al., Science 242:423-426 (1988), regarding single chain antibodies.

In addition, functional fragments of antibodies, including fragments of chimeric, humanized, primatized or single chain antibodies, can also be produced. Functional fragments of the subject antibodies retain at least one binding function and/or modulation function of the full-length antibody from which they are derived. Preferred functional fragments retain an antigen-binding function of a corresponding full-length antibody (such as for example, ability of antibody that binds C5 to bind C5).

General methods for the immunization of animals (in this case with C5 and/or C5b, etc.), isolation of antibody producing cells, fusion of such cells with immortal cells (e.g., myeloma cells) to generate hybridomas secreting monoclonal antibodies, screening of

Samsung Bioepis Exhibit No. 1002
Page 10919

hybridoma supernatants for reactivity of secreted monoclonal antibodies with a desired antigen (in this case the immunogen or a molecule containing the immunogen), the preparation of quantities of such antibodies in hybridoma supernatants or ascites fluids, and for the purification and storage of such monoclonal antibodies, can be found in numerous publications. These include: Coligan, et al., eds. Current Protocols In Immunology, John Wiley & Sons, New York, 1992; Harlow and Lane, Antibodies, A Laboratory Manual, Cold Spring Harbor Laboratory, New York, 1988; Liddell and Cryer, A Practical Guide To Monoclonal Antibodies, John Wiley & Sons, Chichester, West Sussex, England, 1991; Montz et al., Cellular Immunol. 127:337-351 (1990); Wurzner et al., Complement Inflamm. 8:328-340 (1991); and Mollnes et al., Scand. J. Immunol. 28:307-312 (1988).

VI Methods of Treatment

Methods of the application may be used to treat paroxysmal nocturnal hemoglobinuria associated symptoms. Methods of the application may be used to treat anemia associated symptoms. Treatment of paroxysmal nocturnal hemoglobinuria and/or anemia may be administered by standard means. Treatments of the application may be used in combination with other treatments of the application or known treatments for paroxysmal nocturnal hemoglobinuria and/or anemia. Treatments of the application may be co-administered with other treatments that treat symptoms of paroxysmal nocturnal hemoglobinuria and/or anemia.

VII Pharmaceutical Formulations and Uses

Methods of administration of small molecules, proteins, and nucleic acids are well-known to those of skill in the art. Methods of administration of antibodies are well-known to those of skill in the art. To achieve the desired inhibition, the antibodies can be administered in a variety of unit dosage forms. The dose will vary according to the particular antibody. For example, different antibodies may have different masses and/or affinities, and thus require different dosage levels. Antibodies prepared as Fab fragments will also require differing dosages than the equivalent intact immunoglobulins, as they are of considerably smaller mass than intact immunoglobulins, and thus require lower dosages to reach the same molar levels in the patient's blood. The dose will also vary depending on the manner of administration, the particular symptoms of the patient being treated, the overall health, condition, size, and age of the patient, and the judgment of the prescribing

Samsung Bioepis Exhibit No. 1002
Page 10920

physician. Dosage levels of the antibodies for human subjects are generally between about 1 mg per kg and about 100 mg per kg per patient per treatment, and preferably between about 5 mg per kg and about 50 mg per kg per patient per treatment. In terms of plasma concentrations, the antibody concentrations are preferably in the range from about 25 μg/mL to about 500 μg/mL. However, greater amounts may be required for extreme cases and smaller amounts may be sufficient for milder cases.

In certain embodiments, the pharmaceutical composition is in a single unit dosage form. In certain embodiments, the single unit dosage form is a 300 mg unit dosage form. In certain embodiments, the pharmaceutical composition is lyophilized. In certain embodiments, the pharmaceutical composition is a sterile solution. In certain embodiments, the pharmaceutical composition is a preservative free formulation. In certain embodiments, the pharmaceutical composition comprises a 300 mg single-use formulation of 30 ml of a 10 mg/ml sterile, preservative free solution. In certain embodiments, the antibody is administered according to the following protocol: 600 mg via 25 to 45 minute IV infusion every 7 ± 2 days for the first 4 weeks, followed by 900 mg for the fifth dose 7 ± 2 days later, then 900 mg every 14 ± 2 days thereafter. Antibody is administered via IV infusion over 25 to 45 minute.

Administration of the anti-C5 antibodies will generally be performed by an intravascular route, e.g., via intravenous infusion by injection. Other routes of administration may be used if desired but an intravenous route will be the most preferable. Formulations suitable for injection are found in Remington's Pharmaceutical Sciences, Mack Publishing Company, Philadelphia, Pa., 17th ed. (1985). Such formulations must be sterile and non-pyrogenic, and generally will include a pharmaceutically effective carrier, such as saline, buffered (e.g., phosphate buffered) saline, Hank's solution, Ringer's solution, dextrose/saline, glucose solutions, and the like. The formulations may contain pharmaceutically acceptable auxiliary substances as required, such as, tonicity adjusting agents, wetting agents, bactericidal agents, preservatives, stabilizers, and the like. In certain embodiments, complement inhibitors such as eculizumab may be administered via IV infusion and diluted to a final concentration of 5 mg/ml prior to administration.

Administration of the antibodies capable of inhibiting complement such as an antibody that binds C5 will generally be performed by a parenteral route, typically via injection such as intra-articular or intravascular injection (e.g., intravenous infusion) or intramuscular injection. Other routes of administration, e.g., oral (p.o.), may be used if

Samsung Bioepis Exhibit No. 1002
Page 10921

desired and practicable for the particular antibody capable of inhibiting complement to be administered. Antibodies capable of inhibiting complement such as an antibody that binds C5 can also be administered in a variety of unit dosage forms and their dosages will also vary with the size, potency, and in vivo half-life of the particular antibody capable of inhibiting complement being administered. Doses of antibodies capable of inhibiting complement such as an antibody that binds C5 will also vary depending on the manner of administration, the particular symptoms of the patient being treated, the overall health, condition, size, and age of the patient, and the judgment of the prescribing physician.

In certain embodiments, a typical therapeutic treatment includes a series of doses, which will usually be administered concurrently with the monitoring of clinical endpoints with the dosage levels adjusted as needed to achieve the desired clinical outcome. In certain embodiments, treatment is administered in multiple dosages over at least a week. In certain embodiments, treatment is administered in multiple dosages over at least a month. In certain embodiments, treatment is administered in multiple dosages over at least a year. In certain embodiments, treatment is administered in multiple dosages over the remainder of the patient's life.

The frequency of administration may also be adjusted according to various parameters. These include the clinical response, the plasma half-life of the therapeutic of the disclosure, and the levels of the antibody in a body fluid, such as, blood, plasma, serum, or synovial fluid. To guide adjustment of the frequency of administration, levels of the therapeutic of the disclosure in the body fluid may be monitored during the course of treatment.

In certain embodiments, the frequency of administration may be adjusted according to an assay measuring cell-lysing ability of complement present in one or more of the patient's body fluids. The cell-lysing ability can be measured as percent hemolysis in hemolytic assays of the types described herein. A 10% or 25% or 50% reduction in the cell-lysing ability of complement present in a body fluid after treatment with the antibody capable of inhibiting complement used in the practice of the application means that the percent hemolysis after treatment is 90, 75, or 50 percent, respectively, of the percent hemolysis before treatment.

For the treatment of hemolytic diseases such as PNH by systemic administration of an antibody capable of inhibiting complement such as an antibody that binds C5 (as opposed to local administration), administration of a large initial dose is specific, i.e., a

Samsung Bioepis Exhibit No. 1002
Page 10922

single initial dose sufficient to yield a substantial reduction, and more preferably an at least about 50% reduction, in the hemolytic activity of the patient's serum. Such a large initial dose is preferably followed by regularly repeated administration of tapered doses as needed to maintain substantial reductions of serum hemolytic titer. In another embodiment, the initial dose is given by both local and systemic routes, followed by repeated systemic administration of tapered doses as described above.

Formulations particularly useful for antibody-based therapeutic agents are also described in U.S. Patent App. Publication Nos. 20030202972, 20040091490 and 20050158316. In certain embodiments, the liquid formulations of the application are substantially free of surfactant and/or inorganic salts. In another specific embodiment, the liquid formulations have a pH ranging from about 5.0 to about 7.0. In yet another specific embodiment, the liquid formulations comprise histidine at a concentration ranging from about 1 mM to about 100 mM. In still another specific embodiment, the liquid formulations comprise histidine at a concentration ranging from 1 mM to 100 mM. It is also contemplated that the liquid formulations may further comprise one or more excipients such as a saccharide, an amino acid (e.g., arginine, lysine, and methionine) and a polyol. Additional descriptions and methods of preparing and analyzing liquid formulations can be found, for example, in PCT publications WO 03/106644, WO 04/066957, and WO 04/091658.

Wetting agents, emulsifiers and lubricants, such as sodium lauryl sulfate and magnesium stearate, as well as coloring agents, release agents, coating agents, sweetening, flavoring and perfuming agents, preservatives and antioxidants can also be present in the pharmaceutical compositions of the application.

In certain embodiments, formulations of the subject antibodies are pyrogen-free formulations which are substantially free of endotoxins and/or related pyrogenic substances. Endotoxins include toxins that are confined inside microorganisms and are released when the microorganisms are broken down or die. Pyrogenic substances also include fever-inducing, thermostable substances (glycoproteins) from the outer membrane of bacteria and other microorganisms. Both of these substances can cause fever, hypotension and shock if administered to humans. Due to the potential harmful effects, it is advantageous to remove even low amounts of endotoxins from intravenously administered pharmaceutical drug solutions. The Food & Drug Administration ("FDA") has set an upper limit of 5 endotoxin units (EU) per dose per kilogram body weight in a

Samsung Bioepis Exhibit No. 1002
Page 10923

single one hour period for intravenous drug applications (The United States Pharmacopeial Convention, Pharmacopeial Forum 26 (1):223 (2000)). When therapeutic proteins are administered in amounts of several hundred or thousand milligrams per kilogram body weight, as can be the case with monoclonal antibodies, it is advantageous to remove even trace amounts of endotoxin.

Formulations of the subject antibodies include those suitable for oral, dietary, topical, parenteral (e.g., intravenous, intraarterial, intramuscular, subcutaneous injection), ophthalmologic (e.g., topical or intraocular), inhalation (e.g., intrabronchial, intranasal or oral inhalation, intranasal drops), rectal, and/or intravaginal administration. Other suitable methods of administration can also include rechargeable or biodegradable devices and controlled release polymeric devices. Stents, in particular, may be coated with a controlled release polymer mixed with an agent of the application. The pharmaceutical compositions of this disclosure can also be administered as part of a combinatorial therapy with other agents (either in the same formulation or in a separate formulation).

The amount of the formulation which will be therapeutically effective can be determined by standard clinical techniques. In addition, *in vitro* assays may optionally be employed to help identify optimal dosage ranges. The precise dose to be employed in the formulation will also depend on the route of administration, and the seriousness of the disease or disorder, and should be decided according to the judgment of the practitioner and each patient's circumstances. Effective doses may be extrapolated from dose-response curves derived from in vitro or animal model test systems. The dosage of the compositions to be administered can be determined by the skilled artisan without undue experimentation in conjunction with standard dose-response studies. Relevant circumstances to be considered in making those determinations include the condition or conditions to be treated, the choice of composition to be administered, the age, weight, and response of the individual patient, and the severity of the patient's symptoms. For example, the actual patient body weight may be used to calculate the dose of the formulations in milliliters (mL) to be administered. There may be no downward adjustment to "ideal" weight. In such a situation, an appropriate dose may be calculated by the following formula: Dose (mL) = [patient weight (kg) x dose level (mg/kg)/ drug concentration (mg/mL)]

To achieve the desired treatment results, anti-C5 antibodies can be administered in a variety of unit dosage forms. The dose will vary according to the particular antibody. For example, different antibodies may have different masses and/or affinities, and thus require

Samsung Bioepis Exhibit No. 1002
Page 10924

different dosage levels. Antibodies prepared as Fab' fragments or single chain antibodies will also require differing dosages than the equivalent native immunoglobulins, as they are of considerably smaller mass than native immunoglobulins, and thus require lower dosages to reach the same molar levels in the patient's blood.

Other therapeutics of the disclosure can also be administered in a variety of unit dosage forms and their dosages will also vary with the size, potency, and *in vivo* half-life of the particular therapeutic being administered.

Doses of therapeutics of the disclosure will also vary depending on the manner of administration, the particular symptoms of the patient being treated, the overall health, condition, size, and age of the patient, and the judgment of the prescribing physician.

The formulations of the application can be distributed as articles of manufacture comprising packaging material and a pharmaceutical agent which comprises the antibody capable of inhibiting complement and a pharmaceutically acceptable carrier as appropriate to the mode of administration. The packaging material may include a label which indicates that the formulation is for use in the treatment of hemolytic diseases such as PNH. Although antibodies are preferred, especially anti-C5 antibodies which have already been shown to be safe and effective at decreasing the accumulation of downstream complement components in persons, the use of other complement inhibitors is also contemplated by this disclosure. The pharmaceutical formulations and uses of the disclosure may be combined with any known complement inhibitors or hemolytic diseases treatments known in the art.

In certain aspects, the application provides kits comprising a pharmaceutical composition of the application. In some embodiments, the kit further comprises at least one component of a closed sterile system. Components of the closed sterile system include, but are not limited to, needles, syringes, catheter based syringes, needle based injection devices, needle-less injection devices, filters, tubing, valves and cannulas. In a related embodiment, the kit comprise components for the removal of a preservative from the composition. Such components include filters, syringes, vials, containers, tubing, etc.

Samsung Bioepis Exhibit No. 1002
Page 10925

EXEMPLIFICATION

METHODS

Patient Selection

The TRIUMPH trial consisted of a 2-week screening period, an observation period of up to 3 months duration, and a 26-week treatment period.

During the screening period, patients were evaluated with respect to inclusion and exclusion criteria. Men and women, 18 years or older, diagnosed as having PNH with a type III erythrocyte population of ≥10%, and who had received at least 4 transfusions in the previous 12 months were eligible. Concomitant administration of erythropoietin, immunosuppressants, corticosteroids, coumadin, low molecular weight heparin, iron supplements, and folic acid were not reasons for exclusion, provided the doses were steady prior to the first visit and throughout the duration of the study. Because of the increased frequency of neisserial infections in individuals genetically deficient in terminal complement proteins, all patients were vaccinated against *Neisseria meningitidas*. Patients were to avoid conception. The protocol was approved by an Investigational Review Board at each clinical site and written informed consent was obtained from all patients enrolled.

Patients transfused with a mean pre-transfusion hemoglobin level >10.5 g/dL over the previous 12 months, and those who showed evidence of having a suppressed immune response, complement deficiency, or active bacterial infection, including any history of meningococcal disease, were excluded from the study. Patients were also not eligible if they had previously received a bone marrow transplant or if they had participated in another trial or received another investigational drug within 30 days of the first visit. An individualized transfusion algorithm was calculated for each patient based on their prior 12-month transfusion history; the written algorithm documented the number of packed red blood cell (PRBC) units transfused for given hemoglobin values and served as a prospectively determined guide for transfusion during observation and treatment periods.

Each patient considered eligible entered an observation period of up to 13 weeks in order to confirm their PBRC transfusion dependence. At least one transfusion --termed the "qualifying" transfusion-- during the 13-week observation period at a hemoglobin value at or below 9 g/dL with symptoms, or at or below 7 g/dL with or without symptoms, in accordance with the transfusion algorithm indicated for each patient, was a requirement to

Samsung Bioepis Exhibit No. 1002
Page 10926

proceed to randomization. The hemoglobin value at which each individual's qualifying transfusion was administered, was defined as the hemoglobin "set point" for that individual for the purpose of the primary efficacy variable. A platelet count ≥100,000/mL and a LDH level ≥1.5 times the upper limit of the normal range were also required either at screening or during the observation period for eligibility.

Study Design

Patients were randomly assigned on a one-on-one basis to receive either placebo or eculizumab (Soliris™, Alexion Pharmaceuticals, Inc.) within 10 days of the qualifying transfusion. Study medication was dosed in a blinded fashion as follows: 600 mg eculizumab for patients randomly assigned to active drug, or placebo for those patients randomly assigned to placebo, respectively via IV infusion every 7±1 days for 4 doses; followed by 900 mg eculizumab, or placebo, respectively, via IV infusion 7±1 day later; followed by a maintenance dose of 900 mg eculizumab, or placebo, respectively, via IV infusion every 14±2 days for a total of 26 weeks of treatment.

Measures of Clinical Efficacy

There were two co-primary endpoints in the study: (1) stabilization of hemoglobin levels, defined as a hemoglobin value maintained above the individual hemoglobin set point in the absence of transfusions for the entire 26-week treatment period, and (2) reduction in units of PRBCs transfused during the 26-week treatment phase of the study. The trigger for transfusion during the study period remained unchanged for each patient, as compared with their care before entry into the study: patients received blood transfusions when they had symptoms resulting from anemia and reached their individualized, pre-determined "set point". Pre-specified secondary endpoints included transfusion avoidance, hemolysis as measured by LDH area under the curve from baseline to 26 weeks, and QoL changes as measured from baseline to 26 weeks using the Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-Fatigue) instrument.[13] Pre-specified exploratory analyses included assessment of the EORTC QLQ-C30 instrument,[14] the change in LDH from baseline through week 26, and thrombosis. Other pre-specified measurements included pharmacokinetics, pharmacodynamics, and immunogenicity of eculizumab. Time to first transfusion during the 26-week treatment phase and the proportion of PNH type III blood cells were also assessed.

Safety Assessments

Samsung Bioepis Exhibit No. 1002
Page 10927

Treatment-emergent adverse events, clinical laboratory tests (e.g., serum chemical analyses and complete blood counts), electrocardiogram data, and vital signs were assessed. Adverse events were defined using the MedDRA preferred terms and tabulated as incidence rates per treatment group.

Statistical Analysis

For co-primary endpoints, analyses were performed according to the intention to treat using the data from all patients who were randomized and received study drug; stabilization of hemoglobin levels was analyzed using the Fisher's exact test and total PRBC units transfused were analyzed with the Wilcoxon's rank sum test. For comparison of treatment effect on transfusion avoidance, the Fisher's exact test was used on the incidence and the log rank test was used for time to first transfusion. For LDH area under the curve the Wilcoxon's rank sum test was used.

Quality of life measure of fatigue was assessed using the scoring guidelines for the FACIT-Fatigue instrument.[15] Assessment of quality of life measures based on the EORTC QLQ-C30 instrument was conducted in accordance with the appropriate scoring guidelines.[16] The changes of FACIT-Fatigue and EORTC QLQ-C30 scores from baseline through 26 weeks were analyzed using a mixed model, with baseline as covariate, treatment and time as fixed effects, and patient as a random effect. Changes in LDH levels and PNH type III erythrocytes from baseline through 26 weeks were analyzed using the same mixed model. Two-sided tests were used for all analyses. The adverse events and long-term safety checklist were tabulated separately and compared between treatments using the Fisher's exact test. A p-value ≤ 0.05 was considered to be statistically significant.

RESULTS

Characteristics of Patients

A total of 115 PNH patients were screened. Six patients did not meet the inclusion/exclusion criteria during the screening period. Twenty-one other patients did not receive a qualifying transfusion and were not randomized into the treatment phase. One patient who did not meet the inclusion criteria was inadvertently randomized, but did not receive study medication. Thus 87 hemolytic PNH patients (35 men and 52 women) were enrolled and randomized to receive either eculizumab (N=43) or placebo (N=44), exceeding the original target of 75 randomized patients.

Samsung Bioepis Exhibit No. 1002
Page 10928

Patient characteristics were similar in the eculizumab- and placebo-treated cohorts; median age, 41 (range 20-85) and 35 (range 18-78) years; median duration of PNH, 4.2 (range 0.8 to 29.7) and 9.2 (range 0.4 to 38.3) years; patients with history of aplastic anemia, 4 and 11; history of myelodysplastic syndrome, 1 and 0; and history of thrombosis, 9 (16 events) and 8 (11 events). Stable usage of concomitant medications at baseline in the eculizumab- and placebo-treated groups included the following: erythropoietin, 3 patients and 0 patients; cyclosporine, 1 and 1; anticoagulants (coumarins or heparins) 21 and 11; and steroids (glucocorticoids or androgenic steroids), 12 and 12, respectively.

Of the 87 patients randomized, 85 completed the trial. Two patients who did not complete the trial had been randomized to the eculizumab arm: one patient discontinued due to the inconvenience of travel to the study site and the second patient became pregnant. Ten patients in the placebo-treatment group discontinued infusions, in all cases due to perceived lack of efficacy, but they remained in the study for monitoring purposes.

Pharmacokinetics/Pharmacodynamics

In 42 of the 43 eculizumab-treated patients the levels of drug during the maintenance period (900 mg every 2 weeks±2 days) were sufficient to completely block serum hemolytic activity (mean trough value at week 26 of 101.8 μg/mL). A single patient did not sustain therapeutic trough levels of eculizumab and demonstrated a breakthrough in complement blockade during the last few days of each dosing interval. These breakthroughs were clinically manageable and quickly resolved following the next dose.

Hemolytic Efficacy Variables

The impact of terminal complement inhibition with eculizumab on chronic intravascular hemolysis in PNH patients was demonstrated in this study by an immediate (one week) and sustained decrease in mean levels of LDH (Figure 1A). The median LDH area under the curve during the 26-week study period was reduced 85.8% in eculizumab-relative to placebo-treated patients ($P<0.001$). The mean LDH level decreased from 2199.7±157.7 IU/L at baseline to 327.3±67.6 IU/L by 26 weeks in eculizumab-treated patients while levels in placebo-treated patients remained consistently elevated with values of 2259.0±158.5 IU/L at baseline and 2418.9±140.3 IU/L at 26 weeks ($P<0.001$, for eculizumab versus placebo). A second biochemical measure of hemolysis, serum aspartate aminotransferase (AST), also showed a statistically significant improvement following eculizumab- versus placebo-treatment (data not shown). Haptoglobin levels were statistically significantly increased in eculizumab- as compared to placebo-treated patients

Samsung Bioepis Exhibit No. 1002
Page 10929

but mean levels of haptoglobin were still below normal levels in eculizumab-treated patients (data not shown).

Figure 1A shows the degree of intravascular hemolysis in PNH patients, demonstrated by mean lactate dehydrogenase (LDH) levels (±standard error) from baseline (study week 0) to week 26 for both eculizumab- and placebo-treated patient populations. Screening occurred up to 3 months prior to study week 0. The upper limit of the normal range (103-223 IU/L) for LDH is indicated by a dashed line. LDH was reduced to a mean level just above the upper limit of normal at week 26 for eculizumab-treated patients; 15 of 41 patients who completed the study demonstrated LDH levels within the normal range. All placebo-treated patients remained at least 5 times above the upper limit of normal at week 26. The P value is based on a mixed model analysis from baseline through week 26. Figure 1B shows the mean proportion (±standard error) of PNH type III erythrocytes assessed for placebo- and eculizumab-treated patients. The screening visit occurred up to 3 months prior to study week 0. The P value is based on a mixed model analysis from baseline through week 26.

A corollary to the reduction in intravascular hemolysis during eculizumab treatment was an observed increase in the PNH type III erythrocyte population (Figure 1B). The mean proportions of type III erythrocytes increased from 28.1±2.0% at baseline to 56.9±3.6% by week 26 for eculizumab-treated patients while proportions in the placebo group remained constant with mean values of 35.7±2.8% before treatment to 35.5±2.8% at 26 weeks ($P<0.001$, for eculizumab versus placebo). By contrast, the proportions of PNH type III granulocytes and monocytes did not change significantly between the treatment groups during the treatment period and were greater than 90% at week 26.

CLINICAL EFFICACY

Co-primary endpoints

The co-primary efficacy endpoints in the TRIUMPH trial were stabilization of hemoglobin levels and reduction in PRBC units transfused. At the end of the treatment period, 48.8% of eculizumab-treated patients had maintained levels of hemoglobin above the pre-specified set-point (median set-point value of 7.7 g/dL for both treatment groups) in the absence of transfusions, whereas stabilization of hemoglobin did not occur in any of the patients in the placebo group ($P<0.001$; Table 1). By week 26, the median of PRBC units transfused per patient was 0 in the eculizumab group and 10.0 in the placebo cohort

Samsung Bioepis Exhibit No. 1002
Page 10930

(P<0.001), while the mean of PRBC units transfused was 3.0 and 11.0 in the eculizumab and placebo cohorts, respectively. In the 6-month period prior to the study, the median of PRBC units transfused per patient was 9.0 in the eculizumab cohort and 8.5 in placebo patients while the mean of PRBC units transfused was 9.6±0.6 and 9.7±0.7, respectively. Mean hemoglobin levels were similar between the treatment groups at baseline (10.0±1.8 g/dL in eculizumab-treated patients and 9.7±1.8 g/dL in placebo-treated patients) and did not substantially change by week 26 (10.1±2.5 g/dL and 8.9±2.2 g/dL in eculizumab and placebo cohorts, respectively).

The median time to first transfusion was not reached during the study period in eculizumab-treated patients (it was greater than 26 weeks) while the placebo group reached the median time to first transfusion in only 4 weeks (P<0.001; Figure 2). Transfusion avoidance was achieved in 51.2% and 0% of the eculizumab and placebo cohorts, respectively (P<0.001). By the end of the 26-week treatment period, the total PRBC units transfused were 131 in eculizumab-treated patients versus 482 in the placebo group (Table 1). By contrast, in the 6-month period prior to the study, total PRBC units transfused in the eculizumab- and placebo-cohorts were 413 and 417, respectively.

Table 1

Stabilization of Hemoglobin Levels and Reduction

in Transfusion Requirements during Eculizumab Treatment

	PRE-TREATMENT HISTORY*		TREATMENT PERIOD		
	Placebo	Eculizumab	Placebo	Eculizumab	P Value
†Stabilization of Hemoglobin Levels in the absence of transfusions (percent of patients)	NA	NA	0	48.8	<0.001‡
†Units Transfused per Patient					
Median	8.5	9.0	10	0	<0.001§
Mean±SE	9.7±0.7	9.6±0.6	11.0±0.83	3.0±0.67	
Total Units Transfused per Group	417	413	482	131	

*Twelve month historical transfusion data normalized to 6 months

†Co-primary endpoints

‡Base on 2-sided Fisher's exact test

§Based on Wilcoxon's rank sum test

NA, not applicable

Improvements in quality of life measures

Assessments of quality of life in PNH patients during eculizumab treatment were performed using two different instruments, FACIT-Fatigue and the EORTC QLQ-C30. Eculizumab-treated patients showed a mean increase (improvement) in the FACIT-Fatigue score of 6.4±1.2 points from baseline to 26-weeks while the mean score in placebo patients decreased by 4.0±1.7 points, a total difference between the treatment groups of 10.4 points (Figure 3). Mixed model analysis of covariance demonstrated a statistically significant difference between treatment groups (P<0.001).

For the EORTC instrument, improvements were observed with eculizumab-treatment in each subscale. Statistically significant improvements with eculizumab-compared with placebo-treated groups were observed in the following quality of life

Samsung Bioepis Exhibit No. 1002
Page 10932

subscales (Table 2): global health status (P<0.001), physical functioning (P<0.001), emotional functioning (P=0.008), cognitive functioning (P=0.002), role functioning (P<0.001), social functioning (P=0.003), fatigue (P<0.001), pain (P=0.002), dyspnea (P<0.001), appetite loss (P<0.001), and insomnia (P=0.014). The improvements with eculizumab treatment in the other scales, including nausea and vomiting, diarrhea, constipation, and financial difficulties, did not reach statistical significance.

Table 2

Effect of Eculizumab Treatment on

Quality of Life Assessed by the EORTC QLQ-C30 Instrument

	Mean Change from Baseline to Week 26*			
	Placebo	Eculizumab	Absolute Difference	P Value†
Global Health Status	-8.5	10.9	19.4	<0.001
Functional				
Role	-6.9	17.9	24.8	<0.001
Social	2.0	16.7	14.6	=0.003
Cognitive	-6.1	7.9	14.0	=0.002
Physical	-3.5	9.4	13.0	<0.001
Emotional	-3.7	7.5	11.2	=0.008
Symptoms/Single Items				
Fatigue	10.0	-16.9	27.0	<0.001
Pain	5.3	-12.3	17.6	=0.002
Dyspnea	8.9	-7.9	16.9	<0.001
Appetite Loss	3.3	-10.3	13.6	<0.001
Insomnia	4.9	-7.9	12.8	=0.014

Samsung Bioepis Exhibit No. 1002
Page 10933

Financial Difficulties	0.0	-10.3	10.3	=0.186
Constipation	0.0	-6.3	6.3	=0.199
Nausea/vomiting	2.8	-0.4	3.2	=0.056
Diarrhea	5.7	4.8	0.9	=0.147

*A positive change indicates an improvement in global health status and functional scales and a negative change indicates an improvement in symptom and single item scales.

†Based on a mixed analysis-of-covariance model with visit as a fixed effect, patient as a random effect and baseline as a covariate.

Relationship between FACIT-Fatigue quality of life and intravascular hemolysis

In order to determine if there was a treatment independent relationship between the FACIT-Fatigue quality of life instrument and intravascular hemolysis, an analysis was performed whereby the mean LDH level (through the 26 week study period) for each TRIUMPH patient was analyzed as a function of the patient's respective mean change in FACIT-Fatigue score from baseline (through the 26 week study period) (see Table 3). For this analysis, mean levels of LDH were divided into 4 groups that included: normal levels, 1-2 times the upper limit of normal (ULN), 2-10 times the upper limit of normal, and greater than 10 times the upper limit of normal. The analysis demonstrated that patients who maintained normal LDH levels throughout the study experienced significant improvements in fatigue when compared to patients who had incrementally higher levels of LDH throughout the study (p=0.0048). These data establish a clear link between increasing intravascular hemolysis as measured by LDH levels and decreased quality of life as measured by the FACIT-Fatigue quality of life instrument.

Samsung Bioepis Exhibit No. 1002
Page 10934

Table 3

Relationship between FACIT-Fatigue and Intravascular Hemolysis

Treatment Group	LDH Category	Change of FACIT from Baseline		
		< 4	>= 4	P-Value
Combined	Normal	4 (30.77%)	9 (69.23%)	.0048
	1 - 2 X ULN	18 (61.54%)	10 (38.46%)	
	2 - 10 X ULN	18 (72.00%)	7 (28.00%)	
	> 10 X ULN	16 (80.00%)	4 (20.00%)	

Safety

There were no deaths in the study. Serious adverse events (SAEs) were reported for 13 patients, of which 4 occurred in the eculizumab-treated cohort and 9 were in the placebo-treated cohort (see Table 4). All patients recovered without sequelae.

The most common AEs reported for eculizumab-treated patients were headache, nasopharyngitis, back pain, and upper respiratory tract infection. Headache and back pain occurred more commonly in the eculizumab-treatment group compared with the placebo group. However, the increase in headaches was limited to the first 2 weeks of therapy and was mild to moderate. There were no statistically significant differences in incidents rates between treatment groups for any AEs reported.

One episode of thrombosis (Budd-Chiari) occurred in a placebo-treated patient. There were no thromboses in eculizumab-treated patients.

Only one patient showed a detectable level of anti-eculizumab antibodies in the eculizumab-treated cohort; this response was weak (did not titrate), occurred at only one time point and did not result in a disruption of complement blockade.

Samsung Bioepis Exhibit No. 1002
Page 10935

Table 4

Adverse Event Reporting

SERIOUS ADVERSE EVENTS*	Placebo Patients n (percent)	Eculizumab Patients n (percent)
Total	9 (20.5)	4 (9.3)
Eculizumab treatment emergent		
Exacerbation of PNH	3 (6.8)	1 (2.3)
Renal colic	0	1 (2.3)
Lumbar sacral disc prolapse	0	1 (2.3)
Alpha streptococcal bacteremia	0	1 (2.3)
Central line infection and UTI	1 (2.3)	0 (0)
Upper respiratory tract infection	1 (2.3)	0 (0)
Probable viral infection	1 (2.3)	0 (0)
Neutropenia	1 (2.3)	0 (0)
Cellulitis / folliculitis / neutropenia	1 (2.3)	0 (0)
Anemia and pyrexia	1 (2.3)	0 (0)
MOST FREQUENT ADVERSE EVENTS*†		
Headache§	12 (27.3)	19‡ (44.2)
Nasopharyngitis	8 (18.2)	10 (23.3)
Upper respiratory tract infection	10 (22.7)	6 (14)
Back pain	4 (9.1)	8 (18.6)
Nausea	5 (11.4)	7 (16.3)
Cough	4 (9.1)	5 (11.6)
Diarrhea	5 (11.4)	4 (9.3)
Arthralgia	5 (11.4)	3 (7.0)
Abdominal pain	5 (11.4)	2 (4.7)
Dizziness	5 (11.4)	2 (4.7)
Vomiting	5 (11.4)	2 (4.7)
Fatigue	1 (2.3)	5 (11.6)

Samsung Bioepis Exhibit No. 1002
Page 10936

Viral infection	5 (11.4)	1 (2.3)

*By preferred terms

†Occurring in 10% or more of patients

‡Sixteen of 19 patients experienced headache within 48 hours of infusion

§Following the first 2 weeks of dosing, 20.9% of eculizumab- and 22.7% of placebo-treated patients experienced headache

DISCUSSION

Chronic intravascular hemolysis with periods of acute exacerbation are the classical manifestations of PNH, frequently resulting in anemia, the need for transfusions to sustain hemoglobin levels, and deterioration in quality of life. In the phase III pivotal TRIUMPH study, we examined the effect of terminal complement inhibition with eculizumab on hemoglobin levels and transfusion requirements in patients with PNH. Forty-nine percent of patients treated with eculizumab over the 6-month period demonstrated stabilization of hemoglobin in the absence of transfusions compared to no patients in the placebo arm of the trial. Over 50% of eculizumab-treated patients were transfusion independent during the entire study compared to none in the placebo arm, and the overall mean transfusion rate was reduced by 73%. Moreover, even in patients who did not achieve transfusion independence, eculizumab treatment was associated with a 44% reduction in the rate of transfusion (data now shown).

Lactate dehydrogenase, a biochemical marker of hemolysis in PNH,[9] was immediately and consistently decreased in all eculizumab-treated patients, while patients in the placebo cohort continued to hemolyze with levels of LDH exceeding 5 times the upper limit of the normal range in all patients at the study end. Levels of LDH were reduced into the normal range in approximately one-third of eculizumab-treated patients, while the remainder stabilized at a level just above the upper limit of normal suggesting residual low level hemolysis in some patients. Levels of haptoglobin, a more sensitive marker of the presence of cell free hemoglobin in the circulation, were undetectable in most patients. Low level hemolysis in a subset of eculizumab-treated patients is possibly due to an inherent decrease in survival of these cells or C3b-mediated, extravascular clearance of PNH erythrocytes through the reticuloendothelial system.[17]

Samsung Bioepis Exhibit No. 1002
Page 10937

Before eculizumab treatment, hemoglobin levels in study patients were artificially maintained by frequent transfusion. Therefore, stabilization of hemoglobin levels with a concomitant cessation of or reduction in transfusions represents a net increase in endogenous hemoglobin levels. Our data suggest that resolution of hemolysis with eculizumab results in a new steady state hemoglobin level determined by a balance between the extent of the underlying bone marrow dysfunction, the number of PNH erythrocytes that are preserved by eculizumab therapy and the new level (if any) of transfusion requirement.

Patients with PNH generally experience markedly impaired quality of life characterized by fatigue, anemia, thrombosis, and pulmonary hypertension as well as smooth muscle dystonia including abdominal pain, dysphagia, and erectile dysfunction.[9,10,18] These symptoms have been attributed to both excessive intravascular hemolysis and downstream scavenging of nitric oxide by cell free hemoglobin in plasma. The reduction of intravascular hemolysis in eculizumab-treated patients in the current study was associated with significant improvements in the fatigue component of quality of life relative to placebo-treated patients as assessed via the FACIT-Fatigue instrument. Further, eculizumab therapy was associated with a median increase of 6.4 points over baseline values established before treatment. It has previously been demonstrated that an increase of 3 or more points from baseline represents a clinically important difference in this quality of life instrument.[19] Patients who received eculizumab also experienced a significant improvement in most domains of the EORTC QLQ-30 relative to the placebo-treated cohort including global health status, physical functioning, emotional functioning, cognitive functioning, role functioning, social functioning, fatigue, pain, dyspnea, appetite loss, and insomnia. Improvement in the fatigue component of the EORTC QLQ-30 provides support for the improvement demonstrated in the FACIT-Fatigue instrument during eculizumab therapy. Importantly, these improvements in quality of life in the eculizumab-treated patients occurred despite similar levels of erythrocyte hemoglobin in the two treatment groups, further supporting the contribution of hemolysis per se, as opposed to anemia, in mediating the poor quality of life in PNH patients. Clinical assessment of additional life quality-related symptoms of PNH, including abdominal pain, dysphagia, and erectile dysfunction, have also been reported to improve during eculizumab therapy.[20]

Samsung Bioepis Exhibit No. 1002
Page 10938

Eculizumab was safe and well-tolerated. There were no deaths in the study and only a single thrombotic event which occurred in a placebo patient in a site (the hepatic veins) which is typical of the thrombosis in PNH. The relative brief duration of this study was not sufficient to address the relevant issue of a possible protection from thrombosis by terminal complement inhibition with eculizumab.

Adverse events were generally mild with headache occurring at increased frequency in the eculizumab-treated patients; however, this increased frequency did not persist following the first two doses of therapy. There were 4 SAEs in the eculizumab treatment group and 9 SAEs in the placebo group. There was no evidence of increased infection risk in eculizumab-treated patients during the study period. One eculizumab-treated patient showed a low level of anti-eculizumab antibodies at one time point during the study which did not persist and did not result in a disruption of complement blockade. There were no AEs associated with eculizumab withdrawal in the 2 eculizumab-treated patients who did not complete the trial. Additional safety assessments, as well as efficacy measures, are being examined in an ongoing multi-center, open-label Phase III safety trial of eculizumab (SHEPHERD) in approximately 95 patients with PNH.

Results from the current randomized, double-blind, placebo-controlled, global study show that terminal complement inhibition with eculizumab appears to be a safe and effective therapy for patients with the rare disorder PNH. Treatment with eculizumab reduced intravascular hemolysis, and stabilized hemoglobin levels despite a reduction of transfusions, to the point where most PNH patients were rendered transfusion independent. Substantial and clinically meaningful improvements in fatigue and other key quality of life parameters were also demonstrated. All of the 85 patients who completed the study elected to receive eculizumab in an open-label extension study and all currently remain on drug. The results of the TRIUMPH study indicate that terminal complement inhibition with eculizumab safely and effectively addresses an important consequence of the underlying genetic defect in PNH hematopoietic stem cells by providing a therapeutic replacement for the terminal complement inhibitor deficiency.

The present invention provides among other things treatment with an inhibitor of complement. Many variations of the invention will become apparent to those skilled in the art upon review of this specification. The full scope of the invention should be determined by reference to the claims, along with their full scope of equivalents, and the specification, along with such variations.

Samsung Bioepis Exhibit No. 1002
Page 10939

All publications and patents mentioned herein, including those items listed below, are hereby incorporated by reference in their entirety as if each individual publication or patent was specifically and individually indicated to be incorporated by reference. In case of conflict, the present application, including any definitions herein, will control.

1. Takeda J, Miyata T, Kawagoe K et al. Deficiency of the GPI anchor caused by a somatic mutation of the PIG-A gene in paroxysmal nocturnal hemoglobinuria. Cell 1993;73:703-11.

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Samsung Bioepis Exhibit No. 1002
Page 10940

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16. Fayers PM, Aaronson NK, Bjordal K et al. The EORTC QLQ-C30 Scoring Manual (3rd Edition). Brussels: European Organisation for Research and Treatment of Cancer, 2001.

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Ref Type: Abstract

19. Cella D, Eton DT, Lai JS, Peterman AH, Merkel DE. Combining anchor and distribution-based methods to derive minimal clinically important differences on the Functional Assessment of Cancer Therapy (FACT) anemia and fatigue scales. J Pain Symptom Manage 2002;24:547-61.

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Samsung Bioepis Exhibit No. 1002
Page 10942

SEQUENCES

SEQ ID NO: 1 – Eculizumab V_H

QVQLVQSGAEVKKPGASVKVSCKASGYIFSNYWIQWVRQAPGQGLEWMGEILPG
SGSTEYTENFKDRVTMTRDTSTSTVYMELSSLRSEDTAVYYCARYFFGSSPNWYF
DVWGQGTLVTVSSA

SEQ ID NO: 2 – Eculizumab Heavy chain

QVQLVQSGAEVKKPGASVKVSCKASGYIFSNYWIQWVRQAPGQGLEWMGEILPG
SGSTEYTENFKDRVTMTRDTSTSTVYMELSSLRSEDTAVYYCARYFFGSSPNWYF
DVWGQGTLVTVSSASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNS
GALTSGVHTFPAVLQSSGLYSLSSVVTVPSSNFGTQTYTCNVDHKPSNTKVDKTVE
RKCCVECPPCPAPPVAGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQFN
WYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLP
SSIEKTISKAKGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQ
PENNYKTTPPVLDSDGSFFLYSRLTVDKSRWQEGNVFSCSVMHEALHNHYTQKSL
SLSLGK

SEQ ID NO: 3 – Eculizumab V_L

MDMRVPAQLLGLLLLWLRGARCDIQMTQSPSSLSASVGDRVTITCGASENIYGAL
NWYQQKPGKAPKLLIYGATNLADGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCQ
NVLNTPLTFGQGTKVEIKRT

SEQ ID NO: 4 – Eculizumab Light chain

MDMRVPAQLLGLLLLWLRGARCDIQMTQSPSSLSASVGDRVTITCGASENIYGAL
NWYQQKPGKAPKLLIYGATNLADGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCQ
NVLNTPLTFGQGTKVEIKRTVAAPSVFIPPPSDEQLKSGTASVVCLLNNFYPREAKV
QWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQG
LSSPVTKSFNRGEC

SEQ ID NO: 5 – Eculizumab CDRH1

NYWIQ

Samsung Bioepis Exhibit No. 1002
Page 10943

SEQ ID NO: 6 – Eculizumab CDRH2
EILPGSGSTEYTENFKD

SEQ ID NO: 7 – Eculizumab CDRH3
YFFGSSPNWYFDV

SEQ ID NO: 8 – Eculizumab CDRL1
GASENIYGALN

SEQ ID NO: 9 – Eculizumab CDRL2
GATNLAD

SEQ ID NO: 10 – Eculizumab CDRL3
QNVLNTPLT

Samsung Bioepis Exhibit No. 1002
Page 10944

WHAT IS CLAIMED IS:

1. An antibody that binds C5 comprising a heavy chain consisting of SEQ ID NO: 2 and a light chain consisting of SEQ ID NO: 4.

Samsung Bioepis Exhibit No. 1002
Page 10945

TREATMENT OF PAROXYSMAL NOCTURNAL HEMOGLOBINURIA PATIENTS BY AN INHIBITOR OF COMPLEMENT

Eculizumab, a humanized monoclonal antibody against C5 that inhibits terminal complement activation, showed activity in a preliminary 12-week open-label trial in a small cohort of patients with paroxysmal nocturnal hemoglobinuria (PNH). The present study examined whether chronic eculizumab therapy could reduce intravascular hemolysis, stabilize hemoglobin levels, reduce transfusion requirements, and improve quality of life in a double-blind, randomized, placebo-controlled, multi-center global Phase III trial. It has been found that eculizumab stabilized hemoglobin levels, decreased the need for transfusions, and improved quality of life in PNH patients via reduced intravascular hemolysis. Chronic eculizumab treatment appears to be a safe and effective therapy for PNH.

Samsung Bioepis Exhibit No. 1002
Page 10946

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DECLARATION (37 CFR 1.63) FOR UTILITY OR DESIGN APPLICATION USING AN APPLICATION DATA SHEET (37 CFR 1.76)

Title of Invention	TREATMENT OF PAROXYSMAL NOCTURNAL HEMOGLOBINURIA PATIENTS BY AN INHIBITOR OF COMPLEMENT

As the below named inventor, I hereby declare that:

This declaration is directed to:
- [ ] The attached application, or
- [x] United States application or PCT international application number 15/148,839 filed on 05/06/2016

The above-identified application was made or authorized to be made by me.

I believe that I am the original inventor or an original joint inventor of a claimed invention in the application.

I hereby acknowledge that any willful false statement made in this declaration is punishable under 18 U.S.C. 1001 by fine or imprisonment of not more than five (5) years, or both.

WARNING:

Petitioner/applicant is cautioned to avoid submitting personal information in documents filed in a patent application that may contribute to identity theft. Personal information such as social security numbers, bank account numbers, or credit card numbers (other than a check or credit card authorization form PTO-2038 submitted for payment purposes) is never required by the USPTO to support a petition or an application. If this type of personal information is included in documents submitted to the USPTO, petitioners/applicants should consider redacting such personal information from the documents before submitting them to the USPTO. Petitioner/applicant is advised that the record of a patent application is available to the public after publication of the application (unless a non-publication request in compliance with 37 CFR 1.213(a) is made in the application) or issuance of a patent. Furthermore, the record from an abandoned application may also be available to the public if the application is referenced in a published application or an issued patent (see 37 CFR 1.14). Checks and credit card authorization forms PTO-2038 submitted for payment purposes are not retained in the application file and therefore are not publicly available.

LEGAL NAME OF INVENTOR

Inventor: Leonard Bell Date (Optional): _____

Signature: _____

Note: An application data sheet (PTO/SB/14 or equivalent), including naming the entire inventive entity, must accompany this form or must have been previously filed. Use an additional PTO/AIA/01 form for each additional inventor.

Doc code: Oath
Document Description: Oath or declaration filed

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SUBSTITUTE STATEMENT IN LIEU OF AN OATH OR DECLARATION FOR UTILITY OR DESIGN PATENT APPLICATION (35 U.S.C. 115(d) AND 37 CFR 1.64)

Title of Invention	TREATMENT OF PAROXYSMAL NOCTURNAL HEMOGLOBINURIA PATIENTS BY AN INHIBITOR OF COMPLEMENT

This statement is directed to:

[ ] The attached application,

OR

[X] United States application or PCT international application number 15/148,839 filed on 05/06/2016.

LEGAL NAME of inventor to whom this substitute statement applies:

(*E.g.*, Given Name (first and middle (if any)) and Family Name or Surname)

Russell P. ROTHER

Residence (except for a deceased or legally incapacitated inventor):

City	State	Country
Oklahoma City	OK	United States of America

Mailing Address (except for a deceased or legally incapacitated inventor):

10325 Forest Meadow Drive

City	State	Zip	Country
Oklahoma City	OK	73151	United States of America

I believe the above-named inventor or joint inventor to be the original inventor or an original joint inventor of a claimed invention in the application.

The above-identified application was made or authorized to be made by me.

I hereby acknowledge that any willful false statement made in this statement is punishable under 18 U.S.C. 1001 by fine or imprisonment of not more than five (5) years, or both.

Relationship to the inventor to whom this substitute statement applies:

[ ] Legal Representative (for deceased or legally incapacitated inventor only),

[X] Assignee,

[ ] Person to whom the inventor is under an obligation to assign,

[ ] Person who otherwise shows a sufficient proprietary interest in the matter (petition under 37 CFR 1.46 is required), or

[ ] Joint Inventor.

Samsung Bioepis Exhibit No. 1002
Page 10948

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SUBSTITUTE STATEMENT

Circumstances permitting execution of this substitute statement:

- [ ] Inventor is deceased,
- [ ] Inventor is under legal incapacity,
- [ ] Inventor cannot be found or reached after diligent effort, or
- [x] Inventor has refused to execute the oath or declaration under 37 CFR 1.63.

If there are joint inventors, please check the appropriate box below:

- [x] An application data sheet under 37 CFR 1.76 (PTO/AIA/14 or equivalent) naming the entire inventive entity has been or is currently submitted.

OR

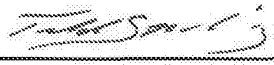
- [ ] An application data sheet under 37 CFR 1.76 (PTO/AIA/14 or equivalent) has not been submitted. Thus, a Substitute Statement Supplemental Sheet (PTO/AIA/11 or equivalent) naming the entire inventive entity and providing inventor information is attached. See 37 CFR 1.64(b).

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PERSON EXECUTING THIS SUBSTITUTE STATEMENT:

Name: Todd Spalding	Date (Optional):

Signature: 

APPLICANT NAME AND TITLE OF PERSON EXECUTING THIS SUBSTITUTE STATEMENT:

If the applicant is a juristic entity, list the applicant name and the title of the signer:

Applicant Name: Alexion Pharmaceuticals, Inc.

Title of Person Executing This Substitute Statement: Vice President, Head of Intellectual Property

The signer, whose title is supplied above, is authorized to act on behalf of the applicant.

Residence of the signer (unless provided in an application data sheet, PTO/AIA/14 or equivalent):

City	State	Country

Mailing Address of the signer (unless provided in an application data sheet, PTO/AIA/14 or equivalent)

100 College St.

City	State	Zip	Country
New Haven	CT	06510	US

Note: Use an additional PTO/AIA/02 form for each inventor who is deceased, legally incapacitated, cannot be found or reached after diligent effort, or has refused to execute the oath or declaration under 37 CFR 1.63.

Samsung Bioepis Exhibit No. 1002
Page 10949

1/4

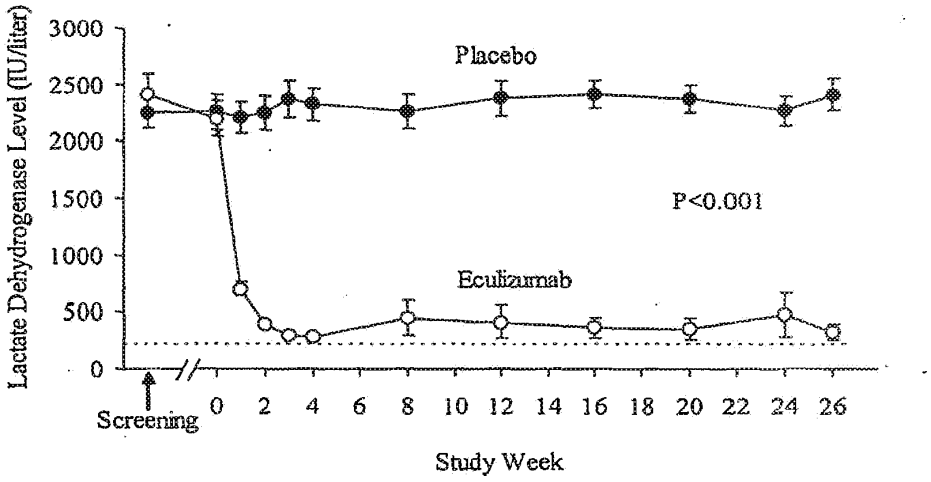

Lactate Dehydrogenase Level (IU/liter)
3000
2500
2000
1500
1000
500
0
Placebo
P<0.001
Eculizumab
Screening
0 2 4 6 8 10 12 14 16 18 20 22 24 26
Study Week

FIGURE 1A

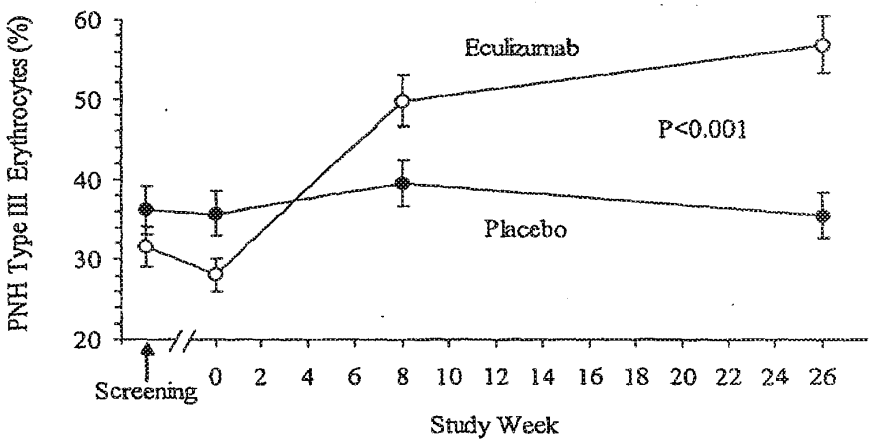

PNH Type III Erythrocytes (%)
60
50
40
30
20
Eculizumab
P<0.001
Placebo
Screening
0 2 4 6 8 10 12 14 16 18 20 22 24 26
Study Week

FIGURE 1B

PATIENTS AVOIDING TRANSFUSION (%)
100
90
80
70
60
50
40
30
20
10
0
ECULIZUMAB
PLACEBO
P<0.001
0
2
4
6
8
10
12
14
16
18
20
22
24
26
STUDY WEEK

FIGURE 2

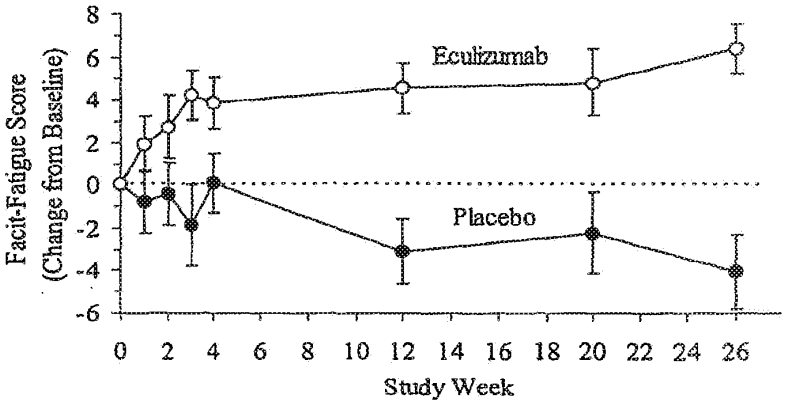

Facit-Fatigue Score
(Change from Baseline)
8
6
4
2
0
-2
-4
-6
0 2 4 6 8 10 12 14 16 18 20 22 24 26
Study Week
Eculizumab
Placebo

FIGURE 3

DocCode – SCORE

SCORE Placeholder Sheet for IFW Content

Application Number: 15284015 Document Date: 10/03/2016

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Form Revision Date: August 26, 2013

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Page 10954

DocCode – SEQ.TXT

SCORE Placeholder Sheet for IFW Content

Application Number: 15284015 Document Date: 10/03/2016

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Page 10955

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PATENT APPLICATION FEE DETERMINATION RECORD Substitute for Form PTO-875	Application or Docket Number 15/284,015	Filing Date 10/03/2016	☐ To be Mailed

ENTITY: ☒ LARGE ☐ SMALL ☐ MICRO

APPLICATION AS FILED – PART I

	(Column 1)	(Column 2)		
FOR	NUMBER FILED	NUMBER EXTRA	RATE ($)	FEE ($)
☐ BASIC FEE (37 CFR 1.16(a), (b), or (c))	N/A	N/A	N/A	
☐ SEARCH FEE (37 CFR 1.16(k), (i), or (m))	N/A	N/A	N/A	
☐ EXAMINATION FEE (37 CFR 1.16(o), (p), or (q))	N/A	N/A	N/A	
TOTAL CLAIMS (37 CFR 1.16(i))	minus 20 =	*	X $ =	
INDEPENDENT CLAIMS (37 CFR 1.16(h))	minus 3 =	*	X $ =	
☐ APPLICATION SIZE FEE (37 CFR 1.16(s))	If the specification and drawings exceed 100 sheets of paper, the application size fee due is $310 ($155 for small entity) for each additional 50 sheets or fraction thereof. See 35 U.S.C. 41(a)(1)(G) and 37 CFR 1.16(s).			
☐ MULTIPLE DEPENDENT CLAIM PRESENT (37 CFR 1.16(j))				
* If the difference in column 1 is less than zero, enter "0" in column 2.			TOTAL	

APPLICATION AS AMENDED – PART II

AMENDMENT	10/03/2016	(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	RATE ($)	ADDITIONAL FEE ($)
	Total (37 CFR 1.16(i))	* 1	Minus	** 20	= 0	X $80 =	0
	Independent (37 CFR 1.16(h))	* 1	Minus	***3	= 0	X $420 =	0
	☐ Application Size Fee (37 CFR 1.16(s))						
	☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))						
						TOTAL ADD'L FEE	**0**

AMENDMENT		(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	RATE ($)	ADDITIONAL FEE ($)
	Total (37 CFR 1.16(i))	*	Minus	**	=	X $ =	
	Independent (37 CFR 1.16(h))	*	Minus	***	=	X $ =	
	☐ Application Size Fee (37 CFR 1.16(s))						
	☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))						
						TOTAL ADD'L FEE	

* If the entry in column 1 is less than the entry in column 2, write "0" in column 3.
** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 20, enter "20".
*** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 3, enter "3".
The "Highest Number Previously Paid For" (Total or Independent) is the highest number found in the appropriate box in column 1.

LDRC
CARMEN WILLIAMS

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Reviewer: Anjum, Durreshwar (CGI Federal)
Timestamp: [year=2016; month=10; day=6; hr=10; min=5; sec=17; ms=646; ]
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Samsung Bioepis Exhibit No. 1002
Page 10957

Validated By CRFValidator v 1.0.5

Application No: 15284015 Version No: 1.0

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Finished: 2016-10-03 16:51:05.193
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Total Errors: 1
No. of SeqIDs Defined: 10
Actual SeqID Count: 10

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Samsung Bioepis Exhibit No. 1002
Page 10958

SEQUENCE LISTING

<110> ALEXION PHARMACEUTICALS, INC.

<120> TREATMENT OF PAROXYSMAL NOCTURNAL HEMOGLOBINURIA PATIENTS
BY AN INHIBITOR OF COMPLEMENT

<130> AXJ-114BUSCN4

<140> US 15/284,015
<141> 2016-10-03

<150> 15/260,888
<151> 2016-09-09

<150> 15/148,839
<151> 2016-05-06

<150> 13/426,973
<151> 2012-03-22

<150> 12/225,040
<151> 2009-05-13

<150> PCT/US2007/006606
<151> 2007-03-15

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<220>
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Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Ile Phe Ser Asn Tyr
20 25 30

Trp Ile Gln Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
35 40 45

Gly Glu Ile Leu Pro Gly Ser Gly Ser Thr Glu Tyr Thr Glu Asn Phe
50 55 60

Samsung Bioepis Exhibit No. 1002
Page 10959

```
Lys Asp Arg Val Thr Met Thr Arg Asp Thr Ser Thr Ser Thr Val Tyr
65                  70                  75                  80

Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95

Ala Arg Tyr Phe Phe Gly Ser Ser Pro Asn Trp Tyr Phe Asp Val Trp
            100                 105                 110

Gly Gln Gly Thr Leu Val Thr Val Ser Ser Ala
        115                 120
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Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Ile Phe Ser Asn Tyr
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Trp Ile Gln Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
        35                  40                  45

Gly Glu Ile Leu Pro Gly Ser Gly Ser Thr Glu Tyr Thr Glu Asn Phe
    50                  55                  60

Lys Asp Arg Val Thr Met Thr Arg Asp Thr Ser Thr Ser Thr Val Tyr
65                  70                  75                  80

Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95

Ala Arg Tyr Phe Phe Gly Ser Ser Pro Asn Trp Tyr Phe Asp Val Trp
            100                 105                 110

Gly Gln Gly Thr Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro
        115                 120                 125
```


Samsung Bioepis Exhibit No. 1002
Page 10960

```
Ser Val Phe Pro Leu Ala Pro Cys Ser Arg Ser Thr Ser Glu Ser Thr
    130                 135                 140

Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr
145                 150                 155                 160

Val Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro
                165                 170                 175

Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr
            180                 185                 190

Val Pro Ser Ser Asn Phe Gly Thr Gln Thr Tyr Thr Cys Asn Val Asp
        195                 200                 205

His Lys Pro Ser Asn Thr Lys Val Asp Lys Thr Val Glu Arg Lys Cys
    210                 215                 220

Cys Val Glu Cys Pro Pro Cys Pro Ala Pro Pro Val Ala Gly Pro Ser
225                 230                 235                 240

Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg
                245                 250                 255

Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser Gln Glu Asp Pro
            260                 265                 270

Glu Val Gln Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala
        275                 280                 285

Lys Thr Lys Pro Arg Glu Glu Gln Phe Asn Ser Thr Tyr Arg Val Val
    290                 295                 300

Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr
305                 310                 315                 320

Lys Cys Lys Val Ser Asn Lys Gly Leu Pro Ser Ser Ile Glu Lys Thr
                325                 330                 335

Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu
            340                 345                 350
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Samsung Bioepis Exhibit No. 1002
Page 10961

```
Pro Pro Ser Gln Glu Glu Met Thr Lys Asn Gln Val Ser Leu Thr Cys
        355                 360                 365

Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser
    370                 375                 380

Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp
385                 390                 395                 400

Ser Asp Gly Ser Phe Phe Leu Tyr Ser Arg Leu Thr Val Asp Lys Ser
                405                 410                 415

Arg Trp Gln Glu Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala
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Leu Ser Ala Ser Val Gly Asp Arg Val Thr Ile Thr Cys Gly Ala Ser
        35                  40                  45

Glu Asn Ile Tyr Gly Ala Leu Asn Trp Tyr Gln Gln Lys Pro Gly Lys
    50                  55                  60

Ala Pro Lys Leu Leu Ile Tyr Gly Ala Thr Asn Leu Ala Asp Gly Val
65                  70                  75                  80

Pro Ser Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr
                85                  90                  95
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Samsung Bioepis Exhibit No. 1002
Page 10962

```
Ile Ser Ser Leu Gln Pro Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Asn
            100                 105                 110

Val Leu Asn Thr Pro Leu Thr Phe Gly Gln Gly Thr Lys Val Glu Ile
        115                 120                 125

Lys Arg Thr
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Leu Ser Ala Ser Val Gly Asp Arg Val Thr Ile Thr Cys Gly Ala Ser
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Glu Asn Ile Tyr Gly Ala Leu Asn Trp Tyr Gln Gln Lys Pro Gly Lys
    50                  55                  60

Ala Pro Lys Leu Leu Ile Tyr Gly Ala Thr Asn Leu Ala Asp Gly Val
65                  70                  75                  80

Pro Ser Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr
                85                  90                  95

Ile Ser Ser Leu Gln Pro Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Asn
            100                 105                 110

Val Leu Asn Thr Pro Leu Thr Phe Gly Gln Gly Thr Lys Val Glu Ile
        115                 120                 125

Lys Arg Thr Val Ala Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp
    130                 135                 140
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Samsung Bioepis Exhibit No. 1002
Page 10963

```
Glu Gln Leu Lys Ser Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn
145                 150                 155                 160

Phe Tyr Pro Arg Glu Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu
                165                 170                 175

Gln Ser Gly Asn Ser Gln Glu Ser Val Thr Glu Gln Asp Ser Lys Asp
            180                 185                 190

Ser Thr Tyr Ser Leu Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr
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Glu Lys His Lys Val Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser
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Asp

Samsung Bioepis Exhibit No. 1002
Page 10964

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<210> 9
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Gln Asn Val Leu Asn Thr Pro Leu Thr
1 5

Samsung Bioepis Exhibit No. 1002
Page 10965

Samsung Bioepis Exhibit No. 1002
Page 10966

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United States Patent and Trademark Office
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Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NUMBER	FILING or 371(c) DATE	GRP ART UNIT	FIL FEE REC'D	ATTY.DOCKET.NO	TOT CLAIMS	IND CLAIMS
15/284,015	10/03/2016	1615	1600	AXJ-114BUSCN4	1	1

CONFIRMATION NO. 1040

133485
Nelson Mullins Riley & Scarborough LLP/Alexion
One Post Office Square
30th Floor
Boston, MA 02109-2127

FILING RECEIPT

OC000000086415992

Date Mailed: 10/13/2016

Receipt is acknowledged of this non-provisional patent application. The application will be taken up for examination in due course. Applicant will be notified as to the results of the examination. Any correspondence concerning the application must include the following identification information: the U.S. APPLICATION NUMBER, FILING DATE, NAME OF APPLICANT, and TITLE OF INVENTION. Fees transmitted by check or draft are subject to collection. Please verify the accuracy of the data presented on this receipt. **If an error is noted on this Filing Receipt, please submit a written request for a Filing Receipt Correction. Please provide a copy of this Filing Receipt with the changes noted thereon. If you received a "Notice to File Missing Parts" for this application, please submit any corrections to this Filing Receipt with your reply to the Notice. When the USPTO processes the reply to the Notice, the USPTO will generate another Filing Receipt incorporating the requested corrections**

Inventor(s)

Leonard BELL, Woodbridge, CT;
Russell P. ROTHER, Oklahoma City, OK;

Applicant(s)

Alexion Pharmaceuticals, Inc., New Haven, CT;

Power of Attorney: None

Domestic Priority data as claimed by applicant

This application is a CON of 15/260,888 09/09/2016
which is a CON of 15/148,839 05/06/2016
which is a CON of 13/426,973 03/22/2012
which is a CON of 12/225,040 05/13/2009 ABN
which is a 371 of PCT/US2007/006606 03/15/2007

Foreign Applications for which priority is claimed (You may be eligible to benefit from the **Patent Prosecution Highway** program at the USPTO. Please see http://www.uspto.gov for more information.) - None.
Foreign application information must be provided in an Application Data Sheet in order to constitute a claim to foreign priority. See 37 CFR 1.55 and 1.76.

Permission to Access Application via Priority Document Exchange: Yes

Permission to Access Search Results: Yes

Applicant may provide or rescind an authorization for access using Form PTO/SB/39 or Form PTO/SB/69 as appropriate.

If Required, Foreign Filing License Granted: 10/12/2016

The country code and number of your priority application, to be used for filing abroad under the Paris Convention, is **US 15/284,015**

Projected Publication Date: 01/19/2017

Non-Publication Request: No

Early Publication Request: No

Title

TREATMENT OF PAROXYSMAL NOCTURNAL HEMOGLOBINURIA PATIENTS BY AN INHIBITOR OF COMPLEMENT

Preliminary Class

424

Statement under 37 CFR 1.55 or 1.78 for AIA (First Inventor to File) Transition Applications: No

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Since the rights granted by a U.S. patent extend only throughout the territory of the United States and have no effect in a foreign country, an inventor who wishes patent protection in another country must apply for a patent in a specific country or in regional patent offices. Applicants may wish to consider the filing of an international application under the Patent Cooperation Treaty (PCT). An international (PCT) application generally has the same effect as a regular national patent application in each PCT-member country. The PCT process **simplifies** the filing of patent applications on the same invention in member countries, but **does not result** in a grant of "an international patent" and does not eliminate the need of applicants to file additional documents and fees in countries where patent protection is desired.

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Applicants may wish to consult the USPTO booklet, "General Information Concerning Patents" (specifically, the section entitled "Treaties and Foreign Patents") for more information on timeframes and deadlines for filing foreign patent applications. The guide is available either by contacting the USPTO Contact Center at 800-786-9199, or it can be viewed on the USPTO website at http://www.uspto.gov/web/offices/pac/doc/general/index.html.

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Title 35, United States Code, Section 184

Title 37, Code of Federal Regulations, 5.11 & 5.15

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PATENT APPLICATION FEE DETERMINATION RECORD

Substitute for Form PTO-875

Application or Docket Number: 15/284,015

APPLICATION AS FILED - PART I

FOR	(Column 1) NUMBER FILED	(Column 2) NUMBER EXTRA	SMALL ENTITY RATE($)	SMALL ENTITY FEE($)	OR	OTHER THAN SMALL ENTITY RATE($)	OTHER THAN SMALL ENTITY FEE($)
BASIC FEE (37 CFR 1.16(a), (b), or (c))	N/A	N/A	N/A			N/A	280
SEARCH FEE (37 CFR 1.16(k), (i), or (m))	N/A	N/A	N/A			N/A	600
EXAMINATION FEE (37 CFR 1.16(o), (p), or (q))	N/A	N/A	N/A			N/A	720
TOTAL CLAIMS (37 CFR 1.16(i))	1 minus 20 =	*			OR	x 80 =	0.00
INDEPENDENT CLAIMS (37 CFR 1.16(h))	1 minus 3 =	*				x 420 =	0.00
APPLICATION SIZE FEE (37 CFR 1.16(s))	If the specification and drawings exceed 100 sheets of paper, the application size fee due is $310 ($155 for small entity) for each additional 50 sheets or fraction thereof. See 35 U.S.C. 41(a)(1)(G) and 37 CFR 1.16(s).						0.00
MULTIPLE DEPENDENT CLAIM PRESENT (37 CFR 1.16(j))							0.00
* If the difference in column 1 is less than zero, enter "0" in column 2.			TOTAL			TOTAL	1600

APPLICATION AS AMENDED - PART II

AMENDMENT A

	(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	SMALL ENTITY RATE($)	SMALL ENTITY ADDITIONAL FEE($)	OR	OTHER THAN SMALL ENTITY RATE($)	OTHER THAN SMALL ENTITY ADDITIONAL FEE($)
Total (37 CFR 1.16(i))	*	Minus	**	=	x =		OR	x =	
Independent (37 CFR 1.16(h))	*	Minus	***	=	x =		OR	x =	
Application Size Fee (37 CFR 1.16(s))									
FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))							OR		
					TOTAL ADD'L FEE		OR	TOTAL ADD'L FEE	

AMENDMENT B

	(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	RATE($)	ADDITIONAL FEE($)	OR	RATE($)	ADDITIONAL FEE($)
Total (37 CFR 1.16(i))	*	Minus	**	=	x =		OR	x =	
Independent (37 CFR 1.16(h))	*	Minus	***	=	x =		OR	x =	
Application Size Fee (37 CFR 1.16(s))									
FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))							OR		
					TOTAL ADD'L FEE		OR	TOTAL ADD'L FEE	

* If the entry in column 1 is less than the entry in column 2, write "0" in column 3.

** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 20, enter "20".

*** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 3, enter "3".

The "Highest Number Previously Paid For" (Total or Independent) is the highest found in the appropriate box in column 1.

Samsung Bioepis Exhibit No. 1002
Page 10970

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
15/284,015	10/03/2016	Leonard BELL	AXJ-114BUSCN4	1040

133485 7590 10/20/2016

Nelson Mullins Riley & Scarborough LLP/Alexion
One Post Office Square
30th Floor
Boston, MA 02109-2127

EXAMINER	
ROGERS, JAMES L	

ART UNIT	PAPER NUMBER
1644	

NOTIFICATION DATE	DELIVERY MODE
10/20/2016	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

ipboston.docketing@nelsonmullins.com
chris.schlauch@nelsonmullins.com
ipqualityassuranceboston@nelsonmullins.com

UNITED STATES PATENT AND TRADEMARK OFFICE

Commissioner for Patents
United States Patent and Trademark Office
P.O. Box 1450
Alexandria, VA 22313-1450
www.uspto.gov

Doc Code:
TRACK1.GRANT

Decision Granting Request for Prioritized Examination (Track I or After RCE)	Application No.: 15/284,015

1. THE REQUEST FILED 10/03/16 IS **GRANTED.**

The above-identified application has met the requirements for prioritized examination
A. ☒ for an original nonprovisional application (Track I).
B. ☐ for an application undergoing continued examination (RCE).

2. **The above-identified application will undergo prioritized examination.** The application will be accorded special status throughout its entire course of prosecution until one of the following occurs:

A. filing a **petition for extension of time** to extend the time period for filing a reply;
B. filing an **amendment to amend the application to contain more than four independent claims, more than thirty total claims**, or a multiple dependent claim;
C. filing a **request for continued examination**;
D. filing a notice of appeal;
E. filing a request for suspension of action;
F. mailing of a notice of allowance;
G. mailing of a final Office action;
H. completion of examination as defined in 37 CFR 41.102; or
I. abandonment of the application.

Telephone inquiries with regard to this decision should be directed to Terri Johnson at 571-272-2991. In his/her absence, calls may be directed to Brian Brown at 571-272-5338.

/Terri Johnson/ — [*Signature*]

Paralegal Specialist — (Title)

U.S. Patent and Trademark Office
PTO-2298 (Rev. 02-2012)

Samsung Bioepis Exhibit No. 1002
Page 10972

Office of Petitions: Routing Sheet



Application No. 15/284,015

This application is being forwarded to your office for further processing. A decision has been rendered on a petition filed in this application, as indicated below. For details of this decision, please see the document PET.OP.DEC filed on the same date as this document.

- [X] **GRANTED**
- [ ] **DISMISSED**
- [ ] **DENIED**

Samsung Bioepis Exhibit No. 1002
Page 10973

Office of Petitions: Decision Count Sheet

Mailing Month: 10

Application No.: 15284015

15284015

For US serial numbers: enter number only, no slashes or commas. Ex: 10123456

For PCT: enter "51+single digit of year of filing+last 5 numbers", Ex. for PCT/US05/12345, enter 51512345

Deciding Official: Johnson, Terri

Count (1) - Palm Credit 15/284,015

Decision: GRANT

FINANCE WORK NEEDED

☐ Select Check Box for YES

GRANT

Decision Type: 643 - Track One request

643

Notes:

Count (2)

Decision: n/a

FINANCE WORK NEEDED

☑ Select Check Box for YES

Decision Type: NONE

Notes:

Count (3)

Decision: n/a

FINANCE WORK NEEDED

☐ Select Check Box for YES

Decision Type: NONE

Notes:

Initials of Approving Official (if required)

If more than 3 decisions, attach 2nd count sheet & mark this box ☐

Printed on: *10/14/2016*

Office of Petitions Internal Document - Ver. 5.0

Samsung Bioepis Exhibit No. 1002
Page 10974

I hereby certify that this paper (along with any paper referred to as being attached or enclosed) is being transmitted via the Office electronic filing system in accordance with 37 CFR § 1.6(a)(4).

Dated: October 21, 2016
Electronic Signature for Jill Gorny Sloper, Esq.: /Jill Gorny Sloper, Esq./

Docket No.: AXJ-114BUSCN4
(PATENT)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of:
Leonard Bell *et al.*

Application No.: 15/284,015

Confirmation No.: 1040

Filed: October 3, 2016

Art Unit: 1644

For: TREATMENT OF PAROXYSMAL NOCTURNAL HEMOGLOBINURIA PATIENTS BY AN INHIBITOR OF COMPLEMENT

Examiner: J. L. Rogers

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

INFORMATION DISCLOSURE STATEMENT (IDS)

Dear Sir:

In compliance with 37 C.F.R. § 1.56, 1.97 and 1.98, the attention of the Patent and Trademark Office is hereby directed to the documents listed on the attached PTO/SB/08. It is respectfully requested that the documents listed on the PTO/SB/08 be expressly considered by the Examiner during the prosecution of this application, and that the documents be made of record therein and appear among the "References Cited" on any patent to issue therefrom.

The present application is a continuation of U.S. Application No. 15/148,839, filed May 6, 2016 (Atty. Docket No. AXJ-114BUSCN2). For the Examiner's convenience in reviewing this continuation application, Applicant submits a consolidated PTO Form SB/08, listing all references cited during the prosecution of the parent applications [U.S. Application No. 15/148,839, filed September 9, 2016 (Atty. Docket No. AXJ-114BUSCN3), U.S. Application No. 15/260,888, filed 15/260,888(Atty. Docket No. AXJ-114BUSCN2), U.S. Application No. 13/426,973, filed March 22, 2012 (Atty. Docket No. AXJ-114BUSCN), and U.S. Application No. 12/225,040, filed May 13, 2009 (Atty. Docket No. AXJ-0114BUS)].

Samsung Bioepis Exhibit No. 1002
Page 10975

Copies of the references previously cited by or submitted to the Office in the parent applications are not enclosed, but will be provided upon request, in accordance with 37 CFR §1.98(d). In addition, Applicant submits herewith copies of foreign patents and non-patent literature references, but has not included copies of U.S. patents and U.S. patent applications, in accordance with 37 C.F.R. § 1.98(a)(2)(i)-(iv).

Additionally, Applicant calls to the attention of the Examiner the following Applications and Office Actions cited therein:

Applications				
Examiner's Initials	*Serial No.*	*Filing Date*	*First Named Inventor*	*Docket No.*
	15/260,888	09-09-2016	Leonard Bell	AXJ-114BUSCN3
	15/148,839	05-06-2016	Leonard Bell	AXJ-114BUSCN2
	13/426,973	03-22-2012	Leonard Bell	AXJ-114BUSCN
	12/225,040	05-13-2009	Leonard Bell	AXJ-114BUS
	12/621,792	11-19-2009	Leonard Bell	AXJ-114DV
	10/771,552	02-03-2004	Leonard Bell	AXJ-114RCE
	11/050,543	02-03-2005	Leonard Bell	AXJ-114CPRCE
	11/595,118	11-08-2006	Leonard Bell	AXJ-114CP2
	12/902,617	10-12-2010	Leonard Bell	AXJ-114CPCN
	13/335,518	12-22-2011	Leonard Bell	AXJ-114CPCN2RCE

Office Actions (copies enclosed)			
Examiner's Initials	Serial No.	Date Mailed from USPTO	Examiner
	15/148,839	08-16-2016	J. Rogers
	13/426,973	01-27-2014	J. Rogers
	13/426,973	05-31-2013	J. Rogers
	13/426,973	08-20-2012	J. Rogers
	12/225,040	09-22-2011	J. Rogers
	12/225,040	06-01-2011	J. Rogers
	12/225,040	04-11-2011	J. Rogers
	12/621,792	09-30-2010	P. Gambel
	10/771,552	12-22-2008	F. Vandervegt
	10/771,552	03-21-2008	F. Vandervegt
	10/771,552	08-10-2007	F. Vandervegt
	10/771,552	02-26-2007	F. Vandervegt
	10/771,552	09-26-2006	F. Vandervegt

	11/050,543	07-09-2010	P. Gambel
	11/050,543	04-02-2008	F. Vandervegt
	11/050,543	10-10-2007	F. Vandervegt
	11/050,543	06-11-2007	F. Vandervegt
	11/595,118	01-21-2011	P. Gambel
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	11/595,118	07-07-2010	P. Gambel
	11/595,118	04-03-2009	F. Vandervegt
	12/902,617	06-23-2011	P. Gambel
	12/902,617	04-04-2011	P. Gambel
	13/335,518	08-22-2016	P. Gambel
	13/335,518	09-12-2014	P. Gambel
	13/335,518	02-06-2014	P. Gambel
	13/335,518	11-07-2013	P. Gambel

The Examiner is requested to review the file histories of these applications, including cited references, Office Actions, Responses, etc., and is asked to contact Applicant's Attorney if the Examiner would like the Applicant to supply copies of any or all of the information included in any of these applications. For any of these applications, if Applicant's Attorney is not contacted by the Examiner with such a request, then it will be concluded that the Examiner has reviewed or will review the file content of these applications.

Applicant respectfully requests that the Examiner initial the blank columns next to the cited Applications and Office Actions, to indicate that the information has been considered by the Examiner. Alternatively, Applicant requests that the Examiner insert the phrase, "All references considered except where lined through," on each page of the Information Disclosure Statement, along with the Examiner's initials.

The filing of this Information Disclosure Statement is not to be interpreted as a representation that the cited documents are material, that an exhaustive search has been conducted, or that no other relevant information exists. Nor shall the citation of any documents herein be construed *per se* as a representation that such document is prior art. Moreover, Applicant understands the Examiner will make an independent evaluation of the cited documents.

This Information Disclosure Statement is filed within three months of the U.S. filing date (37 C.F.R. § 1.97(b)(1)). The Director is hereby authorized to charge any deficiency in the fees filed, asserted to be filed or which should have been filed herewith (or with any paper hereafter filed in this application by this firm) to our Deposit Account No. 12-0080, under Order No. AXJ-114BUSCN4.

Dated: October 21, 2016

Respectfully submitted,

Electronic signature: /Jill Gorny Sloper, Esq./
Jill Gorny Sloper, Esq.
Registration No.: 60,760
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INFORMATION DISCLOSURE STATEMENT BY APPLICANT
(Not for submission under 37 CFR 1.99)

Application Number	15284015
Filing Date	2016-10-03
First Named Inventor	Leonard BELL
Art Unit	1644
Examiner Name	J. L. Rogers
Attorney Docket Number	AXJ-114BUSCN4

U.S.PATENTS Remove

Examiner Initial*	Cite No	Patent Number	Kind Code[1]	Issue Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear
	1	6355245		2002-03-12	Evans et al.	
	2	4686100		1987-08-11	Raffin et al.	
	3	5135916		1992-08-04	Sims et al.	
	4	5660825		1997-08-26	Sims et al.	
	5	7361339		2008-04-22	Bell	
	6	7482435		2009-01-27	Bowdish et al.	

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Examiner Initial*	Cite No	Publication Number	Kind Code[1]	Publication Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
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	Art Unit	1644
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	1	20050271660	A1	2005-12-08	Wang	
	2	20030049683	A1	2003-03-13	Bowdish et al.	
	3	20050191298	A1	2005-09-01	Bell et al.	
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	6	20090220508	A1	2009-09-03	Bell et al.	
	7	20100068202	A1	2010-03-18	Bell et al.	
	8	20050169921	A1	2005-08-04	Bell et al.	
	9	20070116710	A1	2007-05-24	Bell et al.	
	10	20110086040	A1	2011-04-14	Bell et al.	
	11	20120308559	A1	2012-12-06	Bell et al.	

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	12	20160244516	A1	2016-08-25	BELL et al.	
	13	20030049260	A1	2003-03-13	Bell	
	14	20040038308		2004-02-26	Rother et al.	
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	16	20040253242	A1	2004-12-16	Bowdish et al.	
	17	20050036991	A1	2005-02-17	Fodor	
	18	20050226870	A1	2005-10-13	Wang et al.	
	19	20060057679	A1	2006-03-16	O'Keefe et al.	
	20	20060263349	A1	2006-11-23	McCutcheon et al.	

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FOREIGN PATENT DOCUMENTS Remove

Examiner Initial*	Cite No	Foreign Document Number[3]	Country Code[2] i	Kind Code[4]	Publication Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear	T[5]

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	1	2004/029207	WO	A2	2004-04-08	Xencor Inc		
	2	0411306	EP	A1	1991-02-06	GOETZE OTTO		X
	3	2005074607	WO	A2	2005-08-18	Alexion Pharmaceuticals, Inc		☐
	4	2007005612	WO	A2	2007-01-11	Medimmune, Inc		☐
	5	2007002571	WO	A2	2007-01-04	Alexion Pharmaceuticals, Inc		☐
	6	2005110481	WO	A2	2005-11-24	Alexion Pharmaceuticals, Inc		☐

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NON-PATENT LITERATURE DOCUMENTS Remove

Examiner Initials*	Cite No	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc), date, pages(s), volume-issue number(s), publisher, city and/or country where published.	T5
	1	Adis International Limited, "Eculizumab: 5G1.1, h5G1.1, Long-Acting Anti-C5 Monoclonal Antibody 5G1-1, Long-Acting Anti-C5 Monoclonal Antibody 5G1.1," Drugs in Research and Development, vol. 8 (1): 61-68 (2007).	
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	34	COLLARD et al., "Endothelial nuclear factor-KB translocation and vascular cell adhesion molecule- 1 induction by complement: inhibition with anti-human C5 therapy or cGMP analogues," Art. Thromb. Vas., vol. 19:2623-2629 (1999).	
	35	CORVINI M. et al., "Complement C7 deficiency presenting as recurrent aseptic meningitis," Database accession no. NLM15328683,1 page (2004) DATABASE MEDLINE [Online] US NATIONAL LIBRARY OF MEDICINE (NLM),; BETHESDA, MD, US; October 1992 (1992-10);	
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	37	European Decision Revoking The European Patent (Art. 101(2). (3)(b) EPC). 12 pages. dated July 1. 2014.	
	38	European Medicines Agency, EMA/HMPC/16633/2009 section 2, Historical Data on Medicinal Use, 2010, pages 1-40.	
	39	FIGUEROA, "Infectious Diseases Associated with Complement Deficiencies,"; Clinical Microbiology Reviews, Vol. 4 (3), pp. 359-395 (1991).;	
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	45	Grounds of Appeal filed on November 11,2014 in the related European Opposition, European Patent No. 1720571, pages 1-15.	
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If you wish to add additional non-patent literature document citation information please click the Add button Add

EXAMINER SIGNATURE

Examiner Signature		Date Considered	

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through a citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

[1] See Kind Codes of USPTO Patent Documents at www.USPTO.GOV or MPEP 901.04. [2] Enter office that issued the document, by the two-letter code (WIPO Standard ST.3). [3] For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. [4] Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16 if possible. [5] Applicant is to place a check mark here if English language translation is attached.

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CERTIFICATION STATEMENT

Please see 37 CFR 1.97 and 1.98 to make the appropriate selection(s):

That each item of information contained in the information disclosure statement was first cited in any communication from a foreign patent office in a counterpart foreign application not more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(1).

OR

☐ That no item of information contained in the information disclosure statement was cited in a communication from a foreign patent office in a counterpart foreign application, and, to the knowledge of the person signing the certification after making reasonable inquiry, no item of information contained in the information disclosure statement was known to any individual designated in 37 CFR 1.56(c) more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(2).

See attached certification statement.

The fee set forth in 37 CFR 1.17 (p) has been submitted herewith.

☒ A certification statement is not submitted herewith.

SIGNATURE

A signature of the applicant or representative is required in accordance with CFR 1.33, 10.18. Please see CFR 1.4(d) for the form of the signature.

Signature	/Jill Gorny Sloper, Esq./	Date (YYYY-MM-DD)	2016-10-21
Name/Print	Jill Gorny Sloper, Esq.	Registration Number	60,760

This collection of information is required by 37 CFR 1.97 and 1.98. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 1 hour to complete, including gathering, preparing and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

Privacy Act Statement

The Privacy Act of 1974 (P.L. 93-579) requires that you be given certain information in connection with your submission of the attached form related to a patent application or patent. Accordingly, pursuant to the requirements of the Act, please be advised that: (1) the general authority for the collection of this information is 35 U.S.C. 2(b)(2); (2) furnishing of the information solicited is voluntary; and (3) the principal purpose for which the information is used by the U.S. Patent and Trademark Office is to process and/or examine your submission related to a patent application or patent. If you do not furnish the requested information, the U.S. Patent and Trademark Office may not be able to process and/or examine your submission, which may result in termination of proceedings or abandonment of the application or expiration of the patent.

The information provided by you in this form will be subject to the following routine uses:

1. The information on this form will be treated confidentially to the extent allowed under the Freedom of Information Act (5 U.S.C. 552) and the Privacy Act (5 U.S.C. 552a). Records from this system of records may be disclosed to the Department of Justice to determine whether the Freedom of Information Act requires disclosure of these record s.

2. A record from this system of records may be disclosed, as a routine use, in the course of presenting evidence to a court, magistrate, or administrative tribunal, including disclosures to opposing counsel in the course of settlement negotiations.

3. A record in this system of records may be disclosed, as a routine use, to a Member of Congress submitting a request involving an individual, to whom the record pertains, when the individual has requested assistance from the Member with respect to the subject matter of the record.

4. A record in this system of records may be disclosed, as a routine use, to a contractor of the Agency having need for the information in order to perform a contract. Recipients of information shall be required to comply with the requirements of the Privacy Act of 1974, as amended, pursuant to 5 U.S.C. 552a(m).

5. A record related to an International Application filed under the Patent Cooperation Treaty in this system of records may be disclosed, as a routine use, to the International Bureau of the World Intellectual Property Organization, pursuant to the Patent Cooperation Treaty.

6. A record in this system of records may be disclosed, as a routine use, to another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c)).

7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (i.e., GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.

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Application Number	15284015
Filing Date	2016-10-03
First Named Inventor	Leonard BELL
Art Unit	1644
Examiner Name	J. L. Rogers
Attorney Docket Number	AXJ-114BUSCN4

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See attached certification statement.

The fee set forth in 37 CFR 1.17 (p) has been submitted herewith.

A certification statement is not submitted herewith.

SIGNATURE

A signature of the applicant or representative is required in accordance with CFR 1.33, 10.18. Please see CFR 1.4(d) for the form of the signature.

Signature	/Jill Gorny Sloper, Esq./	Date (YYYY-MM-DD)	2016-10-21
Name/Print	Jill Gorny Sloper, Esq.	Registration Number	60,760

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Application Number:	15284015
International Application Number:	
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1	Foreign Reference	WO2005110481A2.pdf	3921591 2ee498bfad15b6303219e24a66f5e92a577661bf	no	73

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Samsung Bioepis Exhibit No. 1002
Page 11002

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Samsung Bioepis Exhibit No. 1002
Page 11003

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Samsung Bioepis Exhibit No. 1002
Page 11004

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Samsung Bioepis Exhibit No. 1002
Page 11005

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Samsung Bioepis Exhibit No. 1002
Page 11006

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Samsung Bioepis Exhibit No. 1002
Page 11007

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Samsung Bioepis Exhibit No. 1002
Page 11008

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Samsung Bioepis Exhibit No. 1002
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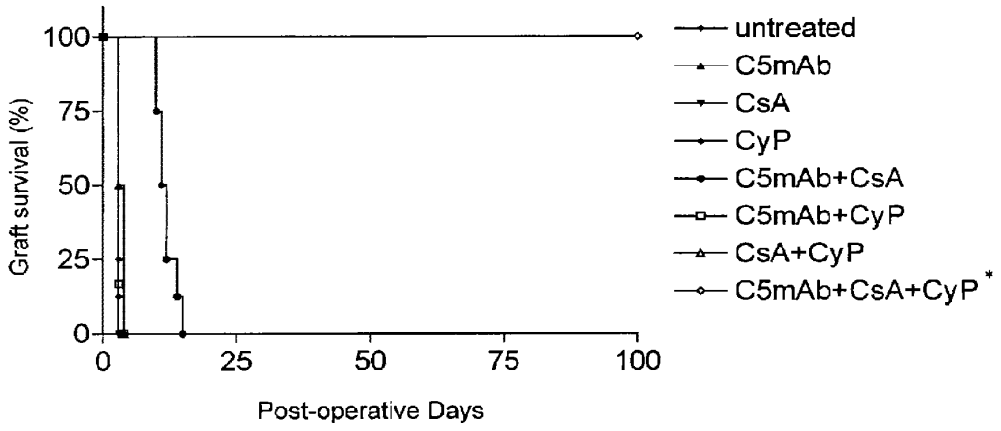
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(54) **Title:** PROLONGATION OF SURVIVAL OF AN ALLOGRAFT BY INHIBITING COMPLEMENT ACTIVITY



(57) **Abstract:** Methods of prolonging survival of allotransplanted cells, tissues or organs are presented. These methods are directed to administering to the allotransplant recipient an inhibitor of complement activity together with one or more immunosuppressants. The inhibitor of complement activity is administered chronically. These methods have been determined to aid in preventing chronic rejection of allografts. These methods can additionally be used in cases in which the recipient has been presensitized to the allograft or in which there is an ABO mismatch between the allograft and the recipient.

WO 2005/110481 A2

Samsung Bioepis Exhibit No. 1002
Page 11010

PROLONGATION OF SURVIVAL OF AN ALLOGRAFT BY INHIBITING COMPLEMENT ACTIVITY

RELATED APPLICATIONS

This application claims the benefit of and priority to U.S. Provisional Patent Application No. 60/571,444, filed May 14, 2004, the disclosure of which is incorporated herein by reference in its entirety.

TECHNICAL FIELD

The present disclosure relates to methods for prolonging survival of an allograft in a mammal. In particular, the present disclosure relates to prolonging survival of an allograft by administering an inhibitor of complement or terminal complement formation, especially an inhibitor of complement C5 cleavage, in addition to one or more drugs that are immunosuppressant.

BACKGROUND

Organ transplantation is the preferred treatment for most patients with chronic organ failure. Although transplantation of kidney, liver, lung, and heart offers an excellent opportunity for rehabilitation as recipients return to a more normal lifestyle, it is limited by the medical/surgical suitability of potential recipients, an increasing shortage of donors, and premature failure of transplanted organ function.

Transplantation of cells, tissues and organs has become very common and is often a life-saving procedure. Organ transplantation is the preferred treatment for most patients with chronic organ failure. Despite great improvement in treatments to inhibit rejection, rejection continues to be the single largest impediment to successful organ transplantation. Rejection includes not only acute rejection but also chronic rejection. One-year survival rates for transplanted kidneys average 88.3% with kidneys from deceased donors and 94.4% with kidneys received from living donors. The corresponding five year survival rates for the transplanted kidneys are 63.3% and 76.5% (OPTN/SRTR Annual Report, 2002). For livers the one year survival rates are 80.2% and 76.5% for livers from deceased and living donors, respectively. The corresponding five year liver graft survival rates are 63.5% and 73.0% (OPTN/SRTR Annual Report, 2002). The use of immunosuppressant drugs, especially cyclosporin A and more recently tacrolimus, has dramatically improved the success rate of organ transplantation especially by preventing acute rejection. But as the numbers above

Samsung Bioepis Exhibit No. 1002
Page 11011

show, there is still a need to improve the success rates, both short-term and especially long-term. As seen from the above numbers for kidney and liver transplants, the five year failure rates for these transplanted organs are on the order of 25-35%. In the year 2001 alone there were more than 23,000 patients who received an organ transplant of which approximately 19,000 were kidney or liver (OPTN/SRTR Annual Report, 2002). For this one year of transplants alone, with present techniques it can be expected that approximately 5,000-6,000 of these transplanted kidneys and livers will fail within 5 years. These numbers do not even include other transplanted organs or transplanted tissues or cells such as bone marrow.

There are multiple types of transplants. These are described in Abbas et al., 2000. A graft transplanted from one individual to the same individual is called an autologous graft or autograft. A graft transplanted between two genetically identical or syngeneic individual is called a syngeneic graft. A graft transplanted between two genetically different individuals of the same species is called an allogeneic graft or allograft. A graft transplanted between individuals of different species is called a xenogeneic graft or xenograft. The molecules that are recognized as foreign on allografts are called alloantigens and those on xenografts are called xenoantigens. The lymphocytes or antibodies that react with alloantigens or xenoantigens are described as being alloreactive or xenoreactive, respectively.

Currently more than 40,000 kidney, heart, lung, liver and pancreas transplants are performed in the United States each year (Abbas et al., 2000). Other possible transplants include, but are not limited to, vascular tissue, eye, cornea, lens, skin, bone marrow, muscle, connective tissue, gastrointestinal tissue, nervous tissue, bone, stem cells, islets, cartilage, hepatocytes, and hematopoietic cells. Unfortunately, there are many more candidates for a transplant than there are donors. To overcome this shortage, a major effort is being made to learn how to use xenografts. While progress is being made in this field, the fact is that at present most transplants are allografts. An allogeneic transplant, while presently being more likely to be successful than a xenogeneic transplant, must surmount numerous obstacles to be successful. There are several types of immunological attacks made by the recipient against the donor organ which can lead to rejection of the allograft. These include hyperacute rejection, acute vascular rejection (including accelerated humoral rejection and de novo acute humoral rejection), and chronic rejection. Rejection is normally a result of T-cell mediated or humoral antibody attack, but may include additional secondary factors such as the effects of complement and cytokines.

Samsung Bioepis Exhibit No. 1002
Page 11012

An ever growing gap between the number of patients requiring organ transplantation and the number of donor organs available has become a major problem throughout the world. Park et al., 2003. Individuals who have developed anti-HLA antibodies are said to be immunized or sensitized. Gloor, 2005. HLA sensitization is the major barrier to optimal utilization of organs from living donors in clinical transplantation (Warren et al., 2004) due to the development of severe antibody-mediated rejection (ABMR). For example, more than 50% of all individuals awaiting kidney transplantation are presensitized patients (Glotz et al., 2002) who have elevated levels of broadly reactive alloantibodies, resulting from multiple transfusions, prior failed allografts, or pregnancy (Kupiec-Weglinski, 1996). The role of ABMR is currently one of the most dynamic areas of study in transplantation, due to recognition that this type of rejection can lead to either acute or chronic loss of allograft function. Mehra et al., 2003. Numerous cases of ABMR, including hyperacute rejection (HAR) or accelerated humoral rejection (ACHR), have been reported that are characterized by acute allograft injury that is resistant to potent anti-T cell therapy, the detection of circulating donor specific antibodies, and the deposition of complement components in the graft. ABMR with elevated circulating alloantibodies and complement activation that occurs in 20-30% of acute rejection cases has a poorer prognosis than cellular rejection. Mauiyyedi et al., 2002.

Highly presensitized patients, who exhibit high levels of alloantibodies, usually suffer an immediate and aggressive HAR. In clinical practice, with great efforts and significant advances in technology, HAR is avoided by obtaining a pretransplant lymphocytotoxic cross-match to identify sensitized patients with antibodies specific for donor HLA antigens. However, circulating antibodies against donor HLA or other non-MHC endothelial antigens may also be responsible for a delayed form of acute humoral rejection, which is associated with an increased incidence of graft loss. Collins et al., 1999. Therefore, development of a novel presensitized animal model to mimic ABMR in clinical settings would be beneficial to studies on the mechanism, and to the much needed progress in the management of allograft rejection in presensitized hosts.

Some highly presensitized patients can benefit from intervention programs such as immunoadsorption (Palmer et al.,1989; Ross et al., 1993; Kriaa et al., 1995), plasmapheresis and intravenous immunoglobulin (Sonnenday et al., 2002; Rocha et al., 2003), that have been designed and implemented to temporarily eliminate anti-donor antibodies. However, in addition to their benefits, the aforementioned therapies carry with them numerous drawbacks

Samsung Bioepis Exhibit No. 1002
Page 11013

as some individuals are less susceptible to their effects (Kriaa et al., 1995; Hakim et al., 1990; Glotz et al., 1993; Tyan et al., 1994); they are extremely expensive, time-consuming, and risky (Salama et al., 2001). Moreover, the transient and variable effect of these protocols has limited their impact. Glotz et al., 2002; Kupin et al., 1991; Schweitzer et al., 2000. Therefore, developing novel strategies to reduce the risk and cost in prevention of ABMR would be beneficial to presensitized recipients receiving an allograft.

SUMMARY

Accordingly, methods of prolonging survival of transplanted cells, tissues or organs are provided. In particular, methods of prolonging survival of allotransplanted cells, tissues or organs are provided. These methods are directed to using one or more immunosuppressants in addition to an inhibitor of complement activity. Use of one or more immunosuppressants and an inhibitor of complement activity in the manufacture of one or more medicaments or medicament packages is also provided. Such medicaments or medicament packages are useful in prolonging survival of an allograft in a subject mammal.

In certain embodiments, the inhibition of complement activity is effected by chronic administration of a drug directed against complement C5. A preferred drug that inhibits complement activity is an antibody specific to one or more components of complement, for example, C5. In certain preferred embodiments, the antibody inhibits the cleavage of C5 and thereby inhibits the formation of both C5a and C5b-9. The antibody may be, e.g., a monoclonal antibody, a chimeric antibody (e.g., a humanized antibody), an antibody fragment (e.g., Fab), a single chain antibody, an Fv, or a domain antibody. The recipient is also treated with one or more immunosuppressive drugs, for example, cyclosporin A.

In certain embodiments, either an MHC mismatched recipient (i.e., a mammalian recipient of an MHC mismatched allograft), a presensitized recipient or an ABO mismatched recipient (i.e., a mammalian recipient of an AMB mismatched allograft) is treated. In this model, the recipient is again chronically treated with a complement inhibitor, preferably an anti-C5 monoclonal antibody, together with immunosuppressive drugs, preferably a chronic administration of cyclosporin A and a short-term administration of cyclophosphamide. This triple therapy results in extended graft survival in the presensitized allotransplant recipient.

The present disclosure also provides methods of prolonging survival of an allograft in a mammalian recipient by administering to the recipient agents that modulate the level and/or ratio of subclasses and/or isotypes of anti-donor immunoglobulins (Ig) in the recipient. In

Samsung Bioepis Exhibit No. 1002
Page 11014

certain embodiments, an agent that reduces the level of anti-donor IgG1 in the recipient is preferred. In certain embodiments, an agent that increases the level of anti-donor IgG2a and/or IgG2b in the recipient is preferred. In certain embodiments, an agent that reduces the ratio of anti-donor IgG1/anti-donor IgG2a or IgG2b in the recipient is preferred.

The present disclosure also provides a method of prolonging survival of an allograft in a second mammalian recipient using an allograft that has been accommodated in a first mammalian recipient (i.e., the allograft has prolonged survival in the first recipient). The present disclosure further provides an allograft that is resistant to anti-donor antibodies in a mammalian recipient, and the allograft is prepared from a first recipient that has accommodated the allograft. In preferred embodiments, the first recipient has accommodated the allograft by receiving a treatment as described herein, such a triple therapy treatment involving administering to the first recipient a drug that inhibits complement activity and two immunosuppressive agents.

Further provided are pharmaceutical packages. A pharmaceutical package of the present disclosure may comprise a drug that inhibits complement activity and at least one immunosuppressive agent. The pharmaceutical package may further comprise a label for chronic administration. The pharmaceutical package may also comprise a label for self-administration by a patient, for example, a recipient of a transplant graft, or instructions for a caretaker of a recipient of a transplant graft. In certain embodiments, the drug and the agent in the pharmaceutical package are in a formulation or separate formulations that are suitable for chronic administration and/or self-administration.

The present disclosure also provides lyophilized formulations and formulations suitable for injection. Certain embodiments provide a lyophilized antibody formulation comprising an antibody that inhibits complement activity and a lyoprotectant. In preferred embodiments, the antibody formulation is suitable for chronic administration, for example, the antibody formulation is stable. Alternative embodiments provide an injection system comprising a syringe; the syringe comprises a cartridge containing an antibody that inhibits complement activity and is in a formulation suitable for injection.

An antibody employed in various embodiments of the present disclosure preferably inhibits the formation of terminal complement or C5a. In certain embodiments, antibody inhibits formation of terminal complement or C5a is a whole antibody or an antibody fragment. The whole antibody or antibody fragment may be a human, humanized,

Samsung Bioepis Exhibit No. 1002
Page 11015

chimerized or deimmunized antibody or antibody fragment. In certain embodiments, the whole antibody or antibody fragment may inhibit cleavage of complement C5. In certain embodiments, the antibody fragment is a Fab, an F(ab')2, an Fv, a domain antibody, or a single-chain antibody. In preferred embodiments, the antibody fragment is pexelizumab. In alternative preferred embodiments, the whole antibody is eculizumab.

In certain embodiments, a drug, such as an antibody, that inhibits complement activity is present in unit dosage form, which can be particularly suitable for self-administration. Similarly, an immunosuppressive agent of the present disclosure may also be present in unit dosage form.

BRIEF DESCRIPTION OF THE DRAWINGS

Figures 1A-1D show anti-donor antibody levels in presensitized versus unsensitized recipients under different treatments.

Figures 2A and 2B show comparison between triple therapy using anti-C5 antibody, CsA and CyP in presensitized allograft recipients and combination therapy using only anti-C5 antibody and CsA in presensitized allograft recipients. Figure 2A compares heart-allograft survival in various recipients under different treatments as indicated. Figure 2B shows histology and immunohistology, for example, for lymphocyte infiltration in heart allografts of recipients in different groups.

Figure 3 shows blocked terminal complement activity by anti-C5 antibody as compared to immunosuppressive agents.

Figures 4A-4D compare levels of anti-donor antibodies in presensitized recipients of allografts under monotherapy with anti-C5 antibody alone, double combination therapy with anti-C5 antibody and CsA, and triple combination therapy with anti-C5 antibody, CsA and CyP.

Figures 5A and 5B show change of ratios of IgG isotypes in allograft recipients that were untreated or under different treatments.

Figure 6 shows high-level expression of Bcl-2 and Bcl-xl proteins in long-term surviving heart grafts as compared to heart grafts of untreated animals.

Figure 7 shows improved second transplantation (re-transplantation) of an accommodated graft from a first transplantation recipient.

Figure 8 shows results from re-transplantation experiments.

Samsung Bioepis Exhibit No. 1002
Page 11016

Figure 9 shows results from re-transplantation experiments.

DETAILED DESCRIPTION

Overview: Rejection of Transplants or Grafts

Hyperacute rejection occurs within minutes to hours after transplant and is due to preformed antibodies to the transplanted tissue antigens. It is characterized by hemorrhage and thrombotic occlusion of the graft vasculature. The binding of antibody to endothelium activates complement, and antibody and complement induce a number of changes in the graft endothelium that promote intravascular thrombosis and lead to vascular occlusion, the result being that the grafted organ suffers irreversible ischemic damage (Abbas et al., 2000). Hyperacute rejection is often mediated by preexisting IgM alloantibodies, e.g., those directed against the ABO blood group antigens expressed on red blood cells. This type of rejection, mediated by natural antibodies, is the main reason for rejection of xenotransplants. Hyperacute rejection due to natural IgM antibodies is no longer a major problem with allografts because allografts are usually selected to match the donor and recipient ABO type. Hyperacute rejection of an ABO matched allograft may still occur, usually mediated by IgG antibodies directed against protein alloantigens, such as foreign MHC molecules, or against less well defined alloantigens expressed on vascular endothelial cells. Such antibodies may arise as a result of prior exposure to alloantigens through blood transfusion, prior transplantation, or multiple pregnancies (this prior exposure being referred to as "presensitization"). Abbas et al., 2000.

Acute rejection is a process of vascular and parenchymal injury mediated by T cells, macrophages, and antibodies that usually begins after the first week of transplantation. Abbas et al., 2001. T lymphocytes play a central role in acute rejection by responding to alloantigens, including MHC molecules, present on vascular endothelial and parenchymal cells. The activated T cells cause direct lysis of graft cells or produce cytokines that recruit and activate inflammatory cells, which cause necrosis. Both $CD4^+$ and $CD8^+$ cells may contribute to acute rejection. The destruction of allogeneic cells in a graft is highly specific and a hallmark of $CD8^+$ cytotoxic T lymphocyte killing. Abbas et al., 2000. $CD4^+$ T cells may be important in mediating acute graft rejection by secreting cytokines and inducing delayed-type hypersensitivity-like reactions in grafts, with some evidence available that indicates that $CD4^+$ T cells are sufficient to mediate acute rejection. Abbas et al., 2000. Antibodies can also mediate acute rejection after a graft recipient mounts a humoral immune

Samsung Bioepis Exhibit No. 1002
Page 11017

response to vessel wall antigens and the antibodies that are produced bind to the vessel wall and activate complement. Abbas et al., 2000.

Chronic rejection is characterized by fibrosis with loss of normal organ structures occurring over a prolonged period. The pathogenesis of chronic rejection is less well understood than that of acute rejection. Graft arterial occlusion may occur as a result of the proliferation of intimal smooth muscle cells (Abbas et al., 2000). This process is called accelerated or graft arteriosclerosis and can develop in any vascularized organ transplant within 6 months to a year after transplantation.

For a transplant to be successful, the several modes of rejection must be overcome. Multiple approaches are utilized in preventing rejection. This may require administration of immunosuppressants, often several types to prevent the various modes of attack, e.g., inhibition of T-cell attack, antibodies, and cytokine and complement effects. Prescreening of donors to match them with recipients is also a major factor in preventing rejection, especially in preventing hyperacute rejection. Immunoadsorption of anti-HLA antibodies prior to grafting may reduce hyperacute rejection. Prior to transplantation the recipient or host may be administered anti-T cell reagents, e.g., the monoclonal antibody OKT3, Anti-Thymocyte Globulin (ATG), cyclosporin A, or tacrolimus (FK 506). Additionally, glucocorticoids and/or azathioprine may be administered to the host prior to transplant. Drugs used to aid in preventing transplant rejection include, but are not limited to, ATG or ALG, OKT3, daclizumab, basiliximab, corticosteroids, 15-deoxyspergualin, cyclosporins, tacrolimus, azathioprine, methotrexate, mycophenolate mofetil, 6-mercaptopurine, bredinin, brequinar, leflunamide, cyclophosphamide, sirolimus, anti-CD4 monoclonal antibodies, CTLA4-Ig, anti-CD154 monoclonal antibodies, anti-LFA1 monoclonal antibodies, anti-LFA-3 monoclonal antibodies, anti-CD2 monoclonal antibodies, and anti-CD45.

Allografts are rejected in part by the activation of T cells. The transplant recipient mounts a rejection response following $CD4^+$ T cell recognition of foreign antigens in the allograft. These antigens are encoded by the major histocompatibility complex (MHC). There are both Class I and Class II MHC molecules. In humans the class I MHC molecules are HLA-A, HLA-B, and HLA-C. The class II MHC molecules in humans are called HLA-DR, HLA-DQ and HLA-DP. In mice the class I MHC molecules are H-2K, H-2D and H-2L and the class II MHC molecules are I-A and I-E. When $CD4^+$ T cells bind the foreign MHC antigens they are activated and undergo clonal proliferation. The activated T cells secrete cytokines which aid in activating monocytes/macrophages, B cells and cytotoxic $CD8^+$ T

Samsung Bioepis Exhibit No. 1002
Page 11018

cells. The activated monocytes/macrophages release agents which result in tissue damage, the B cells produce alloantibodies which lead to complement mediated tissue destruction, and the $CD8^+$ T cells kill graft cells in an antigen-specific manner through induction of apoptosis and cell lysis.

Immunosuppressive Agents

The numerous drugs utilized to delay graft rejection (i.e., to prolong their survival) work in a variety of ways. Immunosuppressive agents are widely used. See Stepkowski, 2000, for a review of the mechanism of action of several immunosuppressive drugs. Cyclosporin A is one of the most widely used immunosuppressive drugs for inhibiting graft rejection. It is an inhibitor of interleukin-2 or IL-2 (it prevents mRNA transcription of interleukin-2). More directly, cyclosporin inhibits calcineurin activation that normally occurs upon T cell receptor stimulation. Calcineurin dephosphorylates NFAT (nuclear factor of activated T cells) enabling it to enter the nucleus and bind to interleukin-2 promoter. By blocking this process, cyclosporin A inhibits the activation of the $CD4^+$ T cells and the resulting cascade of events which would otherwise occur. Tacrolimus is another immunosuppressant that acts by inhibiting the production of interleukin-2.

Rapamycin (Sirolimus), SDZ RAD, and interleukin-2 receptor blockers are drugs that inhibit the action of interleukin-2 and therefore prevent the cascade of events described above.

Inhibitors of purine or pyrimidine biosynthesis are also used to inhibit graft rejection. These prevent DNA synthesis and thereby inhibit cell division including the ability of T cells to divide. The result is the inhibition of T cell activity by preventing the formation of new T cells. Inhibitors of purine synthesis include azathioprine, methotrexate, mycophenolate mofetil (MMF) and mizoribine (bredinin). Inhibitors of pyrimidine synthesis include brequinar sodium and leflunomide. Cyclophosphamide is an inhibitor of both purine and pyrimidine synthesis.

Yet another method for inhibiting T cell activation is to treat the recipient with antibodies to T cells. OKT3 is a murine monoclonal antibody against CD3 which is part of the T cell receptor. This antibody inhibits the T cell receptor and suppresses T cell activation.

Numerous other drugs and methods for delaying allotransplant rejection are known to and used by those of skill in the art. One approach has been to deplete T cells, e.g., by irradiation. This has often been used in bone marrow transplants, especially if there is a

Samsung Bioepis Exhibit No. 1002
Page 11019

partial mismatch of major HLA. Administration to the recipient of an inhibitor (blocker) of the CD40 ligand-CD40 interaction and/or a blocker of the CD28-B7 interaction has been used (U.S. Patent 6,280,957). Published PCT patent application WO 01/37860 teaches the administration of an anti-CD3 monoclonal antibody and IL-5 to inhibit the Th1 immune response. Published PCT patent application WO 00/27421 teaches a method for prophylaxis or treatment of corneal transplant rejection by administering a tumor necrosis factor-α antagonist. Glotz et al. (2002) show that administration of intravenous immunoglobulins (IVIg) can induce a profound and sustained decrease in the titers of anti-HLA antibodies thereby allowing a transplant of an HLA-mismatched organ. Similar protocols have included plasma exchanges (Taube et al., 1984) or immunoadsorption techniques coupled to immunosuppressive agents (Hiesse et al., 1992) or a combination of these (Montgomery et al., 2000). Changelian et al. (2003) teach a model in which immunosuppression is caused by an oral inhibitor of Janus kinase 3 (JAK3) which is an enzyme necessary for the proper signaling of cytokine receptors which use the common gamma chain (γc) (Interleukins-2, -4, -7, -9, -15, -21), the result being an inhibition of T cell activation. Antisense nucleic acids against ICAM-1 have been used alone or in combination with a monoclonal antibody specific for leukocyte-function associated antigen 1 (LFA-1) in a study of heart allograft transplantation (Stepkowski, 2000). Similarly, an anti-ICAM-1 antibody has been used in combination with anti-LFA-1 antibody to treat heart allografts (Stepkowski, 2000). Antisense oligonucleotides have additionally been used in conjunction with cyclosporin in rat heart or kidney allograft models, resulting in a synergistic effect to prolong the survival of the grafts (Stepkowski, 2000). Chronic transplant rejection has been treated by administering an antagonist of TGF-β which is a cytokine involved in differentiation, proliferation and apoptosis (U.S. Patent Application Publication US 2003/0180301).

Complement and Transplant/Graft Rejection

The role of complement in transplant rejection is well known. This is especially true in the case of xenotransplantation, but complement also plays a role in allotransplant rejection. For review, see Platt and Saadi, 1999. One aspect of complement's role is that ischemia-reperfusion injury may occur at the time that an organ graft is reperfused with the blood of the recipient. Complement may also cause some manifestations of allograft rejection.

The complement system is described in detail in U.S. Patent 6,355,245. The complement system acts in conjunction with other immunological systems of the body to

Samsung Bioepis Exhibit No. 1002
Page 11020

defend against intrusion of cellular and viral pathogens. There are at least 25 complement proteins, which are found as a complex collection of plasma proteins and membrane cofactors. The plasma proteins make up about 10% of the globulins in vertebrate serum. Complement components achieve their immune defensive functions by interacting in a series of intricate but precise enzymatic cleavage and membrane binding events. The resulting complement cascade leads to the production of products with opsonic, immunoregulatory, and lytic functions.

The complement cascade progresses via the classical pathway or the alternative pathway. These pathways share many components and, while they differ in their initial steps, they converge and share the same "terminal complement" components (C5 through C9) responsible for the activation and destruction of target cells.

The classical complement pathway is typically initiated by antibody recognition of and binding to an antigenic site on a target cell. The alternative pathway is usually antibody independent and can be initiated by certain molecules on pathogen surfaces. Both pathways converge at the point where complement component C3 is cleaved by an active protease (which is different in each pathway) to yield C3a and C3b. Other pathways activating complement attack can act later in the sequence of events leading to various aspects of complement function.

C3a is an anaphylatoxin. C3b binds to bacterial and other cells, as well as to certain viruses and immune complexes, and tags them for removal from the circulation. C3b in this role is known as opsonin. The opsonic function of C3b is considered to be the most important anti-infective action of the complement system. Patients with genetic lesions that block C3b function are prone to infection by a broad variety of pathogenic organisms, while patients with lesions later in the complement cascade sequence, i.e., patients with lesions that block C5 functions, are found to be more prone only to Neisseria infection, and then only somewhat more prone (Fearon, 1983).

C3b also forms a complex with other components unique to each pathway to form classical or alternative C5 convertase, which cleaves C5 into C5a and C5b. C3 is thus regarded as the central protein in the complement reaction sequence since it is essential to both the alternative and classical pathways (Wurzner et al., 1991). This property of C3b is regulated by the serum protease Factor I, which acts on C3b to produce iC3b. While still functional as opsonin, iC3b cannot form an active C5 convertase.

Samsung Bioepis Exhibit No. 1002
Page 11021

C5 is a 190 kDa beta globulin found in normal serum at approximately 75 μg/mL (0.4 μM). C5 is glycosylated, with about 1.5-3 percent of its mass attributed to carbohydrate. Mature C5 is a heterodimer of a 999 amino acid 115 kDa alpha chain that is disulfide linked to a 656 amino acid 75 kDa beta chain. C5 is synthesized as a single chain precursor protein product of a single copy gene (Haviland et al., 1991). The cDNA sequence of the transcript of this gene predicts a secreted pro-C5 precursor of 1659 amino acids along with an 18 amino acid leader sequence.

The pro-C5 precursor is cleaved after amino acid 655 and 659, to yield the beta chain as an amino terminal fragment (amino acid residues +1 to 655) and the alpha chain as a carboxyl terminal fragment (amino acid residues 660 to 1658), with four amino acids deleted between the two.

C5a is cleaved from the alpha chain of C5 by either alternative or classical C5 convertase as an amino terminal fragment comprising the first 74 amino acids of the alpha chain (i.e., amino acid residues 660-733). Approximately 20 percent of the 11 kDa mass of C5a is attributed to carbohydrate. The cleavage site for convertase action is at or immediately adjacent to amino acid residue 733. A compound that would bind at or adjacent to this cleavage site would have the potential to block access of the C5 convertase enzymes to the cleavage site and thereby act as a complement inhibitor.

C5 can also be activated by means other than C5 convertase activity. Limited trypsin digestion (Minta and Man, 1977; Wetsel and Kolb, 1982) and acid treatment (Yamamoto and Gewurz, 1978; Vogt et al., 1989) can also cleave C5 and produce active C5b.

C5a is another anaphylatoxin. C5b combines with C6, C7, and C8 to form the C5b-8 complex at the surface of the target cell. Upon binding of several C9 molecules, the membrane attack complex (MAC, C5b-9, terminal complement complex-TCC) is formed. When sufficient numbers of MACs insert into target cell membranes the openings they create (MAC pores) mediate rapid osmotic lysis of the target cells. Lower, non-lytic concentrations of MACs can produce other effects. In particular, membrane insertion of small numbers of the C5b-9 complexes into endothelial cells and platelets can cause deleterious cell activation. In some cases activation may precede cell lysis.

As mentioned above, C3a and C5a are anaphylatoxins. These activated complement components can trigger mast cell degranulation, which releases histamine and other mediators of inflammation, resulting in smooth muscle contraction, increased vascular

Samsung Bioepis Exhibit No. 1002
Page 11022

permeability, leukocyte activation, and other inflammatory phenomena including cellular proliferation resulting in hypercellularity. C5a also functions as a chemotactic peptide that serves to attract pro-inflammatory granulocytes to the site of complement activation.

Complement-binding recipient antibodies to donor alloantigens are considered to be the main cause of hyperacute graft rejection. Owing to pretransplant crossmatch testing, this prototype of humoral rejection is now rarely observed (Regele et al., 2001). Data are now showing that humoral immune mechanisms might contribute to other types of allograft rejection (Regele et al., 2001). High levels of panel reactive antibodies indicating humoral presensitization were found to be associated with inferior kidney graft survival (Opelz, 1992), the appearance of alloantibodies during the post-transplant period has been reported to predict poor graft outcome (Jeannet et al., 1970; Halloran et al., 1992), and selective removal of recipient IgG by immunoadsorption reversed some rejection episodes indicating the contribution of humoral immune mechanisms to rejection (Persson et al., 1995; Böhmig et al., 2000). Complement activation within a graft might indicate antibody-mediated graft injury. The complement cleavage product C4d is a marker for activation of the antibody-dependent classical pathway. Capillary C4d deposits in kidney allograft biopsies were associated with poor graft outcome.

Recently increasing evidence indicates that complement activation significantly contributes to the sensitization of allograft recipients and the development of tissue injury in allografts (Platt et al., 1999). Antibodies are the most thoroughly investigated mediators of activating the classical complement pathway. Clinically, alloantibodies are known to activate complement (Baldwin et al., 2001). Halloran and Collins indicate that C4d deposition in peritubular capillaries of renal allografts is a sensitive and diagnostic marker of acute humoral rejection that correlates strongly with the presence of circulating donor-specific antibodies (Collins et al., 1999; Halloran, 2003). Further supporting evidence is seen in animals with complement inhibition (Pratt et al., 1996; Pruitt et al., 1991; Forbes et al., 1978) or deficiency (Pratt et al., 2000; Baurer et al., 1995) which exhibit significantly reduced inflammatory injury and lowered anti-donor immune responses. In ABMR, complement is suggested to be activated by the classical pathway and to play a key role in the pathogenesis (Collard et al., 1997). Although the role of complement in HAR or acute vascular rejection (AVR) following xenotransplantation has been well documented (Platt et al., 1999), precise mechanisms of complement in the pathogenesis of ABMR following allotransplantation has not yet been elucidated.

Samsung Bioepis Exhibit No. 1002
Page 11023

The C5 component of complement is cleaved to form products with multiple proinflammatory effects and thus represents an attractive target for complement inhibition within the immune-mediated inflammatory response. As described above, C5a is a powerful anaphylatoxin and chemotactic factor. Cellular activation by C5a induces the release of multiple additional inflammatory mediators (Jose et al., 1983). The complement activation pathways (classical, alternative, or mannan-binding lectin pathway) ultimately lead to the formation of the cytolytic membrane attack complex C5b-9 (Kirschfunk, 2001), which can mediate both direct tissue injury by cell lysis, and proinflammatory cell activation at sublytic doses (Saadi et al., 1995; Papadimitriou et al., 1991). Therefore, blocking both C5a and C5b-9 generation may be required for the optimal inhibition of complement-mediated inflammatory response following transplantation. At the same time, inhibition of the complement cascade at C5 does not impair the generation of C3b, preserving C3b-mediated opsonization of pathogenic microorganisms as well as solubilization and clearance of immune complexes (Liszewski, 1993).

The beneficial effect of anti-C5 mAb has previously been reported in several experimental models including myocardial reperfusion (Vakeva et al., 1998), systemic lupus erythematosus (Wang et al., 1996) and rheumatoid arthritis (Wang et al., 1995); as well as in human clinical trials (Kirschfink, 2001) of autoimmune disease, cardiopulmonary bypass and acute myocardial infarction. In addition, complement inactivation by a functionally blocking anti-C5 monoclonal Ab (mAb) prevented HAR in xenotransplantation models (Kroshus et al., 1995; Wang et al., 1999).

Methods of delaying allotransplant rejection by administration of complement inhibitors have been tested. Published PCT patent application WO 92/10205 discloses the use of a combination of cyclosporin and a soluble complement receptor (sCR1) to inhibit rejection of a cardiac allotransplant in a presensitized rat model. Complement receptor 1 binds complements C3b and C4b. Soluble forms of complement receptor 1 occur naturally or can be generated via recombinant DNA procedures. These soluble complement receptors have inhibited in vitro the consequences of complement activation (U.S. Patent 6,057,131). In WO 92/10205, rats, which had been presensitized to the cardiac allograft they were receiving, were administered cyclosporin A intramuscularly at 10 mg/kg/day beginning two days prior to transplant and continued until the time of graft rejection. Additionally, soluble complement receptor 1 (sCR1) was administered as a single intravenous bolus at 15 mg/kg immediately prior to reperfusion of the graft. Control animals with no drug treatment had the

Samsung Bioepis Exhibit No. 1002
Page 11024

graft rejected at an average of 3.8 days. Those administered cyclosporin A alone rejected the grafts at an average of 57 days (this was quite variable with two rats rejecting quickly at 2 and 4 days and a third rat rejecting at 166 days). Rats administered sCR1 alone rejected the grafts at an average of 44 days. Those rats administered the combination of cyclosporin A and sCR1 rejected the grafts at an average of 147 days. The combination of chronic cyclosporin A and single bolus sCR1 was seen to result in a synergistic effect greatly prolonging the time until graft rejection. Earlier studies by Pruitt and Bollinger (1991) used a similar model of a presensitized rat allograft to show that administration of sCR1 alone to inactivate complement resulted in increased time before graft rejection.

Sims et al. (U.S. Patent 5,135,916) suggest using inhibitors of complement, e.g., CD59 or antibodies against C7 or C9 to block the formation of the C5b-9 complex, to treat the vascular endothelium of organs and tissues to be transplanted. This would prevent the C5b-9 initiated cell necrosis. The C5b-9 inactivators would be added to the perfusate or storage medium to protect the vascular lining cells from ongoing complement activation during in vitro storage. Additionally the organ or tissue would be protected from the cytolytic and thrombotic effects arising from complement activation initiated upon transplantation, thereby circumventing complement mediated acute rejection. Sims et al. (U.S. Patent 5,573,940 and U.S. Patent 6,100,443) also teach a method of expressing CD59 in the transplanted tissue or organ to protect the transplanted organ from rejection. This can be accomplished by transfecting the cells being transplanted.

Although the several drugs developed to date in combination with methods of prescreening donors and recipients to match the donor allograft to the recipient have over time increased the average length of time of survival of allografts, many allografts are nonetheless rejected during the life-time of the recipient. In general, the prior art advances have mainly been directed to overcoming acute graft rejection. Further, the role of activated terminal complement components in antibody-mediated allograft rejection has not been examined using inhibitors that specifically target the complement cascade at the C5 protein level. The methods described herein and as exemplified in the Examples advance the allotransplant art by inhibiting chronic rejection of allografts, in particular, allografts in a presensitized recipient. New methods are presented for further prolonging allograft survival by using a proper combination of immunosuppressive drugs in combination with a chronic administration of a complement inhibitor.

Samsung Bioepis Exhibit No. 1002
Page 11025

Methods and Uses

The methods disclosed herein are used to prolong allograft survival. The methods generally include administering an inhibitor of complement activity in combination with one or more immunosuppressants.

Suitable complement inhibitors are known to those of skill in the art. Antibodies can be made to individual components of activated complement, e.g., antibodies to C5a, C7, C9, etc. (see, e.g., U.S. Patent 6,534,058; published U.S. patent application US 2003/0129187; and U.S. Patent 5,660,825). Proteins are known which inhibit complement-mediated lysis, including CD59, CD55, CD46 and other inhibitors of C8 and C9 (see, e.g., U.S. Patent 6,100,443). U.S. Patent 6,355,245 teaches an antibody which binds to C5 and prevents it from being cleaved into C5a and C5b thereby preventing the formation not only of C5a but also the C5b-9 complex. Proteins known as complement receptors and which bind complement are also known (see, Published PCT Patent Application WO 92/10205 and U.S. Patent 6,057,131). Use of soluble forms of complement receptors, e.g., soluble CR1, can inhibit the consequences of complement activation such as neutrophil oxidative burst, complement mediated hemolysis, and C3a and C5a production. Those of skill in the art recognize the above as some, but not all, of the known methods of inhibiting complement and its activation.

Suitable immunosuppressants include, but are not limited to, ATG or ALG, OKT3, daclizumab, basiliximab, corticosteroids, 15-deoxyspergualin, cyclosporins, tacrolimus, azathioprine, methotrexate, mycophenolate mofetil, 6-mercaptopurine, bredinin, brequinar, leflunamide, cyclophosphamide, sirolimus, anti-CD4 monoclonal antibodies, CTLA4-Ig, anti-CD154 monoclonal antibodies, anti-LFA1 monoclonal antibodies, anti-LFA-3 monoclonal antibodies, anti-CD2 monoclonal antibodies, and anti-CD45.

An allograft can include a transplanted organ, part of an organ, tissue or cell. These include, but are not limited to, heart, kidney, lung, pancreas, liver, vascular tissue, eye, cornea, lens, skin, bone marrow, muscle, connective tissue, gastrointestinal tissue, nervous tissue, bone, stem cells, islets, cartilage, hepatocytes, and hematopoietic cells.

At least part of the reason for the failure of allografts is that one response by the recipient of an allograft is the activation of complement. This results in the formation of C5a and C5b-9 which are potent proinflammatory molecules which aid in causing graft failure. Without wishing to be bound by any proposed theory, Applicants theorized that inhibiting the

Samsung Bioepis Exhibit No. 1002
Page 11026

formation of C5a and C5b-9 or inhibiting C5a and C5b-9 which was present would aid in preventing graft failure. Furthermore, it was theorized that so long as the allograft is present, the recipient will continue to attempt to mount an immune response against the graft, and this response will include attempts to produce C5a and C5b-9. If not prevented, this complement response will lead to acute vascular rejection in the short term and could contribute to chronic graft rejection in the long term. Prior art methods of using inhibitors of complement activity were limited to administering these inhibitors only at the time of transplant. This was helpful in preventing acute rejection, but as the results disclosed herein illustrate, improved results are obtained by administration of such inhibitors for a longer term. This long-term administration aids in preventing a chronic rejection of the allograft as opposed to only aiding in preventing an acute rejection. The result is a longer term survival of the allograft as compared to either not administering an inhibitor of complement activity or administering such an inhibitor only at the time of transplant of the allograft. Although very commonly it is desirable that the allograft will survive for the remaining lifetime of the recipient, there are times when the allograft is needed only for a shorter length of time, e.g., a bridge organ to bridge the time until the recipient's own organ can recover on its own, at which time the allograft will no longer be needed. The length of time such a graft will be needed will vary, but will usually be longer than the time at which acute rejection would occur and may be long enough for chronic rejection to occur. This period of desired survival for a bridge graft may be several months, e.g., six months.

To prove that long-term inhibition of complement activity will prolong allograft survival, experiments were performed in which complement activation was inhibited in a chronic fashion and not merely at the time of transplant. Chronic treatment means treatment during an extended period up to the lifetime of the allograft. This can be daily treatment but is not limited to daily treatment. Chronic treatment will maintain an effective amount of the drug in the allograft recipient. For example, a preferred method is to include the anti-C5 monoclonal antibody eculizumab in the treatment. In studies of persons suffering from paroxysmal nocturnal hemoglobinuria (PNH), eculizumab has been administered at a dose of 900 mg/patient once every 12-14 days. This dosing has been found to completely and consistently block terminal complement activity and has greatly inhibited the symptoms of PNH (Hillmen et al., 2004). The administered dose is able to block the effects of complement for approximately two weeks before the eculizumab is inactivated or removed from the body. Therefore, a chronic treatment of eculizumab may be, e.g., the administration

Samsung Bioepis Exhibit No. 1002
Page 11027

of 900 mg to the allograft recipient once every two weeks for the remaining life-time of the patient. Similarly, other drugs can be delivered chronically as needed, whether this is on a daily basis or another schedule is required to maintain an effective amount of the drug in the allograft recipient. Because it is well known that graft rejection can be caused by more than just complement activation, e.g., by T cell activity, the experiments included immunosuppressants such as cyclosporin to further aid in preventing graft rejection.

A preferred method of inhibiting complement activity is to use a monoclonal antibody which binds to complement C5 and prevents C5 from being cleaved. This prevents the formation of both C5a and C5b-9 while at the same time allowing the formation of C3a and C3b which are beneficial to the recipient. Such antibodies that are specific to human complement are known (U.S. Patent 6,355,245). These antibodies disclosed in U.S. Patent 6,355,245 include both a whole or full-length antibody (now named eculizumab) and a single-chain antibody (now named pexelizumab). A similar antibody against mouse C5 is called BB5.1 (Frei et al., 1987). BB5.1 was utilized in the experiments set forth below. Antibodies to inhibit complement activity need not be monoclonal antibodies. They can be, e.g., polyclonal antibodies. They may additionally be antibody fragments. An antibody fragment includes, but is not limited to, an Fab, F(ab'), $F(ab')_2$, a single-chain antibody, a domain antibody and an Fv. Furthermore, it is well known by those of skill in the art that antibodies can be humanized (Jones et al., 1986), chimerized, or deimmunized. An antibody may also comprise a mutated Fc portion, such that the mutant Fc does not activate complement. The antibodies to be used in the present disclosure may be any of these. It is preferable to use humanized antibodies when the recipient of the allograft is a human.

Administration and Formulations

Administration of the inhibitor of complement activity is performed according to methods known to those of skill in the art. These inhibitors are administered preferably before the time of allograft transplantation or at the time of transplantation with administration continuing in a chronic fashion. These inhibitors can additionally be administered during a rejection episode in the event such an episode does occur.

The present disclosure also provides uses of a drug that inhibits complement activity and an immunosuppressive agent in the manufacture of a medicament or medicament package. Such medicament or medicament package is useful in prolonging allograft survival in a recipient, in particular, chronic survival of the allograft. In preferred embodiments, the

Samsung Bioepis Exhibit No. 1002
Page 11028

medicament or medicament package is formulated and prepared such that it is suitable for chronic administration to the recipient of the allograft, for example, stable formulations are employed. In certain embodiments, the medicament or medicament package is formulated and prepared such that it is suitable for concurrent administration of the drug that inhibits complement activity and the immunosuppressive drug to the recipient of the allograft. In certain embodiments, the medicament or medicament package is formulated and prepared such that it is suitable for sequential (in either order) administration of the drug that inhibits complement activity and the immunosuppressive drug to the recipient of the allograft.

A pharmaceutical package of the present disclosure may comprise a drug that inhibits complement activity and at least one immunosuppressive agent. The pharmaceutical package may further comprise a label for chronic administration. The pharmaceutical package may also comprise a label for self-administration by a patient, for example, a recipient of a transplant graft, or instructions for a caretaker of a recipient of a transplant graft. In certain embodiments, the drug and the agent in the pharmaceutical package are in a formulation or separate formulations that are suitable for chronic administration and/or self-administration.

The present disclosure also provides lyophilized formulations and formulations suitable for injection. Certain embodiments provide a lyophilized antibody formulation comprising an antibody that inhibits complement activity and a lyoprotectant. In preferred embodiments, the antibody formulation is suitable for chronic administration, for example, the antibody formulation stable. Alternative embodiments provide an injection system comprising a syringe; the syringe comprises a cartridge containing an antibody that inhibits complement activity and is in a formulation suitable for injection.

An antibody employed in various embodiments of the present disclosure preferably inhibits the formation of terminal complement or C5a. In certain embodiments, antibody inhibits formation of terminal complement or C5a is a whole antibody or an antibody fragment. The whole antibody or antibody fragment may be a human, humanized, chimerized or deimmunized antibody or antibody fragment. In certain embodiments, the whole antibody or antibody fragment may inhibit cleavage of complement C5. In certain embodiments, the antibody fragment is a Fab, an F(ab')2, an Fv, a domain antibody, or a single-chain antibody. In preferred embodiments, the antibody fragment is pexelizumab. In alternative preferred embodiments, the whole antibody is eculizumab.

Samsung Bioepis Exhibit No. 1002
Page 11029

In certain embodiments, a drug, such as an antibody, that inhibits complement activity is present in unit dosage form, which can be particularly suitable for self-administration. Similarly, an immunosuppressive agent of the present disclosure may also be present in unit dosage form. A formulated product of the present disclosure can be included within a container, typically, for example, a vial, cartridge, prefilled syringe or disposable pen. A doser such as the doser device described in U.S. Patent 6,302,855 may also be used, for example, with an injection system of the present disclosure.

A "stable" formulation is one in which the drug (e.g., an antibody) or agent therein essentially retains its physical and chemical stability and integrity upon storage. Various analytical techniques for measuring protein stability are available in the art and are reviewed in Peptide and Protein Drug Delivery, 247-301, Vincent Lee Ed., Marcel Dekker, Inc., New York, N.Y., Pubs. (1991) and Jones, A. Adv. Drug Delivery Rev. 10: 29-90 (1993). Stability can be measured at a selected temperature for a selected time period. For example, the extent of aggregation following lyophilization and storage can be used as an indicator of protein stability. For example, a "stable" formulation may be one wherein less than about 10% and preferably less than about 5% of the protein is present as an aggregate in the formulation. In other embodiments, any increase in aggregate formation following lyophilization and storage of the lyophilized formulation can be determined. For example, a "stable" lyophilized formulation may be one wherein the increase in aggregate in the lyophilized formulation is less than about 5% and preferably less than about 3%, when the lyophilized formulation is stored at 2-8 °C for at least one year. In other embodiments, stability of the protein formulation may be measured using a biological activity assay.

A "reconstituted" formulation is one which has been prepared by dissolving a lyophilized protein formulation in a diluent such that the protein is dispersed in the reconstituted formulation. The reconstituted formulation in suitable for administration (e.g. parenteral administration) to a patient to be treated with the protein of interest and, in certain embodiments of the invention, may be one which is suitable for subcutaneous administration.

An isotonic reconstituted formulation is preferable in certain embodiments. By "isotonic" is meant that the formulation of interest has essentially the same osmotic pressure as human blood. Isotonic formulations will generally have an osmotic pressure from about 250 to 350 mOsm. Isotonicity can be measured using a vapor pressure or ice-freezing type osmometer, for example.

Samsung Bioepis Exhibit No. 1002
Page 11030

A "lyoprotectant" is a molecule which, when combined with a drug (e.g., antibody) of interest, significantly prevents or reduces chemical and/or physical instability of the drug (e.g., antibody) upon lyophilization and subsequent storage. Exemplary lyoprotectants include sugars such as sucrose or trehalose; an amino acid such as monosodium glutamate or histidine; a methylamine such as betaine; a lyotropic salt such as magnesium sulfate; a polyol such as trihydric or higher sugar alcohols, e.g. glycerin, erythritol, glycerol, arabitol, xylitol, sorbitol, and mannitol; propylene glycol; polyethylene glycol; Pluronics; and combinations thereof. The preferred lyoprotectant is a non-reducing sugar, such as trehalose or sucrose.

The lyoprotectant is added to the pre-lyophilized formulation in a "lyoprotecting amount" which means that, following lyophilization of the drug (e.g., antibody) in the presence of the lyoprotecting amount of the lyoprotectant, the drug (e.g., antibody) essentially retains its physical and chemical stability and integrity upon lyophilization and storage.

The "diluent" of interest herein is one which is pharmaceutically acceptable (safe and non-toxic for administration to a human) and is useful for the preparation of a reconstituted formulation. Exemplary diluents include sterile water, bacteriostatic water for injection (BWFI), a pH buffered solution (e.g. phosphate-buffered saline), sterile saline solution, Ringer's solution or dextrose solution.

A "preservative" is a compound which can be added to the diluent to essentially reduce bacterial action in the reconstituted formulation, thus facilitating the production of a multi-use reconstituted formulation, for example. Examples of potential preservatives include octadecyldimethylbenzyl ammonium chloride, hexamethonium chloride, benzalkonium chloride (a mixture of alkylbenzyldimethylammonium chlorides in which the alkyl groups are long-chain compounds), and benzethonium chloride. Other types of preservatives include aromatic alcohols such as phenol, butyl and benzyl alcohol, alkyl parabens such as methyl or propyl parahen, catechol, resorcinol, cyclohexanol, 3-pentanol, and m-cresol.

A "bulking agent" is a compound which adds mass to the lyophilized mixture and contributes to the physical structure of the lyophilized cake (e.g. facilitates the production of an essentially uniform lyophilized cake which maintains an open pore structure). Exemplary bulking agents include mannitol, glycine, polyethylene glycol and xorbitol.

Accordingly, a stable lyophilized antibody formulation can be prepared using a lyoprotectant (preferably a sugar such as sucrose or trehalose), which lyophilized formulation

Samsung Bioepis Exhibit No. 1002
Page 11031

can be reconstituted to generate a stable reconstituted formulation having an antibody concentration which is significantly higher (e.g. from about 2-40 times higher, preferably 3-10 times higher and most preferably 3-6 times higher) than the antibody concentration in the pre-lyophilized formulation. Such high protein concentrations in the reconstituted formulation are considered to be particularly useful where the formulation is intended for subcutaneous administration. Despite the very high protein concentration in the reconstituted formulation, the reconstituted formulation can be stable (i.e. fails to display significant or unacceptable levels of chemical or physical instability of the protein) at 2-8 °C. for at least about 30 days. See U.S. Patent 6,821,515. In certain embodiments, the reconstituted formulation is isotonic.

When reconstituted with a diluent comprising a preservative (such as bacteriostatic water for injection, BWFI), the reconstituted formulation may be used as a multi-use formulation. Such a formulation is useful, for example, where a subject patient requires frequent administrations of the drug or antibody and/or agent to treat a chronic medical condition. The advantage of a multi-use formulation is that it facilitates ease of use for the patient, reduces waste by allowing complete use of vial contents, and results in a significant cost savings for the manufacturer since several doses are packaged in a single vial (lower filling and shipping costs).

The present disclosure also provides a method for preparing a formulation comprising the steps of: (a) lyophilizing a mixture of an antibody and a lyoprotectant; and (b) reconstituting the lyophilized mixture of step (a) in a diluent such that the reconstituted formulation is isotonic and stable.

An article of manufacture is also provided herein which comprises: (a) a container which holds a lyophilized mixture of an antibody and a lyoprotectant; and (b) instructions for reconstituting the lyophilized mixture with a diluent to a desirable antibody concentration in the reconstituted formulation. The article of manufacture may further comprise a second container which holds a diluent (e.g. bacteriostatic water for injection (BWFI) comprising an aromatic alcohol).

An injection system of the present disclosure may employ a medication delivery pen as described in U.S. Patent 5,308,341. Medication delivery pens have been developed to facilitate the self-administration of medication. A medication of the present disclosure can be a drug that inhibits complement activity, for example an antibody specific to complement C5,

Samsung Bioepis Exhibit No. 1002
Page 11032

and/or an immunosuppressive agent. One medication delivery pen includes a vial holder into which a vial of insulin or other medication may be received. The vial holder is an elongate generally tubular structure with proximal and distal ends. The distal end of the vial holder includes mounting means for engaging a double-ended needle cannula. The proximal end also includes mounting means for engaging a pen body which includes a driver and dose setting apparatus. A disposable medication containing vial for use with the prior art vial holder includes a distal end having a pierceable elastomeric septum that can be pierced by one end of a double-ended needle cannula. The proximal end of this vial includes a stopper slidably disposed in fluid tight engagement with the cylindrical wall of the vial. This medication delivery pen is used by inserting the vial of medication into the vial holder. A pen body then is connected to the proximal end of the vial holder. The pen body includes a dose setting apparatus for designating a dose of medication to be delivery by the pen and a driving apparatus for urging the stopper of the vial distally for a distance corresponding to the selected dose.

The user of the pen mounts a double-ended needle cannula to the distal end of the vial holder such that the proximal point of the needle cannula pierces the septum on the vial. The patient then selects a dose and operates the pen to urge the stopper distally to deliver the selected dose. The dose selecting apparatus returns to zero upon injection of the selected dose. The patient then removes and discards the needle cannula, and keeps the prior art medication delivery pen in a convenient location for the next required medication administration. The medication in the vial will become exhausted after several such administrations of medication. The patient then separates the vial holder from the pen body. The empty vial may then be removed and discarded. A new vial can be inserted into the vial holder, and the vial holder and pen body can be reassembled and used as explained above.

Accordingly, a medication delivery pen generally has a drive mechanism for accurate dosing and ease of use. A dosage mechanism such as a rotatable knob allows the user to accurately adjust the amount of medication that will be injected by the pen from a prepackaged vial of medication. To inject the dose of medication, the user inserts the needle under the skin and depresses the knob once as far as it will depress. The pen may be an entirely mechanical device or it may be combined with electronic circuitry to accurately set and/or indicate the dosage of medication that is injected into the user. See U.S. Patent 6,192,891.

Samsung Bioepis Exhibit No. 1002
Page 11033

The present disclosure also presents controlled-release or extended-release formulations suitable for chronic and/or self-administration of a medication.

The various formulations can be administered to a patient in need of treatment (e.g., a recipient of an allograft) with the medication (e.g., an antibody of the present disclosure and at least one immunosuppressive agent) by intravenous administration as a bolus or by continuous infusion over a period of time, by intramuscular, intraperitoneal, intracerobrospinal, subcutaneous, intra-articular, intrasynovial, intrathecal, oral, topical, or inhalation routes.

In certain embodiments, a formulation is administered to the patient by subcutaneous (i.e. beneath the skin) administration. For such purposes, the formulation may be injected using a syringe. However, other devices for administration of the formulation are available such as injection devices (e.g. the Inject-ease® and Genject® devices); injector pens (such as the GenPen®); needleless devices (e.g. MediJector® and BioJector®); and subcutaneous patch delivery systems.

The present methods and uses are described with reference to the following Examples, which are offered by way of illustration and are not intended to limit the disclosure in any manner. Standard techniques well known in the art or the techniques specifically described below are utilized. The following abbreviations are used herein: ABMR, antibody-mediated rejection; ACHR, accelerated humoral rejection; ACR, acute cellular rejection; AVR, acute vascular rejection; CsA, cyclosporin; CyP, cyclophosphamide; HAR, hyperacute rejection; MCP-1, monocyte chemotactic protein 1; MST, mean survival time; POD, postoperative day.

Example 1

Methods

Animals and Immunosuppressive Drugs Male adult C3H (H-2^k) mice and BALB/c (H-2^d) mice (Jackson Labs, Bar Harbor, Maine) weighing 25-30 g were chosen as donors and recipients, respectively. In the groups receiving immunosuppression, the recipients were injected with CsA (15 mg/kg/day, s.c., daily from day 0 to endpoint rejection or until day 100), or with CyP (40 mg/kg/day, i.v., on day 0 and 1), or with anti-C5 mAb (clone BB5.1, Alexion Pharmaceuticals Inc., 40 mg/kg/day, i.p., day 0–2, followed by twice a week, day 0-60). Animals were housed under conventional conditions at the Animal Care Facility,

Samsung Bioepis Exhibit No. 1002
Page 11034

University of Western Ontario, and were cared for in accordance with the guidelines established by the Canadian Council on Animal Care. Olfert et al., 1993.

Skin Presensitization Full-thickness skin grafts taken from C3H donors were cut into square pieces of 1×1 cm^2 and transplanted onto the back of the BALB/c recipients' thorax one week prior to heart transplantation from the same donors. Rejection was defined as complete necrosis of the skin grafts.

Abdominal and Cervical Cardiac Transplantation Seven days after skin presensitization, C3H mouse hearts were transplanted into the abdomen of presensitized BALB/c recipients by anastomosing the donor aorta and recipient aorta, and the donor pulmonary artery and recipient inferior vena cava. In the groups with re-transplantation, second heart grafts harvested from either naive C3H mice or long-term surviving presensitized BALB/c recipients were transplanted into the cervical area of the recipients carrying a long-term surviving first abdominal heart graft by anastomosing the donor aorta and recipient carotid artery, and the donor pulmonary artery and recipient external jugular vein (end-to-side). The heart grafts were monitored daily until rejection unless otherwise indicated and rejection was defined as complete cessation of pulsation.

Experimental Groups Presensitized recipients were randomly assigned to eight groups, each consisting of eight animals: Group 1, mice with no treatment; Group 2, mice treated with CsA; Group 3, mice treated with CyP; Group 4, mice treated with CsA plus CyP; Group 5, mice treated with anti-C5 mAb; Group 6, mice treated with anti-C5 mAb plus CsA; Group 7, mice treated with anti-C5 mAb plus CyP; Group 8, mice treated with anti-C5 mAb in combination of CsA and CyP. When cardiac impulses were no longer palpable or at POD100, the grafts were removed for routine histology, immunohistochemistry and western blot analysis, serum samples were collected for flow cytometric analysis and complement hemolytic assay. Five additional animals were placed and sacrificed in groups 6 and 8 on POD3 (MST for groups 1-5, 7) to allow for comparisons at a uniform time point. Serum samples were also collected on POD 11, 21, 28 and 60 in Group 8 for detecting the sequential changes of anti-donor antibody levels and complement activity. In addition, when triple therapy treated presensitized recipients carried a first heart graft for 100 days, they were re-transplanted with a second heart. A naive C3H heart or a 100-day surviving C3H heart from another presensitized BALB/c recipient was used as the second heart. Eight animals were included in each re-transplant group.

Samsung Bioepis Exhibit No. 1002
Page 11035

Graft Histology Tissue samples were fixed in 10% buffered formaldehyde. Specimens were then embedded in paraffin, and sectioned for H&E staining. The microscopic sections were examined in a blinded fashion for severity of rejection by a pathologist. Criteria for graft rejection included the presence of vasculitis, thrombosis, hemorrhage and lymphocyte infiltration. These changes were scored as: 0, no change; 1, minimum change; 2, mild change; 3, moderate change; or 4, marked change.

Immunohistochemistry Four micrometer sections were cut from tissue samples embedded in Tissue-Tek O.C.T gel (Optimum Cutting Temperature, Skura Finetek, Torrance, CA) mounted on gelatin-coated glass microscope slides and stained by a standard indirect avidin-biotin immunoperoxidase staining method using an Elite Vectastain ABC kit (Vector Laboratories Inc., Burlingame, CA). Specimens were stained for $CD4^+$ and $CD8^+$ cells with biotin-conjugated rat anti-mouse CD4 mAb (clone YTS 191.1.2, Cedarlane Laboratories Ltd., Hornby, Ontario, Canada) and biotin-conjugated rat anti-mouse CD8 mAb (clone 53-6.7, Pharmingen, Franklin Lakes, NJ), respectively. Intragraft monocyte/macrophage infiltration was detected by staining with biotin-conjugated rat anti-mouse Mac-1 mAb (Cedarlane Laboratories Ltd., Hornby, Ontario, Canada). Mouse IgG and IgM deposition in grafts was detected using biotin-conjugated goat anti-mouse-IgG and goat anti-mouse-IgM (Cedarlane). For identification of complement deposition, sections were serially incubated with goat anti-C3 or anti-C5 polyclonal Abs (Quidel, San Diego, CA), biotinylated rabbit anti-goat IgG (Vector Laboratories), and HRP-conjugated-streptavidin (Zymed Laboratories, South San Francisco, CA). Slides were washed with phosphate-buffered saline between steps, and examined under light microscopy. Negative controls were performed by omitting the primary antibodies. The immunostaining was scored in five high-power fields of each section, and five independent experiments were performed. The sections of immunoperoxidase staining were graded from 0 to 4+ according to the staining intensity: 0, negative; 1+, equivocal; 2+, weak staining; 3+, moderate staining; and 4+, very intensive staining.

Flow Cytometry The circulating anti-donor specific IgG and IgM antibodies were evaluated in the recipient serum by FACScan flow cytometry (Becton Dickinson, Mountain View, CA). Glotz et al., (1993); Tyan et al. (1994). Briefly, C3H mouse splenocytes were isolated and incubated at 37 °C for 30 minutes with serum from naive control and experimental groups. To stain for total IgG, IgG1, IgG2a, IgG2b and IgM, the cells were washed and incubated with FITC-conjugated goat antibody specific for the Fc portion of mouse IgG or with

Samsung Bioepis Exhibit No. 1002
Page 11036

phycoerythrin-conjugated goat antibody specific for the μ-chain of mouse IgM (Jackson ImmunoResearch Laboratories, West Grove, PA), or with FITC-conjugated goat anti-mouse IgG1 (CALTAG Laboratories, Burlingame, CA), or with FITC-conjugated goat anti-mouse IgG2a (CALTAG), or with FITC-conjugated goat anti-mouse IgG2b (CALTAG). After 1 hour of staining at 4 °C, the cells were washed with PBS, resuspended at 5×10^6/mL, and analyzed by flow cytometry for mean channel fluorescence intensity, which represents the antibody-binding reactivity.

Complement Hemolytic Assay The purified anti-C5 mAb was serially diluted twofold (175-0.1 μg/ml) in GVB^{2+} buffer (gelatin Veronal-buffered saline: 0.1% gelatin, 141 mM NaCl, 0.5 mM $MgCl_2$, 0.15 mM $CaCl_2$, and 1.8 mM sodium barbital) and added in triplicate (50 μl/well) to a 96-well plate. BALB/c mouse serum was diluted to 40% v/v with GVB^{2+} buffer and added (50 μl/ml) to the rows of the same 96-well plate such that the final concentration of BALB/c mouse serum in each well was 20%. The plate was then incubated at room temperature for approximately 30 min while chicken erythrocytes were prepared. Chicken erythrocytes were washed 5×1 ml with GVB^{2+} buffer and resuspended to a final concentration of 5×10^7/ml in GVB^{2+}. Four milliliters of the chicken erythrocytes were sensitized by adding anti-chicken RBC polyclonal antibody (Intercell Technologies, Hopewell, NJ, 0.1% v/v) and the cells were incubated at 4 °C for 15 min with frequent vortexing. The cells were then washed 2×1 ml with GVB^{2+} and resuspended to a final volume of 2.4 ml in GVB^{2+}. The chicken erythrocytes (30 μl/well, 2.5×10^6 cells) were added to the plate containing serum and anti-C5 mAb as described above, mixed well, and incubated at 37 °C for 30 min. The plate was then centrifuged at 1000×g for 2 min, and 85 μl of the supernatant was transferred to a new 96-well microtiter plate. The plate was read at OD 415 nm using a microplate reader and the percentage of hemolysis was determined using this formula:

$$\%\ \text{hemolysis} = 100 \times \frac{(\text{OD sample}) - (\text{OD } GVB^{2+} \text{ control})}{(\text{OD 100\% lysed control}) - (\text{OD } GVB^{2+} \text{ control})}$$

with 100% lysed control obtained by the addition of 100 μl GVB^{2+} containing 0.1% NP-40 to the 30 μg/ml of chicken erythrocytes as prepared above.

Samsung Bioepis Exhibit No. 1002
Page 11037

Western Blot Analysis Sonication of frozen heart samples was performed in RIPA lysis buffer (Santa Cruz Biotechnology, Inc.) at 4 °C for 1 minute at 10-second intervals, followed by microcentrifugation at 13,000 rpm for 10 minutes at 4 °C. Clarified supernatants were immediately quantitated in triplicate for protein content using Detergent-compatible protein assay kit (BIO-RAD). Heart lysates (10μg protein/well) were separated on NuPAGE, 4-12% gradient Bis-Tris gels and MES buffer system (Invitrogen) and transferred to polyvinylidene difluoride (PVDF) membrane (0.45 μm pore size; Invitrogen) using a semi-dry transfer apparatus (BIO-RAD). Membranes were cut appropriately at the correct molecular weights to allow the development of the blots with two different primary antibodies per blot such that each blot was exposed to a test antibody and an internal control antibody to insure equal sample loading. The test primary antibodies including anti-Bcl-2 (N-19) rabbit polyclonal sera (Santa Cruz Biotechnology, Inc.) and anti-Bcl-XS/L (M-125) rabbit polyclonal sera (Santa Cruz Biotechnology, Inc.) were used to detect intragraft expression of Bcl-2 and Bcl-xl proteins. Anti-calsequestrin rabbit polyclonal sera (Calbiochem) were used as internal control primary antibody (Kobayashi et al., 1999). Detection of primary antibody binding was performed as previously described (Arp et al., 1996) by exposing washed incubated blots to a polyclonal goat anti-rabbit IgG fraction conjugated to horseradish peroxidase (HRP; Roche Laboratories) and then appropriately developed by exposure to enhance chemiluminescence for HRP-conjugated antibodies (Roche Laboratories).

Statistical Analysis The data were reported as the mean ± SD. Allograft survival among experimental groups was compared using the rank-log test. Histological and immunohistological findings were analyzed using the Mann-Whitney U test. Flow cytometric data and western blot data were analyzed using one-way ANOVA. Differences with p values less than 0.05 were considered significant.

Example 2

Presensitization with C3H donor skin graft induces antibody-mediated ACHR in heart allografts of BALB/c recipients.

To develop a suitable small animal model that mimics presensitized patients in the clinic and to study ABMR, a novel, fully MHC-mismatched mouse ABMR model has been developed through presensitization of mouse recipients. In this model, BALB/c recipients were presensitized with C3H donor skin grafts one week prior to heart transplantation from the same donor. Seven days after donor skin presensitization, serum level of anti-donor IgG,

Samsung Bioepis Exhibit No. 1002
Page 11038

but not IgM antibody was markedly elevated and reached to a peak level in the presensitized BALB/c recipients (Figure 1A). Heart transplantation from same donor was then performed in these highly sensitized recipients. Without immunosuppression, C3H heart grafts were rapidly rejected in 3.1 ± 0.4 days by ACHR, characterized by severe thrombosis, hemorrhage and infarction (Figure 1B-a). In contrast, same heart grafts in unsensitized BALB/c recipients (with mean survival time, MST of 8.2 ± 0.8 days) show the normal histology on post-operative day (POD) 3 (Figure 1B-b). When compared to unsensitized BALB/c recipients at the same day, heart grafts in presensitized animals revealed massive IgG antibody and complement (C3 and C5) deposition, but minimal $CD4^+$ and $CD8^+$ cell infiltration (Table 1). Furthermore, circulating anti-donor IgG levels in presensitized recipients were significantly higher than those of unsensitized same recipients receiving a heart graft on POD3 ($P< 0.01$, Figure 1C). However, anti-donor IgM remained at very low levels both in circulation (Figure 1C) and in heart grafts (Table 1) and it showed no significant difference between unsensitized and presensitized recipients. In addition, normal levels of complement hemolytic activity were shown in both presensitized and unsensitized heart recipients without treatment (Figure 1D). These data indicate that this is an ideal transplant model to study ABMR in presensitized recipients in which complement plays an important role in the pathogenesis.

Table 1.

Comparison of immunohistological changes of C3H heart allografts in unsensitized and presensitized BALB/c recipients on POD3

Groups	Unsensitized	Presensitized
IgG	1+	4+
IgM	1+	1+
C3	2+	3+
C5	2+	3+
CD4	0	1+
CD8	0	1+

Samsung Bioepis Exhibit No. 1002
Page 11039

Grades for immunoperoxidase staining: 0, negative; 1+, equivocal; 2+, weak; 3+, moderate; 4+, intense.

Anti-C5 mAb in combination with CsA and CyP prevents ABMR and achieves indefinite heart allograft survival in presensitized mouse recipients.

Complement has been shown to play an important role in ABMR. However, the inhibitory effect of functionally blocking terminal complement cascade at the C5 level in highly sensitized recipients is unknown. In the study presented herein, the presensitized model was used to study the efficacy of anti-C5 mAb either alone or combined with CsA and /or CyP in prevention of ABMR. As presented in Figure 2A, treatment with either CsA or CyP or the two drugs in combination did not prevent ABMR and grafts were rejected in 3.0 ± 0.0 days, 3.3 ± 0.5 days and 3.5 ± 0.6 days, respectively with typical pathological features of ACHR including intravascular thrombosis and interstitial hemorrhage (Figure 2B-b, c, d), which were indistinguishable from heart grafts in untreated presensitized BALB/c recipients (Figure 2B-a). Anti-C5 monotherapy or combined with CyP was not able to improve graft survival and heart grafts were rejected by ACHR (Figure 2B-e, f) in 3.5 ± 0.6 days and 3.2 ± 0.4 days, respectively (Figure 2A). Although the combination therapy of anti-C5 mAb and CsA, the protocol capable of inducing long-term heart allograft survival in unsensitized animals, marginally prolonged graft survival in this presensitized model, heart grafts were also rejected by severe humoral rejection with vasculitis, thrombosis, hemorrhage and minimal cell infiltration (Figure 2B-g) in 11.9 ± 1.8 days (Figure 2A). In contrast, triple therapy of anti-C5 mAb in combination of CsA and CyP achieved indefinite heart graft survival over 100 days (Figure 2A) in presensitized animals ($P<0.01$ vs. the animals without treatment or treated with either monotherapy or two drugs in combination) with no evidence of rejection (Figure 2B-h). In this presensitized mouse model, as shown in Table 2, only minor intragraft $CD4^+$ and $CD8^+$ cell infiltration was observed in the recipients that rejected their heart grafts within 3 days. However, the number of these T cells was slightly increased if heart grafts survived longer in anti-C5 mAb plus CsA-treated recipients at the time of rejection (POD11) and in triple therapy-treated recipients at early stages of graft survival (e.g. POD11). Furthermore, with continuous treatment of CsA in the triple therapy group, $CD4^+$ and $CD8^+$ cell infiltration was inhibited in long-term surviving heart grafts on POD60 and 100. In addition, moderate intragraft Mac-1^+ cell infiltration, including monocytes and macrophages, was found in untreated and CsA-, CyP- or CsA plus CyP-treated animals,

Samsung Bioepis Exhibit No. 1002
Page 11040

while the infiltration of these cells was significantly reduced in anti-C5 mAb treated animals (Table 2). These results indicate that functionally blocking anti-C5 mAb enables the use and efficacy of conventional immunosuppressive agents, thereby preventing ABMR and achieving indefinite heart graft survival in presensitized recipients.

Table 2.

Grades for immunoperoxidase staining of heart allografts

in presensitized mouse recipients at necropsy

Groups	Date for sample collection (POD)	C3	C5	**CD4**	CD8	Mac-1	IgG	IgM
Untreated	3	3+	3+	1+	1+	3+	4+	1+
CsA	3	3+	3+	1+	1+	3+	4+	1+
CyP	3	3+	3+	1+	1+	3+	3+	1+
CsA+CyP	3	3+	3+	1+	1+	3+	3+	1+
Anti-C5mAb	3	3+	0	1+	1+	2+	4+	1+
Anti-C5mAb+CsA	11	3+	0	2+	2+	2+	4+	1+
Anti-C5mAb+CyP	3	3+	0	1+	1+	2+	3+	1+
Anti-C5mAb+CsA+CyP	3	3+	0	1+	1+	2+	3+	1+
Anti-C5mAb+CsA+CyP	11	3+	0	2+	2+	1+	3+	1+
Anti-C5mAb+CsA+CyP	60	3+	0	1+	1+	0	2+	1+
Anti-C5mAb+CsA+CyP	100	3+	2+	0	0	0	2+	1+

Grades: 0, negative; 1+, equivocal; 2+, weak; 3+, moderate; 4+, intense.

Anti-C5 mAb completely inhibits total complement hemolytic activity and local C5 deposition in presensitized recipients receiving a heart allograft.

Anti-C5 mAb was previously shown to block the cleavage of complement protein C5 into the proinflammatory molecules C5a and C5b-9 (Kroshus et al., 1995), and to completely and consistently block terminal complement activity in mice (Wang et al., 1999). In the current study, terminal complement activity was measured by assessing the ability of

Samsung Bioepis Exhibit No. 1002
Page 11041

recipient mouse sera to lyse antibody presensitized chicken erythrocytes and was compared at the same time-point (POD3). Treatment of mice with either CsA or CyP or the two drugs in combination had no effect on terminal complement activity, while treatment with anti-C5 mAb either alone or combined with CsA or/and CyP completely inhibited this activity (Figure 3; $P<0.01$, vs. naive and untreated animals, as well as CsA-, CyP-, or CsA plus CyP-treated animals). In addition, sera obtained from anti-C5 mAb treated animals at several earlier time points showed similarly diminished hemolytic activity, suggesting that serum terminal complement was inhibited throughout the treatment period. Furthermore, local C5 deposition in heart grafts was completely prevented in the anti-C5 mAb treated presensitized recipients, but not in untreated, or CsA-, CyP- and CsA plus CyP-treated presensitized animals (Table 2). As predicted, treatment with anti-C5 mAb did not prevent C3 deposition in the grafts (Table 2). These results suggest anti-C5 therapy completely blocks total complement activity after cardiac allografting in highly sensitized recipients.

Long-term surviving heart grafts in presensitized animals are resistant to humoral injury in the presence of low level of anti-donor antibodies and complement- a situation of accommodation.

To further investigate the role of anti-C5 mAb in humoral rejection, anti-donor alloantibody levels were measured in recipient sera by flow cytometry and intragraft antibody deposition by using immunostaining techniques in different groups. Figure 4A shows that on POD3 untreated presensitized BALB/c recipients had high levels of circulating anti-donor IgG antibodies. When presensitized recipients receiving either monotherapy or two drugs in combination, CsA and/or CyP partially down-regulated circulating anti-donor IgG levels, while treatment with anti-C5 mAb either alone or combined with CsA or CyP did not further affect anti-donor antibody levels at the same day. In contrast, with triple therapy of anti-C5 mAb, CsA and CyP, a high level of circulating anti-donor IgG was gradually downregulated and reached a low level on POD60, thereafter remaining at this level until day 100 (Figure 4B). Similar to levels of circulating antibodies in the different treatment groups, Table 2 shows that strong deposition of anti-mouse IgG was present in the rapidly rejected heart grafts of presensitized animals with no treatment or treated with monotherapy or two drugs in combination therapy. Interestingly, with triple therapy, IgG antibody deposition was gradually attenuated to a mild level in the long-term surviving heart grafts on POD 100 (Figure 4C-a, Table 2). In this model, IgM remained at very low levels in either circulation (Figure 4A, B) or transplanted heart grafts (Figure 4C-b, Table 2) in presensitized recipients

Samsung Bioepis Exhibit No. 1002
Page 11042

with or without treatment. In addition, treatment with anti-C5 mAb eliminated complement activity to an undetectable level until day 60, followed by a progressive recovery to predepletion levels on POD 100 after discontinuation of anti-C5 therapy in presensitized mouse recipients receiving triple therapy (Figure 4D). Furthermore, intragraft C5 deposition was also detected in 100-day surviving presensitized animals (Table 2). These data demonstrate that ongoing transplant accommodation occurs in triple therapy treated presensitized recipients despite the presence of anti-graft antibodies and complement activation.

Anti-C5 mAb in combination with CsA and CyP reduces the IgG1/IgG2a ratio and leads to a shift in IgG subclass to IgG2b in recipients with accommodated grafts.

To determine whether anti-C5 mAb-based triple therapy would induce a shift in IgG subclass, which may be associated with accommodation, serum levels of anti-donor IgG subclasses of IgG1, IgG2a and IgG2b were compared between untreated recipients and the recipients with accommodated heart graft. Sera from untreated recipients contained predominant IgG1 isotype, indicated by a high ratio of IgG1/IgG2a (Figure 5A). In contrast, a significant reduction in the ratio of IgG1/IgG2a was observed in the recipients carrying accommodated grafts (Figure 5A, $P<0.01$). Furthermore, presensitized recipients with the accommodated heart grafts displayed an increased level of anti-donor IgG2b as compared to the same recipients with rejected grafts (Figure 5B, $P<0.01$). In addition, the pattern of IgG isotypes in the recipients treated with either monotherapy or two drugs in combination is indistinguishable from that of untreated animals. These data indicate that anti-donor IgG1 isotype may be associated with graft rejection, while production of anti-donor IgG2b subclass may function as a protective antibody and plays an important role in the induction of accommodation.

Anti-C5 mAb in combination with CsA and CyP induces intragraft Bcl-2 and Bcl-xl expression in highly sensitized mouse recipients.

To determine whether a causal relationship exists between intragraft expression of protective proteins and graft resistance to humoral injury in this model, western blot analysis was employed to detect proteins of interest in heart graft tissues from highly sensitized mouse recipients. Long-term surviving heart grafts were found to express high levels of Bcl-2 and Bcl-xl proteins on POD100, and these proteins were detected as early as 12 days after heart transplantation in highly sensitized recipients receiving anti-C5 mAb-based triple therapy

Samsung Bioepis Exhibit No. 1002
Page 11043

(Figure 6). In contrast, there were no Bcl-2 and Bcl-xl proteins expressed on heart grafts of untreated animals (Figure 6) or animals treated with either monotherapy or two drugs in combination therapy. This result suggests that graft resistance to humoral injury in indefinite surviving animals is associated with the protection provided by Bcl-2 and Bcl-xl proteins in this presensitized model.

Presensitized recipients with an accommodating first heart graft accept a second accommodated heart graft but reject a second naive heart graft from the same donors.

The ability of accommodated grafts to resist rejection has not been tested directly under pathophysiological conditions where naive grafts undergo rejection following allotransplantation. In this model, to determine whether presensitized recipients with an accommodating first heart graft will accept a second accommodated graft but reject a second naive graft, we performed re-transplantation scenarios. After the accommodated C3H heart grafts have survived to the 100-day point, the time at which low levels of alloantibodies were detected (Figure 4B) and complement activity has returned to pretreatment levels (Figure 4D), in presensitized BALB/c recipient treated with anti-C5 mAb-based triple therapy, these recipients received a second heart graft. Specifically, either a naive (Figure 7A) or a 100-day accommodated C3H heart (Figure 7B) from another presensitized BALB/c recipient was transplanted into the neck of the presensitized recipients carrying an accommodating first C3H heart. These recipients rejected a second naive heart at 6.6 ± 1.1 days (Figure 8A) with severe AVR (Figure 8B-a) while the first heart continued to survive. In contrast, when the accommodated hearts that had been already surviving for 100 days in different presensitized mice were used as second grafts, these grafts were accepted by the presensitized recipients carrying an accommodating first heart graft (Figure 8A). There was no sign of rejection in those accommodated second heart grafts 90 days after second transplantation (Figure 8B-b). These data indicate that accommodated grafts become resistant to the effects of anti-donor antibodies and complement that normally mediate allograft rejection in these presensitized recipients. Furthermore, the fact that the host of the accommodated graft rejected a new graft suggests that accommodation involves changes to the graft.

Presensitized recipients being treated with CsA reject accommodated heart grafts.

Another re-transplantation was performed to determine whether accommodation in this presensitized model would be caused by the changes in the grafts and/or the recipients. Specifically, after C3H heart grafts have been accommodated in presensitized BALB/c mice

Samsung Bioepis Exhibit No. 1002
Page 11044

for 100 days, the accommodated heart graft will then be re-transplanted into a second presensitized BALB/c recipient being treated with CsA alone (Figure 7C), a therapy that can prevent cellular rejection but cannot prevent accelerated humoral rejection of a fresh C3H heart in presensitized recipients. The accommodated C3H heart grafts were rapidly rejected in CsA treated presensitized BALB/c recipients. After re-transplantation, the pathology in accommodated heart grafts was changed from normal (Figure 9A) to severe ACHR with massive interstitial hemorrhage but few cell infiltrates (Figure 9B). In addition, high levels of anti-donor IgG and normal levels of complement hemolytic activity in these recipients receiving an accommodated C3H heart were similar to those of CsA treated presensitized recipients receiving a naive C3H heart. This result further indicates that accommodation induced by anti-C5 mAb-based triple therapy can originate from mechanisms involving changes not only to the graft, but also to the recipient.

Example 3

Acute Vascular Rejection in a Heart Transplantation Model

Experiments were performed to determine whether inclusion of an inhibitor of formation of terminal complement would attenuate acute vascular rejection and whether the use of such an inhibitor in conjunction with an immunosuppressant would achieve long-term allograft survival. In this set of experiments an anti-C5 monoclonal antibody was used in conjunction with cyclosporin. The model used was an allograft heterotopic heart transplant from C3H mice into BALB/c mice. This model is a stringent acute vascular rejection model with the C3H and BALB/c mice being strongly MHC mismatched. The transplantations and other methods were performed as described in Wang et al. (2003).

Heterotopic Cardiac Transplantation

Intra-abdominal heterotopic cardiac transplantation was performed as previously described by Wang et al. (2003). Briefly, a median sternotomy was performed on the donor, and the heart graft was slowly perfused in situ with 1.0 ml of cold heparinized Ringer's lactate solution through the inferior vena cava and aorta before the superior vena cava and pulmonary veins were ligated and divided. The ascending aorta and pulmonary artery were transected, and the graft was removed from the donor. The graft was then revascularized with end-to-side anastomoses between the donor's pulmonary artery and the recipient's inferior vena cava as well as the donor's aorta and the recipient's abdominal aorta using 11-0 nylon suture. The beating of the grafted heart was monitored daily by direct abdominal palpation.

Samsung Bioepis Exhibit No. 1002
Page 11045

The degree of pulsation was scored as: A, beating strongly; B, noticeable decline in the intensity of pulsation; or C, complete cessation of cardiac impulses. When cardiac impulses were no longer palpable, the graft was removed for routine histology. In certain instances, mice in which the graft was still functioning were sacrificed to perform histology.

Results

Mice (male 8-12 week old mice weighing 25 – 30 g) were split into six experimental groups with six to eight mice per group. Transplant occurred on day 0. Histological changes were checked at the endpoint (the endpoint being graft failure) or in some cases a mouse was sacrificed prior to graft failure. The dosage of BB5.1 which was administered (40 mg/kg body weight three times per week) was known from prior studies to completely inhibit terminal complement activity.

Group 1' (control) - mice were administered 0.75 mL of saline intraperitoneally on days -1, 0, 1 and 2. Subsequently these mice were treated with 0.75 mL of saline intraperitoneally three times per week (Monday, Wednesday, Friday) until the endpoint.

Group 2' (cyclosporin A alone) - mice were administered 15 mg/kg body weight of cyclosporin A subcutaneously on a daily basis beginning at day 0 (day of transplant) until the endpoint.

Group 3' (anti-complement antibody alone) - mice were administered the anti-mouse C5 antibody BB5.1 (Frei et al., 1987) at 40 mg/kg body weight intraperitoneally on days -1, 0, 1 and 2 followed by 40 mg/kg body weight administered three times per week (Monday, Wednesday, Friday) until the endpoint.

Group 4' (anti-complement antibody until day 14 post-transplant plus cyclosporin A) - mice were administered the anti-mouse C5 antibody BB5.1 at 40 mg/kg body weight intravenously on days -1 through day 14 and were also administered cyclosporin A at 15 mg/kg of body weight on a daily basis beginning at day 0 until the endpoint. Note that this differs from the other groups in that the BB5.1 was administered intravenously and on a daily basis.

Group 5' (anti-complement antibody until day 28 post-transplant plus cyclosporin A) - mice were administered the anti-mouse C5 antibody BB5.1 at 40 mg/kg body weight intraperitoneally on days -1, 0, 1 and 2 followed by 40 mg/kg body weight administered three times per week (Monday, Wednesday, Friday) until day 28 and were also administered

Samsung Bioepis Exhibit No. 1002
Page 11046

cyclosporin A at 15 mg/kg of body weight on a daily basis beginning at day 0 until the endpoint.

Group 6' (anti-complement antibody chronically until 100 days plus cyclosporin) - mice were administered the anti-mouse C5 antibody BB5.1 at 40 mg/kg body weight intraperitoneally on days -1, 0, 1 and 2 followed by 40 mg/kg body weight administered three times per week (Monday, Wednesday, Friday) until 100 days and were also administered cyclosporin A at 15 mg/kg of body weight on a daily basis beginning at day 0 until 100 days.

The results of this experiment are shown in Tables 3 and 4. Table 3 shows the survival time for the grafts. Table 4 sets forth the histological scores.

Table 3

Allograft Survival

Group (Treatment)	Individual Survival (days)	Mean Survival Time (days)
1'. Saline	8, 8, 8, 8, 8, 9	8.3 ± 0.5
2'. Cyclosporin A	14, 15, 15, 16, 16, 16, 17	15.5 ± 1.1
3'. BB5.1	7, 8, 8, 8, 8, 9	8.0 ± 0.6
4'. BB5.1 until day 14 + cyclosporin A	35, 38, 43, 45, 46, 47	42.3 ± 4.8
5'. BB5.1 until day 28 + cyclosporin A	77, 80, 80, 81, 82	80 ±1.9
6'. BB5.1 until day 100 + cyclosporin A	>100 days (7 mice; one sacrificed for histology)	> 100 days

Samsung Bioepis Exhibit No. 1002
Page 11047

Table 4

Median Scores of Histological Changes of Heart Allografts at Necropsy

Groups	Vasc*	Infarc	Lymph	Throm	Hemo	Fibrin	PMN
1'. Saline (endpoint)	3.0	3.0	1.0	4.0	3.0	3.0	3.0
2'. Cyclosporin A (endpoint)	2.0	1.0	2.0	3.0	2.0	2.0	3.0
3'. BB5.1 (endpoint)	2.0	1.0	2.0	2.0	1.0	0.0	0.0
4'. BB5.1 until day 14 + cyclosporin A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
5'. BB5.1 28 days + Cyclosporin A (post-operative day 8)	0.0	0.0	0.0	0.0	0.0	0.0	0.0
5'. BB5.1 28 days + Cyclosporin A (endpoint)	0.0	0.0	1.0	1.0	2.0	1.0	0.0
6'. BB5.1 until day 100 + Cyclosporin A (post-operative day 100)	0.0	0.0	0.0	0.0	0.0	0.0	0.0

Median scores: 0 - normal; 1- minimum change; 2 - mild change; 3 - moderate change; 4 - marked change. N/A - not available.

*Vasc - vasculitis; Infar - infarction; Lymph - lymphocyte infiltration; Throm - thrombosis; Hemo - hemorrhage; Fibrin - fibrin deposition; PMN - polymorphonuclear cell infiltrate

The results indicate the synergistic effects of using a complement inhibiting drug in addition to an immunosuppressant. In untreated mice the grafts were rejected in about 8 days. Use of the immunosuppressant cyclosporin A alone on a daily, chronic basis resulted

Samsung Bioepis Exhibit No. 1002
Page 11048

in an increase in graft survival until approximately 15 days post-transplant. The use of the anti-C5 antibody BB5.1 to inhibit formation of terminal complement had no effect on its own, graft rejection occurring at 8 days post-transplant as in the control group (Group 1'). The combination of BB5.1 through day 28 post-transplant plus cyclosporin A showed a synergistic effect with graft survival being extended until approximately day 80. A more surprising result is that of Group 5' in which BB5.1 and cyclosporin A were each administered chronically post-transplant. In this case the graft survival was for more than 100 days (as much data as presently available). Additionally, the histological results shown in Table 4 indicate that the administration of both BB5.1 and cyclosporin A protected the graft from changes much better than either BB5.1 or cyclosporin A alone, and that the chronic administration of BB5.1 and cyclosporin A protected the graft to such an extent that even at 100 days post-transplant there were no histological changes seen in the engrafted hearts. A survival time of 100 days in these models is considered to be the gold standard. A survival of 100 days in the model is believed to indicate that there will be an indefinite survival of the allograft. When BB5.1 administration was stopped after 28 days, the grafts were protected but they did begin to show some minimal to mild histological changes by about day 80 which was the time at which graft failure occurred.

The Group 4' mice were treated differently in that they were administered BB5.1 on a daily basis by an intravenous administration. These animals became ill, showing weight loss and urine retention and were sacrificed at a time at which the grafted hearts were still beating although their function had declined. This was the first group of mice studied and it is unknown why these ill effects were seen. These ill effects were not seen when the BB5.1 was administered intraperitoneally with a schedule of three times per week. As seen below in Example 4, daily administration of BB5.1 via an intraperitoneal route did not cause ill effects. Also, intravenous administration was not necessarily the cause of the illness in these animals. Intravenous administration of eculizumab (a human equivalent antibody to BB5.1 in that it binds to human C5) has been successfully administered intravenously without ill effects to humans in a study of PNH (Hillmen et al., 2004). Complement inhibitors may be administered by other routes in addition to intravenous and intraperitoneal, with all such routes being well known by those skilled in the art.

Example 4

Samsung Bioepis Exhibit No. 1002
Page 11049

Accelerated Rejection in a Presensitized Heart Transplantation Model

A second set of experiments similar to those of Example 3 was performed but the recipient mouse was presensitized to the donor organ. In these experiments, the presensitization was brought about by prior transplantation of a skin graft. In general, presensitization can occur not only as a result of having received an earlier allograft, but can also be caused by having received multiple blood transfusions or in women who have been pregnant. Besides such presensitization methods, allografts with an ABO mismatch will be rapidly attacked and rejected because of preformed antibodies to the ABO antigens unless steps are taken to prevent such an attack.

Some mice in these studies were administered cyclophosphamide in addition to BB5.1 and/or cyclosporin A. For these experiments BALB/c recipient mice were presensitized with C3H skin grafts one week prior to heart transplantation from the same donor (using the method of Pruitt and Bollinger, 1991). This model is designed to mimic presensitized transplantation in humans, especially in relation to accelerated humoral rejection. Recipient mice were split into eight groups of six to eight mice each. The treatments were as follow.

Group 1" (control) - mice (male 8-12 week old mice weighing 25 – 30 g) were administered 0.75 mL saline intraperitoneally on a daily basis beginning at day -1 and continuing until the endpoint (graft rejection).

Group 2" (cyclosporin A alone) - mice were administered cyclosporin A subcutaneously at a dose of 15 mg/kg body weight beginning on day 0 (day of transplant) until the endpoint.

Group 3" (BB5.1 alone) - mice were administered the anti-mouse complement monoclonal antibody BB5.1 at a dose of 40 mg/kg body weight delivered intraperitoneally on a daily basis beginning at day -1 and continuing until the endpoint.

Group 4" (cyclophosphamide alone) - mice were administered cyclophosphamide intravenously at a dose of 40 mg/kg body weight on each of days 0 and 1.

Group 5" (BB5.1 plus cyclosporin A) - mice were administered BB5.1 intraperitoneally at a dose of 40 mg/kg body weight on a daily basis beginning at day -1 and continuing until the endpoint. These mice were additionally administered cyclosporin A subcutaneously at a dose of 15 mg/kg body weight on a daily basis from day 0 until the endpoint.

Samsung Bioepis Exhibit No. 1002
Page 11050

Group 6" (BB5.1 plus cyclophosphamide) - mice were administered BB5.1 intraperitoneally at a dose of 40 mg/kg body weight on a daily basis beginning at day -1 and continuing until the endpoint. These mice were additionally administered cyclophosphamide intravenously at a dose of 40 mg/kg body weight on each of days 0 and 1.

Group 7" (cyclosporin A plus cyclophosphamide) - mice were administered cyclosporin A subcutaneously at a dose of 15 mg/kg body weight on a daily basis from day 0 until the endpoint. These mice were additionally administered cyclophosphamide intravenously at a dose of 40 mg/kg body weight on each of days 0 and 1.

Group 8" (BB5.1 plus cyclosporin A plus cyclophosphamide) - mice were administered BB5.1 intraperitoneally at a dose of 40 mg/kg body weight on a daily basis beginning at day -1 and continuing until 100 days. These mice were also administered cyclosporin A subcutaneously at a dose of 15 mg/kg body weight on a daily basis from day 0 until 100 days. These mice were additionally administered cyclophosphamide intravenously at a dose of 40 mg/kg body weight on each of days 0 and 1. Two mice in this group were sacrificed at day 60 for histological studies (no rejection had yet occurred) and the four remaining mice still had not rejected their grafts by day 100.

Additionally a control group of mice which was not presensitized and received only the saline treatment as for Group 1" was tested.

The results of these experiments are shown in Tables 5 and 6. Table 5 lists survival times for the grafts and Table 6 summarizes the histological results.

Samsung Bioepis Exhibit No. 1002
Page 11051

Table 5

Allograft Survival

Groups (Treatment)	Individual survival (days)	Mean survival time (days)
No presensitization	8, 8, 8, 8, 8, 9	8.3 ± 0.5*
1". One skin presensitization	3, 3, 3, 3, 3, 3, 3, 4	3.1 ± 0.4
2". Cyclosporin A	3, 3, 3, 3	3.0 ± 0.0
3". BB5.1	3, 3, 4, 4	3.5 ± 0.6
4". Cyclophosphamide	3, 3, 3, 4	3.3 ± 0.5
5". BB5.1 + Cyclosporin A	10, 10, 11, 11, 12, 12, 14, 15	11.9 ± 1.8**
6". BB5.1 + Cyclophosphamide	3, 3, 3, 3, 3, 4	3.2 ± 0.4
7". Cyclosporin A + Cyclophosphamide	3, 3, 3, 4, 4, 4	3.5 ± 0.6
8". BB5.1 + Cyclosporin A + Cyclophosphamide	> 100 days (4 mice)	> 100***

*P < 0.01 group 1" vs. no presensitization

**P < 0.01 group 5" vs. groups 1"-4" and 6"-7".

***P<0.01 group 8" vs. groups 1"-7".

Samsung Bioepis Exhibit No. 1002
Page 11052

Table 6

Median Scores of Histological Changes of Heart Allografts at Necropsy

Groups	Vasc*	Infar	Lymph	Throm	Hemo	Fibrin	PMN
No presensitization (endpoint)	3.0	3.0	1.0	4.0	3.0	3.0	3.0
1". One skin presensitization (endpoint)	0.0	4.0	1.0	4.0	3.0	0.0	0.0
2". Cyclosporin A (endpoint)	0.0	4.0	0.0	3.0	3.0	N/A	N/A
3". BB5.1 (endpoint)	2.0	2.0	2.0	2.0	3.0	N/A	N/A
4". Cyclophosphamide (endpoint)	2.0	4.0	0.0	3.0	2.0	N/A	N/A
5". BB5.1 + Cyclosporin A (post-operative day 3)	0.0	1.0	1.0	0.0	0.0	0.0	0.0
5". BB5.1 + Cyclosporin A (endpoint)	2.0	2.0	2.0	2.0	2.0	0.0	0.0
6". BB5.1 + Cyclophosphamide (endpoint)	1.0	3.0	0.0	3.0	2.0	N/A	N/A
7". Cyclosporin A + Cyclophosphamide (endpoint)	0.0	1.0	1.0	2.0	3.0	N/A	N/A
8". BB5.1 + Cyclosporin A + Cyclophosphamide (post-operative day 3)	0.0	0.0	1.0	0.0	0.0	N/A	N/A
8. BB5.1 + Cyclosporin A + Cyclophosphamide (post-operative day 12)	0.0	0.0	1.0	0.0	0.0	N/A	N/A
8". BB5.1 + Cyclosporin A + Cyclophosphamide (post-	0.0	0.0	1.0	0.0	0.0	N/A	N/A

Samsung Bioepis Exhibit No. 1002
Page 11053

operative day 60)							
8". BB5.1 + Cyclosporin A + Cyclophosphamide (post-operative day 100)	N/A	N/A	N/A	N/A	N/A	N/A	N/A

Median scores: 0 - normal; 1- minimum change; 2 - mild change; 3 - moderate change; 4 - marked change. N/A - not available.

*Vasc - vasculitis; Infar - infarction; Lymph - lymphocyte infiltration; Throm - thrombosis; Hemo - hemorrhage; Fibrin - fibrin deposition; PMN - polymorphonuclear cell infiltrate

The results shown in Table 5 indicate a difference between the presensitized mouse model and the nonpresensitized mouse model as used in Example 3. The results indicate that in the absence of presensitization, grafts are rejected in approximately 8 days in the absence of treatment with any drugs. Presensitizing the animals causes a more rapid rejection, the rejection of the graft in the presensitized animals being in approximately 3 days in the absence of any drug treatment. Treatment with either BB5.1, cyclosporin A or cyclophosphamide had no effect upon graft survival, with the grafts being rejected in approximately 3-4 days in each of these groups of animals. The combination of BB5.1 and cyclosporin A showed some effect with rejection occurring about day 12. The combination of BB5.1 and cyclophosphamide had no protective effect with rejection occurring about day 3. Similarly the combination of cyclosporin A and cyclophosphamide had essentially no protective effect with rejection occurring at 3-4 days. Very surprisingly, the combination of all three drugs (chronic administration of BB5.1 and cyclosporin plus administration of cyclophosphamide at the time of transplant) showed a highly synergistic effect with all of the mice surviving for more than 100 days. Again, a survival of 100 days in this model is considered to be the gold standard and assumes an indefinite survival.

These results as well as the histological results as shown in Table 6 indicate that the combination of chronic treatment with a complement inhibitor and an immunosuppressant such as cyclosporin A in treating a presensitized mouse results in some attenuation of accelerated rejection. Treatment of these animals additionally with cyclophosphamide at the time of transplant and on the first day after transplant results in a much greater time of survival, no rejection having been seen by at least day 100.

Samsung Bioepis Exhibit No. 1002
Page 11054

It will be appreciated that the methods and compositions of the instant disclosure can be incorporated in the form of a variety of embodiments, only a few of which are disclosed herein. It will be apparent to the artisan that other embodiments exist and do not depart from the spirit of the disclosure. Thus, the described embodiments are illustrative and should not be construed as restrictive.

Samsung Bioepis Exhibit No. 1002
Page 11055

LIST OF REFERENCES

The publications and other materials used herein to illuminate the background of the disclosure, and in particular, cases to provide additional details respecting the practice, are incorporated herein by reference in their entirety, and for convenience, are referenced by author and date in the text and respectively grouped in the following List of References.

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Samsung Bioepis Exhibit No. 1002
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Samsung Bioepis Exhibit No. 1002
Page 11057

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Samsung Bioepis Exhibit No. 1002
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The contents of all references cited herein are incorporated by reference in their entirety.

Samsung Bioepis Exhibit No. 1002
Page 11059

CLAIMS

1. A method to prolong survival of an MHC mismatched allograft in a recipient mammal, said method comprising administering to said mammal a) a drug which inhibits complement activity and b) at least one immunosuppressive drug, wherein said drug which inhibits complement activity is administered chronically.

2. The method of claim 1 wherein said mammal is a human.

3. The method of claim 2 wherein said MHC mismatched allograft is an HLA mismatched allograft.

4. The method of claim 1 wherein said drug which inhibits complement activity inhibits the formation of terminal complement or C5a.

5. The method of claim 4 wherein said drug which inhibits formation of terminal complement or C5a is a whole antibody or an antibody fragment.

6. The method of claim 5 wherein said whole antibody or antibody fragment is a human, humanized, chimerized or deimmunized antibody or antibody fragment.

7. The method of claim 5 wherein said whole antibody or antibody fragment inhibits cleavage of complement C5.

8. The method of claim 5 wherein said antibody fragment is selected from the group consisting of an Fab, an $F(ab')_2$, an Fv, a domain antibody, and a single-chain antibody.

9. The method of claim 5 wherein said antibody fragment is pexelizumab.

10. The method of claim 5 wherein said whole antibody is eculizumab.

11. The method claim 10 wherein said eculizumab is administered once every 2 weeks.

12. The method of claim 1 wherein said inhibitor of complement activity is selected from the group consisting of a i) soluble complement receptor, ii) CD59, iii) CD55, iv) CD46, and v) an antibody to C5, C6, C7, C8, or C9.

13. The method of claim 1 wherein said immunosuppressive drug inhibits T-cell activity or B-cell activity.

Samsung Bioepis Exhibit No. 1002
Page 11060

14. The method of claim 1 wherein said immunosuppressive drug inhibits T-cell activity and B-cell activity.

15. The method of claim 1 wherein said immunosuppressive drug is selected from the group consisting of cyclosporin A, tacrolimus, sirolimus, OKT3, a corticosteroid, daclizumab, basiliximab, azathioprene, mycophenolate mofetil, methotrexate, 6-mercaptopurine, anti-T cell antibodies, cyclophosphamide, leflunamide, brequinar, ATG, ALG, 15-deoxyspergualin, and bredinin.

16. The method of claim 1 wherein more than one immunosuppressive drug is administered.

17. The method of claim 1 wherein said method comprises administering i) a drug which inhibits complement activity and ii) cyclosporin A.

18. The method of claim 17 wherein said drug which inhibits complement activity is an antibody which inhibits cleavage of complement C5.

19. The method of claim 1 wherein said allograft is selected from the group consisting of i) heart, ii) kidney, iii) lung, iv) pancreas, v) liver, vi) vascular tissue, vii) eye, viii) cornea, ix) lens, x) skin, xi) bone marrow, xii) muscle, xiii) connective tissue, xiv) gastrointestinal tissue, xv) nervous tissue, xvi) bone, xvii) stem cells, xviii) islets, xix) cartilage, xx) hepatocytes, and xxi) hematopoietic cells.

20. The method of claim 1 wherein said allograft survives for a time at least 20% longer than would occur if said method were to be performed without said drug which inhibits complement activity.

21. The method of claim 1 wherein said allograft survives for a time at least 40% longer than would occur if said method were to be performed without said drug which inhibits complement activity.

22. The method of claim 1 wherein said allograft survives for the remaining life-time of said mammal.

23. The method of claim 2 wherein said allograft survives for at least six months.

24. The method of claim 2 wherein said allograft survives for at least one year.

25. The method of claim 2 wherein said allograft survives for at least five years.

Samsung Bioepis Exhibit No. 1002
Page 11061

26. The method of claim 2 wherein said allograft survives for the remaining life-time of said human.

27. The method of claim 1 wherein said drug which inhibits complement activity is administered chronically for at least 14 days.

28. The method of claim 1 wherein said drug which inhibits complement activity is administered chronically for at least 28 days.

29. The method of claim 1 wherein said drug which inhibits complement activity is administered chronically for at least 3 months.

30. The method of claim 1 wherein said drug which inhibits complement activity is administered chronically for at least 6 months.

31. The method of claim 1 wherein said drug which inhibits complement activity is administered chronically for at least 1 year.

32. The method of claim 1 wherein said drug which inhibits complement activity is administered chronically for at least 5 years.

33. The method of claim 1 wherein said drug which inhibits complement activity is administered chronically for the remaining life-time of said mammal.

34. The method of claim 1 wherein at least one immunosuppressive drug is administered chronically for the remaining life-time of said mammal.

35. The method of claim 34 wherein at least cyclosporin A is administered chronically for the remaining life-time of said mammal.

36. A method to prolong survival of an allograft in a recipient mammal presensitized to said allograft, said method comprising administering to said mammal a) a drug which inhibits complement activity and b) at least one immunosuppressive drug, wherein said drug which inhibits complement activity is administered chronically.

37. The method of claim 36 wherein said mammal is a human.

38. The method of claim 36 wherein said drug which inhibits complement activity inhibits the formation of terminal complement or C5a.

Samsung Bioepis Exhibit No. 1002
Page 11062

39. The method of claim 38 wherein said drug that inhibits formation of terminal complement or C5a is a whole antibody or an antibody fragment.

40. The method of claim 39 wherein said whole antibody or antibody fragment is a human, humanized, chimerized or deimmunized antibody or antibody fragment.

41. The method of claim 39 wherein said whole antibody or antibody fragment inhibits cleavage of complement C5.

42. The method of claim 39 wherein said antibody fragment is selected from the group consisting of an Fab, an $F(ab')_2$, an Fv, a domain antibody, and a single-chain antibody.

43. The method of claim 39 wherein said antibody fragment is pexelizumab.

44. The method of claim 39 wherein said whole antibody is eculizumab.

45. The method claim 44 wherein said eculizumab is administered once every 2 weeks.

46. The method of claim 36 wherein said inhibitor of complement activity is selected from the group consisting of a i) soluble complement receptor, ii) CD59, iii) CD55, iv) CD46, and v) an antibody to C5, C6, C7, C8, or C9.

47. The method of claim 36 wherein said immunosuppressive drug inhibits T-cell activity or B-cell activity.

48. The method of claim 36 wherein said immunosuppressive drug inhibits T-cell activity and B-cell activity.

49. The method of claim 36 wherein said immunosuppressive drug is selected from the group consisting of cyclosporin A, tacrolimus, sirolimus, OKT3, a corticosteroid, daclizumab, basiliximab, azathioprene, mycophenolate mofetil, methotrexate, 6-mercaptopurine, anti-T cell antibodies, cyclophosphamide, leflunamide, brequinar, ATG, ALG, 15-deoxyspergualin, and bredinin.

50. The method of claim 36 wherein more than one immunosuppressive drug is administered.

51. The method of claim 36 wherein said method comprises administering i) a drug which inhibits complement activity and ii) cyclosporin A.

Samsung Bioepis Exhibit No. 1002
Page 11063

52. The method of claim 51 wherein said method comprises administering i) a drug which inhibits complement activity, ii) cyclosporin A, and iii) cyclophosphamide.

53. The method of claim 51 wherein said drug which inhibits complement activity is an antibody which inhibits cleavage of complement C5.

54. The method of claim 36 wherein said allograft is selected from the group consisting of i) heart, ii) kidney, iii) lung, iv) pancreas, v) liver, vi) vascular tissue, vii) eye, viii) cornea, ix) lens, x) skin, xi) bone marrow, xii) muscle, xiii) connective tissue, xiv) gastrointestinal tissue, xv) nervous tissue, xvi) bone, xvii) stem cells, xviii) islets, xix) cartilage, xx) hepatocytes, and xxi) hematopoietic cells.

55. The method of claim 36 wherein said allograft survives for a time at least 20% longer than would occur if said method were to be performed without said drug which inhibits complement activity.

56. The method of claim 36 wherein said allograft survives for a time at least 40% longer than would occur if said method were to be performed without said drug which inhibits complement activity.

57. The method of claim 36 wherein said allograft survives for the remaining life-time of said mammal.

58. The method of claim 37 wherein said allograft survives for at least six months.

59. The method of claim 37 wherein said allograft survives for at least one year.

60. The method of claim 37 wherein said allograft survives for at least five years.

61. The method of claim 37 wherein said allograft survives for the remaining life-time of said human.

62. The method of claim 36 wherein said drug which inhibits complement activity is administered chronically for at least 14 days.

63. The method of claim 36 wherein said drug which inhibits complement activity is administered chronically for at least 28 days.

64. The method of claim 36 wherein said drug which inhibits complement activity is administered chronically for at least 3 months.

Samsung Bioepis Exhibit No. 1002
Page 11064

65. The method of claim 36 wherein said drug which inhibits complement activity is administered chronically for at least 6 months.

66. The method of claim 36 wherein said drug which inhibits complement activity is administered chronically for at least 1 year.

67. The method of claim 36 wherein said drug which inhibits complement activity is administered chronically for at least 5 years.

68. The method of claim 36 wherein said drug which inhibits complement activity is administered chronically for the remaining life-time of said mammal.

69. The method of claim 36 wherein at least one immunosuppressive drug is administered chronically for the remaining life-time of said mammal.

70. The method of claim 69 wherein at least cyclosporin A is administered chronically for the remaining life-time of said mammal.

71. A method to prolong survival of an allograft in a recipient mammal which is an ABO mismatch to said allograft, said method comprising administering to said mammal a) a drug which inhibits complement activity and b) at least one immunosuppressive drug, wherein said drug which inhibits complement activity is administered chronically.

72. The method of claim 71 wherein said mammal is a human.

73. The method of claim 71 wherein said drug which inhibits complement activity inhibits the formation of terminal complement or C5a.

74. The method of claim 73 wherein said drug which inhibits formation of terminal complement or C5a is a whole antibody or an antibody fragment.

75. The method of claim 74 wherein said whole antibody or antibody fragment is a human, humanized, chimerized or deimmunized antibody or antibody fragment.

76. The method of claim 74 wherein said whole antibody or antibody fragment inhibits cleavage of complement C5.

77. The method of claim 74 wherein said antibody fragment is selected from the group consisting of an Fab, an $F(ab')_2$, an Fv, a domain antibody, and a single-chain antibody.

Samsung Bioepis Exhibit No. 1002
Page 11065

78. The method of claim 74 wherein said antibody fragment is pexelizumab.

79. The method of claim 74 wherein said whole antibody is eculizumab.

80. The method claim 79 wherein said eculizumab is administered once every 2 weeks.

81. The method of claim 71 wherein said inhibitor of complement activity is selected from the group consisting of a i) soluble complement receptor, ii) CD59, iii) CD55, iv) CD46, and v) an antibody to C5, C6, C7, C8, or C9.

82. The method of claim 71 wherein said immunosuppressive drug inhibits T-cell activity or B-cell activity.

83. The method of claim 71 wherein said immunosuppressive drug inhibits T-cell activity and B-cell activity.

84. The method of claim 71 wherein said immunosuppressive drug is selected from the group consisting of cyclosporin A, tacrolimus, sirolimus, OKT3, a corticosteroid, daclizumab, basiliximab, azathioprene, mycophenolate mofetil, methotrexate, 6-mercaptopurine, anti-T cell antibodies, cyclophosphamide, leflunamide, brequinar, ATG, ALG, 15-deoxyspergualin, and bredinin.

85. The method of claim 71 wherein more than one immunosuppressive drug is administered.

86. The method of claim 71 wherein said method comprises administering i) a drug which inhibits complement activity and ii) cyclosporin A.

87. The method of claim 86 wherein said method comprises administering i) a drug which inhibits complement activity, ii) cyclosporin A, and iii) cyclophosphamide.

88. The method of claim 86 wherein said drug that inhibits complement activity is an antibody that inhibits cleavage of complement C5.

89. The method of claim 71 wherein said allograft is selected from the group consisting of i) heart, ii) kidney, iii) lung, iv) pancreas, v) liver, vi) vascular tissue, vii) eye, viii) cornea, ix) lens, x) skin, xi) bone marrow, xii) muscle, xiii) connective tissue, xiv) gastrointestinal tissue, xv) nervous tissue, xvi) bone, xvii) stem cells, xviii) islets, xix) cartilage, xx) hepatocytes, and xxi) hematopoietic cells.

Samsung Bioepis Exhibit No. 1002
Page 11066

90. The method of claim 71 wherein said allograft survives for a time at least 20% longer than would occur if said method were to be performed without said drug that inhibits complement activity.

91. The method of claim 71 wherein said allograft survives for a time at least 40% longer than would occur if said method were to be performed without said drug that inhibits complement activity.

92. The method of claim 71 wherein said allograft survives for the remaining life-time of said mammal.

93. The method of claim 72 wherein said allograft survives for at least six months.

94. The method of claim 72 wherein said allograft survives for at least one year.

95. The method of claim 72 wherein said allograft survives for at least five years.

96. The method of claim 72 wherein said allograft survives for the remaining life-time of said human.

97. The method of claim 71 wherein said drug which inhibits complement activity is administered chronically for at least 14 days.

98. The method of claim 71 wherein said drug which inhibits complement activity is administered chronically for at least 28 days.

99. The method of claim 71 wherein said drug which inhibits complement activity is administered chronically for at least 3 months.

100. The method of claim 71 wherein said drug which inhibits complement activity is administered chronically for at least 6 months.

101. The method of claim 71 wherein said drug which inhibits complement activity is administered chronically for at least 1 year.

102. The method of claim 71 wherein said drug which inhibits complement activity is administered chronically for at least 5 years.

103. The method of claim 71 wherein said drug which inhibits complement activity is administered chronically for the remaining life-time of said mammal.

Samsung Bioepis Exhibit No. 1002
Page 11067

104. The method of claim 71 wherein at least one immunosuppressive drug is administered chronically for the remaining life-time of said mammal.

105. The method of claim 104 wherein at least cyclosporin A is administered chronically for the remaining life-time of said mammal.

106. Use of a drug that inhibits complement activity and an immunosuppressive drug in the manufacture of a medicament or medicament package for prolong survival of an allograft in a mammal.

107. The use of claim 106, wherein more than one immunosuppressive drug is included in said medicament or medicament package.

108. The use of claim 106, wherein said drug that inhibits complement activity and said immunosuppressive drug are in a formulation suitable for concurrent administration to said mammal.

109. The use of claim 106, wherein said drug that inhibits complement activity and said immunosuppressive drug are in a formulation or formulations suitable for sequential administration to said mammal.

110. The use of claim 106, wherein said drug that inhibits complement activity is in a formulation suitable for chronic administration to said mammal.

111. The use of claim 106, wherein said immunosuppressive drug is in a formulation suitable for chronic administration to said mammal.

112. A method to prolong survival of allograft in a recipient mammal, comprising preparing an allograft from a first allograft accommodated by a first recipient mammal, wherein said first recipient mammal, after receiving said first allograft, has been treated with a drug that inhibits complement activity and at least one immunosuppressive agent.

113. An allograft that has prolonged survival in a recipient mammal, wherein said allograft is prepared from a first recipient mammal and was transplanted to the first recipient mammal that has been treated with a drug that inhibits complement activity and at least one immunosuppressive agent.

Samsung Bioepis Exhibit No. 1002
Page 11068

114. A pharmaceutical package comprising a drug that inhibits complement activity and at least one immunosuppressive agent, wherein said drug and said agent are formulated for chronic administration.

115. The pharmaceutical package of claim 114, wherein said drug is an antibody in a lyophilized formulation comprising the antibody and a lyoprotectant.

116. The pharmaceutical package of claim 114, wherein said agent is in a lyophilized formulation comprising the agent and a lyoprotectant.

117. The pharmaceutical package of claim 114, wherein said drug and said agent are in the same lyophilized formulation comprising said drug, said agent, and a lyoprotectant.

118. The pharmaceutical package of claim 114, wherein said drug is in an injection system comprising a syringe that comprises a cartridge, wherein said cartridge contains said drug in a formulation suitable for injection.

119. The pharmaceutical package of claim 114, wherein said agent is in an injection system comprising a syringe that comprises a cartridge, wherein said cartridge contains said agent in a formulation suitable for injection.

120. The pharmaceutical package of claim 114, wherein said drug and said agent are in an injection system comprising a syringe that comprises a cartridge, wherein said cartridge contains said drug and said agent in a formulation suitable for injection.

121. The pharmaceutical package of claim 114, wherein said drug is present in unit dosage form.

122. The pharmaceutical package of claim 114, wherein said agent is present in unit dosage form.

123. A lyophilized antibody formulation comprising an antibody that inhibits complement activity and a lyoprotectant, wherein said antibody formulation is suitable for chronic administration.

124. The lyophilized antibody formulation of claim 123, wherein the antibody inhibits the formation of terminal complement or C5a.

Samsung Bioepis Exhibit No. 1002
Page 11069

125. The lyophilized antibody formulation of claim 123, wherein the antibody is a whole antibody or an antibody fragment.

126. The lyophilized antibody formulation of claim 125, wherein the antibody wherein said whole antibody or antibody fragment is a human, humanized, chimerized or deimmunized antibody or antibody fragment.

127. The lyophilized antibody formulation of claim 125, wherein said whole antibody or antibody fragment inhibits cleavage of complement C5.

128. The lyophilized antibody formulation of claim 125, wherein said antibody fragment is selected from the group consisting of an Fab, an $F(ab')_2$, an Fv, a domain antibody, and a single-chain antibody.

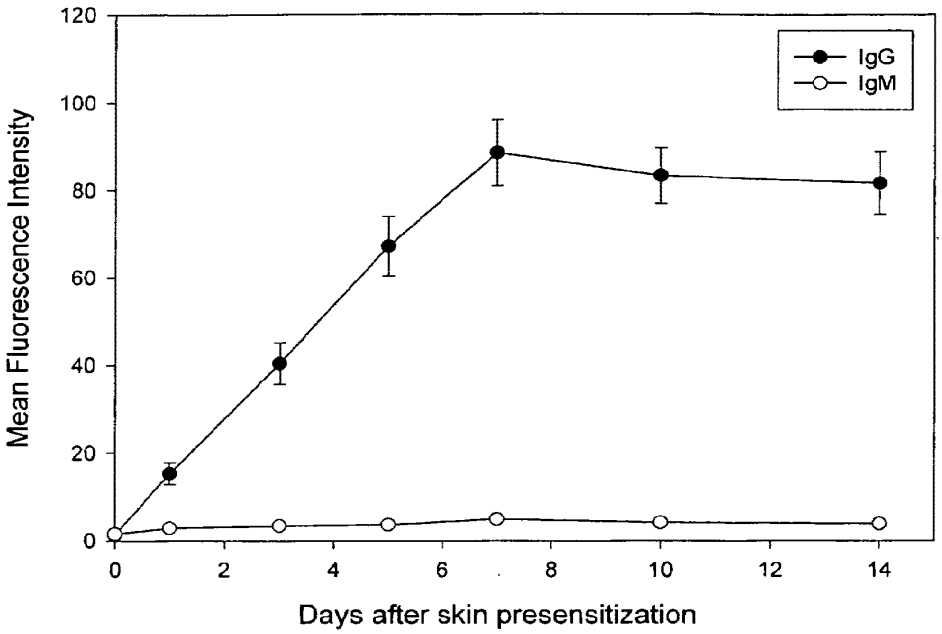
129. The lyophilized antibody formulation of claim 125, wherein said antibody fragment is pexelizumab.

130. The lyophilized antibody formulation of claim 125, wherein said whole antibody is eculizumab.

131. An injection system comprising a syringe, wherein said syringe comprises a cartridge containing an antibody that inhibits complement activity and is formulated suitable for injection.

Samsung Bioepis Exhibit No. 1002
Page 11070

A



B

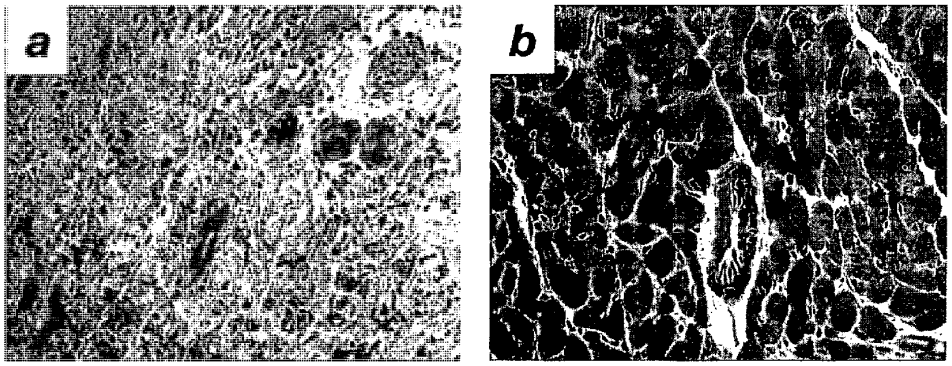


Figure 1A, B

Samsung Bioepis Exhibit No. 1002
Page 11071

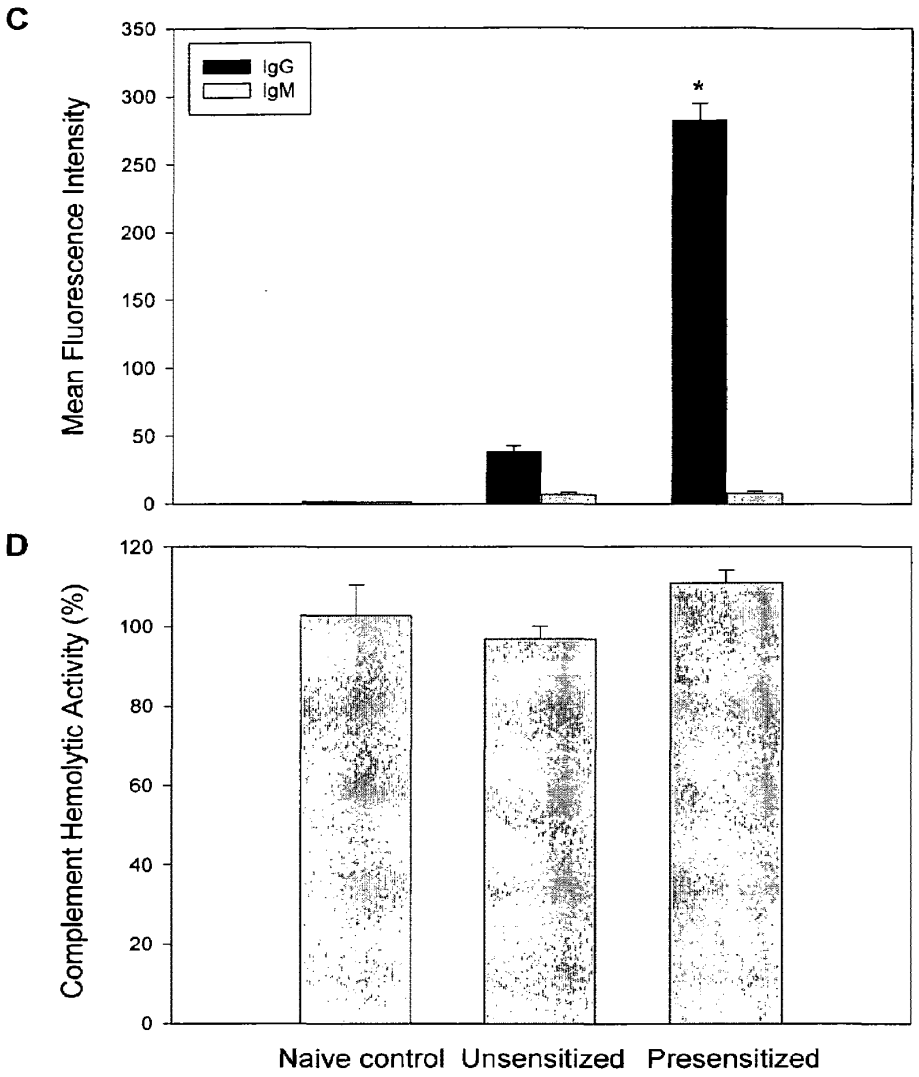


Figure 1C, D

Samsung Bioepis Exhibit No. 1002
Page 11072

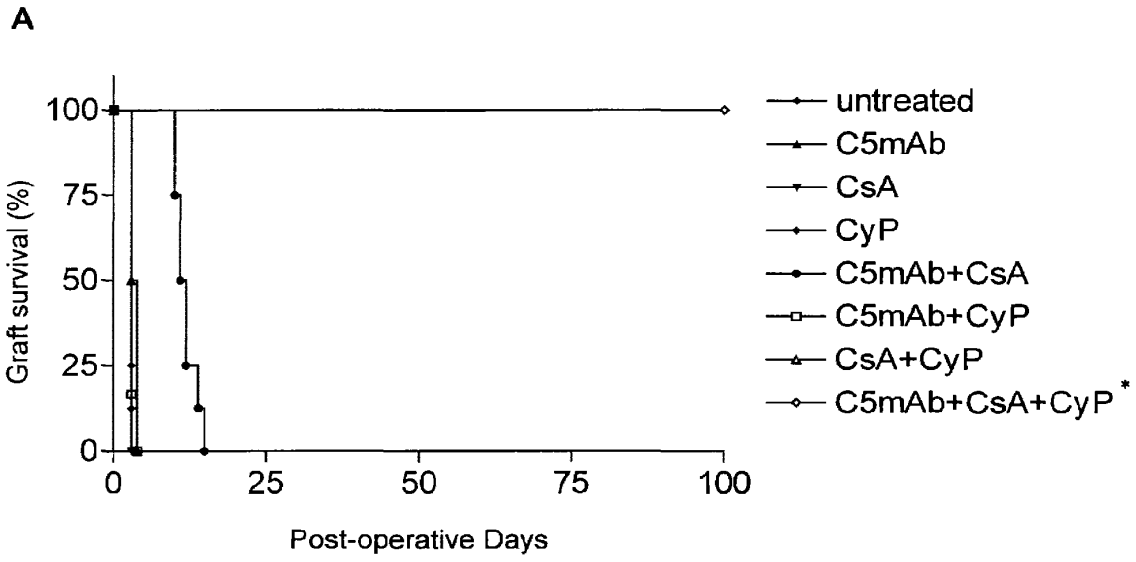


Figure 2A

Samsung Bioepis Exhibit No. 1002
Page 11073

B

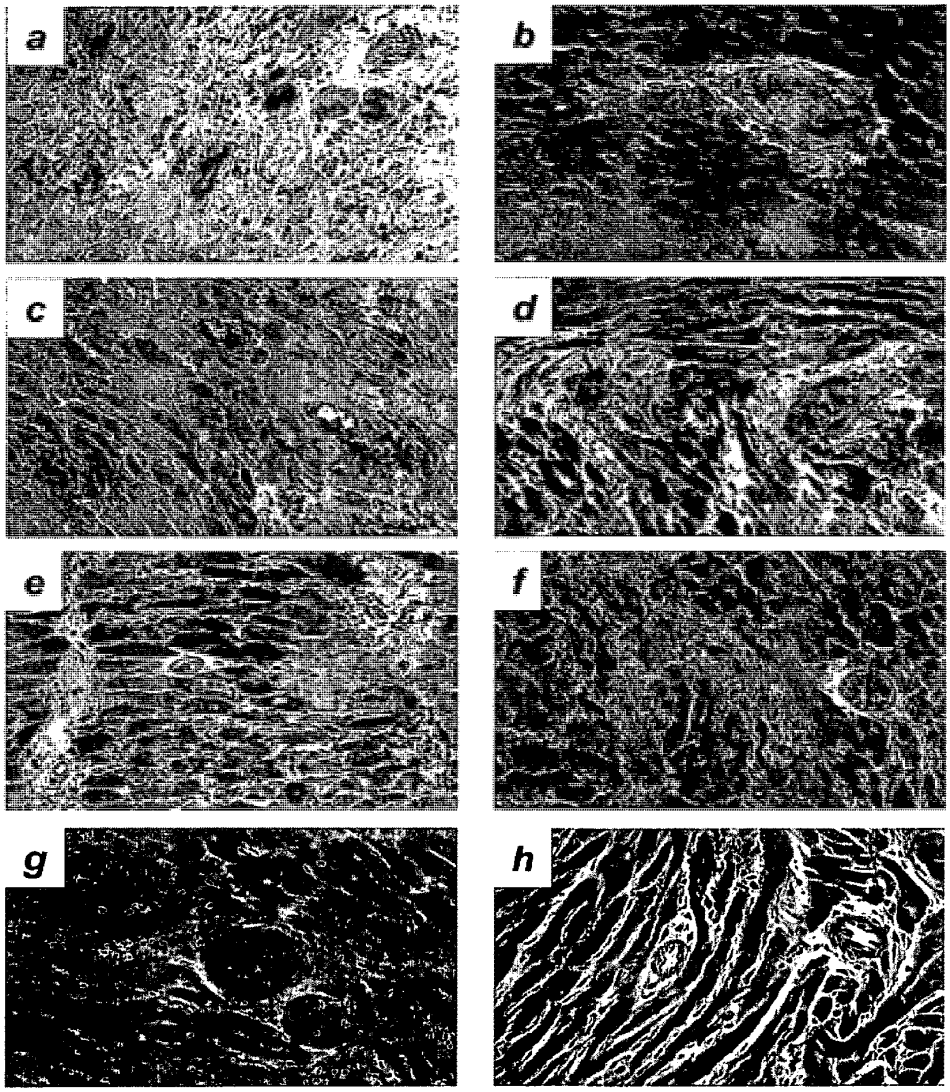


Figure 2B

Samsung Bioepis Exhibit No. 1002
Page 11074

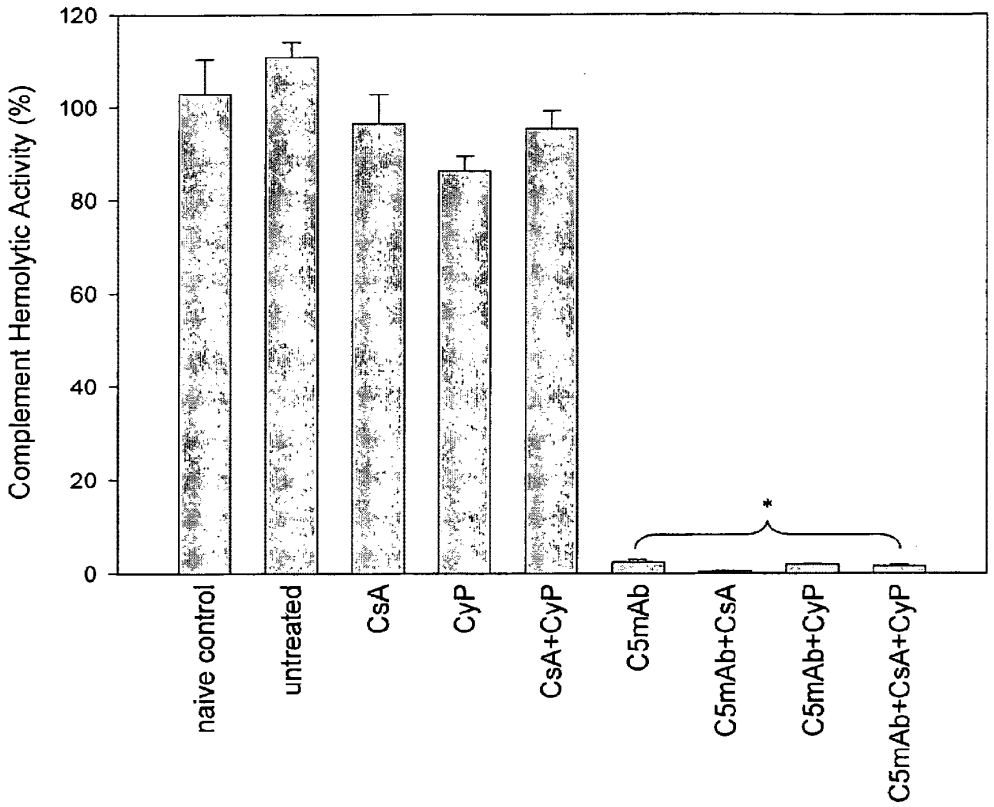


Figure 3

Samsung Bioepis Exhibit No. 1002
Page 11075

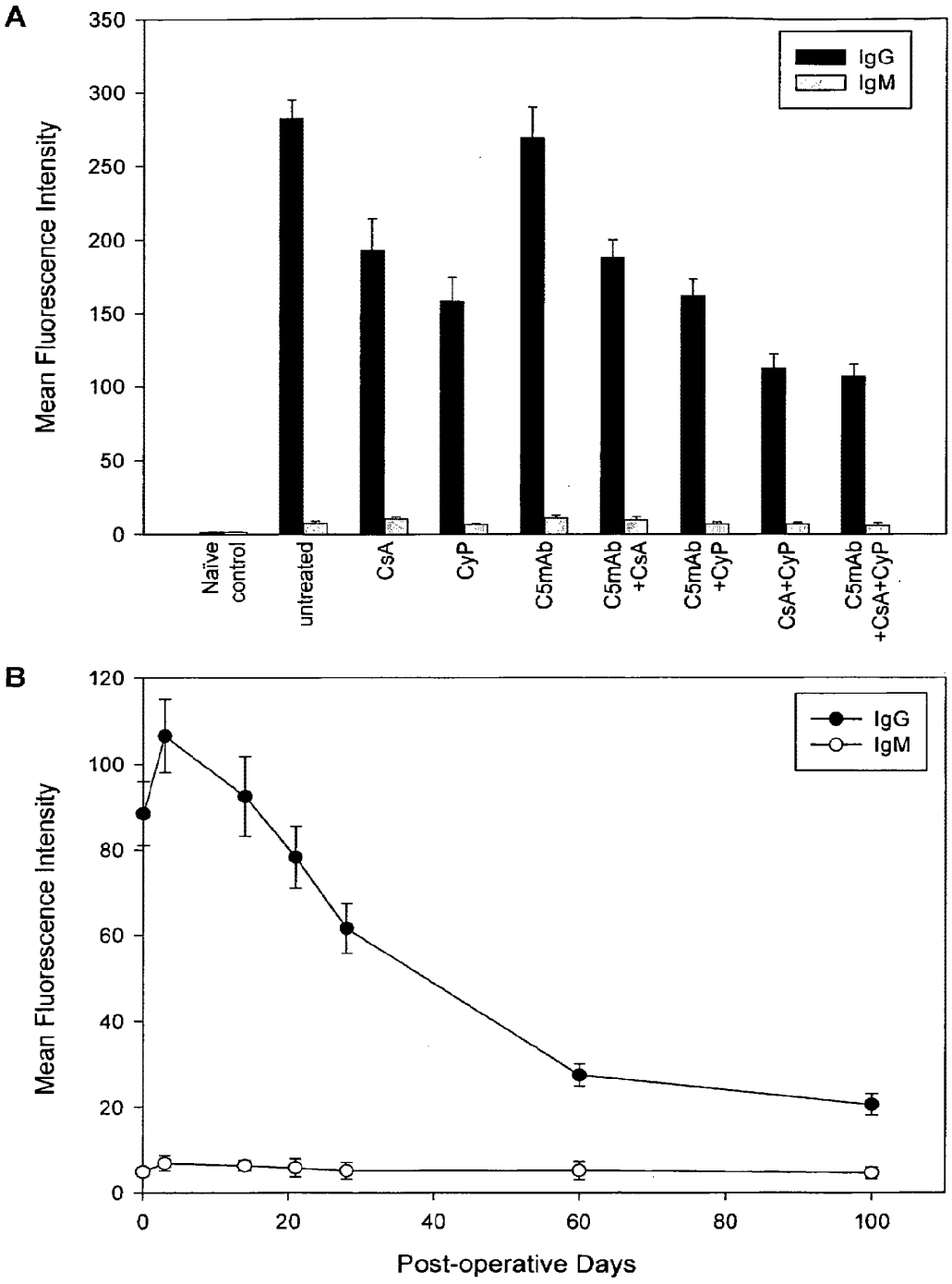
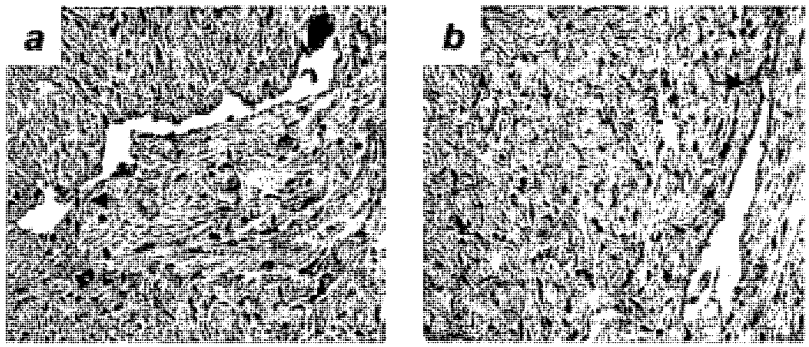


Figure 4A, B

Samsung Bioepis Exhibit No. 1002
Page 11076

C



D

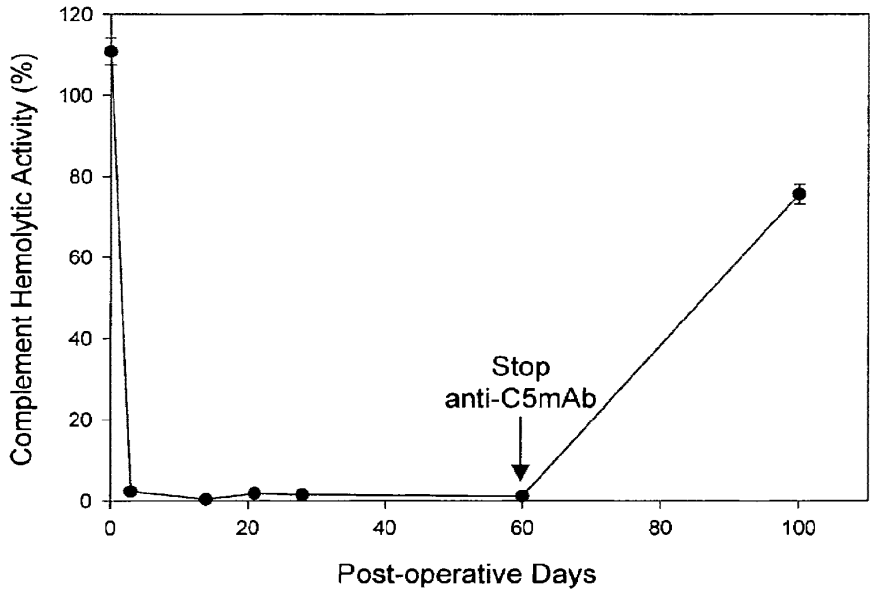


Figure 4C, D

Samsung Bioepis Exhibit No. 1002
Page 11077

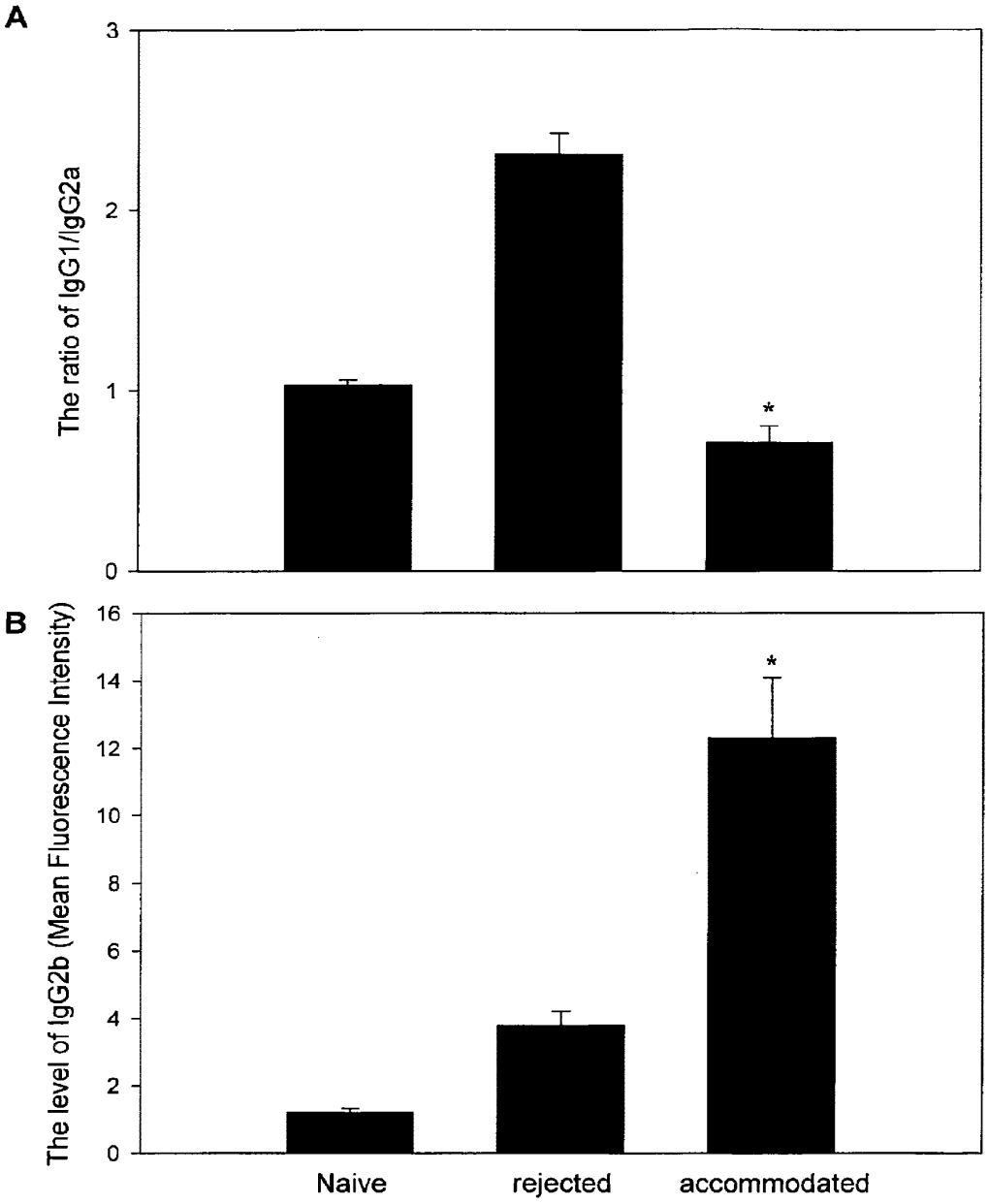


Figure 5A, B

Samsung Bioepis Exhibit No. 1002
Page 11078

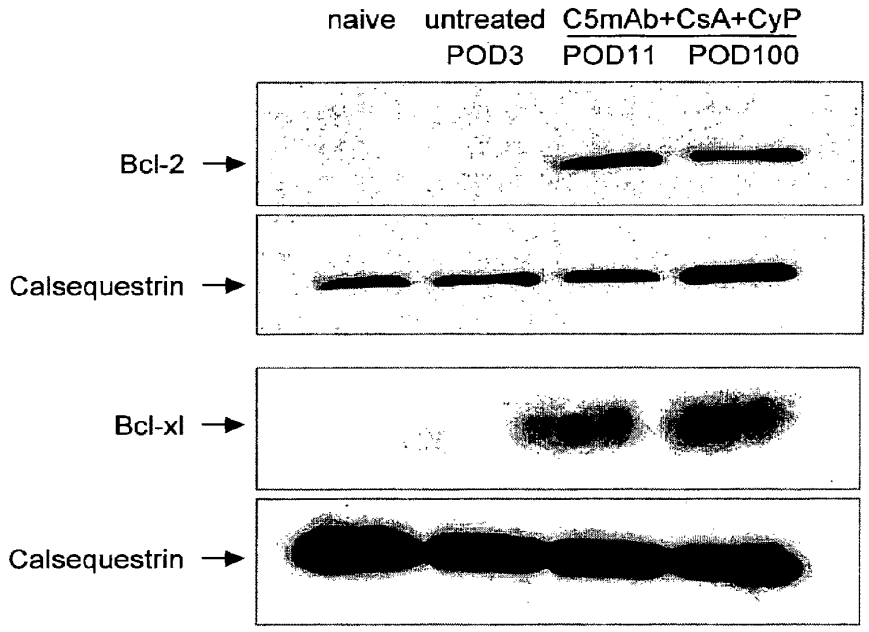


Figure 6

Samsung Bioepis Exhibit No. 1002
Page 11079

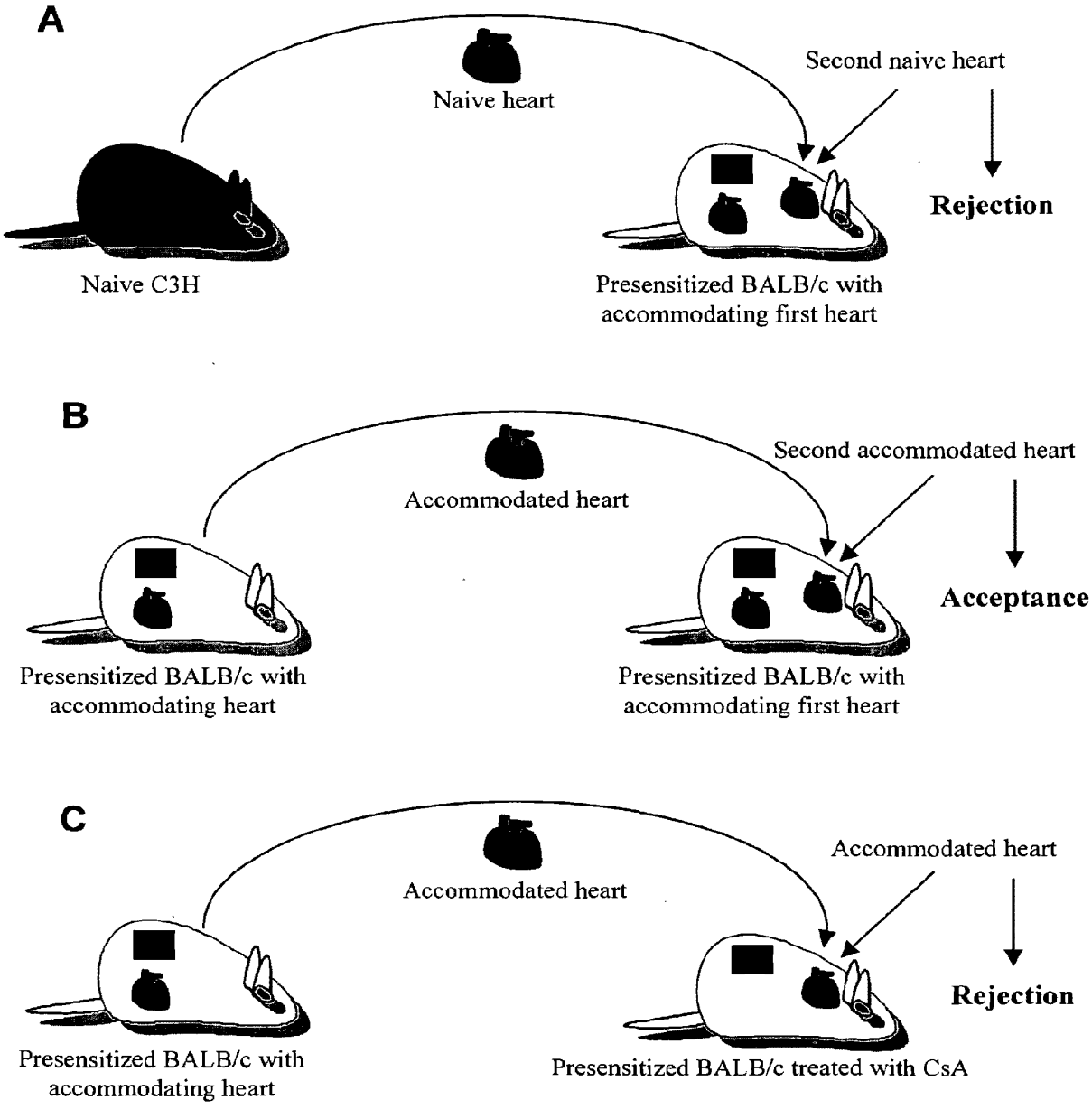
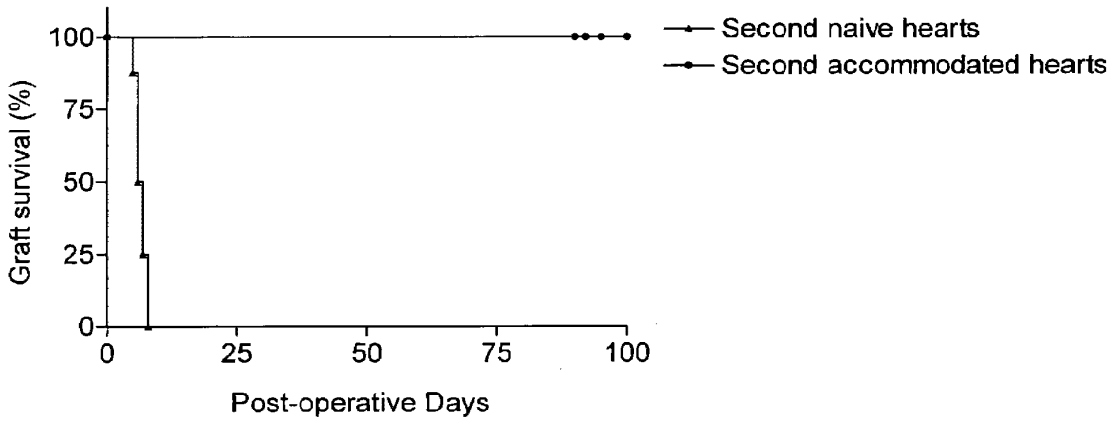


Figure 7

Samsung Bioepis Exhibit No. 1002
Page 11080

A



B

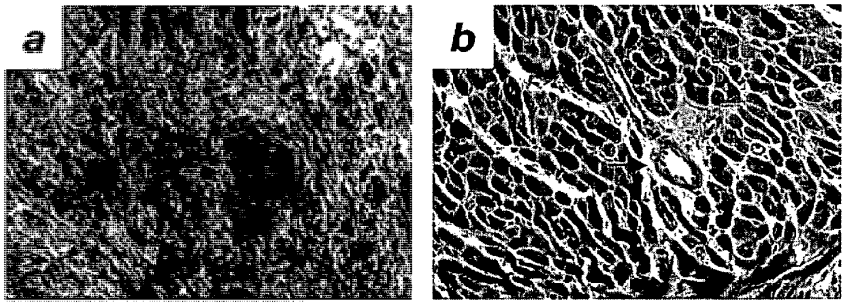


Figure 8

Samsung Bioepis Exhibit No. 1002
Page 11081

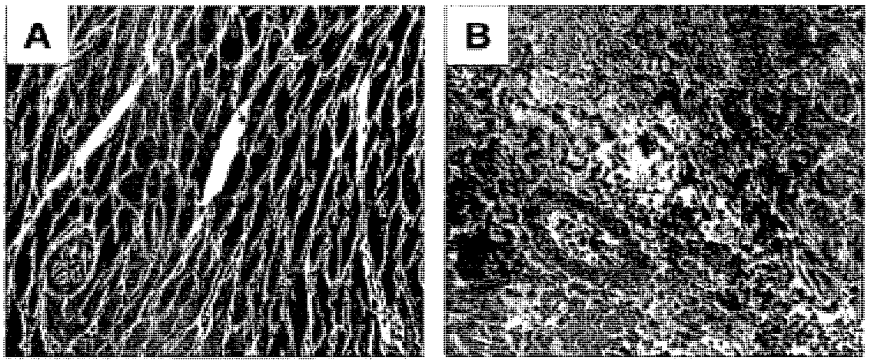


Figure 9

Samsung Bioepis Exhibit No. 1002
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(54) Title: OPTIMIZED FC VARIANTS AND METHODS FOR THEIR GENERATION

(57) Abstract: The present invention relates to optimized Fc variants, methods for their generation, and antibodies and Fc fusions comprising optimized Fc variants.

WO 2004/029207 A2

Samsung Bioepis Exhibit No. 1002
Page 11083

OPTIMIZED Fc VARIANTS AND METHODS FOR THEIR GENERATION

[001] This application claims benefit under 35 U.S.C. §199(e) to USSNs 60/477,839 filed June 12, 2003; 60/467,606, filed May 2, 2003; 60/414,433 filed September 27, 2002; and 60/442,301 filed January 23, 2003, all of which are expressly incorporated by reference in their entirety.

FIELD OF THE INVENTION

[002] The present invention relates to novel optimized Fc variants, engineering methods for their generation, and their application, particularly for therapeutic purposes.

BACKGROUND OF THE INVENTION

[003] Antibodies are immunological proteins that bind a specific antigen. In most mammals, including humans and mice, antibodies are constructed from paired heavy and light polypeptide chains. Each chain is made up of individual immunoglobulin (Ig) domains, and thus the generic term immunoglobulin is used for such proteins. Each chain is made up of two distinct regions, referred to as the variable and constant regions. The light and heavy chain variable regions show significant sequence diversity between antibodies, and are responsible for binding the target antigen. The constant regions show less sequence diversity, and are responsible for binding a number of natural proteins to elicit important biochemical events. In humans there are five different classes of antibodies including IgA (which includes subclasses IgA1 and IgA2), IgD, IgE, IgG (which includes subclasses IgG1, IgG2, IgG3, and IgG4), and IgM. The distinguishing features between these antibody classes are their constant regions, although subtler differences may exist in the V region. Figure 1 shows an IgG1 antibody, used here as an example to describe the general structural features of immunoglobulins. IgG antibodies are tetrameric proteins composed of two heavy chains and two light chains. The IgG heavy chain is composed of four immunoglobulin domains linked from N- to C-terminus in the order V_H-Cγ1-Cγ2-Cγ3, referring to the heavy chain variable domain, constant gamma 1 domain, constant gamma 2 domain, and constant gamma 3 domain respectively. The IgG light chain is composed of two immunoglobulin domains linked from N- to C-terminus in the order V_L-C_L, referring to the light chain variable domain and the light chain constant domain respectively.

[004] The variable region of an antibody contains the antigen binding determinants of the molecule, and thus determines the specificity of an antibody for its target antigen. The variable region is so named because it is the most distinct in sequence from other antibodies within the same class. The majority of sequence variability occurs in the complementarity determining regions (CDRs). There are 6 CDRs total, three each per heavy and light chain, designated V_H CDR1, V_H CDR2, V_H CDR3, V_L

Samsung Bioepis Exhibit No. 1002
Page 11084

CDR1, V_L CDR2, and V_L CDR3. The variable region outside of the CDRs is referred to as the framework (FR) region. Although not as diverse as the CDRs, sequence variability does occur in the FR region between different antibodies. Overall, this characteristic architecture of antibodies provides a stable scaffold (the FR region) upon which substantial antigen binding diversity (the CDRs) can be explored by the immune system to obtain specificity for a broad array of antigens. A number of high-resolution structures are available for a variety of variable region fragments from different organisms, some unbound and some in complex with antigen. The sequence and structural features of antibody variable regions are well characterized (Morea *et al.*, 1997, *Biophys Chem* 68:9-16; Morea *et al.*, 2000, *Methods* 20:267-279), and the conserved features of antibodies have enabled the development of a wealth of antibody engineering techniques (Maynard *et al.*, 2000, *Annu Rev Biomed Eng* 2:339-376). For example, it is possible to graft the CDRs from one antibody, for example a murine antibody, onto the framework region of another antibody, for example a human antibody. This process, referred to in the art as "humanization", enables generation of less immunogenic antibody therapeutics from nonhuman antibodies. Fragments comprising the variable region can exist in the absence of other regions of the antibody, including for example the antigen binding fragment (Fab) comprising V_H-Cγ1 and V_H-C_L, the variable fragment (Fv) comprising V_H and V_L, the single chain variable fragment (scFv) comprising V_H and V_L linked together in the same chain, as well as a variety of other variable region fragments (Little *et al.*, 2000, *Immunol Today* 21:364-370).

[005] The Fc region of an antibody interacts with a number of Fc receptors and ligands, imparting an array of important functional capabilities referred to as effector functions. For IgG the Fc region, as shown in Figure 1, comprises Ig domains Cγ2 and Cγ3 and the N-terminal hinge leading into Cγ2. An important family of Fc receptors for the IgG class are the Fc gamma receptors (FcγRs). These receptors mediate communication between antibodies and the cellular arm of the immune system (Raghavan *et al.*, 1996, *Annu Rev Cell Dev Biol* 12:181-220; Ravetch *et al.*, 2001, *Annu Rev Immunol* 19:275-290). In humans this protein family includes FcγRI (CD64), including isoforms FcγRIa, FcγRIb, and FcγRIc; FcγRII (CD32), including isoforms FcγRIIa (including allotypes H131 and R131), FcγRIIb (including FcγRIIb-1 and FcγRIIb-2), and FcγRIIc; and FcγRIII (CD16), including isoforms FcγRIIIa (including allotypes V158 and F158) and FcγRIIIb (including allotypes FcγRIIIb-NA1 and FcγRIIIb-NA2) (Jefferis *et al.*, 2002, *Immunol Lett* 82:57-65). These receptors typically have an extracellular domain that mediates binding to Fc, a membrane spanning region, and an intracellular domain that may mediate some signaling event within the cell. These receptors are expressed in a variety of immune cells including monocytes, macrophages, neutrophils, dendritic cells, eosinophils, mast cells, platelets, B cells, large granular lymphocytes, Langerhans' cells, natural killer (NK) cells, and $\gamma\gamma$ T cells. Formation of the Fc/FcγR complex recruits these effector cells to sites of bound antigen, typically resulting in signaling events within the cells and important subsequent immune responses such as release of inflammation mediators, B cell activation, endocytosis, phagocytosis, and cytotoxic attack. The ability to mediate cytotoxic and phagocytic effector functions is a potential mechanism by which antibodies destroy targeted cells. The cell-mediated reaction wherein nonspecific cytotoxic

cells that express FcγRs recognize bound antibody on a target cell and subsequently cause lysis of the target cell is referred to as antibody dependent cell-mediated cytotoxicity (ADCC) (Raghavan *et al.*, 1996, *Annu Rev Cell Dev Biol* 12:181-220; Ghetie *et al.*, 2000, *Annu Rev Immunol* 18:739-766; Ravetch *et al.*, 2001, *Annu Rev Immunol* 19:275-290). The cell-mediated reaction wherein nonspecific cytotoxic cells that express FcγRs recognize bound antibody on a target cell and subsequently cause phagocytosis of the target cell is referred to as antibody dependent cell-mediated phagocytosis (ADCP). A number of structures have been solved of the extracellular domains of human FcγRs, including FcγRIIa (pdb accession code 1H9V)(Sondermann *et al.*, 2001, *J Mol Biol* 309:737-749) (pdb accession code 1FCG)(Maxwell *et al.*, 1999, *Nat Struct Biol* 6:437-442), FcγRIIb (pdb accession code 2FCB)(Sondermann *et al.*, 1999, *Embo J* 18:1095-1103); and FcγRIIIb (pdb accession code 1E4J)(Sondermann *et al.*, 2000, *Nature* 406:267-273.). All FcγRs bind the same region on Fc, at the N-terminal end of the Cγ2 domain and the preceding hinge, shown in Figure 2. This interaction is well characterized structurally (Sondermann *et al.*, 2001, *J Mol Biol* 309:737-749), and several structures of the human Fc bound to the extracellular domain of human FcγRIIIb have been solved (pdb accession code 1E4K)(Sondermann *et al.*, 2000, *Nature* 406:267-273.) (pdb accession codes 1IIS and 1IIX)(Radaev *et al.*, 2001, *J Biol Chem* 276:16469-16477), as well as has the structure of the human IgE Fc/Fc□RI□ complex (pdb accession code 1F6A)(Garman *et al.*, 2000, *Nature* 406:259-266).

[006] The different IgG subclasses have different affinities for the FcγRs, with IgG1 and IgG3 typically binding substantially better to the receptors than IgG2 and IgG4 (Jefferis *et al.*, 2002, *Immunol Lett* 82:57-65). All FcγRs bind the same region on IgG Fc, yet with different affinities: the high affinity binder FcγRI has a Kd for IgG1 of 10^{-8} M^{-1}, whereas the low affinity receptors FcγRII and FcγRIII generally bind at 10^{-6} and 10^{-5} respectively. The extracellular domains of FcγRIIIa and FcγRIIIb are 96% identical, however FcγRIIIb does not have a intracellular signaling domain. Furthermore, whereas FcγRI, FcγRIIa/c, and FcγRIIIa are positive regulators of immune complex-triggered activation, characterized by having an intracellular domain that has an immunoreceptor tyrosine-based activation motif (ITAM), FcγRIIb has an immunoreceptor tyrosine-based inhibition motif (ITIM) and is therefore inhibitory. Thus the former are referred to as activation receptors, and FcγRIIb is referred to as an inhibitory receptor. The receptors also differ in expression pattern and levels on different immune cells. Yet another level of complexity is the existence of a number of FcγR polymorphisms in the human proteome. A particularly relevant polymorphism with clinical significance is V158/F158 FcγRIIIa. Human IgG1 binds with greater affinity to the V158 allotype than to the F158 allotype. This difference in affinity, and presumably its effect on ADCC and/or ADCP, has been shown to be a significant determinant of the efficacy of the anti-CD20 antibody rituximab (Rituxan®, a registered trademark of IDEC Pharmaceuticals Corporation). Patients with the V158 allotype respond favorably to rituximab treatment; however, patients with the lower affinity F158 allotype respond poorly (Cartron *et al.*, 2002, *Blood* 99:754-758). Approximately 10-20% of humans are V158/V158

Samsung Bioepis Exhibit No. 1002
Page 11086

homozygous, 45% are V158/F158 heterozygous, and 35-45% of humans are F158/F158 homozygous (Lehrnbecher *et al.*, 1999, *Blood* 94:4220-4232; Cartron *et al.*, 2002, *Blood* 99:754-758). Thus 80-90% of humans are poor responders, that is they have at least one allele of the F158 FcγRIIIa.

[007] An overlapping but separate site on Fc, shown in Figure 1, serves as the interface for the complement protein C1q. In the same way that Fc/FcγR binding mediates ADCC, Fc/C1q binding mediates complement dependent cytotoxicity (CDC). C1q forms a complex with the serine proteases C1r and C1s to form the C1 complex. C1q is capable of binding six antibodies, although binding to two IgGs is sufficient to activate the complement cascade. Similar to Fc interaction with FcγRs, different IgG subclasses have different affinity for C1q, with IgG1 and IgG3 typically binding substantially better to the FcγRs than IgG2 and IgG4 (Jefferis *et al.*, 2002, *Immunol Lett* 82:57-65). There is currently no structure available for the Fc/C1q complex; however, mutagenesis studies have mapped the binding site on human IgG for C1q to a region involving residues D270, K322, K326, P329, and P331, and E333 (Idusogie *et al.*, 2000, *J Immunol* 164:4178-4184; Idusogie *et al.*, 2001, *J Immunol* 166:2571-2575).

[008] A site on Fc between the Cγ2 and Cγ3 domains, shown in Figure 1, mediates interaction with the neonatal receptor FcRn, the binding of which recycles endocytosed antibody from the endosome back to the bloodstream (Raghavan *et al.*, 1996, *Annu Rev Cell Dev Biol* 12:181-220; Ghetie *et al.*, 2000, *Annu Rev Immunol* 18:739-766). This process, coupled with preclusion of kidney filtration due to the large size of the full length molecule, results in favorable antibody serum half-lives ranging from one to three weeks. Binding of Fc to FcRn also plays a key role in antibody transport. The binding site for FcRn on Fc is also the site at which the bacterial proteins A and G bind. The tight binding by these proteins is typically exploited as a means to purify antibodies by employing protein A or protein G affinity chromatography during protein purification. Thus the fidelity of this region on Fc is important for both the clinical properties of antibodies and their purification. Available structures of the rat Fc/FcRn complex (Martin *et al.*, 2001, *Mol Cell* 7:867-877), and of the complexes of Fc with proteins A and G (Deisenhofer, 1981, *Biochemistry* 20:2361-2370; Sauer-Eriksson *et al.*, 1995, *Structure* 3:265-278; Tashiro *et al.*, 1995, *Curr Opin Struct Biol* 5:471-481) provide insight into the interaction of Fc with these proteins.

[009] A key feature of the Fc region is the conserved N-linked glycosylation that occurs at N297, shown in Figure 1. This carbohydrate, or oligosaccharide as it is sometimes referred, plays a critical structural and functional role for the antibody, and is one of the principle reasons that antibodies must be produced using mammalian expression systems. While not wanting to be limited to one theory, it is believed that the structural purpose of this carbohydrate may be to stabilize or solubilize Fc, determine a specific angle or level of flexibility between the Cγ3 and Cγ2 domains, keep the two Cγ2 domains from aggregating with one another across the central axis, or a combination of these.

Samsung Bioepis Exhibit No. 1002
Page 11087

Efficient Fc binding to FcγR and C1q requires this modification, and alterations in the composition of the N297 carbohydrate or its elimination affect binding to these proteins (Umaña *et al.*, 1999, *Nat Biotechnol* 17:176-180; Davies *et al.*, 2001, *Biotechnol Bioeng* 74:288-294; Mimura *et al.*, 2001, *J Biol Chem* 276:45539-45547.; Radaev *et al.*, 2001, *J Biol Chem* 276:16478-16483; Shields *et al.*, 2001, *J Biol Chem* 276:6591-6604; Shields *et al.*, 2002, *J Biol Chem* 277:26733-26740; Simmons *et al.*, 2002, *J Immunol Methods* 263:133-147). Yet the carbohydrate makes little if any specific contact with FcγRs (Radaev *et al.*, 2001, *J Biol Chem* 276:16469-16477), indicating that the functional role of the N297 carbohydrate in mediating Fc/FcγR binding may be via the structural role it plays in determining the Fc conformation. This is supported by a collection of crystal structures of four different Fc glycoforms, which show that the composition of the oligosaccharide impacts the conformation of Cγ2 and as a result the Fc/FcγR interface (Krapp *et al.*, 2003, *J Mol Biol* 325:979-989).

[010] The features of antibodies discussed above - specificity for target, ability to mediate immune effector mechanisms, and long half-life in serum - make antibodies powerful therapeutics. Monoclonal antibodies are used therapeutically for the treatment of a variety of conditions including cancer, inflammation, and cardiovascular disease. There are currently over ten antibody products on the market and hundreds in development. In addition to antibodies, an antibody-like protein that is finding an expanding role in research and therapy is the Fc fusion (Chamow *et al.*, 1996, *Trends Biotechnol* 14:52-60; Ashkenazi *et al.*, 1997, *Curr Opin Immunol* 9:195-200). An Fc fusion is a protein wherein one or more polypeptides is operably linked to Fc. An Fc fusion combines the Fc region of an antibody, and thus its favorable effector functions and pharmacokinetics, with the target-binding region of a receptor, ligand, or some other protein or protein domain. The role of the latter is to mediate target recognition, and thus it is functionally analogous to the antibody variable region. Because of the structural and functional overlap of Fc fusions with antibodies, the discussion on antibodies in the present invention extends directly to Fc fusions.

[011] Despite such widespread use, antibodies are not optimized for clinical use. Two significant deficiencies of antibodies are their suboptimal anticancer potency and their demanding production requirements. These deficiencies are addressed by the present invention

[012] There are a number of possible mechanisms by which antibodies destroy tumor cells, including anti-proliferation via blockage of needed growth pathways, intracellular signaling leading to apoptosis, enhanced down regulation and/or turnover of receptors, CDC, ADCC, ADCP, and promotion of an adaptive immune response (Cragg *et al.*, 1999, *Curr Opin Immunol* 11:541-547; Glennie *et al.*, 2000, *Immunol Today* 21:403-410). Anti-tumor efficacy may be due to a combination of these mechanisms, and their relative importance in clinical therapy appears to be cancer dependent. Despite this arsenal of anti-tumor weapons, the potency of antibodies as anti-cancer agents is unsatisfactory, particularly given their high cost. Patient tumor response data show that monoclonal

Samsung Bioepis Exhibit No. 1002
Page 11088

antibodies provide only a small improvement in therapeutic success over normal single-agent cytotoxic chemotherapeutics. For example, just half of all relapsed low-grade non-Hodgkin's lymphoma patients respond to the anti-CD20 antibody rituximab (McLaughlin *et al.*, 1998, *J Clin Oncol* 16:2825-2833). Of 166 clinical patients, 6% showed a complete response and 42% showed a partial response, with median response duration of approximately 12 months. Trastuzumab (Herceptin®, a registered trademark of Genentech), an anti-HER2/neu antibody for treatment of metastatic breast cancer, has less efficacy. The overall response rate using trastuzumab for the 222 patients tested was only 15%, with 8 complete and 26 partial responses and a median response duration and survival of 9 to 13 months (Cobleigh *et al.*, 1999, *J Clin Oncol* 17:2639-2648). Currently for anticancer therapy, any small improvement in mortality rate defines success. Thus there is a significant need to enhance the capacity of antibodies to destroy targeted cancer cells.

[013] A promising means for enhancing the anti-tumor potency of antibodies is via enhancement of their ability to mediate cytotoxic effector functions such as ADCC, ADCP, and CDC. The importance of FcγR-mediated effector functions for the anti-cancer activity of antibodies has been demonstrated in mice (Clynes *et al.*, 1998, *Proc Natl Acad Sci U S A* 95:652-656; Clynes *et al.*, 2000, *Nat Med* 6:443-446), and the affinity of interaction between Fc and certain FcγRs correlates with targeted cytotoxicity in cell-based assays (Shields *et al.*, 2001, *J Biol Chem* 276:6591-6604; Presta *et al.*, 2002, *Biochem Soc Trans* 30:487-490; Shields *et al.*, 2002, *J Biol Chem* 277:26733-26740). Additionally, a correlation has been observed between clinical efficacy in humans and their allotype of high (V158) or low (F158) affinity polymorphic forms of FcγRIIIa (Cartron *et al.*, 2002, *Blood* 99:754-758). Together these data suggest that an antibody with an Fc region optimized for binding to certain FcγRs may better mediate effector functions and thereby destroy cancer cells more effectively in patients. The balance between activating and inhibiting receptors is an important consideration, and optimal effector function may result from an Fc with enhanced affinity for activation receptors, for example FcγRI, FcγRIIa/c, and FcγRIIIa, yet reduced affinity for the inhibitory receptor FcγRIIb. Furthermore, because FcγRs can mediate antigen uptake and processing by antigen presenting cells, enhanced Fc/FcγR affinity may also improve the capacity of antibody therapeutics to elicit an adaptive immune response.

[014] Mutagenesis studies have been carried out on Fc towards various goals, with substitutions typically made to alanine (referred to as alanine scanning) or guided by sequence homology substitutions (Duncan *et al.*, 1988, *Nature* 332:563-564; Lund *et al.*, 1991, *J Immunol* 147:2657-2662; Lund *et al.*, 1992, *Mol Immunol* 29:53-59; Jefferis *et al.*, 1995, *Immunol Lett* 44:111-117; Lund *et al.*, 1995, *Faseb J* 9:115-119; Jefferis *et al.*, 1996, *Immunol Lett* 54:101-104; Lund *et al.*, 1996, *J Immunol* 157:4963-4969; Armour *et al.*, 1999, *Eur J Immunol* 29:2613-2624; Shields *et al.*, 2001, *J Biol Chem* 276:6591-6604; Jefferis *et al.*, 2002, *Immunol Lett* 82:57-65) (US 5,624,821; US 5,885,573; PCT WO 00/42072; PCT WO 99/58572). The majority of substitutions reduce or ablate binding with FcγRs.

Samsung Bioepis Exhibit No. 1002
Page 11089

However some success has been achieved at obtaining Fc variants with higher FcγR affinity. (See for example US 5,624,821, and PCT WO 00/42072). For example, Winter and colleagues substituted the human amino acid at position 235 of mouse IgG2b antibody (a glutamic acid to leucine mutation) that increased binding of the mouse antibody to human FcγRI by100-fold (Duncan *et al.*, 1988, *Nature* 332:563-564) (US 5,624,821). Shields *et al.* used alanine scanning mutagenesis to map Fc residues important to FcγR binding, followed by substitution of select residues with non-alanine mutations (Shields *et al.*, 2001, *J Biol Chem* 276:6591-6604; Presta *et al.*, 2002, *Biochem Soc Trans* 30:487-490) (PCT WO 00/42072). Several mutations disclosed in this study, including S298A, E333A, and K334A, show enhanced binding to the activating receptor FcγRIIIa and reduced binding to the inhibitory receptor FcγRIIb. These mutations were combined to obtain double and triple mutation variants that show additive improvements in binding. The best variant disclosed in this study is a S298A/E333A/K334A triple mutant with approximately a 1.7-fold increase in binding to F158 FcγRIIIa, a 5-fold decrease in binding to FcγRIIb, and a 2.1-fold enhancement in ADCC.

[015] Enhanced affinity of Fc for FcγR has also been achieved using engineered glycoforms generated by expression of antibodies in engineered or variant cell lines (Umaña *et al.*, 1999, *Nat Biotechnol* 17:176-180; Davies *et al.*, 2001, *Biotechnol Bioeng* 74:288-294; Shields *et al.*, 2002, *J Biol Chem* 277:26733-26740; Shinkawa *et al.*, 2003, *J Biol Chem* 278:3466-3473). This approach has generated substantial enhancements of the capacity of antibodies to bind FcγRIIIa and to mediate ADCC. Although there are practical limitations such as the growth efficiency of the expression strains under large scale production conditions, this approach for enhancing Fc/FcγR affinity and effector function is promising. Indeed, coupling of these alternate glycoform technologies with the Fc variants of the present invention may provide additive or synergistic effects for optimal effector function.

[016] Although there is a need for greater effector function, for some antibody therapeutics reduced or eliminated effector function may be desired. This is often the case for therapeutic antibodies whose mechanism of action involves blocking or antagonism but not killing of the cells bearing target antigen. In these cases depletion of target cells is undesirable and can be considered a side effect. For example, the ability of anti-CD4 antibodies to block CD4 receptors on T cells makes them effective anti-inflammatories, yet their ability to recruit FcγR receptors also directs immune attack against the target cells, resulting in T cell depletion (Reddy *et al.*, 2000, *J Immunol* 164:1925-1933). Effector function can also be a problem for radiolabeled antibodies, referred to as radioconjugates, and antibodies conjugated to toxins, referred to as immunotoxins. These drugs can be used to destroy cancer cells, but the recruitment of immune cells via Fc interaction with FcγRs brings healthy immune cells in proximity to the deadly payload (radiation or toxin), resulting in depletion of normal lymphoid tissue along with targeted cancer cells (Hutchins *et al.*, 1995, *Proc Natl Acad Sci U S A* 92:11980-11984; White *et al.*, 2001, *Annu Rev Med* 52:125-145). This problem can potentially be circumvented by using IgG isotypes that poorly recruit complement or effector cells, for example IgG2

Samsung Bioepis Exhibit No. 1002
Page 11090

and IgG4. An alternate solution is to develop Fc variants that reduce or ablate binding (Alegre *et al.*, 1994, *Transplantation* 57:1537-1543; Hutchins *et al.*, 1995, *Proc Natl Acad Sci U S A* 92:11980-11984; Armour *et al.*, 1999, *Eur J Immunol* 29:2613-2624; Reddy *et al.*, 2000, *J Immunol* 164:1925-1933; Xu *et al.*, 2000, *Cell Immunol* 200:16-26; Shields *et al.*, 2001, *J Biol Chem* 276:6591-6604) (US 6,194,551; US 5,885,573; PCT WO 99/58572). A critical consideration for the reduction or elimination of effector function is that other important antibody properties not be perturbed. Fc variants should be engineered that not only ablate binding to FcγRs and/or C1q, but also maintain antibody stability, solubility, and structural integrity, as well as ability to interact with other important Fc ligands such as FcRn and proteins A and G.

[017] The present invention addresses another major shortcoming of antibodies, namely their demanding production requirements (Garber, 2001, *Nat Biotechnol* 19:184-185; Dove, 2002, *Nat Biotechnol* 20:777-779). Antibodies must be expressed in mammalian cells, and the currently marketed antibodies together with other high-demand biotherapeutics consume essentially all of the available manufacturing capacity. With hundreds of biologics in development, the majority of which are antibodies, there is an urgent need for more efficient and cheaper methods of production. The downstream effects of insufficient antibody manufacturing capacity are three-fold. First, it dramatically raises the cost of goods to the producer, a cost that is passed on to the patient. Second, it hinders industrial production of approved antibody products, limiting availability of high demand therapeutics to patients. Finally, because clinical trials require large amounts of a protein that is not yet profitable, the insufficient supply impedes progress of the growing antibody pipeline to market.

[018] Alternative production methods have been explored in attempts at alleviating this problem. Transgenic plants and animals are being pursued as potentially cheaper and higher capacity production systems (Chadd *et al.*, 2001, *Curr Opin Biotechnol* 12:188-194). Such expression systems, however, can generate glycosylation patterns significantly different from human glycoproteins. This may result in reduced or even lack of effector function because, as discussed above, the carbohydrate structure can significantly impact FcγR and complement binding. A potentially greater problem with nonhuman glycoforms may be immunogenicity; carbohydrates are a key source of antigenicity for the immune system, and the presence of nonhuman glycoforms has a significant chance of eliciting antibodies that neutralize the therapeutic, or worse cause adverse immune reactions. Thus the efficacy and safety of antibodies produced by transgenic plants and animals remains uncertain. Bacterial expression is another attractive solution to the antibody production problem. Expression in bacteria, for example *E. coli*, provides a cost-effective and high capacity method for producing proteins. For complex proteins such as antibodies there are a number of obstacles to bacterial expression, including folding and assembly of these complex molecules, proper disulfide formation, and solubility, stability, and functionality in the absence of glycosylation because proteins expressed in bacteria are not glycosylated. Full length unglycosylated antibodies that bind antigen have been successfully expressed in *E. coli* (Simmons *et al.*, 2002, *J Immunol*

Samsung Bioepis Exhibit No. 1002
Page 11091

Methods 263:133-147), and thus, folding, assembly, and proper disulfide formation of bacterially expressed antibodies are possible in the absence of the eukaryotic chaperone machinery. However the ultimate utility of bacterially expressed antibodies as therapeutics remains hindered by the lack of glycosylation, which results in lack effector function and may result in poor stability and solubility. This will likely be more problematic for formulation at the high concentrations for the prolonged periods demanded by clinical use.

[019] An aglycosylated Fc with favorable solution properties and the capacity to mediate effector functions would be significantly enabling for the alternate production methods described above. By overcoming the structural and functional shortcomings of aglycosylated Fc, antibodies can be produced in bacteria and transgenic plants and animals with reduced risk of immunogenicity, and with effector function for clinical applications in which cytotoxicity is desired such as cancer. The present invention describes the utilization of protein engineering methods to develop stable, soluble Fc variants with effector function. Currently, such Fc variants do not exist in the art.

[020] In summary, there is a need for antibodies with enhanced therapeutic properties. Engineering of optimized or enhanced Fc variants is a promising approach to meeting this need. Yet a substantial obstacle to engineering Fc variants with the desired properties is the difficulty in predicting what amino acid modifications, out of the enormous number of possibilities, will achieve the desired goals, coupled with the inefficient production and screening methods for antibodies. Indeed one of the principle reasons for the incomplete success of the prior art is that approaches to Fc engineering have thus far involved hit-or-miss methods such as alanine scans or production of glycoforms using different expression strains. In these studies, the Fc modifications that were made were fully or partly random in hopes of obtaining variants with favorable properties. The present invention provides a variety of engineering methods, many of which are based on more sophisticated and efficient techniques, which may be used to overcome these obstacles in order to develop Fc variants that are optimized for the desired properties. The described engineering methods provide design strategies to guide Fc modification, computational screening methods to design favorable Fc variants, library generation approaches for determining promising variants for experimental investigation, and an array of experimental production and screening methods for determining the Fc variants with favorable properties.

SUMMARY OF THE INVENTION

[021] The present invention provides Fc variants that are optimized for a number of therapeutically relevant properties.

Samsung Bioepis Exhibit No. 1002
Page 11092

[022] It is an object of the present invention to provide novel Fc positions at which amino acid modifications may be made to generate optimized Fc variants. Said Fc positions include 240, 244, 245, 247, 262, 263, 266, 299, 313, 325, 328, and 332, wherein the numbering of the residues in the Fc region is that of the EU index as in Kabat. The present invention describes any amino acid modification at any of said novel Fc positions in order to generate an optimized Fc variant.

[023] It is a further object of the present invention to provide Fc variants that have been screened computationally. A computationally screened Fc variant is one that is predicted by the computational screening calculations described herein as having a significantly greater potential than random for being optimized for a desired property. In this way, computational screening serves as a prelude to or surrogate for experimental screening, and thus said computationally screened Fc variants are considered novel.

[024] It is a further object of the present invention to provide Fc variants that have been characterized using one or more of the experimental methods described herein. In one embodiment, said Fc variants comprise at least one amino acid substitution at a position selected from the group consisting of: 234, 235, 239, 240, 241, 243, 244, 245, 247, 262, 263, 264, 265, 266, 267, 269, 296, 297, 298, 299, 313, 325, 327, 328, 329, 330, and 332, wherein the numbering of the residues in the Fc region is that of the EU index as in Kabat. In a preferred embodiment, said Fc variants comprise at least one substitution selected from the group consisting of L234D, L234E, L234N, L234Q, L234T, L234H, L234Y, L234I, L234V, L234F, L235D, L235S, L235N, L235Q, L235T, L235H, L235Y, L235I, L235V, L235F, S239D, S239E, S239N, S239Q, S239F, S239T, S239H, S239Y, V240I, V240A, V240T, V240M, F241W, F241L, F241Y, F241E, F241R, F243W, F243L F243Y, F243R, F243Q, P244H, P245A, P247V, P247G, V262I, V262A, V262T, V262E, V263I, V263A, V263T, V263M, V264L, V264I, V264W, V264T, V264R, V264F, V264M, V264Y, V264E, D265G, D265N, D265Q, D265Y, D265F, D265V, D265I, D265L, D265H, D265T, V266I, V266A, V266T, V266M, S267Q, S267L, E269H, E269Y, E269F, E269R, Y296E, Y296Q, Y296D, Y296N, Y296S, Y296T, Y296L, Y296I, Y296H, N297S, N297D, N297E, A298H, T299I, T299L, T299A, T299S, T299V, T299H, T299F, T299E, W313F, N325Q, N325L, N325I, N325D, N325E, N325A, N325T, N325V, N325H, A327N, A327L, L328M, L328D, L328E, L328N, L328Q, L328F, L328I, L328V, L328T, L328H, L328A, P329F, A330L, A330Y, A330V, A330I, A330F, A330R, A330H, I332D, I332E, I332N, I332Q, I332T, I332H, I332Y, and I332A, wherein the numbering of the residues in the Fc region is that of the EU index as in Kabat. In a mostly preferred embodiment, said Fc variants are selected from the group consisting of V264L, V264I, F241W, F241L, F243W, F243L, F241L/F243L/V262I/V264I, F241W/F243W, F241W/F243W/V262A/V264A, F241L/V262I, F243L/V264I, F243L/V262I/V264W, F241Y/F243Y/V262T/V264T, F241E/F243R/V262E/V264R, F241E/F243Q/V262T/V264E, F241R/F243Q/V262T/V264R, F241E/F243Y/V262T/V264R, L328M, L328E, L328F, I332E, L328M/I332E, P244H, P245A, P247V, W313F, P244H/P245A/P247V, P247G, V264I/I332E, F241E/F243R/V262E/V264R/I332E, F241E/F243Q/V262T/V264E/I332E,

10

Samsung Bioepis Exhibit No. 1002
Page 11093

F241R/F243Q/V262T/V264R/I332E, F241E/F243Y/V262T/V264R/I332E, S298A/I332E, S239E/I332E, S239Q/I332E, S239E, D265G, D265N, S239E/D265G, S239E/D265N, S239E/D265Q, Y296E, Y296Q, T299I, A327N, S267Q/A327S, S267L/A327S , A327L, P329F, A330L, A330Y, I332D, N297S, N297D, N297S/I332E, N297D/I332E, N297E/I332E, D265Y/N297D/I332E, D265Y/N297D/T299L/I332E, D265F/N297E/I332E, L328I/I332E, L328Q/I332E, I332N, I332Q, V264T, V264F, V240I, V263I, V266I, T299A, T299S, T299V, N325Q, N325L, N325I, S239D, S239N, S239F, S239D/I332D, S239D/I332E, S239D/I332N, S239D/I332Q, S239E/I332D, S239E/I332N, S239E/I332Q, S239N/I332D, S239N/I332E, S239N/I332N, S239N/I332Q, S239Q/I332D, S239Q/I332N, S239Q/I332Q, Y296D, Y296N, F241Y/F243Y/V262T/V264T/N297D/I332E, A330Y/I332E, V264I/A330Y/I332E, A330L/I332E, V264I/A330L/I332E, L234D, L234E, L234N, L234Q, L234T, L234H, L234Y, L234I, L234V, L234F, L235D, L235S, L235N, L235Q, L235T, L235H, L235Y, L235I, L235V, L235F, S239T, S239H, S239Y, V240A, V240T, V240M, V263A, V263T, V263M, V264M, V264Y, V266A, V266T, V266M, E269H, E269Y, E269F, E269R, Y296S, Y296T, Y296L, Y296I, A298H, T299H, A330V, A330I, A330F, A330R, A330H, N325D, N325E, N325A, N325T, N325V, N325H, L328D/I332E, L328E/I332E, L328N/I332E, L328Q/I332E, L328V/I332E, L328T/I332E, L328H/I332E, L328I/I332E, L328A, I332T, I332H, I332Y, I332A, S239E/V264I/I332E, S239Q/V264I/I332E, S239E/V264I/A330Y/I332E, S239E/V264I/S298A/A330Y/I332E, S239D/N297D/I332E, S239E/N297D/I332E, S239D/D265V/N297D/I332E, S239D/D265I/N297D/I332E, S239D/D265L/N297D/I332E, S239D/D265F/N297D/I332E, S239D/D265Y/N297D/I332E, S239D/D265H/N297D/I332E, S239D/D265T/N297D/I332E, V264E/N297D/I332E, Y296D/N297D/I332E, Y296E/N297D/I332E, Y296N/N297D/I332E, Y296Q/N297D/I332E, Y296H/N297D/I332E, Y296T/N297D/I332E, N297D/T299V/I332E, N297D/T299I/I332E, N297D/T299L/I332E, N297D/T299F/I332E, N297D/T299H/I332E, N297D/T299E/I332E, N297D/A330Y/I332E, N297D/S298A/A330Y/I332E, S239D/A330Y/I332E, S239N/A330Y/I332E, S239D/A330L/I332E, S239N/A330L/I332E, V264I/S298A/I332E, S239D/S298A/I332E, S239N/S298A/I332E, S239D/V264I/I332E, S239D/V264I/S298A/I332E, and S239D/V264I/A330L/I332E, wherein the numbering of the residues in the Fc region is that of the EU index as in Kabat.

[025] It is a further object of the present invention to provide an Fc variant that binds with greater affinity to one or more FcγRs. In one embodiment, said Fc variants have affinity for an FcγR that is more than 1-fold greater than that of the parent Fc polypeptide. In an alternate embodiment, said Fc variants have affinity for an FcγR that is more than 5-fold greater than that of the parent Fc polypeptide. In a preferred embodiment, said Fc variants have affinity for an FcγR that is between 5-fold and 300-fold greater than that of the parent Fc polypeptide. In one embodiment, said Fc variants comprise at least one amino acid substitution at a position selected from the group consisting of: 234, 235, 239, 240, 243, 264, 266, 328, 330, 332, and 325, wherein the numbering of the residues in the Fc region is that of the EU index as in Kabat. In a preferred embodiment, said Fc variants comprise at least one amino acid substitution selected from the group consisting of: L234E, L234Y, L234I, L235D,

L235S, L235Y, L235I, S239D, S239E, S239N, S239Q, S239T, V240I, V240M, F243L, V264I, V264T, V264Y, V266I, L328M, L328I, L328Q, L328D, L328V, L328T, A330Y, A330L, A330I, I332D, I332E, I332N, I332Q, and N325T, wherein the numbering of the residues in the Fc region is that of the EU index as in Kabat. In a mostly preferred embodiment, said Fc variants are selected from the group consisting of V264I, F243L/V264I, L328M, I332E, L328M/I332E, V264I/I332E, S298A/I332E, S239E/I332E, S239Q/I332E, S239E, A330Y, I332D, L328I/I332E, L328Q/I332E, V264T, V240I, V266I, S239D, S239D/I332D, S239D/I332E, S239D/I332N, S239D/I332Q, S239E/I332D, S239E/I332N, S239E/I332Q, S239N/I332D, S239N/I332E, S239Q/I332D, A330Y/I332E, V264I/A330Y/I332E, A330L/I332E, V264I/A330L/I332E, L234E, L234Y, L234I, L235D, L235S, L235Y, L235I, S239T, V240M, V264Y, A330I, N325T, L328D/I332E, L328V/I332E, L328T/I332E, L328I/I332E, S239E/V264I/I332E, S239Q/V264I/I332E, S239E/V264I/A330Y/I332E, S239D/A330Y/I332E, S239N/A330Y/I332E, S239D/A330L/I332E, S239N/A330L/I332E, V264I/S298A/I332E, S239D/S298A/I332E, S239N/S298A/I332E, S239D/V264I/I332E, S239D/V264I/S298A/I332E, and S239D/V264I/A330L/I332E, wherein the numbering of the residues in the Fc region is that of the EU index as in Kabat.

[026] It is a further object of the present invention to provide Fc variantd that have a FcγRIIIa-fold:FcγRIIb-fold ratio greater than 1:1. In one embodiment, said Fc variants have a FcγRIIIa-fold:FcγRIIb-fold ratio greater than 11:1. In a preferred embodiment, said Fc variants have a FcγRIIIa-fold:FcγRIIb-fold ratio between 11:1 and 86:1. In one embodiment, said Fc variants comprise at least one amino acid substitution at a position selected from the group consisting of: 234, 235, 239, 240, 264, 296, 330, and I332, wherein the numbering of the residues in the Fc region is that of the EU index as in Kabat. In a preferred embodiment, said Fc variants comprise at least one amino acid substitution selected from the group consisting of: L234Y, L234I, L235I, S239D, S239E, S239N, S239Q, V240A, V240M, V264I, V264Y, Y296Q, A330L, A330Y, A330I, I332D, and I332E, wherein the numbering of the residues in the Fc region is that of the EU index as in Kabat. In a mostly preferred embodiment, said Fc variants are selected from the group consisting of: I332E, V264I/I332E, S239E/I332E, S239Q/I332E, Y296Q, A330L, A330Y, I332D, S239D, S239D/I332E, A330Y/I332E, V264I/A330Y/I332E, A330L/I332E, V264I/A330L/I332E, L234Y, L234I, L235I, V240A, V240M, V264Y, A330I, S239D/A330L/I332E, S239D/S298A/I332E, S239N/S298A/I332E, S239D/V264I/I332E, S239D/V264I/S298A/I332E, and S239D/V264I/A330L/I332E, wherein the numbering of the residues in the Fc region is that of the EU index as in Kabat.

[027] It is a further object of the present invention to provide Fc variants that mediate effector function more effectively in the presence of effector cells. In one embodiment, said Fc variants mediate ADCC that is greater than that mediated by the parent Fc polypeptide. In a preferred embodiment, said Fc variants mediate ADCC that is more than 5-fold greater than that mediated by the parent Fc polypeptide. In a mostly preferred embodiment, said Fc variants mediate ADCC that is between 5-fold and 50-fold greater than that mediated by the parent Fc polypeptide. In one

Samsung Bioepis Exhibit No. 1002
Page 11095

embodiment, said Fc variants comprise at least one amino acid substitution at a position selected from the group consisting of: 234, 235, 239, 240, 243, 264, 266, 328, 330, 332, and 325, wherein the numbering of the residues in the Fc region is that of the EU index as in Kabat. In a preferred embodiment, said Fc variants comprise at least one amino acid substitutions selected from the group consisting of: L234E, L234Y, L234I, L235D, L235S, L235Y, L235I, S239D, S239E, S239N, S239Q, S239T, V240I, V240M, F243L, V264I, V264T, V264Y, V266I, L328M, L328I, L328Q, L328D, L328V, L328T, A330Y, A330L, A330I, I332D, I332E, I332N, I332Q, and N325T, wherein the numbering of the residues in the Fc region is that of the EU index as in Kabat. In a mostly preferred embodiment, said Fc variants are selected from the group consisting of: V264I, F243L/V264I, L328M, I332E, L328M/I332E, V264I/I332E, S298A/I332E, S239E/I332E, S239Q/I332E, S239E, A330Y, I332D, L328I/I332E, L328Q/I332E, V264T, V240I, V266I, S239D, S239D/I332D, S239D/I332E, S239D/I332N, S239D/I332Q, S239E/I332D, S239E/I332N, S239E/I332Q, S239N/I332D, S239N/I332E, S239Q/I332D, A330Y/I332E, V264I/A330Y/I332E, A330L/I332E, V264I/A330L/I332E, L234E, L234Y, L234I, L235D, L235S, L235Y, L235I, S239T, V240M, V264Y, A330I, N325T, L328D/I332E, L328V/I332E, L328T/I332E, L328I/I332E, S239E/V264I/I332E, S239Q/V264I/I332E, S239E/V264I/A330Y/I332E, S239D/A330Y/I332E, S239N/A330Y/I332E, S239D/A330L/I332E, S239N/A330L/I332E, V264I/S298A/I332E, S239D/S298A/I332E, S239N/S298A/I332E, S239D/V264I/I332E, S239D/V264I/S298A/I332E, and S239D/V264I/A330L/I332E, wherein the numbering of the residues in the Fc region is that of the EU index as in Kabat.

[028] It is a further object of the present invention to provide Fc variants that bind with weaker affinity to one or more FcγRs. In one embodiment, said Fc variants comprise at least one amino acid substitution at a position selected from the group consisting of: 234, 235, 239, 240, 241, 243, 244, 245, 247, 262, 263, 264, 265, 266, 267, 269, 296, 297, 298, 299, 313, 325, 327, 328, 329, 330, and 332, wherein the numbering of the residues in the Fc region is that of the EU index as in Kabat. In a preferred embodiment, said Fc variants comprise an amino acid substitution at a position selected from the group consisting of: L234D, L234N, L234Q, L234T, L234H, L234V, L234F, L235N, L235Q, L235T, L235H, L235V, L235F, S239E, S239N, S239Q, S239F, S239H, S239Y, V240A, V240T, F241W, F241L, F241Y, F241E, F241R, F243W, F243L F243Y, F243R, F243Q, P244H, P245A, P247V, P247G, V262I, V262A, V262T, V262E, V263I, V263A, V263T, V263M, V264L, V264I, V264W, V264T, V264R, V264F, V264M, V264E, D265G, D265N, D265Q, D265Y, D265F, D265V, D265I, D265L, D265H, D265T, V266A, V266T, V266M, S267Q, S267L, E269H, E269Y, E269F, E269R, Y296E, Y296Q, Y296D, Y296N, Y296S, Y296T, Y296L, Y296I, Y296H, N297S, N297D, N297E, A298H, T299I, T299L, T299A, T299S, T299V, T299H, T299F, T299E, W313F, N325Q, N325L, N325I, N325D, N325E, N325A, N325V, N325H, A327N, A327L, L328M, 328E, L328N, L328Q, L328F, L328H, L328A, P329F, A330L, A330V, A330F, A330R, A330H, I332N, I332Q, I332T, I332H, I332Y, and I332A, wherein the numbering of the residues in the Fc region is that of the EU index as in Kabat. In a mostly preferred embodiment, said Fc variants are selected from the group consisting of: V264L, F241W, F241L, F243W, F243L, F241L/F243L/V262I/V264I, F241W/F243W, F241W/F243W/V262A/V264A, F241L/V262I, F243L/V262I/V264W, F241Y/F243Y/V262T/V264T,

Samsung Bioepis Exhibit No. 1002
Page 11096

F241E/F243R/V262E/V264R, F241E/F243Q/V262T/V264E, F241R/F243Q/V262T/V264R, F241E/F243Y/V262T/V264R, L328M, L328E, L328F, P244H, P245A, P247V, W313F, P244H/P245A/P247V, P247G, F241E/F243R/V262E/V264R/I332E, F241E/F243Y/V262T/V264R/I332E, D265G, D265N, S239E/D265G, S239E/D265N, S239E/D265Q, Y296E, Y296Q, T299I, A327N, S267Q/A327S, S267L/A327S , A327L, P329F, A330L, N297S, N297D, N297S/I332E, I332N, I332Q, V264F, V263I, T299A, T299S, T299V, N325Q, N325L, N325I, S239N, S239F, S239N/I332N, S239N/I332Q, S239Q/I332N, S239Q/I332Q, Y296D, Y296N, L234D, L234N, L234Q, L234T, L234H, L234V, L234F, L235N, L235Q, L235T, L235H, L235V, L235F, S239H, S239Y, V240A, V263T, V263M, V264M, V266A, V266T, V266M, E269H, E269Y, E269F, E269R, Y296S, Y296T, Y296L, Y296I, A298H, T299H, A330V, A330F, A330R, A330H, N325D, N325E, N325A, N325V, N325H, L328E/I332E, L328N/I332E, L328Q/I332E, L328H/I332E, L328A, I332T, I332H, I332Y, and I332A, wherein the numbering of the residues in the Fc region is that of the EU index as in Kabat.

[029] It is a further object of the present invention to provide Fc variants that mediate ADCC in the presence of effector cells less effectively. In one embodiment, said Fc variants comprise at least one amino acid substitution at a position selected from the group consisting of: 234, 235, 239, 240, 241, 243, 244, 245, 247, 262, 263, 264, 265, 266, 267, 269, 296, 297, 298, 299, 313, 325, 327, 328, 329, 330, and 332, wherein the numbering of the residues in the Fc region is that of the EU index as in Kabat. In a preferred embodiment, said Fc variants comprise at least one amino acid substitution at a position selected from the group consisting of: L234D, L234N, L234Q, L234T, L234H, L234V, L234F, L235N, L235Q, L235T, L235H, L235V, L235F, S239E, S239N, S239Q, S239F, S239H, S239Y, V240A, V240T, F241W, F241L, F241Y, F241E, F241R, F243W, F243L F243Y, F243R, F243Q, P244H, P245A, P247V, P247G, V262I, V262A, V262T, V262E, V263I, V263A, V263T, V263M, V264L, V264I, V264W, V264T, V264R, V264F, V264M, V264E, D265G, D265N, D265Q, D265Y, D265F, D265V, D265I, D265L, D265H, D265T, V266A, V266T, V266M, S267Q, S267L, E269H, E269Y, E269F, E269R, Y296E, Y296Q, Y296D, Y296N, Y296S, Y296T, Y296L, Y296I, Y296H, N297S, N297D, N297E, A298H, T299I, T299L, T299A, T299S, T299V, T299H, T299F, T299E, W313F, N325Q, N325L, N325I, N325D, N325E, N325A, N325V, N325H, A327N, A327L, L328M, 328E, L328N, L328Q, L328F, L328H, L328A, P329F, A330L, A330V, A330F, A330R, A330H, I332N, I332Q, I332T, I332H, I332Y, and I332A, wherein the numbering of the residues in the Fc region is that of the EU index as in Kabat. In a mostly preferred embodiment, said Fc variants are selected from the group consisting of: V264L, F241W, F241L, F243W, F243L, F241L/F243L/V262I/V264I, F241W/F243W, F241W/F243W/V262A/V264A, F241L/V262I, F243L/V262I/V264W, F241Y/F243Y/V262T/V264T, F241E/F243R/V262E/V264R, F241E/F243Q/V262T/V264E, F241R/F243Q/V262T/V264R, F241E/F243Y/V262T/V264R, L328M, L328E, L328F, P244H, P245A, P247V, W313F, P244H/P245A/P247V, P247G, F241E/F243R/V262E/V264R/I332E, F241E/F243Y/V262T/V264R/I332E, D265G, D265N, S239E/D265G, S239E/D265N, S239E/D265Q, Y296E, Y296Q, T299I, A327N, S267Q/A327S, S267L/A327S , A327L, P329F, A330L, N297S, N297D, N297S/I332E, I332N, I332Q, V264F, V263I, T299A, T299S, T299V, N325Q, N325L, N325I,

Samsung Bioepis Exhibit No. 1002
Page 11097

S239N, S239F, S239N/I332N, S239N/I332Q, S239Q/I332N, S239Q/I332Q, Y296D, Y296N, L234D, L234N, L234Q, L234T, L234H, L234V, L234F, L235N, L235Q, L235T, L235H, L235V, L235F, S239H, S239Y, V240A, V263T, V263M, V264M, V266A, V266T, V266M, E269H, E269Y, E269F, E269R, Y296S, Y296T, Y296L, Y296I, A298H, T299H, A330V, A330F, A330R, A330H, N325D, N325E, N325A, N325V, N325H, L328E/I332E, L328N/I332E, L328Q/I332E, L328H/I332E, L328A, I332T, I332H, I332Y, and I332A, wherein the numbering of the residues in the Fc region is that of the EU index as in Kabat.

[030] It is a further object of the present invention to provide Fc variants that have improved function and/or solution properties as compared to the aglycosylated form of the parent Fc polypeptide. Improved functionality herein includes but is not limited to binding affinity to an Fc ligand. Improved solution properties herein includes but is not limited to stability and solubility. In one embodiment, said aglycosylated Fc variants bind to an FcγR with an affinity that is comparable to or better than the glycosylated parent Fc polypeptide. In an alternate embodiment, said Fc variants bind to an FcγR with an affinity that is within 0.4-fold of the glycosylated form of the parent Fc polypeptide. In one embodiment, said Fc variants comprise at least one amino acid substitution at a position selected from the group consisting of: 239, 241, 243, 262, 264, 265, 296, 297, 330, and 332, wherein the numbering of the residues in the Fc region is that of the EU index as in Kabat. In a preferred embodiment, said Fc variants comprise an amino acid substitution selected from the group consisting of: S239D, S239E, F241Y, F243Y, V262T, V264T, V264E, D265Y, D265H, Y296N, N297D, A330Y, and I332E, wherein the numbering of the residues in the Fc region is that of the EU index as in Kabat. In a mostly preferred embodiment, said Fc variants are selected from the group consisting of: N297D/I332E, F241Y/F243Y/V262T/V264T/N297D/I332E, S239D/N297D/I332E, S239E/N297D/I332E, S239D/D265Y/N297D/I332E, S239D/D265H/N297D/I332E, V264E/N297D/I332E, Y296N/N297D/I332E, and N297D/A330Y/I332E, wherein the numbering of the residues in the Fc region is that of the EU index as in Kabat.

[031] The present invention also provides methods for engineering optimized Fc variants. It is an object of the present invention to provide design strategies that may be used to guide Fc optimization. It is a further object of the present invention to provide computational screening methods that may be used to design Fc variants. It is a further object of the present invention to provide methods for generating libraries for experimental testing. It is a further object of the present invention to provide experimental production and screening methods for obtaining optimized Fc variants.

[032] The present invention provides isolated nucleic acids encoding the Fc variants described herein. The present invention provides vectors comprising said nucleic acids, optionally, operably linked to control sequences. The present invention provides host cells containing the vectors, and methods for producing and optionally recovering the Fc variants.

Samsung Bioepis Exhibit No. 1002
Page 11098

[033] The present invention provides novel antibodies and Fc fusions that comprise the Fc variants disclosed herein. Said novel antibodies and Fc fusions may find use in a therapeutic product.

[034] The present invention provides compositions comprising antibodies and Fc fusions that comprise the Fc variants described herein, and a physiologically or pharmaceutically acceptable carrier or diluent.

[035] The present invention contemplates therapeutic and diagnostic uses for antibodies and Fc fusions that comprise the Fc variants disclosed herein.

BRIEF DESCRIPTION OF THE DRAWINGS

[036] Figure 1. Antibody structure and function. Shown is a model of a full length human IgG1 antibody, modeled using a humanized Fab structure from pdb accession code 1CE1 (James *et al.*, 1999, *J Mol Biol* 289:293-301) and a human IgG1 Fc structure from pdb accession code 1DN2 (DeLano *et al.*, 2000, *Science* 287:1279-1283). The flexible hinge that links the Fab and Fc regions is not shown. IgG1 is a homodimer of heterodimers, made up of two light chains and two heavy chains. The Ig domains that comprise the antibody are labeled, and include V_L and C_L for the light chain, and V_H, Cgamma1 (Cγ1), Cgamma2 (Cγ2), and Cgamma3 (Cγ3) for the heavy chain. The Fc region is labeled. Binding sites for relevant proteins are labeled, including the antigen binding site in the variable region, and the binding sites for FcγRs, FcRn, C1q, and proteins A and G in the Fc region.

[037] Figure 2. The Fc/FcγRIIIb complex structure 1IIS. Fc is shown as a gray ribbon diagram, and FcγRIIIb is shown as a black ribbon. The N297 carbohydrate is shown as black sticks.

[038] Figure 3. The amino acid sequence of the heavy chain of the antibody alemtuzumab (Campath®, a registered trademark of Ilex Pharmaceuticals LP), illustrating positions numbered sequentially (2 lines above the amino acid sequence) and positions numbered according to the EU index as in Kabat (2 lines below the amino acid sequence. The approximate beginnings of Ig domains VH1, Cγ1, the hinge, Cγ2, and Cγ3 are also labeled above the sequential numbering. Polymorphisms have been observed at a number of Fc positions, including but not limited to Kabat 270, 272, 312, 315, 356, and 358, and thus slight differences between the presented sequence and sequences in the prior art may exist.

Samsung Bioepis Exhibit No. 1002
Page 11099

[039] Figure 4. Experimental library residues mapped onto the Fc/FcγRIIIb complex structure 1IIS. Fc is shown as a gray ribbon diagram, and FcγRIIIb is shown as a black ribbon. Experimental library residues are shown as black ball and sticks. The N297 carbohydrate is shown as black sticks.

[040] Figure 5. The human IgG1 Fc sequence showing positions relevant to the design of the Fc variant experimental library. The sequence includes the hinge region, domain Cγ2, and domain Cγ3. Residue numbers are according to the EU index as in Kabat. Positions relevant to the experimental library are underlined. Because of observed polymorphic mutations at a number of Fc positions, slight differences between the presented sequence and sequences in the literature may exist.

[041] Figure 6. Expression of Fc variant and wild type (WT) proteins of alemtuzumab in 293T cells. Plasmids containing alemtuzumab heavy chain genes (WT or variants) were co-transfected with plasmid containing the alemtuzumab light chain gene. Media were harvested 5 days after transfection. For each transfected sample, 10ul medium was loaded on a SDS-PAGE gel for Western analysis. The probe for Western was peroxidase-conjugated goat-anti human IgG (Jackson Immuno-Research, catalog # 109-035-088). WT: wild type alemtuzumab; 1-10: alemtuzumab variants. H and L indicate antibody heavy chain and light chain, respectively.

[042] Figure 7. Purification of alemtuzumab using protein A chromatography. WT alemtuzumab proteins was expressed in 293T cells and the media was harvested 5 days after transfection. The media were diluted 1:1 with PBS and purified with protein A (Pierce, Catalog # 20334). O: original sample before purification; FT: flow through; E: elution; C: concentrated final sample. The left picture shows a Simple Blue-stained SDS-PAGE gel, and the right shows a western blot labeled using peroxidase-conjugated goat-anti human IgG.

[043] Figure 8. Production of deglycosylated antibodies. Wild type and variants of alemtuzumab were expressed in 293T cells and purified with protein A chromatography. Antibodies were incubated with peptide-N-glycosidase (PNGase F) at 37°C for 24h. For each antibody, a mock treated sample (-PNGase F) was done in parallel. WT: wild-type alemtuzumab; #15, #16, #17, #18, #22: alemtuzumab variants F241E/F243R/V262E/V264R, F241E/F243Q/V262T/V264E, F241R/F243Q/V262T/V264R, F241E/F243Y/V262T/V264R, and I332E respectively. The faster migration of the PNGase F treated versus the mock treated samples represents the deglycosylated heavy chains.

[044] Figure 9. Alemtuzumab expressed from 293T cells binds its antigen. The antigenic CD52 peptide, fused to GST, was expressed in *E. coli* BL21 (DE3) under IPTG induction. Both uninduced and induced samples were run on a SDS-PAGE gel, and transferred to PVDF membrane. For western analysis, either alemtuzumab from Sotec (□-CD52, Sotec) (final concentration 2.5ng/ul) or

Samsung Bioepis Exhibit No. 1002
Page 11100

media of transfected 293T cells (Campath, Xencor) (final alemtuzumab concentration approximately 0.1-0.2ng/ul) were used as primary antibody, and peroxidase-conjugated goat-anti human IgG was used as secondary antibody. M: pre-stained marker; U: un-induced sample for GST-CD52; I: induced sample for GST-CD52.

[045] Figure 10. Expression and purification of extracellular region of human V158 FcγRIIIa. Tagged FcγRIIIa was transfected in 293T cells, and media containing secreted FcγRIIIa were harvested 3 days later and purified using affinity chromatography. 1: media; 2: flow through; 3: wash; 4-8: serial elutions. Both simple blue-stained SDS-PAGE gel and western result are shown. For the western blot, membrane was probed with anti-GST antibody.

[046] Figure 11. Binding to human V158 FcγRIIIa by select alemtuzumab Fc variants from the experimental library as determined by the AlphaScreen™ assay, described in Example 2. In the presence of competitor antibody (Fc variant or WT alemtuzumab) a characteristic inhibition curve is observed as a decrease in luminescence signal. Phosphate buffer saline (PBS) alone was used as the negative control. These data were normalized to the maximum and minimum luminescence signal provided by the baselines at low and high concentrations of competitor antibody respectively. The curves represent the fits of the data to a one site competition model using nonlinear regression. These fits provide IC50s for each antibody, illustrated for WT and S239D by the dotted lines.

[047] Figures 12. AlphaScreen™ assay showing binding of select alemtuzumab Fc variants to human FcγRIIb. The data were normalized, and the curves represent the fits of the data to a one site competition model. PBS was used as a negative control.

[048] Figures 13. AlphaScreen™ assay showing binding of select alemtuzumab Fc variants to human Val158 FcγRIIIa. The data were normalized, and the curves represent the fits of the data to a one site competition model. PBS was used as a negative control.

[049] Figure 14. AlphaScreen™ assay measuring binding to human V158 FcγRIIIa by select Fc variants in the context of rituximab. The data were normalized, and the curves represent the fits of the data to a one site competition model. PBS was used as a negative control.

[050] Figure 15. AlphaScreen™ assay measuring binding to human V158 FcγRIIIa by select Fc variants in the context of trastuzumab. The data were normalized, and the curves represent the fits of the data to a one site competition model. PBS was used as a negative control.

Samsung Bioepis Exhibit No. 1002
Page 11101

[051] Figures 16a – 16b. AlphaScreen™ assay comparing binding of select alemtuzumab Fc variants to human V158 FcγRIIIa (Figure 16a) and human FcγRIIb (Figure 16b). The data were normalized, and the curves represent the fits of the data to a one site competition model. PBS was used as a negative control.

[052] Figure 17. AlphaScreen™ assay measuring binding to human V158 FcγRIIIa by select Fc variants in the context of trastuzumab. The data were normalized, and the curves represent the fits of the data to a one site competition model.

[053] Figures 18. AlphaScreen™ assay showing binding of select alemtuzumab Fc variants to human R131 FcγRIIa. The data were normalized, and the curves represent the fits of the data to a one site competition model.

[054] Figures 19a and 19b. AlphaScreen™ assay showing binding of select alemtuzumab Fc variants to human V158 FcγRIIIa. The data were normalized, and the curves represent the fits of the data to a one site competition model. PBS was used as a negative control.

[055] Figure 20. AlphaScreen™ assay showing binding of aglycosylated alemtuzumab Fc variants to human V158 FcγRIIIa. The data were normalized, and the curves represent the fits of the data to a one site competition model. PBS was used as a negative control.

[056] Figure 21. AlphaScreen™ assay comparing human V158 FcγRIIIa binding by select alemtuzumab Fc variants in glycosylated (solid symbols, solid lines) and deglycosylated (open symbols, dotted lines). The data were normalized, and the curves represent the fits of the data to a one site competition model.

[057] Figures 22a – 22b. AlphaScreen™ assay showing binding of select alemtuzumab Fc variants to the V158 (Figure 22a) and F158 (Figure 22b) allotypes of human FcγRIIIa. The data were normalized, and the curves represent the fits of the data to a one site competition model. PBS was used as a negative control.

[058] Figures 23a – 23d. Figures 23a and 23b show the correlation between SPR Kd's and AlphaScreen™ IC50's from binding of select alemtuzumab Fc variants to V158 FcγRIIIa (Figure 23a)

Samsung Bioepis Exhibit No. 1002
Page 11102

and F158 FcγRIIIa (Figure 23b). Figures 23c and 23d show the correlation between SPR and AlphaScreen™ fold-improvements over WT for binding of select alemtuzumab Fc variants to V158 FcγRIIIa (Figure 23c) and F158 FcγRIIIa (Figure 23d). Binding data are presented in Table 62. The lines through the data represent the linear fits of the data, and the r^2 values indicate the significance of these fits.

[059] Figures 24a – 24b. Cell-based ADCC assays of select Fc variants in the context of alemtuzumab. ADCC was measured using the DELFIA® EuTDA-based cytotoxicity assay (Perkin Elmer, MA), as described in Example 7, using DoHH-2 lymphoma target cells and 50-fold excess human PBMCs. Figure 24a is a bar graph showing the raw fluorescence data for the indicated alemtuzumab antibodies at 10 ng/ml. The PBMC bar indicates basal levels of cytotoxicity in the absence of antibody. Figure 24b shows the dose-dependence of ADCC on antibody concentration for the indicated alemtuzumab antibodies, normalized to the minimum and maximum fluorescence signal provided by the baselines at low and high concentrations of antibody respectively. The curves represent the fits of the data to a sigmoidal dose-response model using nonlinear regression.

[060] Figures 25a – 25b. Cell-based ADCC assays of select Fc variants in the context of rituximab. ADCC was measured using the DELFIA® EuTDA-based cytotoxicity assay, as described in Example 7, using WIL2-S lymphoma target cells and 50-fold excess human PBMCs. Figure 25a is a bar graph showing the raw fluorescence data for the indicated rituximab antibodies at 1 ng/ml. The PBMC bar indicates basal levels of cytotoxicity in the absence of antibody. Figure 25b shows the dose-dependence of ADCC on antibody concentration for the indicated rituximab antibodies, normalized to the minimum and maximum fluorescence signal provided by the baselines at low and high concentrations of antibody respectively. The curves represent the fits of the data to a sigmoidal dose-response model using nonlinear regression.

[061] Figures 26a – 26c. Cell-based ADCC assays of select Fc variants in the context of trastuzumab. ADCC was measured using the DELFIA® EuTDA-based cytotoxicity assay, as described in Example 7, using BT474 and Sk-Br-3 breast carcinoma target cells and 50-fold excess human PBMCs. Figure 26a is a bar graph showing the raw fluorescence data for the indicated trastuzumab antibodies at 1 ng/ml. The PBMC bar indicates basal levels of cytotoxicity in the absence of antibody. Figures 26b and 26c show the dose-dependence of ADCC on antibody concentration for the indicated trastuzumab antibodies, normalized to the minimum and maximum fluorescence signal provided by the baselines at low and high concentrations of antibody respectively. The curves represent the fits of the data to a sigmoidal dose-response model using nonlinear regression.

Samsung Bioepis Exhibit No. 1002
Page 11103

[062] Figures 27a – 27b. Capacity of select Fc variants to mediate binding and activation of complement. Figure 27a shows an AlphaScreen™ assay measuring binding of select alemtuzumab Fc variants to C1q. The data were normalized to the maximum and minimum luminescence signal provided by the baselines at low and high concentrations of competitor antibody respectively. The curves represent the fits of the data to a one site competition model using nonlinear regression. Figure 27b shows a cell-based assay measuring capacity of select rituximab Fc variants to mediate CDC. CDC assays were performed using Amar Blue to monitor lysis of Fc variant and WT rituximab - opsonized WIL2-S lymphoma cells by human serum complement (Quidel, San Diego, CA). The dose-dependence on antibody concentration of complement-mediated lysis is shown for the indicated rituximab antibodies, normalized to the minimum and maximum fluorescence signal provided by the baselines at low and high concentrations of antibody respectively. The curves represent the fits of the data to a sigmoidal dose-response model using nonlinear regression.

[063] Figure 28. AlphaScreen™ assay measuring binding of select alemtuzumab Fc variants to bacterial protein A, as described in Example 9. The data were normalized, and the curves represent the fits of the data to a one site competition model. PBS was used as a negative control.

[064] Figure 29. AlphaScreen™ assay measuring binding of select alemtuzumab Fc variants to mouse FcγRIII, as described in Example 10. The data were normalized, and the curves represent the fits of the data to a one site competition model. PBS was used as a negative control.

[065] Figure 30. AlphaScreen™ assay measuring binding to human V158 FcγRIIIa by select trastuzumab Fc variants expressed in 293T and CHO cells, as described in Example 11. The data were normalized, and the curves represent the fits of the data to a one site competition model. PBS was used as a negative control.

[066] Figures 31a – 31c. Sequences showing improved anti-CD20 antibodies. The light and heavy chain sequences of rituximab are presented in Figure 31a and Figure 31b respectively, and are taken from translated Sequence 3 of US 5,736,137. Relevant positions in Figure 31b are bolded, including S239, V240, V264I, N297, S298, A330, and I332. Figure 31c shows the improved anti-CD20 antibody heavy chain sequences, with variable positions designated in bold as X_1, X_2, X_3, X_4, X_5, X_6, and Z_1. The table below the sequence provides possible substitutions for these positions. The improved anti-CD20 antibody sequences comprise at least one non-WT amino acid selected from the group of possible substitutions for X_1, X_2, X_3, X_4, X_5, and X_6. These improved anti-CD20 antibody sequences may also comprise a substitution Z_1. These positions are numbered according to the EU index as in Kabat, and thus do not correspond to the sequential order in the sequence.

Samsung Bioepis Exhibit No. 1002
Page 11104

DETAILED DESCRIPTION OF THE INVENTION

[067] In order that the invention may be more completely understood, several definitions are set forth below. Such definitions are meant to encompass grammatical equivalents.

[068] By "ADCC" or "antibody dependent cell-mediated cytotoxicity" as used herein is meant the cell-mediated reaction wherein nonspecific cytotoxic cells that express FcγRs recognize bound antibody on a target cell and subsequently cause lysis of the target cell.

[069] By "ADCP" or antibody dependent cell-mediated phagocytosis as used herein is meant the cell-mediated reaction wherein nonspecific cytotoxic cells that express FcγRs recognize bound antibody on a target cell and subsequently cause phagocytosis of the target cell.

[070] By "amino acid modification" herein is meant an amino acid substitution, insertion, and/or deletion in a polypeptide sequence. The preferred amino acid modification herein is a substitution. **TT

[071] By "antibody" herein is meant a protein consisting of one or more polypeptides substantially encoded by all or part of the recognized immunoglobulin genes. The recognized immunoglobulin genes, for example in humans, include the kappa (□), lambda (□), and heavy chain genetic loci, which together comprise the myriad variable region genes, and the constant region genes mu (□), delta (□), gamma (γ), sigma (□), and alpha (□) which encode the IgM, IgD, IgG, IgE, and IgA isotypes respectively. Antibody herein is meant to include full length antibodies and antibody fragments, and may refer to a natural antibody from any organism, an engineered antibody, or an antibody generated recombinantly for experimental, therapeutic, or other purposes as further defined below. Thus, "antibody" includes both polyclonal and monoclonal antibody (mAb). Methods of preparation and purification of monoclonal and polyclonal antibodies are known in the art and e.g., are described in Harlow and Lane, Antibodies: A Laboratory Manual (New York: Cold Spring Harbor Laboratory Press, 1988). As outlined herein, "antibody" specifically includes Fc variants described herein, "full length" antibodies including the Fc variant fragments described herein, and Fc variant fusions to other proteins as described herein.

[072] n some embodiments, antibodies can be neutralizing or inhibitory, or stimulatory, and in preferred embodiments, as described herein, the stimulatory activity is measured by an increase in affinitiy of a variant antibody to a receptor, as compared to either the parent antibody (e.g. when a non-naturally occurring variant is used as the starting point for the computation analysis herein), or to the original wild-type antibody. Accordingly, by "neutralization," "neutralize," "neutralizing" and grammatical equivalents herein is meant to inhibit or lessen the biological effect of the antibody, in some cases by binding (e.g. competitively) to a antigen and avoiding or decreasing the biological effect of binding, or by binding that results in decreasing the biological effect of binding.

Samsung Bioepis Exhibit No. 1002
Page 11105

[073] The term "antibody" include antibody fragments, as are known in the art, such as Fab, Fab', F(ab')2, Fcs or other antigen-binding subsequences of antibodies, such as, single chain antibodies (Fv for example), chimeric antibodies, etc., either produced by the modification of whole antibodies or those synthesized de novo using recombinant DNA technologies. Particularly preferred are Fc variants as described herein. The term "antibody" further comprises polyclonal antibodies and mAbs which can be agonist or antagonist antibodies.

[074] The antibodies of the invention specifically bind to Fc receptors, as outlined herein. By "specifically bind" herein is meant that the LC antibodies have a binding constant in the range of at least 10^{-4} - 10^{-6} M^{-1}, with a preferred range being 10^{-7} - 10^{-9} M^{-1}.
In a preferred embodiment, the antibodies of the invention are humanized. Using current monoclonal antibody technology one can produce a humanized antibody to virtually any target antigen that can be identified [Stein, Trends Biotechnol. 15:88-90 (1997)]. Humanized forms of non-human (e.g., murine) antibodies are chimeric molecules of immunoglobulins, immunoglobulin chains or fragments thereof (such as Fv, Fc, Fab, Fab', F(ab')2 or other antigen-binding subsequences of antibodies) which contain minimal sequence derived from non-human immunoglobulin. Humanized antibodies include human immunoglobulins (recipient antibody) in which residues form a complementary determining region (CDR) of the recipient are replaced by residues from a CDR of a non-human species (donor antibody) such as mouse, rat or rabbit having the desired specificity, affinity and capacity. In some instances, Fv framework residues of the human immunoglobulin are replaced by corresponding non-human residues. Humanized antibodies may also comprise residues which are found neither in the recipient antibody nor in the imported CDR or framework sequences. In general, the humanized antibody will comprise substantially all of at least one, and typically two, variable domains, in which all or substantially all of the CDR regions correspond to those of a non-human immunoglobulin and all or substantially all of the FR regions are those of a human immunoglobulin consensus sequence. The humanized antibody optimally also will comprise at least a portion of an immunoglobulin constant region (Fc), typically that of a human immunoglobulin [Jones et al., Nature 321:522-525 (1986); Riechmann et al., Nature 332:323-329 (1988); and Presta, Curr. Op. Struct. Biol. 2:593-596 (1992)]. Methods for humanizing non-human antibodies are well known in the art. Generally, a humanized antibody has one or more amino acid residues introduced into it from a source which is non-human. These non-human amino acid residues are often referred to as import residues, which are typically taken from an import variable domain. Humanization can be essentially performed following the method of Winter and co-workers [Jones et al., supra; Riechmann et al., supra; and Verhoeyen et al., Science, 239:1534-1536 (1988)], by substituting rodent CDRs or CDR sequences for the corresponding sequences of a human antibody. Additional examples of humanized murine monoclonal antibodies are also known in the art, e.g., antibodies binding human protein C [O'Connor et al., Protein Eng. 11:321-8 (1998)], interleukin 2 receptor [Queen et al., Proc. Natl. Acad. Sci., U.S.A. 86:10029-33 (1989)], and human epidermal growth factor receptor 2 [Carter et al., Proc. Natl. Acad. Sci. U.S.A. 89:4285-9 (1992)]. Accordingly, such humanized antibodies are chimeric antibodies (U.S. Patent No. 4,816,567), wherein substantially less than an intact human variable domain has

Samsung Bioepis Exhibit No. 1002
Page 11106

been substituted by the corresponding sequence from a non-human species. In practice, humanized antibodies are typically human antibodies in which some CDR residues and possibly some FR residues are substituted by residues from analogous sites in rodent antibodies.

[075] In a preferred embodiment, the antibodies of the invention are based on human sequences, and are thus human sequences are used as the "base" sequences, against which other sequences, such as rat, mouse and monkey sequences. In order to establish homology to primary sequence or structure, the amino acid sequence of a precursor or parent Fc is directly compared to the human Fc sequence outlined herein. After aligning the sequences, using one or more of the homology alignment programs described herein (for example using conserved residues as between species), allowing for necessary insertions and deletions in order to maintain alignment (i.e., avoiding the elimination of conserved residues through arbitrary deletion and insertion), the residues equivalent to particular amino acids in the primary sequence of human Fc are defined. Alignment of conserved residues preferably should conserve 100% of such residues. However, alignment of greater than 75% or as little as 50% of conserved residues is also adequate to define equivalent residues (sometimes referred to herein as "corresponding residues").

[076] Equivalent residues may also be defined by determining homology at the level of tertiary structure for an Fc fragment whose tertiary structure has been determined by x-ray crystallography. Equivalent residues are defined as those for which the atomic coordinates of two or more of the main chain atoms of a particular amino acid residue of the parent or precursor (N on N, CA on CA, C on C and O on O) are within 0.13 nm and preferably 0.1 nm after alignment. Alignment is achieved after the best model has been oriented and positioned to give the maximum overlap of atomic coordinates of non-hydrogen protein atoms of the Fc variant fragment.

[077] Specifically included within the definition of "antibody" are aglycosylated antibodies. By "aglycosylated antibody" as used herein is meant an antibody that lacks carbohydrate attached at position 297 of the Fc region, wherein numbering is according to the EU system as in Kabat. The aglycosylated antibody may be a deglycosylated antibody, that is an antibody for which the Fc carbohydrate has been removed, for example chemically or enzymatically. Alternatively, the aglycosylated antibody may be a nonglycosylated or unglycosylated antibody, that is an antibody that was expressed without Fc carbohydrate, for example by mutation of one or residues that encode the glycosylation pattern or by expression in an organism that does not attach carbohydrates to proteins, for example bacteria.

[078] Specifically included within the definition of "antibody" are full-length antibodies that contain an Fc variant portion. .By "full length antibody" herein is meant the structure that constitutes the natural biological form of an antibody, including variable and constant regions. For example, in most mammals, including humans and mice, the full length antibody of the IgG class is a tetramer and consists of two identical pairs of two immunoglobulin chains, each pair having one light and one heavy

Samsung Bioepis Exhibit No. 1002
Page 11107

chain, each light chain comprising immunoglobulin domains V_L and C_L, and each heavy chain comprising immunoglobulin domains V_H, $C\gamma1$, $C\gamma2$, and $C\gamma3$. In some mammals, for example in camels and llamas, IgG antibodies may consist of only two heavy chains, each heavy chain comprising a variable domain attached to the Fc region. By "IgG" as used herein is meant a polypeptide belonging to the class of antibodies that are substantially encoded by a recognized immunoglobulin gamma gene. In humans this class comprises IgG1, IgG2, IgG3, and IgG4. In mice this class comprises IgG1, IgG2a, IgG2b, IgG3.

[079] By "amino acid" and "amino acid identity" as used herein is meant one of the 20 naturally occurring amino acids or any non-natural analogues that may be present at a specific, defined position. By "protein" herein is meant at least two covalently attached amino acids, which includes proteins, polypeptides, oligopeptides and peptides. The protein may be made up of naturally occurring amino acids and peptide bonds, or synthetic peptidomimetic structures, i.e. "analogs", such as peptoids (see Simon et al., PNAS USA 89(20):9367 (1992)) particularly when LC peptides are to be administered to a patient. Thus "amino acid", or "peptide residue", as used herein means both naturally occurring and synthetic amino acids. For example, homophenylalanine, citrulline and noreleucine are considered amino acids for the purposes of the invention. "Amino acid" also includes imino acid residues such as proline and hydroxyproline. The side chain may be in either the (R) or the (S) configuration. In the preferred embodiment, the amino acids are in the (S) or L-configuration. If non-naturally occurring side chains are used, non-amino acid substituents may be used, for example to prevent or retard in vivo degradation.

[080] By "computational screening method" herein is meant any method for designing one or more mutations in a protein, wherein said method utilizes a computer to evaluate the energies of the interactions of potential amino acid side chain substitutions with each other and/or with the rest of the protein. As will be appreciated by those skilled in the art, evaluation of energies, referred to as energy calculation, refers to some method of scoring one or more amino acid modifications. Said method may involve a physical or chemical energy term, or may involve knowledge-, statistical-, sequence-based energy terms, and the like. The calculations that compose a computational screening method are herein referred to as "computational screening calculations".

[081] By "effector function" as used herein is meant a biochemical event that results from the interaction of an antibody Fc region with an Fc receptor or ligand. Effector functions include but are not limited to ADCC, ADCP, and CDC. By "effector cell" as used herein is meant a cell of the immune system that expresses one or more Fc receptors and mediates one or more effector functions. Effector cells include but are not limited to monocytes, macrophages, neutrophils, dendritic cells, eosinophils, mast cells, platelets, B cells, large granular lymphocytes, Langerhans' cells, natural killer (NK) cells, and $\gamma\gamma$ T cells, and may be from any organism including but not limited to humans, mice,

Samsung Bioepis Exhibit No. 1002
Page 11108

rats, rabbits, and monkeys. By "library" herein is meant a set of Fc variants in any form, including but not limited to a list of nucleic acid or amino acid sequences, a list of nucleic acid or amino acid substitutions at variable positions, a physical library comprising nucleic acids that encode the library sequences, or a physical library comprising the Fc variant proteins, either in purified or unpurified form.

[082] By "Fc", "Fc region", FC polypeptide", etc. as used herein is meant an antibody as defined herein that includes the polypeptides comprising the constant region of an antibody excluding the first constant region immunoglobulin domain. Thus Fc refers to the last two constant region immunoglobulin domains of IgA, IgD, and IgG, and the last three constant region immunoglobulin domains of IgE and IgM, and the flexible hinge N-terminal to these domains. For IgA and IgM Fc may include the J chain. For IgG, as illustrated in Figure 1, Fc comprises immunoglobulin domains Cgamma2 and Cgamma3 (Cγ2 and Cγ3) and the hinge between Cgamma1 (Cγ1) and Cgamma2 (Cγ2). Although the boundaries of the Fc region may vary, the human IgG heavy chain Fc region is usually defined to comprise residues C226 or P230 to its carboxyl-terminus, wherein the numbering is according to the EU index as in Kabat. Fc may refer to this region in isolation, or this region in the context of an antibody, antibody fragment, or Fc fusion. An Fc may be an antibody, Fc fusion, or an protein or protein domain that comprises Fc. Particularly preferred are Fc variants, which are non-naturally occurring variants of an Fc.

[083] By "Fc fusion" as used herein is meant a protein wherein one or more polypeptides is operably linked to Fc. Fc fusion is herein meant to be synonymous with the terms "immunoadhesin", "Ig fusion", "Ig chimera", and "receptor globulin" (sometimes with dashes) as used in the prior art (Chamow *et al.*, 1996, *Trends Biotechnol* 14:52-60; Ashkenazi *et al.*, 1997, *Curr Opin Immunol* 9:195-200). An Fc fusion combines the Fc region of an immunoglobulin with a fusion partner, which in general can be any protein, including, but not limited to, the target-binding region of a receptor, an adhesion molecule, a ligand, an enzyme, or some other protein or protein domain. The role of the non-Fc part of an Fc fusion is to mediate target binding, and thus it is functionally analogous to the variable regions of an antibody.

[084] By "Fc gamma receptor" or "FcγR" as used herein is meant any member of the family of proteins that bind the IgG antibody Fc region and are substantially encoded by the FcγR genes. In humans this family includes but is not limited to FcγRI (CD64), including isoforms FcγRIa, FcγRIb, and FcγRIc; FcγRII (CD32), including isoforms FcγRIIa (including allotypes H131 and R131), FcγRIIb (including FcγRIIb-1 and FcγRIIb-2), and FcγRIIc; and FcγRIII (CD16), including isoforms FcγRIIIa (including allotypes V158 and F158) and FcγRIIIb (including allotypes FcγRIIIb-NA1 and FcγRIIIb-NA2) (Jefferis *et al.*, 2002, *Immunol Lett* 82:57-65), as well as any undiscovered human FcγRs or FcγR isoforms or allotypes. An FcγR may be from any organism, including but not limited to humans,

Samsung Bioepis Exhibit No. 1002
Page 11109

mice, rats, rabbits, and monkeys. Mouse FcγRs include but are not limited to FcγRI (CD64), FcγRII (CD32), FcγRIII (CD16), and FcγRIII-2 (CD16-2), as well as any undiscovered mouse FcγRs or FcγR isoforms or allotypes.

[085] By "Fc ligand" as used herein is meant a molecule, preferably a polypeptide, from any organism that binds to the Fc region of an antibody to form an Fc-ligand complex. Fc ligands include but are not limited to FcγRs, FcγRs, FcγRs, FcRn, C1q, C3, mannan binding lectin, mannose receptor, *staphylococcal* protein A, *streptococcal* protein G, and viral FcγR. Fc ligands may include undiscovered molecules that bind Fc

[086] By "IgG" as used herein is meant a polypeptide belonging to the class of antibodies that are substantially encoded by a recognized immunoglobulin gamma gene. In humans this class comprises IgG1, IgG2, IgG3, and IgG4. In mice this class comprises IgG1, IgG2a, IgG2b, IgG3. By "immunoglobulin (Ig)" herein is meant a protein consisting of one or more polypeptides substantially encoded by immunoglobulin genes. Immunoglobulins include but are not limited to antibodies. Immunoglobulins may have a number of structural forms, including but not limited to full length antibodies, antibody fragments, and individual immunoglobulin domains. By "immunoglobulin (Ig) domain" herein is meant a region of an immunoglobulin that exists as a distinct structural entity as ascertained by one skilled in the art of protein structure. Ig domains typically have a characteristic □-sandwich folding topology. The known Ig domains in the IgG class of antibodies are V_H, Cγ1, Cγ2, Cγ3, V_L, and C_L.

[087] By "parent polypeptide" or "precursor polypeptide" (including Fc parent or precursors) as used herein is meant a polypeptide that is subsequently modified to generate a variant. Said parent polypeptide may be a naturally occurring polypeptide, or a variant or engineered version of a naturally occurring polypeptide. Parent polypeptide may refer to the polypeptide itself, compositions that comprise the parent polypeptide, or the amino acid sequence that encodes it. Accordingly, by "parent Fc polypeptide" as used herein is meant an unmodified Fc polypeptide that is modified to generate a variant, and by "parent antibody" as used herein is meant an unmodified antibody that is modified to generate a variant antibody.

[088] As outlined above, certain positions of the Fc molecule can be altered. By "position" as used herein is meant a location in the sequence of a protein. Positions may be numbered sequentially, or according to an established format, for example the EU index as in Kabat. For example, position 297 is a position in the human antibody IgG1. Corresponding positions are determined as outlined above, generally through alignment with other parent sequences.

Samsung Bioepis Exhibit No. 1002
Page 11110

[089] By "residue" as used herein is meant a position in a protein and its associated amino acid identity. For example, Daragine 297 (also referred to as N297, also referred to as N297) is a residue in the human antibody IgG1.

[090] By "target antigen" as used herein is meant the molecule that is bound specifically by the variable region of a given antibody. A target antigen may be a protein, carbohydrate, lipid, or other chemical compound.

[091] By "target cell" as used herein is meant a cell that expresses a target antigen.

[092] By "variable region" as used herein is meant the region of an immunoglobulin that comprises one or more Ig domains substantially encoded by any of the V□, V□, and/or V_H genes that make up the kappa, lambda, and heavy chain immunoglobulin genetic loci respectively.

[093] By "variant polypeptide" as used herein is meant a polypeptide sequence that differs from that of a parent polypeptide sequence by virtue of at least one amino acid modification. Variant polypeptide may refer to the polypeptide itself, a composition comprising the polypeptide, or the amino sequence that encodes it. Preferably, the variant polypeptide has at least one amino acid modification compared to the parent polypeptide, e.g. from about one to about ten amino acid modifications, and preferably from about one to about five amino acid modifications compared to the parent. The variant polypeptide sequence herein will preferably possess at least about 80% homology with a parent polypeptide sequence, and most preferably at least about 90% homology, more preferably at least about 95% homology. Accordingly, by "Fc variant" as used herein is meant an Fc sequence that differs from that of a parent Fc sequence by virtue of at least one amino acid modification. An Fc variant may only encompass an Fc region, or may exist in the context of an antibody, Fc fusion, or other polypeptide that is substantially encoded by Fc. Fc variant may refer to the Fc polypeptide itself, compositions comprising the Fc variant polypeptide, or the amino acid sequence that encodes it.

[094] For all positions discussed in the present invention, numbering of an immunoglobulin heavy chain is according to the EU index (Kabat et al., 1991, Sequences of Proteins of Immunological Interest, 5th Ed., United States Public Health Svice, National Institutes of Health, Bethesda). The "EU index as in Kabat" refers to the residue numbering of the human IgG1 EU antibody.

[095] The Fc variants of the present invention may be optimized for a variety of properties. Properties that may be optimized include but are not limited to enhanced or reduced affinity for an

Samsung Bioepis Exhibit No. 1002
Page 11111

FcγR. In a preferred embodiment, the Fc variants of the present invention are optimized to possess enhanced affinity for a human activating FcγR, preferably FcγRI, FcγRIIa, FcγRIIc, FcγRIIIa, and FcγRIIIb, most preferably FcγRIIIa. In an alternately preferred embodiment, the Fc variants are optimized to possess reduced affinity for the human inhibitory receptor FcγRIIb. These preferred embodiments are anticipated to provide antibodies and Fc fusions with enhanced therapeutic properties in humans, for example enhanced effector function and greater anti-cancer potency. In an alternate embodiment, the Fc variants of the present invention are optimized to have reduced or ablated affinity for a human FcγR, including but not limited to FcγRI, FcγRIIa, FcγRIIb, FcγRIIc, FcγRIIIa, and FcγRIIIb. These embodiments are anticipated to provide antibodies and Fc fusions with enhanced therapeutic properties in humans, for example reduced effector function and reduced toxicity. Preferred embodiments comprise optimization of Fc binding to a human FcγR, however in alternate embodiments the Fc variants of the present invention possess enhanced or reduced affinity for FcγRs from nonhuman organisms, including but not limited to mice, rats, rabbits, and monkeys. Fc variants that are optimized for binding to a nonhuman FcγR may find use in experimentation. For example, mouse models are available for a variety of diseases that enable testing of properties such as efficacy, toxicity, and pharmacokinetics for a given drug candidate. As is known in the art, cancer cells can be grafted or injected into mice to mimic a human cancer, a process referred to as xenografting. Testing of antibodies or Fc fusions that comprise Fc variants that are optimized for one or more mouse FcγRs, may provide valuable information with regard to the efficacy of the antibody or Fc fusion, its mechanism of action, and the like. The Fc variants of the present invention may also be optimized for enhanced functionality and/or solution properties in aglycosylated form. In a preferred embodiment, the aglycosylated Fc variants of the present invention bind an Fc ligand with greater affinity than the aglycosylated form of the parent Fc polypeptide. Said Fc ligands include but are not limited to FcγRs, C1q, FcRn, and proteins A and G, and may be from any source including but not limited to human, mouse, rat, rabbit, or monkey, preferably human. In an alternately preferred embodiment, the Fc variants are optimized to be more stable and/or more soluble than the aglycosylated form of the parent Fc polypeptide. An Fc variant that is engineered or predicted to display any of the aforementioned optimized properties is herein referred to as an "optimized Fc variant".

[096] The Fc variants of the present invention may be derived from parent Fc polypeptides that are themselves from a wide range of sources. The parent Fc polypeptide may be substantially encoded by one or more Fc genes from any organism, including but not limited to humans, mice, rats, rabbits, camels, llamas, dromedaries, monkeys, preferably mammals and most preferably humans and mice. In a preferred embodiment, the parent Fc polypeptide composes an antibody, referred to as the parent antibody. The parent antibody may be fully human, obtained for example using transgenic mice (Bruggemann *et al.*, 1997, *Curr Opin Biotechnol* 8:455-458) or human antibody libraries coupled with selection methods (Griffiths *et al.*, 1998, *Curr Opin Biotechnol* 9:102-108). The parent antibody need not be naturally occurring. For example, the parent antibody may be an engineered antibody,

including but not limited to chimeric antibodies and humanized antibodies (Clark, 2000, *Immunol Today* 21:397-402). The parent antibody may be an engineered variant of an antibody that is substantially encoded by one or more natural antibody genes. In one embodiment, the parent antibody has been affinity matured, as is known in the art. Alternatively, the antibody has been modified in some other way, for example as described in USSN 10/339788, filed on March 3, 2003.

[097] The Fc variants of the present invention may be substantially encoded by immunoglobulin genes belonging to any of the antibody classes. In a preferred embodiment, the Fc variants of the present invention find use in antibodies or Fc fusions that comprise sequences belonging to the IgG class of antibodies, including IgG1, IgG2, IgG3, or IgG4. In an alternate embodiment the Fc variants of the present invention find use in antibodies or Fc fusions that comprise sequences belonging to the IgA (including subclasses IgA1 and IgA2), IgD, IgE, IgG, or IgM classes of antibodies. The Fc variants of the present invention may comprise more than one protein chain. That is, the present invention may find use in an antibody or Fc fusion that is a monomer or an oligomer, including a homo- or hetero-oligomer.

[098] The Fc variants of the present invention may be combined with other Fc modifications, including but not limited to modifications that alter effector function. Such combination may provide additive, synergistic, or novel properties in antibodies or Fc fusions. In one embodiment, the Fc variants of the present invention may be combined with other known Fc variants (Duncan *et al.*, 1988, *Nature* 332:563-564; Lund *et al.*, 1991, *J Immunol* 147:2657-2662; Lund *et al.*, 1992, *Mol Immunol* 29:53-59; Alegre *et al.*, 1994, *Transplantation* 57:1537-1543; Hutchins *et al.*, 1995, *Proc Natl Acad Sci U S A* 92:11980-11984; Jefferis *et al.*, 1995, *Immunol Lett* 44:111-117; Lund *et al.*, 1995, *Faseb J* 9:115-119; Jefferis *et al.*, 1996, *Immunol Lett* 54:101-104; Lund *et al.*, 1996, *J Immunol* 157:4963-4969; Armour *et al.*, 1999, *Eur J Immunol* 29:2613-2624; Idusogie *et al.*, 2000, *J Immunol* 164:4178-4184; Reddy *et al.*, 2000, *J Immunol* 164:1925-1933; Xu *et al.*, 2000, *Cell Immunol* 200:16-26; Idusogie *et al.*, 2001, *J Immunol* 166:2571-2575; Shields *et al.*, 2001, *J Biol Chem* 276:6591-6604; Jefferis *et al.*, 2002, *Immunol Lett* 82:57-65; Presta *et al.*, 2002, *Biochem Soc Trans* 30:487-490) (US 5,624,821; US 5,885,573; US 6,194,551; PCT WO 00/42072; PCT WO 99/58572). In an alternate embodiment, the Fc variants of the present invention are incorporated into an antibody or Fc fusion that comprises one or more engineered glycoforms. By "engineered glycoform" as used herein is meant a carbohydrate composition that is covalently attached to an Fc polypeptide, wherein said carbohydrate composition differs chemically from that of a parent Fc polypeptide. Engineered glycoforms may be useful for a variety of purposes, including but not limited to enhancing or reducing effector function. Engineered glycoforms may be generated by any method, for example by using engineered or variant expression strains, by co-expression with one or more enzymes, for example □1–4- N-acetylglucosaminyltransferase III (GnTIII), by expressing an Fc polypeptide in various organisms or cell lines from various organisms, or by modifying carbohydrate(s) after the Fc polypeptide has been expressed. Methods for generating engineered glycoforms are known in the

art, and include but are not limited to (Umaña *et al.*, 1999, *Nat Biotechnol* 17:176-180; Davies *et al.*, 2001, *Biotechnol Bioeng* 74:288-294; Shields *et al.*, 2002, *J Biol Chem* 277:26733-26740; Shinkawa *et al.*, 2003, *J Biol Chem* 278:3466-3473) US 6,602,684; USSN 10/277,370; USSN 10/113,929; PCT WO 00/61739A1; PCT WO 01/29246A1; PCT WO 02/31140A1; PCT WO 02/30954A1; Potelligent™ technology (Biowa, Inc., Princeton, N.J.); GlycoMAb™ glycosylation engineering technology (GLYCART biotechnology AG, Zürich, Switzerland)). Engineered glycoform typically refers to the different carbohydrate or oligosaccharide; thus an Fc polypeptide, for example an antibody or Fc fusion, may comprise an engineered glycoform. Alternatively, engineered glycoform may refer to the Fc polypeptide that comprises the different carbohydrate or oligosaccharide. Thus combinations of the Fc variants of the present invention with other Fc modifications, as well as undiscovered Fc modifications, are contemplated with the goal of generating novel antibodies or Fc fusions with optimized properties.

[099] The Fc variants of the present invention may find use in an antibody. By "antibody of the present invention" as used herein is meant an antibody that comprises an Fc variant of the present invention. The present invention may, in fact, find use in any protein that comprises Fc, and thus application of the Fc variants of the present invention is not limited to antibodies. The Fc variants of the present invention may find use in an Fc fusion. By "Fc fusion of the present invention" as used herein refers to an Fc fusion that comprises an Fc variant of the present invention. Fc fusions may comprise an Fc variant of the present invention operably linked to a cytokine, soluble receptor domain, adhesion molecule, ligand, enzyme, peptide, or other protein or protein domain, and include but are not limited to Fc fusions described in US 5,843,725; US 6,018,026; US 6,291,212; US 6,291,646; US 6,300,099; US 6,323,323; PCT WO 00/24782; and in (Chamow *et al.*, 1996, *Trends Biotechnol* 14:52-60; Ashkenazi *et al.*, 1997, *Curr Opin Immunol* 9:195-200).

[100] Virtually any antigen may be targeted by the antibodies and fusions of the present invention, including but are not limited to the following list of proteins, subunits, domains, motifs, and epitopes belonging to the following list of proteins: CD2; CD3, CD3E, CD4, CD11, CD11a, CD14, CD16, CD18, CD19, CD20, CD22, CD23, CD25, CD28, CD29, CD30, CD32, CD33 (p67 protein), CD38, CD40, CD40L, CD52, CD54, CD56, CD80, CD147, GD3, IL-1, IL-1R, IL-2, IL-2R, IL-4, IL-5, IL-6, IL-6R, IL-8, IL-12, IL-15, IL-18, IL-23, interferon alpha, interferon beta, interferon gamma; TNF-alpha, TNFbeta2, TNFc, TNFalphabeta, TNF-RI, TNF-RII, FasL, CD27L, CD30L, 4-1BBL, TRAIL, RANKL, TWEAK, APRIL, BAFF, LIGHT, VEGI, OX40L, TRAIL Receptor-1, A1 Adenosine Receptor, Lymphotoxin Beta Receptor, TACI, BAFF-R, EPO; LFA-3, ICAM-1, ICAM-3, EpCAM, integrin beta1, integrin beta2, integrin alpha4/beta7, integrin alpha2, integrin alpha3, integrin alpha4, integrin alpha5, integrin alpha6, integrin alphav, alphaVbeta3 integrin, FGFR-3, Keratinocyte Growth Factor, VLA-1, VLA-4, L-selectin, anti-Id, E-selectin, HLA, HLA-DR, CTLA-4, T cell receptor, B7-1, B7-2, VNRintegrin, TGFbeta1, TGFbeta2, eotaxin1, BLyS (B-lymphocyte Stimulator), complement C5, IgE, factor VII, CD64, CBL, NCA 90, EGFR (ErbB-1), Her2/neu (ErbB-2), Her3 (ErbB-3), Her4 (ErbB-4), Tissue

Samsung Bioepis Exhibit No. 1002
Page 11114

Factor, VEGF, VEGFR, endothelin receptor, VLA-4, Hapten NP-cap or NIP-cap, T cell receptor alpha/beta, E-selectin, digoxin, placental alkaline phosphatase (PLAP) and testicular PLAP-like alkaline phosphatase, transferrin receptor, Carcinoembryonic antigen (CEA), CEACAM5, HMFG PEM, mucin MUC1, MUC18, Heparanase I, human cardiac myosin, tumor-associated glycoprotein-72 (TAG-72), tumor-associated antigen CA 125, Prostate specific membrane antigen (PSMA), High molecular weight melanoma-associated antigen (HMW-MAA), carcinoma-associated antigen, Gcoprotein IIb/IIIa (GPIIb/IIIa), tumor-associated antigen expressing Lewis Y related carbohydrate, human cytomegalovirus (HCMV) gH envelope glycoprotein, HIV gp120, HCMV, respiratory syncital virus RSV F, RSVF Fgp, VNRintegrin, IL-8, cytokeratin tumor-associated antigen, Hep B gp120, CMV, gpIIbIIIa, HIV IIIB gp120 V3 loop, respiratory syncytial virus (RSV) Fgp, Herpes simplex virus (HSV) gD glycoprotein, HSV gB glycoprotein, HCMV gB envelope glycoprotein, and *Clostridium perfringens* toxin.

[101] One skilled in the art will appreciate that the aforementioned list of targets refers not only to specific proteins and biomolecules, but the biochemical pathway or pathways that comprise them. For example, reference to CTLA-4 as a target antigen implies that the ligands and receptors that make up the T cell co-stimulatory pathway, including CTLA-4, B7-1, B7-2, CD28, and any other undiscovered ligands or receptors that bind these proteins, are also targets. Thus target as used herein refers not only to a specific biomolecule, but the set of proteins that interact with said target and the members of the biochemical pathway to which said target belongs. One skilled in the art will further appreciate that any of the aforementioned target antigens, the ligands or receptors that bind them, or other members of their corresponding biochemical pathway, may be operably linked to the Fc variants of the present invention in order to generate an Fc fusion. Thus for example, an Fc fusion that targets EGFR could be constructed by operably linking an Fc variant to EGF, TGF□, or any other ligand, discovered or undiscovered, that binds EGFR. Accordingly, an Fc variant of the present invention could be operably linked to EGFR in order to generate an Fc fusion that binds EGF, TGF□, or any other ligand, discovered or undiscovered, that binds EGFR. Thus virtually any polypeptide, whether a ligand, receptor, or some other protein or protein domain, including but not limited to the aforementioned targets and the proteins that compose their corresponding biochemical pathways, may be operably linked to the Fc variants of the present invention to develop an Fc fusion.

[102] A number of antibodies and Fc fusions that are approved for use, in clinical trials, or in development may benefit from the Fc variants of the present invention. Said antibodies and Fc fusions are herein referred to as "clinical products and candidates". Thus in a preferred embodiment, the Fc variants of the present invention may find use in a range of clinical products and candidates. For example, a number of antibodies that target CD20 may benefit from the Fc variants of the present invention. For example the Fc variants of the present invention may find use in an antibody that is substantially similar to rituximab (Rituxan®, IDEC/Genentech/Roche) (see for example US 5,736,137), a chimeric anti-CD20 antibody approved to treat Non-Hodgkin's lymphoma; HuMax-

Samsung Bioepis Exhibit No. 1002
Page 11115

CD20, an anti-CD20 currently being developed by Genmab, an anti-CD20 antibody described in US 5,500,362, AME-133 (Applied Molecular Evolution), hA20 (Immunomedics, Inc.), and HumaLYM (Intracel). A number of antibodies that target members of the family of epidermal growth factor receptors, including EGFR (ErbB-1), Her2/neu (ErbB-2), Her3 (ErbB-3), Her4 (ErbB-4), may benefit from the Fc variants of the present invention. For example the Fc variants of the present invention may find use in an antibody that is substantially similar to trastuzumab (Herceptin®, Genentech) (see for example US 5,677,171), a humanized anti-Her2/neu antibody approved to treat breast cancer; pertuzumab (rhuMab-2C4, Omnitarg™), currently being developed by Genentech; an anti-Her2 antibody described in US 4,753,894; cetuximab (Erbitux®, Imclone) (US 4,943,533; PCT WO 96/40210), a chimeric anti-EGFR antibody in clinical trials for a variety of cancers; ABX-EGF (US 6,235,883), currently being developed by Abgenix/Immunex/Amgen; HuMax-EGFr (USSN 10/172,317), currently being developed by Genmab; 425, EMD55900, EMD62000, and EMD72000 (Merck KGaA) (US 5558864; Murthy et al. 1987, *Arch Biochem Biophys.* 252(2):549-60; Rodeck et al., 1987, *J Cell Biochem.* 35(4):315-20; Kettleborough et al., 1991, *Protein Eng.* 4(7):773-83); ICR62 (Institute of Cancer Research) (PCT WO 95/20045; Modjtahedi et al., 1993, *J. Cell Biophys.* 1993, 22(1-3):129-46; Modjtahedi et al., 1993, *Br J Cancer.* 1993, 67(2):247-53; Modjtahedi et al, 1996, *Br J Cancer*, 73(2):228-35; Modjtahedi et al, 2003, *Int J Cancer,* 105(2):273-80); TheraCIM hR3 (YM Biosciences, Canada and Centro de Immunologia Molecular, Cuba (US 5,891,996; US 6, 506,883; Mateo et al, 1997, *Immunotechnology*, 3(1):71-81); mAb-806 (Ludwig Institue for Cancer Research, Memorial Sloan-Kettering) (Jungbluth et al. 2003, *Proc Natl Acad Sci U S A.* 100(2):639-44); KSB-102 (KS Biomedix); MR1-1 (IVAX, National Cancer Institute) (PCT WO 0162931A2); and SC100 (Scancell) (PCT WO 01/88138). In another preferred embodiment, the Fc variants of the present invention may find use in alemtuzumab (Campath®, Millenium), a humanized monoclonal antibody currently approved for treatment of B-cell chronic lymphocytic leukemia. The Fc variants of the present invention may find use in a variety of antibodies or Fc fusions that are substantially similar to other clinical products and candidates, including but not limited to muromonab-CD3 (Orthoclone OKT3®), an anti-CD3 antibody developed by Ortho Biotech/Johnson & Johnson, ibritumomab tiuxetan (Zevalin®), an anti-CD20 antibody developed by IDEC/Schering AG, gemtuzumab ozogamicin (Mylotarg®), an anti-CD33 (p67 protein) antibody developed by Celltech/Wyeth, alefacept (Amevive®), an anti-LFA-3 Fc fusion developed by Biogen), abciximab (ReoPro®), developed by Centocor/Lilly, basiliximab (Simulect®), developed by Novartis, palivizumab (Synagis®), developed by MedImmune, infliximab (Remicade®), an anti-TNFalpha antibody developed by Centocor, adalimumab (Humira®, an anti-TNFalpha antibody developed by Abbott, Humicade™, an anti-TNFalpha antibody developed by Celltech, etanercept (Enbrel®), an anti-TNFalpha Fc fusion developed by Immunex/Amgen, ABX-CBL, an anti-CD147 antibody being developed by Abgenix, ABX-IL8, an anti-IL8 antibody being developed by Abgenix, ABX-MA1, an anti-MUC18 antibody being developed by Abgenix, Pemtumomab (R1549, ^{90}Y-muHMFG1), an anti-MUC1 In development by Antisoma, Therex (R1550), an anti-MUC1 antibody being developed by Antisoma, AngioMab (AS1405), being developed by Antisoma, HuBC-1, being developed by Antisoma, Thioplatin (AS1407) being developed by Antisoma, Antegren® (natalizumab), an anti-alpha-4-beta-1 (VLA-4) and alpha-4-

Samsung Bioepis Exhibit No. 1002
Page 11116

beta-7 antibody being developed by Biogen, VLA-1 mAb, an anti-VLA-1 integrin antibody being developed by Biogen, LTBR mAb, an anti-lymphotoxin beta receptor (LTBR) antibody being developed by Biogen, CAT-152, an anti-TGF□2 antibody being developed by Cambridge Antibody Technology, J695, an anti-IL-12 antibody being developed by Cambridge Antibody Technology and Abbott, CAT-192, an anti-TGF□1 antibody being developed by Cambridge Antibody Technology and Genzyme, CAT-213, an anti-Eotaxin1 antibody being developed by Cambridge Antibody Technology, LymphoStat-B™ an anti-Blys antibody being developed by Cambridge Antibody Technology and Human Genome Sciences Inc., TRAIL-R1mAb, an anti-TRAIL-R1 antibody being developed by Cambridge Antibody Technology and Human Genome Sciences, Inc., Avastin™ (bevacizumab, rhuMAb-VEGF), an anti-VEGF antibody being developed by Genentech, an anti-HER receptor family antibody being developed by Genentech, Anti-Tissue Factor (ATF), an anti-Tissue Factor antibody being developed by Genentech, Xolair™ (Omalizumab), an anti-IgE antibody being developed by Genentech, Raptiva™ (Efalizumab), an anti-CD11a antibody being developed by Genentech and Xoma, MLN-02 Antibody (formerly LDP-02), being developed by Genentech and Millenium Pharmaceuticals, HuMax CD4, an anti-CD4 antibody being developed by Genmab, HuMax-IL15, an anti-IL15 antibody being developed by Genmab and Amgen, HuMax-Inflam, being developed by Genmab and Medarex, HuMax-Cancer, an anti-Heparanase I antibody being developed by Genmab and Medarex and Oxford GcoSciences, HuMax-Lymphoma, being developed by Genmab and Amgen, HuMax-TAC, being developed by Genmab, IDEC-131, and anti-CD40L antibody being developed by IDEC Pharmaceuticals, IDEC-151 (Clenoliximab), an anti-CD4 antibody being developed by IDEC Pharmaceuticals, IDEC-114, an anti-CD80 antibody being developed by IDEC Pharmaceuticals, IDEC-152, an anti-CD23 being developed by IDEC Pharmaceuticals, anti-macrophage migration factor (MIF) antibodies being developed by IDEC Pharmaceuticals, BEC2, an anti-idiotypic antibody being developed by Imclone, IMC-1C11, an anti-KDR antibody being developed by Imclone, DC101, an anti-flk-1 antibody being developed by Imclone, anti-VE cadherin antibodies being developed by Imclone, CEA-Cide™ (labetuzumab), an anti-carcinoembryonic antigen (CEA) antibody being developed by Immunomedics, LymphoCide™ (Epratuzumab), an anti-CD22 antibody being developed by Immunomedics, AFP-Cide, being developed by Immunomedics, MyelomaCide, being developed by Immunomedics, LkoCide, being developed by Immunomedics, ProstaCide, being developed by Immunomedics, MDX-010, an anti-CTLA4 antibody being developed by Medarex, MDX-060, an anti-CD30 antibody being developed by Medarex, MDX-070 being developed by Medarex, MDX-018 being developed by Medarex, Osidem™ (IDM-1), and anti-Her2 antibody being developed by Medarex and Immuno-Designed Molecules, HuMax™-CD4, an anti-CD4 antibody being developed by Medarex and Genmab, HuMax-IL15, an anti-IL15 antibody being developed by Medarex and Genmab, CNTO 148, an anti-TNF□ antibody being developed by Medarex and Centocor/J&J, CNTO 1275, an anti-cytokine antibody being developed by Centocor/J&J, MOR101 and MOR102, anti-intercellular adhesion molecule-1 (ICAM-1) (CD54) antibodies being developed by MorphoSys, MOR201, an anti-fibroblast growth factor receptor 3 (FGFR-3) antibody being developed by MorphoSys, Nuvion® (visilizumab), an anti-CD3 antibody being developed by Protein Design Labs, HuZAF™, an anti-gamma interferon antibody being developed by Protein Design Labs, Anti-□5□1

Integrin, being developed by Protein Design Labs, anti-IL-12, being developed by Protein Design Labs, ING-1, an anti-Ep-CAM antibody being developed by Xoma, and MLN01, an anti-Beta2 integrin antibody being developed by Xoma.

[103] Application of the Fc variants to the aforementioned antibody and Fc fusion clinical products and candidates is not meant to be constrained to their precise composition. The Fc variants of the present invention may be incorporated into the aforementioned clinical candidates and products, or into antibodies and Fc fusions that are substantially similar to them. The Fc variants of the present invention may be incorporated into versions of the aforementioned clinical candidates and products that are humanized, affinity matured, engineered, or modified in some other way. Furthermore, the entire polypeptide of the aforementioned clinical products and candidates need not be used to construct a new antibody or Fc fusion that incorporates the Fc variants of the present invention; for example only the variable region of a clinical product or candidate antibody, a substantially similar variable region, or a humanized, affinity matured, engineered, or modified version of the variable region may be used. In another embodiment, the Fc variants of the present invention may find use in an antibody or Fc fusion that binds to the same epitope, antigen, ligand, or receptor as one of the aforementioned clinical products and candidates.

[104] The Fc variants of the present invention may find use in a wide range of antibody and Fc fusion products. In one embodiment the antibody or Fc fusion of the present invention is a therapeutic, a diagnostic, or a research reagent, preferably a therapeutic. Alternatively, the antibodies and Fc fusions of the present invention may be used for agricultural or industrial uses. In an alternate embodiment, the Fc variants of the present invention compose a library that may be screened experimentally. This library may be a list of nucleic acid or amino acid sequences, or may be a physical composition of nucleic acids or polypeptides that encode the library sequences. The Fc variant may find use in an antibody composition that is monoclonal or polyclonal. In a preferred embodiment, the antibodies and Fc fusions of the present invention are used to kill target cells that bear the target antigen, for example cancer cells. In an alternate embodiment, the antibodies and Fc fusions of the present invention are used to block, antagonize, or agonize the target antigen, for example for antagonizing a cytokine or cytokine receptor. In an alternately preferred embodiment, the antibodies and Fc fusions of the present invention are used to block, antagonize, or agonize the target antigen and kill the target cells that bear the target antigen.

[105] The Fc variants of the present invention may be used for various therapeutic purposes. In a preferred embodiment, the Fc variant proteins are administered to a patient to treat an antibody-related disorder. A "patient" for the purposes of the present invention includes both humans and other animals, preferably mammals and most preferably humans. Thus the antibodies and Fc fusions of the present invention have both human therapy and veterinary applications. In the preferred embodiment

Samsung Bioepis Exhibit No. 1002
Page 11118

the patient is a mammal, and in the most preferred embodiment the patient is human. The term "treatment" in the present invention is meant to include therapeutic treatment, as well as prophylactic, or suppressive measures for a disease or disorder. Thus, for example, successful administration of an antibody or Fc fusion prior to onset of the disease results in treatment of the disease. As another example, successful administration of an optimized antibody or Fc fusion after clinical manifestation of the disease to combat the symptoms of the disease comprises treatment of the disease. "Treatment" also encompasses administration of an optimized antibody or Fc fusion protein after the appearance of the disease in order to eradicate the disease. Successful administration of an agent after onset and after clinical symptoms have developed, with possible abatement of clinical symptoms and perhaps amelioration of the disease, comprises treatment of the disease. Those "in need of treatment" include mammals already having the disease or disorder, as well as those prone to having the disease or disorder, including those in which the disease or disorder is to be prevented. By "antibody related disorder" or "antibody responsive disorder" or "condition" or "disease" herein are meant a disorder that may be ameliorated by the administration of a pharmaceutical composition comprising an antibody or Fc fusion of the present invention. Antibody related disorders include but are not limited to autoimmune diseases, immunological diseases, infectious diseases, inflammatory diseases, neurological diseases, and oncological and neoplastic diseases including cancer. By "cancer" and "cancerous" herein refer to or describe the physiological condition in mammals that is typically characterized by unregulated cell growth. Examples of cancer include but are not limited to carcinoma, lymphoma, blastoma, sarcoma (including liposarcoma), neuroendocrine tumors, mesothelioma, schwanoma, meningioma, adenocarcinoma, melanoma, and leukemia or lymphoid malignancies. More particular examples of such cancers include squamous cell cancer (e.g. epithelial squamous cell cancer), lung cancer including small-cell lung cancer, non-small cell lung cancer, adenocarcinoma of the lung and squamous carcinoma of the lung, cancer of the peritoneum, hepatocellular cancer, gastric or stomach cancer including gastrointestinal cancer, pancreatic cancer, glioblastoma, cervical cancer, ovarian cancer, liver cancer, bladder cancer, hepatoma, breast cancer, colon cancer, rectal cancer, colorectal cancer, endometrial or uterine carcinoma, salivary gland carcinoma, kidney or renal cancer, prostate cancer, vulval cancer, thyroid cancer, hepatic carcinoma, anal carcinoma, penile carcinoma, testicular cancer, esophagael cancer, tumors of the biliary tract, as well as head and neck cancer. Furthermore, the Fc variants of the present invention may be used to treat conditions including but not limited to congestive heart failure (CHF), vasculitis, rosecea, acne, eczema, myocarditis and other conditions of the myocardium, systemic lupus erythematosus, diabetes, spondylopathies, synovial fibroblasts, and bone marrow stroma; bone loss; Paget's disease, osteoclastoma; multiple myeloma; breast cancer; disuse osteopenia; malnutrition, periodontal disease, Gaucher's disease, Langerhans' cell histiocytosis, spinal cord injury, acute septic arthritis, osteomalacia, Cushing's syndrome, monoostotic fibrous dysplasia, polyostotic fibrous dysplasia, periodontal reconstruction, and bone fractures; sarcoidosis; multiple myeloma; osteolytic bone cancers, breast cancer, lung cancer, kidney cancer and rectal cancer; bone metastasis, bone pain management, and humoral malignant hypercalcemia, ankylosing spondylitisa and other spondyloarthropathies; transplantation rejection, viral infections, hematologic neoplasisas and

Samsung Bioepis Exhibit No. 1002
Page 11119

neoplastic-like conditions for example, Hodgkin's lymphoma; non-Hodgkin's lymphomas (Burkitt's lymphoma, small lymphocytic lymphoma/chronic lymphocytic leukemia, mycosis fungoides, mantle cell lymphoma, follicular lymphoma, diffuse large B-cell lymphoma, marginal zone lymphoma, hairy cell leukemia and lymphoplasmacytic leukemia), tumors of lymphocyte precursor cells, including B-cell acute lymphoblastic leukemia/lymphoma, and T-cell acute lymphoblastic leukemia/lymphoma, thymoma, tumors of the mature T and NK cells, including peripheral T-cell leukemias, adult T-cell leukemia/T-cell lymphomas and large granular lymphocytic leukemia, Langerhans cell histocytosis, myeloid neoplasias such as acute myelogenous leukemias, including AML with maturation, AML without differentiation, acute promyelocytic leukemia, acute myelomonocytic leukemia, and acute monocytic leukemias, myelodysplastic syndromes, and chronic myeloproliferative disorders, including chronic myelogenous leukemia, tumors of the central nervous system, e.g., brain tumors (glioma, neuroblastoma, astrocytoma, medulloblastoma, ependymoma, and retinoblastoma), solid tumors (nasopharyngeal cancer, basal cell carcinoma, pancreatic cancer, cancer of the bile duct, Kaposi's sarcoma, testicular cancer, uterine, vaginal or cervical cancers, ovarian cancer, primary liver cancer or endometrial cancer, and tumors of the vascular system (angiosarcoma and hemagiopericytoma), osteoporosis, hepatitis, HIV, AIDS, spondyloarthritis, rheumatoid arthritis, inflammatory bowel diseases (IBD), sepsis and septic shock, Crohn's Disease, psoriasis, schleraderma, graft versus host disease (GVHD), allogenic islet graft rejection, hematologic malignancies, such as multiple myeloma (MM), myelodysplastic syndrome (MDS) and acute myelogenous leukemia (AML), inflammation associated with tumors, peripheral nerve injury or demyelinating diseases.

[106] In one embodiment, an antibody or Fc fusion of the present invention is administered to a patient having a disease involving inappropriate expression of a protein. Within the scope of the present invention this is meant to include diseases and disorders characterized by aberrant proteins, due for example to alterations in the amount of a protein present, the presence of a mutant protein, or both. An overabundance may be due to any cause, including but not limited to overexpression at the molecular level, prolonged or accumulated appearance at the site of action, or increased activity of a protein relative to normal. Included within this definition are diseases and disorders characterized by a reduction of a protein. This reduction may be due to any cause, including but not limited to reduced expression at the molecular level, shortened or reduced appearance at the site of action, mutant forms of a protein, or decreased activity of a protein relative to normal. Such an overabundance or reduction of a protein can be measured relative to normal expression, appearance, or activity of a protein, and said measurement may play an important role in the development and/or clinical testing of the antibodies and Fc fusions of the present invention.

[107] In one embodiment, an antibody or Fc fusion of the present invention is the only therapeutically active agent administered to a patient. Alternatively, the antibody or Fc fusion of the present invention is administered in combination with one or more other therapeutic agents, including but not limited to cytotoxic agents, chemotherapeutic agents, cytokines, growth inhibitory agents, anti-

Samsung Bioepis Exhibit No. 1002
Page 11120

hormonal agents, kinase inhibitors, anti-angiogenic agents, cardioprotectants, or other therapeutic agents. Such molecules are suitably present in combination in amounts that are effective for the purpose intended. The skilled medical practitioner can determine empirically the appropriate dose or doses of other therapeutic agents useful herein. The antibodies and Fc fusions of the present invention may be administered concomitantly with one or more other therapeutic regimens. For example, an antibody or Fc fusion of the present invention may be administered to the patient along with chemotherapy, radiation therapy, or both chemotherapy and radiation therapy. In one embodiment, the antibody or Fc fusion of the present invention may be administered in conjunction with one or more antibodies or Fc fusions, which may or may not comprise an Fc variant of the present invention.

[108] In one embodiment, the antibodies and Fc fusions of the present invention are administered with a chemotherapeutic agent. By "chemotherapeutic agent" as used herein is meant a chemical compound useful in the treatment of cancer. Examples of chemotherapeutic agents include but are not limited to alkylating agents such as thiotepa and cyclosphosphamide (CYTOXAN™); alkyl sulfonates such as busulfan, improsulfan and piposulfan; aziridines such as benzodopa, carboquone, meturedopa, and uredopa; ethylenimines and methylamelamines including altretamine, triethylenemelamine, trietylenephosphoramide, triethylenethiophosphaoramide and trimethylolomelamine; nitrogen mustards such as chlorambucil, chlornaphazine, cholophosphamide, estramustine, ifosfamide, mechlorethamine, mechlorethamine oxide hydrochloride, melphalan, novembichin, phenesterine, prednimustine, trofosfamide, uracil mustard; nitrosureas such as carmustine, chlorozotocin, fotemustine, lomustine, nimustine, ranimustine; antibiotics such as aclacinomysins, actinomycin, authramycin, azaserine, bleomycins, cactinomycin, calicheamicin, carabicin, caminomycin, carzinophilin, chromomycins, dactinomycin, daunorubicin, detorubicin, 6-diazo-5-oxo-L-norleucine, doxorubicin, epirubicin, esorubicin, idarubicin, marcellomycin, mitomycins, mycophenolic acid, nogalamycin, olivomycins, peplomycin, potfiromycin, puromycin, quelamycin, rodorubicin, streptonigrin, streptozocin, tubercidin, ubenimex, zinostatin, zorubicin; anti-metabolites such as methotrexate and 5-fluorouracil (5-FU); folic acid analogues such as denopterin, methotrexate, pteropterin, trimetrexate; purine analogs such as fludarabine, 6-mercaptopurine, thiamiprine, thioguanine; pyrimidine analogs such as ancitabine, azacitidine, 6-azauridine, carmofur, cytarabine, dideoxyuridine, doxifluridine, enocitabine, floxuridine, 5-FU; androgens such as calusterone, dromostanolone propionate, epitiostanol, mepitiostane, testolactone; anti-adrenals such as aminoglutethimide, mitotane, trilostane; folic acid replenisher such as frolinic acid; aceglatone; aldophosphamide glycoside; aminolevulinic acid; amsacrine; bestrabucil; bisantrene; edatraxate; defofamine; demecolcine; diaziquone; elformithine; elliptinium acetate; etoglucid; gallium nitrate; hydroxyurea; lentinan; lonidamine; mitoguazone; mitoxantrone; mopidamol; nitracrine; pentostatin; phenamet; pirarubicin; podophyllinic acid; 2-ethylhydrazide; procarbazine; PSK®; razoxane; sizofuran; spirogermanium; tenuazonic acid; triaziquone; 2, 2',2"-trichlorotriethylamine; urethan; vindesine; dacarbazine; mannomustine; mitobronitol; mitolactol; pipobroman; gacytosine; arabinoside ("Ara-C"); cyclophosphamide; thiotepa; taxanes, e.g. paclitaxel (TAXOL®, Bristol-Myers Squibb

Samsung Bioepis Exhibit No. 1002
Page 11121

Oncology, Princeton, N.J.) and docetaxel (TAXOTERE®, Rhne-Poulenc Rorer, Antony, France); chlorambucil; gemcitabine; 6-thioguanine; mercaptopurine; methotrexate; platinum analogs such as cisplatin and carboplatin; vinblastine; platinum; etoposide (VP-16); ifosfamide; mitomycin C; mitoxantrone; vincristine; vinorelbine; navelbine; novantrone; teniposide; daunomycin; aminopterin; xeloda; ibandronate; CPT-11; topoisomerase inhibitor RFS 2000; difluoromethylornithine (DMFO); retinoic acid; esperamicins; capecitabine; thymidylate synthase inhibitor (such as Tomudex); cox-2 inhibitors, such as celicoxib (CELEBREX®) or MK-0966 (VIOXX®); and pharmaceutically acceptable salts, acids or derivatives of any of the above. Also included in this definition are anti-hormonal agents that act to regulate or inhibit hormone action on tumors such as anti estrogens including for example tamoxifen, raloxifene, aromatase inhibiting 4(5)-imidazoles, 4-hydroxytamoxifen, trioxifene, keoxifene, LY 117018, onapristone, and toremifene (Fareston); and anti-androgens such as flutamide, nilutamide, bicalutamide, leuprolide, and goserelin; and pharmaceutically acceptable salts, acids or derivatives of any of the above.

[109] A chemotherapeutic or other cytotoxic agent may be administered as a prodrug. By "prodrug" as used herein is meant a precursor or derivative form of a pharmaceutically active substance that is less cytotoxic to tumor cells compared to the parent drug and is capable of being enzymatically activated or converted into the more active parent form. See, for example Wilman, 1986, Biochemical Society Transactions, 615th Meeting Belfast, 14:375-382; and Stella *et al.*, "Prodrugs: A Chemical Approach to Targeted Drug Delivery," Directed Drug Delivery, Borchardt *et al.*, (ed.): 247-267, Humana Press, 1985. The prodrugs that may find use with the present invention include but are not limited to phosphate-containing prodrugs, thiophosphate-containing prodrugs, sulfate-containing prodrugs, peptide-containing prodrugs, D-amino acid-modified prodrugs, glycosylated prodrugs, beta-lactam-containing prodrugs, optionally substituted phenoxyacetamide-containing prodrugs or optionally substituted phenylacetamide-containing prodrugs, 5-fluorocytosine and other 5-fluorouridine prodrugs which can be converted into the more active cytotoxic free drug. Examples of cytotoxic drugs that can be derivatized into a prodrug form for use with the antibodies and Fc fusions of the present invention include but are not limited to any of the aforementioned chemotherapeutic agents.

[110] The antibodies and Fc fusions of the present invention may be combined with other therapeutic regimens. For example, in one embodiment, the patient to be treated with the antibody or Fc fusion may also receive radiation therapy. Radiation therapy can be administered according to protocols commonly employed in the art and known to the skilled artisan. Such therapy includes but is not limited to cesium, iridium, iodine, or cobalt radiation. The radiation therapy may be whole body irradiation, or may be directed locally to a specific site or tissue in or on the body, such as the lung, bladder, or prostate. Typically, radiation therapy is administered in pulses over a period of time from about 1 to 2 weeks. The radiation therapy may, however, be administered over longer periods of time. For instance, radiation therapy may be administered to patients having head and neck cancer for about 6 to about 7 weeks. Optionally, the radiation therapy may be administered as a single dose

or as multiple, sequential doses. The skilled medical practitioner can determine empirically the appropriate dose or doses of radiation therapy useful herein. In accordance with another embodiment of the invention, the antibody or Fc fusion of the present invention and one or more other anti-cancer therapies are employed to treat cancer cells *ex vivo*. It is contemplated that such *ex vivo* treatment may be useful in bone marrow transplantation and particularly, autologous bone marrow transplantation. For instance, treatment of cells or tissue(s) containing cancer cells with antibody or Fc fusion and one or more other anti-cancer therapies, such as described above, can be employed to deplete or substantially deplete the cancer cells prior to transplantation in a recipient patient. It is of course contemplated that the antibodies and Fc fusions of the invention can be employed in combination with still other therapeutic techniques such as surgery.

[111] In an alternate embodiment, the antibodies and Fc fusions of the present invention are administered with a cytokine. By "cytokine" as used herein is meant a generic term for proteins released by one cell population that act on another cell as intercellular mediators. Examples of such cytokines are lymphokines, monokines, and traditional polypeptide hormones. Included among the cytokines are growth hormone such as human growth hormone, N-methionyl human growth hormone, and bovine growth hormone; parathyroid hormone; thyroxine; insulin; proinsulin; relaxin; prorelaxin; glycoprotein hormones such as follicle stimulating hormone (FSH), thyroid stimulating hormone (TSH), and luteinizing hormone (LH); hepatic growth factor; fibroblast growth factor; prolactin; placental lactogen; tumor necrosis factor-alpha and -beta; mullerian-inhibiting substance; mouse gonadotropin-associated peptide; inhibin; activin; vascular endothelial growth factor; integrin; thrombopoietin (TPO); nerve growth factors such as NGF-beta; platelet-growth factor; transforming growth factors (TGFs) such as TGF-alpha and TGF-beta; insulin-like growth factor-I and -II; erythropoietin (EPO); osteoinductive factors; interferons such as interferon-alpha, beta, and -gamma; colony stimulating factors (CSFs) such as macrophage-CSF (M-CSF); granulocyte-macrophage-CSF (GM-CSF); and granulocyte-CSF (G-CSF); interleukins (ILs) such as IL-1, IL-1alpha, IL-2, IL-3, IL-4, IL-5, IL-6, IL-7, IL-8, IL-9, IL-10, IL-11, IL-12; IL-15, a tumor necrosis factor such as TNF-alpha or TNF-beta; and other polypeptide factors including LIF and kit ligand (KL). As used herein, the term cytokine includes proteins from natural sources or from recombinant cell culture, and biologically active equivalents of the native sequence cytokines.

[112] A variety of other therapeutic agents may find use for administration with the antibodies and Fc fusions of the present invention. In one embodiment, the antibody or Fc fusion is administered with an anti-angiogenic agent. By "anti-angiogenic agent" as used herein is meant a compound that blocks, or interferes to some degree, the development of blood vessels. The anti-angiogenic factor may, for instance, be a small molecule or a protein, for example an antibody, Fc fusion, or cytokine, that binds to a growth factor or growth factor receptor involved in promoting angiogenesis. The preferred anti-angiogenic factor herein is an antibody that binds to Vascular Endothelial Growth Factor (VEGF). In an alternate embodiment, the antibody or Fc fusion is administered with a therapeutic

Samsung Bioepis Exhibit No. 1002
Page 11123

agent that induces or enhances adaptive immune response, for example an antibody that targets CTLA-4. In an alternate embodiment, the antibody or Fc fusion is administered with a tyrosine kinase inhibitor. By "tyrosine kinase inhibitor" as used herein is meant a molecule that inhibits to some extent tyrosine kinase activity of a tyrosine kinase. Examples of such inhibitors include but are not limited to quinazolines, such as PD 153035, 4-(3-chloroanilino) quinazoline; pyridopyrimidines; pyrimidopyrimidines; pyrrolopyrimidines, such as CGP 59326, CGP 60261 and CGP 62706; pyrazolopyrimidines, 4-(phenylamino)-7H-pyrrolo(2,3-d) pyrimidines; curcumin (diferuloyl methane, 4,5-bis (4-fluoroanilino)phthalimide); tyrphostines containing nitrothiophene moieties; PD-0183805 (Warner-Lambert); antisense molecules (e.g. those that bind to ErbB-encoding nucleic acid); quinoxalines (US 5,804,396); tryphostins (US 5,804,396); ZD6474 (Astra Zeneca); PTK-787 (Novartis/Schering A G); pan-ErbB inhibitors such as C1-1033 (Pfizer); Affinitac (ISIS 3521; Isis/Lilly); Imatinib mesylate (STI571,Gleevec®; Novartis); PKI 166 (Novartis); GW2016 (Glaxo SmithKline); C1-1033 (Pfizer); EKB-569 (Wyeth); Semaxinib (Sugen); ZD6474 (AstraZeneca); PTK-787 (Novartis/Schering AG); INC-1C11 (Imclone); or as described in any of the following patent publications: US 5,804,396; PCT WO 99/09016 (American Cyanimid); PCT WO 98/43960 (American Cyanamid); PCT WO 97/38983 (Warner-Lambert); PCT WO 99/06378 (Warner-Lambert); PCT WO 99/06396 (Warner-Lambert); PCT WO 96/30347 (Pfizer, Inc); PCT WO 96/33978 (AstraZeneca); PCT WO96/3397 (AstraZeneca); PCT WO 96/33980 (AstraZeneca), gefitinib (IRESSA™, ZD1839, AstraZeneca), and OSI-774 (Tarceva™, OSI Pharmaceuticals/Genentech).

[113] In an alternate embodiment, the antibody or Fc fusion of the present invention is conjugated or operably linked to another therapeutic compound. The therapeutic compound may be a cytotoxic agent, a chemotherapeutic agent, a toxin, a radioisotope, a cytokine, or other therapeutically active agent. Conjugates of the antibody or Fc fusion and cytotoxic agent may be made using a variety of bifunctional protein coupling agents such as N-succinimidyl-3-(2-pyridyldithiol) propionate (SPDP), succinimidyl-4-(N-maleimidomethyl) cyclohexane-1-carboxylate, iminothiolane (IT), bifunctional derivatives of imidoesters (such as dimethyl adipimidate HCL), active esters (such as disuccinimidyl suberate), aldehydes (such as glutareldehyde), bis-azido compounds (such as bis (p-azidobenzoyl) hexanediamine), bis-diazonium derivatives (such as bis-(p-diazoniumbenzoyl)-ethylenediamine), diisocyanates (such as tolyene 2,6-diisocyanate), and bis-active fluorine compounds (such as 1,5-difluoro-2,4-dinitrobenzene). For example, a ricin immunotoxin can be prepared as described in Vitetta et al., 1971, Science 238:1098. Carbon-14-labeled 1-isothiocyanatobenzyl-3-methyldiethylene triaminepentaacetic acid (MX-DTPA) is an exemplary chelating agent for conjugation of radionucleotide to the antibody. See PCT WO 94/11026. The linker may be a cleavable linker facilitating release of the cytotoxic drug in the cell. For example, an acid-labile linker, peptidase-sensitive linker, dimethyl linker or disulfide-containing linker (Chari et al., 1992, Cancer Research 52: 127-131) may be used. Alternatively, the antibody or Fc fusion is operably linked to the therapeutic agent, e.g. by recombinant techniques or peptide synthesis.

Samsung Bioepis Exhibit No. 1002
Page 11124

[114] Chemotherapeutic agents that may be useful for conjugation to the antibodies and Fc fusions of the present invention have been described above. In an alternate embodiment, the antibody or Fc fusion is conjugated or operably linked to a toxin, including but not limited to small molecule toxins and enzymatically active toxins of bacterial, fungal, plant or animal origin, including fragments and/or variants thereof. Small molecule toxins include but are not limited to calicheamicin, maytansine (US 5,208,020), trichothene, and CC1065. In one embodiment of the invention, the antibody or Fc fusion is conjugated to one or more maytansine molecules (e.g. about 1 to about 10 maytansine molecules per antibody molecule). Maytansine may, for example, be converted to May-SS-Me which may be reduced to May-SH3 and reacted with modified antibody or Fc fusion (Chari *et al.*, 1992, *Cancer Research* 52: 127-131) to generate a maytansinoid-antibody or maytansinoid-Fc fusion conjugate. Another conjugate of interest comprises an antibody or Fc fusion conjugated to one or more calicheamicin molecules. The calicheamicin family of antibiotics are capable of producing double-stranded DNA breaks at sub-picomolar concentrations. Structural analogues of calicheamicin that may be used include but are not limited to γ_1^1, $\square_2^1$, $\square_3$, N-acetyl-γ_1^1, PSAG, and Θ^1_1, (Hinman *et al.*, 1993, *Cancer Research* 53:3336-3342; Lode *et al.*, 1998, *Cancer Research* 58:2925-2928) (US 5,714,586; US 5,712,374; US 5,264,586; US 5,773,001). Dolastatin 10 analogs such as auristatin E (AE) and monomethylauristatin E (MMAE) may find use as conjugates for the Fc variants of the present invention (Doronina *et al.*, 2003, *Nat Biotechnol* 21(7):778-84; Francisco *et al.*, 2003 *Blood* 102(4):1458-65). Useful enyzmatically active toxins include but are not limited to diphtheria A chain, nonbinding active fragments of diphtheria toxin, exotoxin A chain (from *Pseudomonas aeruginosa*), ricin A chain, abrin A chain, modeccin A chain, alpha-sarcin, Aleurites fordii proteins, dianthin proteins, Phytolaca americana proteins (PAPI, PAPII, and PAP-S), momordica charantia inhibitor, curcin, crotin, sapaonaria officinalis inhibitor, gelonin, mitogellin, restrictocin, phenomycin, enomycin and the tricothecenes. See, for example, PCT WO 93/21232. The present invention further contemplates a conjugate or fusion formed between an antibody or Fc fusion of the present invention and a compound with nucleolytic activity, for example a ribonuclease or DNA endonuclease such as a deoxyribonuclease (DNase).

[115] In an alternate embodiment, an antibody or Fc fusion of the present invention may be conjugated or operably linked to a radioisotope to form a radioconjugate. A variety of radioactive isotopes are available for the production of radioconjugate antibodies and Fc fusions. Examples include, but are not limited to, At^{211}, I^{131}, I^{125}, Y^{90}, Re^{186}, Re^{188}, Sm^{153}, Bi^{212}, P^{32}, and radioactive isotopes of Lu.

[116] In yet another embodiment, an antibody or Fc fusion of the present invention may be conjugated to a "receptor" (such streptavidin) for utilization in tumor pretargeting wherein the antibody-receptor or Fc fusion-receptor conjugate is administered to the patient, followed by removal of unbound conjugate from the circulation using a clearing agent and then administration of a "ligand" (e.g. avidin) which is conjugated to a cytotoxic agent (e.g. a radionucleotide). In an alternate

Samsung Bioepis Exhibit No. 1002
Page 11125

embodiment, the antibody or Fc fusion is conjugated or operably linked to an enzyme in order to employ Antibody Dependent Enzyme Mediated Prodrug Therapy (ADEPT). ADEPT may be used by conjugating or operably linking the antibody or Fc fusion to a prodrug-activating enzyme that converts a prodrug (e.g. a peptidyl chemotherapeutic agent, see PCT WO 81/01145) to an active anti-cancer drug. See, for example, PCT WO 88/07378 and US 4,975,278. The enzyme component of the immunoconjugate useful for ADEPT includes any enzyme capable of acting on a prodrug in such a way so as to covert it into its more active, cytotoxic form. Enzymes that are useful in the method of this invention include but are not limited to alkaline phosphatase useful for converting phosphate-containing prodrugs into free drugs; arylsulfatase useful for converting sulfate-containing prodrugs into free drugs; cytosine deaminase useful for converting non-toxic 5-fluorocytosine into the anti-cancer drug, 5-fluorouracil; proteases, such as serratia protease, thermolysin, subtilisin, carboxypeptidases and cathepsins (such as cathepsins B and L), that are useful for converting peptide-containing prodrugs into free drugs; D-alanylcarboxypeptidases, useful for converting prodrugs that contain D-amino acid substituents; carbohydrate-cleaving enzymes such as .beta.-galactosidase and neuramimidase useful for converting glycosylated prodrugs into free drugs; beta-lactamase useful for converting drugs derivatized.with .alpha.-lactams into free drugs; and penicillin amidases, such as penicillin V amidase or penicillin G amidase, useful for converting drugs derivatized at their amine nitrogens with phenoxyacetyl or phenylacetyl groups, respectively, into free drugs. Alternatively, antibodies with enzymatic activity, also known in the art as "abzymes", can be used to convert the prodrugs of the invention into free active drugs (see, for example, Massey, 1987, *Nature* 328: 457-458). Antibody-abzyme and Fc fusion-abzyme conjugates can be prepared for delivery of the abzyme to a tumor cell population. Other modifications of the antibodies and Fc fusions of the present invention are contemplated herein. For example, the antibody or Fc fusion may be linked to one of a variety of nonproteinaceous polymers, e.g., polyethylene glycol, polypropylene glycol, polyoxyalkylenes, or copolymers of polyethylene glycol and polypropylene glycol.

[117] Pharmaceutical compositions are contemplated wherein an antibody or Fc fusion of the present invention and and one or more therapeutically active agents are formulated. Formulations of the antibodies and Fc fusions of the present invention are prepared for storage by mixing said antibody or Fc fusion having the desired degree of purity with optional pharmaceutically acceptable carriers, excipients or stabilizers (Remington's Pharmaceutical Sciences 16th edition, Osol, A. Ed.,1980), in the form of lyophilized formulations or aqueous solutions. Acceptable carriers, excipients, or stabilizers are nontoxic to recipients at the dosages and concentrations employed, and include buffers such as phosphate, citrate, acetate, and other organic acids; antioxidants including ascorbic acid and methionine; preservatives (such as octadecyldimethylbenzyl ammonium chloride; hexamethonium chloride; benzalkonium chloride, benzethonium chloride; phenol, butyl orbenzyl alcohol; alkyl parabens such as methyl or propyl paraben; catechol; resorcinol; cyclohexanol; 3-pentanol; and m-cresol); low molecular weight (less than about 10 residues) polypeptides; proteins, such as serum albumin, gelatin, or immunoglobulins; hydrophilic polymers such as polyvinylpyrrolidone; amino acids such as glycine, glutamine, asparagine, histidine, arginine, or lysine;

Samsung Bioepis Exhibit No. 1002
Page 11126

monosaccharides, disaccharides, and other carbohydrates including glucose, mannose, or dextrins; chelating agents such as EDTA; sugars such as sucrose, mannitol, trehalose or sorbitol; sweeteners and other flavoring agents; fillers such as microcrystalline cellulose, lactose, corn and other starches; binding agents; additives; coloring agents; salt-forming counter-ions such as sodium; metal complexes (e.g. Zn-protein complexes); and/or non-ionic surfactants such as TWEEN™, PLURONICS™ or polyethylene glycol (PEG). In a preferred embodiment, the pharmaceutical composition that comprises the antibody or Fc fusion of the present invention is in a water-soluble form, such as being present as pharmaceutically acceptable salts, which is meant to include both acid and base addition salts. "Pharmaceutically acceptable acid addition salt" refers to those salts that retain the biological effectiveness of the free bases and that are not biologically or otherwise undesirable, formed with inorganic acids such as hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid and the like, and organic acids such as acetic acid, propionic acid, glycolic acid, pyruvic acid, oxalic acid, maleic acid, malonic acid, succinic acid, fumaric acid, tartaric acid, citric acid, benzoic acid, cinnamic acid, mandelic acid, methanesulfonic acid, ethanesulfonic acid, p-toluenesulfonic acid, salicylic acid and the like. "Pharmaceutically acceptable base addition salts" include those derived from inorganic bases such as sodium, potassium, lithium, ammonium, calcium, magnesium, iron, zinc, copper, manganese, aluminum salts and the like. Particularly preferred are the ammonium, potassium, sodium, calcium, and magnesium salts. Salts derived from pharmaceutically acceptable organic non-toxic bases include salts of primary, secondary, and tertiary amines, substituted amines including naturally occurring substituted amines, cyclic amines and basic ion exchange resins, such as isopropylamine, trimethylamine, diethylamine, triethylamine, tripropylamine, and ethanolamine. The formulations to be used for *in vivo* administration are preferrably sterile. This is readily accomplished by filtration through sterile filtration membranes or other methods.

[118] The antibodies and Fc fusions disclosed herein may also be formulated as immunoliposomes. A liposome is a small vesicle comprising various types of lipids, phospholipids and/or surfactant that is useful for delivery of a therapeutic agent to a mammal. Liposomes containing the antibody or Fc fusion are prepared by methods known in the art, such as described in Epstein *et al.*, 1985, *Proc Natl Acad Sci USA*, 82:3688; Hwang *et al.*, 1980, *Proc Natl Acad Sci USA*, 77:4030; US 4,485,045; US 4,544,545; and PCT WO 97/38731. Liposomes with enhanced circulation time are disclosed in US 5,013,556. The components of the liposome are commonly arranged in a bilayer formation, similar to the lipid arrangement of biological membranes. Particularly useful liposomes can be generated by the reverse phase evaporation method with a lipid composition comprising phosphatidylcholine, cholesterol and PEG-derivatized phosphatidylethanolamine (PEG-PE). Liposomes are extruded through filters of defined pore size to yield liposomes with the desired diameter. A chemotherapeutic agent or other therapeutically active agent is optionally contained within the liposome (Gabizon *et al.*, 1989, *J National Cancer Inst* 81:1484).

Samsung Bioepis Exhibit No. 1002
Page 11127

[119] The antibodies, Fc fusions, and other therapeutically active agents may also be entrapped in microcapsules prepared by methods including but not limited to coacervation techniques, interfacial polymerization (for example using hydroxymethylcellulose or gelatin-microcapsules, or poly-(methylmethacylate) microcapsules), colloidal drug delivery systems (for example, liposomes, albumin microspheres, microemulsions, nano-particles and nanocapsules), and macroemulsions. Such techniques are disclosed in Remington's Pharmaceutical Sciences 16th edition, Osol, A. Ed., 1980. Sustained-release preparations may be prepared. Suitable examples of sustained-release preparations include semipermeable matrices of solid hydrophobic polymer, which matrices are in the form of shaped articles, e.g. films, or microcapsules. Examples of sustained-release matrices include polyesters, hydrogels (for example poly(2-hydroxyethyl-methacrylate), or poly(vinylalcohol)), polylactides (US 3,773,919), copolymers of L-glutamic acid and gamma ethyl-L-glutamate, non-degradable ethylene-vinyl acetate, degradable lactic acid-glycolic acid copolymers such as the LUPRON DEPOT™ (which are injectable microspheres composed of lactic acid-glycolic acid copolymer and leuprolide acetate), poly-D-(-)-3-hydroxybutyric acid, and ProLease® (commercially available from Alkermes), which is a microsphere-based delivery system composed of the desired bioactive molecule incorporated into a matrix of poly-DL-lactide-co-glycolide (PLG).

[120] The concentration of the therapeutically active antibody or Fc fusion of the present invention in the formulation may vary from about 0.1 to 100 weight %. In a preferred embodiment, the concentration of the antibody or Fc fusion is in the range of 0.003 to 1.0 molar. In order to treat a patient, a therapeutically effective dose of the antibody or Fc fusion of the present invention may be administered. By "therapeutically effective dose" herein is meant a dose that produces the effects for which it is administered. The exact dose will depend on the purpose of the treatment, and will be ascertainable by one skilled in the art using known techniques. Dosages may range from 0.01 to 100 mg/kg of body weight or greater, for example 0.1, 1, 10, or 50 mg/kg of body weight, with 1 to 10mg/kg being preferred. As is known in the art, adjustments for antibody or Fc fusion degradation, systemic versus localized delivery, and rate of new protease synthesis, as well as the age, body weight, general health, sex, diet, time of administration, drug interaction and the severity of the condition may be necessary, and will be ascertainable with routine experimentation by those skilled in the art.

[121] Administration of the pharmaceutical composition comprising an antibody or Fc fusion of the present invention, preferably in the form of a sterile aqueous solution, may be done in a variety of ways, including, but not limited to, orally, subcutaneously, intravenously, intranasally, intraotically, transdermally, topically (e.g., gels, salves, lotions, creams, etc.), intraperitoneally, intramuscularly, intrapulmonary (e.g., AERx® inhalable technology commercially available from Aradigm, or Inhance™ pulmonary delivery system commercially available from Inhale Therapeutics), vaginally, parenterally, rectally, or intraocularly. In some instances, for example for the treatment of wounds, inflammation, etc., the antibody or Fc fusion may be directly applied as a solution or spray. As is known in the art,

the pharmaceutical composition may be formulated accordingly depending upon the manner of introduction.

Engineering Methods

[122] The present invention provides engineering methods that may be used to generate Fc variants. A principal obstacle that has hindered previous attempts at Fc engineering is that only random attempts at modification have been possible, due in part to the inefficiency of engineering strategies and methods, and to the low-throughput nature of antibody production and screening. The present invention describes engineering methods that overcome these shortcomings. A variety of design strategies, computational screening methods, library generation methods, and experimental production and screening methods are contemplated. These strategies, approaches, techniques, and methods may be applied individually or in various combinations to engineer optimized Fc variants.

Design Strategies

[123] The most efficient approach to generating Fc variants that are optimized for a desired property is to direct the engineering efforts toward that goal. Accordingly, the present invention teaches design strategies that may be used to engineer optimized Fc variants. The use of a design strategy is meant to guide Fc engineering, but is not meant to constrain an Fc variant to a particular optimized property based on the design strategy that was used to engineer it. At first thought this may seem counterintuitive; however its validity is derived from the enormous complexity of subtle interactions that determine the structure, stability, solubility, and function of proteins and protein-protein complexes. Although efforts can be made to predict which protein positions, residues, interactions, etc. are important for a design goal, often times critical ones are not predictable. Effects on protein structure, stability, solubility, and function, whether favorable or unfavorable, are often unforeseen. Yet there are innumerable amino acid modifications that are detrimental or deleterious to proteins. Thus often times the best approach to engineering comes from generation of protein variants that are focused generally towards a design goal but do not cause detrimental effects. In this way, a principal objective of a design strategy may be the generation of quality diversity. At a simplistic level this can be thought of as stacking the odds in one's favor. As an example, perturbation of the Fc carbohydrate or a particular domain-domain angle, as described below, are valid design strategies for generating optimized Fc variants, despite the fact that how carbohydrate and domain-domain angles determine the properties of Fc is not well understood. By reducing the number of detrimental amino acid modifications that are screened, i.e. by screening quality diversity, these design strategies become practical. Thus the true value of the design strategies taught in the present invention is their ability to direct engineering efforts towards the generation of valuable Fc variants. The specific value of any one resulting variant is determined after experimentation.

Samsung Bioepis Exhibit No. 1002
Page 11129

[124] One design strategy for engineering Fc variants is provided in which interaction of Fc with some Fc ligand is altered by engineering amino acid modifications at the interface between Fc and said Fc ligand. Fc ligands herein may include but are not limited to FcγRs, C1q, FcRn, protein A or G, and the like. By exploring energetically favorable substitutions at Fc positions that impact the binding interface, variants can be engineered that sample new interface conformations, some of which may improve binding to the Fc ligand, some of which may reduce Fc ligand binding, and some of which may have other favorable properties. Such new interface conformations could be the result of, for example, direct interaction with Fc ligand residues that form the interface, or indirect effects caused by the amino acid modifications such as perturbation of side chain or backbone conformations. Variable positions may be chosen as any positions that are believed to play an important role in determining the conformation of the interface. For example, variable positions may be chosen as the set of residues that are within a certain distance, for example 5 Angstroms (Å), preferrably between 1 and 10 Å, of any residue that makes direct contact with the Fc ligand.

[125] An additional design strategy for generating Fc variants is provided in which the conformation of the Fc carbohydrate at N297 is optimized. Optimization as used in this context is meant to includes conformational and compositional changes in the N297 carbohydrate that result in a desired property, for example increased or reduced affinity for an FcγR. Such a strategy is supported by the observation that the carbohydrate structure and conformation dramatically affect Fc/FcγR and Fc/C1q binding (Umaña *et al.*, 1999, *Nat Biotechnol* 17:176-180; Davies *et al.*, 2001, *Biotechnol Bioeng* 74:288-294; Mimura *et al.*, 2001, *J Biol Chem* 276:45539-45547.; Radaev *et al.*, 2001, *J Biol Chem* 276:16478-16483; Shields *et al.*, 2002, *J Biol Chem* 277:26733-26740; Shinkawa *et al.*, 2003, *J Biol Chem* 278:3466-3473). However the carbohydrate makes no specific contacts with FcγRs. By exploring energetically favorable substitutions at positions that interact with carbohydrate, a quality diversity of variants can be engineered that sample new carbohydrate conformations, some of which may improve and some of which may reduce binding to one or more Fc ligands. While the majority of mutations near the Fc/carbohydrate interface appear to alter carbohydrate conformation, some mutations have been shown to alter the glycosylation composition (Lund *et al.*, 1996, *J Immunol* 157:4963-4969; Jefferis *et al.*, 2002, *Immunol Lett* 82:57-65).

[126] Another design strategy for generating Fc variants is provided in which the angle between the Cγ2 and Cγ3 domains is optimized Optimization as used in this context is meant to describe conformational changes in the Cγ2-Cγ3 domain angle that result in a desired property, for example increased or reduced affinity for an FcγR. This angle is an important determinant of Fc/FcγR affinity (Radaev *et al.*, 2001, *J Biol Chem* 276:16478-16483), and a number of mutations distal to the Fc/FcγR interface affect binding potentially by modulating it (Shields *et al.*, 2001, *J Biol Chem* 276:6591-6604). By exploring energetically favorable substitutions positions that appear to play a key role in determining the Cγ2-Cγ3 angle and the flexibility of the domains relative to one another, a

Samsung Bioepis Exhibit No. 1002
Page 11130

quality diversity of variants can be designed that sample new angles and levels of flexibility, some of which may be optimized for a desired Fc property.

[127] Another design strategy for generating Fc variants is provided in which Fc is reengineered to eliminate the structural and functional dependence on glycosylation. This design strategy involves the optimization of Fc structure, stability, solubility, and/or Fc function (for example affinity of Fc for one or more Fc ligands) in the absence of the N297 carbohydrate. In one approach, positions that are exposed to solvent in the absence of glycosylation are engineered such that they are stable, structurally consistent with Fc structure, and have no tendency to aggregate. The Cγ2 is the only unpaired Ig domain in the antibody (see Figure 1). Thus the N297 carbohydrate covers up the exposed hydrophobic patch that would normally be the interface for a protein-protein interaction with another Ig domain, maintaining the stability and structural integrity of Fc and keeping the Cγ2 domains from aggregating across the central axis. Approaches for optimizing aglycosylated Fc may involve but are not limited to designing amino acid modifications that enhance aglycoslated Fc stability and/or solubility by incorporating polar and/or charged residues that face inward towards the Cγ2-Cγ2 dimer axis, and by designing amino acid modifications that directly enhance the aglycosylated Fc/FcγR interface or the interface of aglycosylated Fc with some other Fc ligand.

[128] An additional design strategy for engineering Fc variants is provided in which the conformation of the Cγ2 domain is optimized Optimization as used in this context is meant to describe conformational changes in the Cγ2 domain angle that result in a desired property, for example increased or reduced affinity for an FcγR. By exploring energetically favorable substitutions at Cγ2 positions that impact the Cγ2 conformation, a quality diversity of variants can be engineered that sample new Cγ2 conformations, some of which may achieve the design goal. Such new Cγ2 conformations could be the result of, for example, alternate backbone conformations that are sampled by the variant. Variable positions may be chosen as any positions that are believed to play an important role in determining C⊓2 structure, stability, solubility, flexibility, function, and the like. For example, Cγ2 hydrophobic core residues, that is Cγ2 residues that are partially or fully sequestered from solvent, may be reengineered. Alternatively, noncore residues may be considered, or residues that are deemed important for determining backbone structure, stability, or flexibility.

[129] An additional design strategy for Fc optimization is provided in which binding to an FcγR, complement, or some other Fc ligand is altered by modifications that modulate the electrostatic interaction between Fc and said Fc ligand. Such modifications may be thought of as optimization of the global electrostatic character of Fc, and include replacement of neutral amino acids with a charged amino acid, replacement of a charged amino acid with a neutral amino acid, or replacement of a charged amino acid with an amino acid of opposite charge (i.e. charge reversal). Such

Samsung Bioepis Exhibit No. 1002
Page 11131

modifications may be used to effect changes in binding affinity between an Fc and one or more Fc ligands, for example FcγRs. In a preferred embodiment, positions at which electrostatic substitutions might affect binding are selected using one of a variety of well known methods for calculation of electrostatic potentials. In the simplest embodiment, Coulomb's law is used to generate electrostatic potentials as a function of the position in the protein. Additional embodiments include the use of Debye-Huckel scaling to account for ionic strength effects, and more sophisticated embodiments such as Poisson-Boltzmann calculations. Such electrostatic calculations may highlight positions and suggest specific amino acid modifications to achieve the design goal. In some cases, these substitutions may be anticipated to variably affect binding to different Fc ligands, for example to enhance binding to activating FcγRs while decreasing binding affinity to inhibitory FcγRs.

Computational Screening

[130] A principal obstacle to obtaining valuable Fc variants is the difficulty in predicting what amino acid modifications, out of the enormous number of possibilities, will achieve the desired goals. Indeed one of the principle reasons that previous attempts at Fc engineering have failed to produce Fc variants of significant clinical value is that approaches to Fc engineering have thus far involved hit-or-miss approaches. The present invention provides computational screening methods that enable quantitative and systematic engineering of Fc variants. These methods typically use atomic level scoring functions, side chain rotamer sampling, and advanced optimization methods to accurately capture the relationships between protein sequence, structure, and function. Computational screening enables exploration of the entire sequence space of possibilities at target positions by filtering the enormous diversity which results. Variant libraries that are screened computationally are effectively enriched for stable, properly folded, and functional sequences, allowing active optimization of Fc for a desired goal. Because of the overlapping sequence constraints on protein structure, stability, solubility, and function, a large number of the candidates in a library occupy "wasted" sequence space. For example, a large fraction of sequence space encodes unfolded, misfolded, incompletely folded, partially folded, or aggregated proteins. This is particularly relevant for Fc engineering because Ig domains are small beta sheet structures, the engineering of which has proven extremely demanding (Quinn *et al.*, 1994, *Proc Natl Acad Sci U S A* 91:8747-8751; Richardson *et al.*, 2002, *Proc Natl Acad Sci U S A* 99:2754-2759). Even seemingly harmless substitutions on the surface of a beta sheet can cause severe packing conflicts, dramatically disrupting folding equilibrium (Smith *et al.*, 1995, *Science* 270:980-982); incidentally, alanine is one of the worst beta sheet formers (Minor *et al.*, 1994, *Nature* 371:264-267). The determinants of beta sheet stability and specificity are a delicate balance between an extremely large number of subtle interactions. Computational screening enables the generation of libraries that are composed primarily of productive sequence space, and as a result increases the chances of identifying proteins that are optimized for the design goal. In effect, computational screening yields an increased hit-rate, thereby decreasing the number of variants that must be screened experimentally. An additional obstacle to Fc engineering is the need for active design of correlated or coupled mutations. For example, the greatest Fc/FcγR affinity

Samsung Bioepis Exhibit No. 1002
Page 11132

enhancement observed thus far is S298A/E333A/K334A, obtained by combining three better binders obtained separately in an alanine scan (Shields *et al.*, 2001, *J Biol Chem* 276:6591-6604). Computational screening is capable of generating such a three-fold variant in one experiment instead of three separate ones, and furthermore is able to test the functionality of all 20 amino acids at those positions instead of just alanine. Computational screening deals with such complexity by reducing the combinatorial problem to an experimentally tractable size.

[131] Computational screening, viewed broadly, has four steps: 1) selection and preparation of the protein template structure or structures, 2) selection of variable positions, amino acids to be considered at those positions, and/or selection of rotamers to model considered amino acids, 3) energy calculation, and 4) combinatorial optimization. In more detail, the process of computational screening can be described as follows. A three-dimensional structure of a protein is used as the starting point. The positions to be optimized are identified, which may be the entire protein sequence or subset(s) thereof. Amino acids that will be considered at each position are selected. In a preferred embodiment, each considered amino acid may be represented by a discrete set of allowed conformations, called rotamers. Interaction energies are calculated between each considered amino acid and each other considered amino acid, and the rest of the protein, including the protein backbone and invariable residues. In a preferred embodiment, interaction energies are calculated between each considered amino acid side chain rotamer and each other considered amino acid side chain rotamer and the rest of the protein, including the protein backbone and invariable residues. One or more combinatorial search algorithms are then used to identify the lowest energy sequence and/or low energy sequences.

[132] In a preferred embodiment, the computational screening method used is substantially similar to Protein Design Automation® (PDA®) technology, as is described in US 6,188,965; US 6,269,312; US 6,403,312; USSN 09/782,004; USSN 09/927,790; USSN 10/218,102; PCT WO 98/07254; PCT WO 01/40091; and PCT WO 02/25588. In another preferred embodiment, a computational screening method substantially similar to Sequence Prediction Algorithm™ (SPA™) technology is used, as is described in (Raha *et al.*, 2000, *Protein Sci* 9:1106-1119), USSN 09/877,695, and USSN 10/071,859. In another preferred embodiment, the computational screening methods described in USSN 10/339788, filed on March 3, 2003, entitled "ANTIBODY OPTIMIZATION", are used. In some embodiments, combinations of different computational screening methods are used, including combinations of PDA® technology and SPA™ technology, as well as combinations of these computational methods in combination with other design tools. Similarly, these computational methods can be used simultaneously or sequentially, in any order.

[133] A template structure is used as input into the computational screening calculations. By "template structure" herein is meant the structural coordinates of part or all of a protein to be

optimized. The template structure may be any protein for which a three dimensional structure (that is, three dimensional coordinates for a set of the protein's atoms) is known or may be calculated, estimated, modeled, generated, or determined. The three dimensional structures of proteins may be determined using methods including but not limited to X-ray crystallographic techniques, nuclear magnetic resonance (NMR) techniques, *de novo* modeling, and homology modeling. If optimization is desired for a protein for which the structure has not been solved experimentally, a suitable structural model may be generated that may serve as the template for computational screening calculations. Methods for generating homology models of proteins are known in the art, and these methods find use in the present invention. See for example, Luo, *et al.* 2002, *Protein Sci* 11: 1218-1226, Lehmann & Wyss, 2001, *Curr Opin Biotechnol* 12(4):371-5.; Lehmann *et al.*, 2000, Biochim Biophys Acta 1543(2):408-415; Rath & Davidson, 2000, *Protein Sci*, 9(12):2457-69; Lehmann *et al.*, 2000, *Protein Eng* 13(1):49-57; Desjarlais & Berg, 1993, *Proc Natl Acad Sci USA* 90(6):2256-60; Desjarlais & Berg, 1992, *Proteins* 12(2):101-4; Henikoff & Henikoff, 2000, *Adv Protein Chem* 54:73-97; Henikoff & Henikoff, 1994, *J Mol Biol* 243(4):574-8; Morea *et al.*, 2000, *Methods* 20:267-269. Protein/protein complexes may also be obtained using docking methods. Suitable protein structures that may serve as template structures include, but are not limited to, all of those found in the Protein Data Base compiled and serviced by the Research Collaboratory for Structural Bioinformatics (RCSB, formerly the Brookhaven National Lab).

[134] The template structure may be of a protein that occurs naturally or is engineered. The template structure may be of a protein that is substantially encoded by a protein from any organism, with human, mouse, rat, rabbit, and monkey preferred. The template structure may comprise any of a number of protein structural forms. In a preferred embodiment the template structure comprises an Fc region or a domain or fragment of Fc. In an alternately preferred embodiment the template structure comprises Fc or a domain or fragment of Fc bound to one or more Fc ligands, with an Fc/FcγR complex being preferred. The Fc in the template structure may be glycosylated or unglycosylated. The template structure may comprise more than one protein chain. The template structure may additionally contain nonprotein components, including but not limited to small molecules, substrates, cofactors, metals, water molecules, prosthetic groups, polymers and carbohydrates. In a preferred embodiment, the template structure is a plurality or set of template proteins, for example an ensemble of structures such as those obtained from NMR. Alternatively, the set of template structures is generated from a set of related proteins or structures, or artificially created ensembles. The composition and source of the template structure depends on the engineering goal. For example, for enhancement of human Fc/FcγR affinity, a human Fc/FcγR complex structure or derivative thereof may be used as the template structure. Alternatively, the uncomplexed Fc structure may be used as the template structure. If the goal is to enhance affinity of a human Fc for a mouse FcγR, the template structure may be a structure or model of a human Fc bound to a mouse FcγR.

Samsung Bioepis Exhibit No. 1002
Page 11134

[135] The template structure may be modified or altered prior to design calculations. A variety of methods for template structure preparation are described in US 6,188,965; US 6,269,312; US 6,403,312; USSN 09/782,004; USSN 09/927,790; USSN 09/877,695; USSN 10/071,859, USSN 10/218,102; PCT WO 98/07254; PCT WO 01/40091; and PCT WO 02/25588. For example, in a preferred embodiment, explicit hydrogens may be added if not included within the structure. In an alternate embodiment, energy minimization of the structure is run to relax strain, including strain due to van der Waals clashes, unfavorable bond angles, and unfavorable bond lengths. Alternatively, the template structure is altered using other methods, such as manually, including directed or random perturbations. It is also possible to modify the template structure during later steps of computational screening, including during the energy calculation and combinatorial optimization steps. In an alternate embodiment, the template structure is not modified before or during computational screening calculations.

[136] Once a template structure has been obtained, variable positions are chosen. By "variable position" herein is meant a position at which the amino acid identity is allowed to be altered in a computational screening calculation. As is known in the art, allowing amino acid modifications to be considered only at certain variable positions reduces the complexity of a calculation and enables computational screening to be more directly tailored for the design goal. One or more residues may be variable positions in computational screening calculations. Positions that are chosen as variable positions may be those that contribute to or are hypothesized to contribute to the protein property to be optimized, for example Fc affinity for an FcγR, Fc stability, Fc solubility, and so forth. Residues at variable positions may contribute favorably or unfavorably to a specific protein property. For example, a residue at an Fc/FcγR interface may be involved in mediating binding, and thus this position may be varied in design calculations aimed at improving Fc/FcγR affinity. As another example, a residue that has an exposed hydrophobic side chain may be responsible for causing unfavorable aggregation, and thus this position may be varied in design calculations aimed at improving solubility. Variable positions may be those positions that are directly involved in interactions that are determinants of a particular protein property. For example, the Fc□R binding site of Fc may be defined to include all residues that contact that particular FγcR. By "contact" herein is meant some chemical interaction between at least one atom of an Fc residue with at least one atom of the bound FcγR, with chemical interaction including, but not limited to van der Waals interactions, hydrogen bond interactions, electrostatic interactions, and hydrophobic interactions. In an alternative embodiment, variable positions may include those positions that are indirectly involved in a protein property, i.e. such positions may be proximal to residues that are known to or hypothesized to contribute to an Fc property. For example, the FcγR binding site of an Fc may be defined to include all Fc residues within a certain distance, for example 4 - 10 Å, of any Fc residue that is in van der Waals contact with the FcγR. Thus variable positions in this case may be chosen not only as residues that directly contact the FcγR, but also those that contact residues that contact the FcγR and thus influence binding indirectly. The specific positions chosen are dependent on the design strategy being employed.

[137] One or more positions in the template structure that are not variable may be floated. By "floated position" herein is meant a position at which the amino acid conformation but not the amino acid identity is allowed to vary in a computational screening calculation. In one embodiment, the floated position may have the parent amino acid identity. For example, floated positions may be positions that are within a small distance, for example 5 Å, of a variable position residue. In an alternate embodiment, a floated position may have a non-parent amino acid identity. Such an embodiment may find use in the present invention, for example, when the goal is to evaluate the energetic or structural outcome of a specific mutation.

[138] Positions that are not variable or floated are fixed. By "fixed position" herein is meant a position at which the amino acid identity and the conformation are held constant in a computational screening calculation. Positions that may be fixed include residues that are not known to be or hypothesized to be involved in the property to be optimized. In this case the assumption is that there is little or nothing to be gained by varying these positions. Positions that are fixed may also include positions whose residues are known or hypothesized to be important for maintaining proper folding, structure, stability, solubility, and/or biological function. For example, positions may be fixed for residues that interact with a particular Fc ligand or residues that encode a glycosylation site in order to ensure that binding to the Fc ligand and proper glycosylation respectively are not perturbed. Likewise, if stability is being optimized, it may be beneficial to fix positions that directly or indirectly interact with an Fc ligand, for example an Fc□R, so that binding is not perturbed. Fixed positions may also include structurally important residues such as cysteines participating in disulfide bridges, residues critical for determining backbone conformation such as proline or glycine, critical hydrogen bonding residues, and residues that form favorable packing interactions.

[139] The next step in computational screening is to select a set of possible amino acid identities that will be considered at each particular variable position. This set of possible amino acids is herein referred to as "considered amino acids" at a variable position. "Amino acids" as used herein refers to the set of natural 20 amino acids and any nonnatural or synthetic analogues. In one embodiment, all 20 natural amino acids are considered. Alternatively, a subset of amino acids, or even only one amino acid is considered at a given variable position. As will be appreciated by those skilled in the art, there is a computational benefit to considering only certain amino acid identities at variable positions, as it decreases the combinatorial complexity of the search. Furthermore, considering only certain amino acids at variable positions may be used to tailor calculations toward specific design strategies. For example, for solubility optimization of aglycosylated Fc, it may be beneficial to allow only polar amino acids to be considered at nonpolar Fc residues that are exposed to solvent in the absence of carbohydrate. Nonnatural amino acids, including synthetic amino acids and analogues of natural amino acids, may also be considered amino acids. For example see Chin *et al.*, 2003, *Science*, 301(5635):964-7; and Chin *et al.*, 2003, *Chem Biol.*10(6):511-9.

Samsung Bioepis Exhibit No. 1002
Page 11136

[140] A wide variety of methods may be used, alone or in combination, to select which amino acids will be considered at each position. For example, the set of considered amino acids at a given variable position may be chosen based on the degree of exposure to solvent. Hydrophobic or nonpolar amino acids typically reside in the interior or core of a protein, which are inaccessible or nearly inaccessible to solvent. Thus at variable core positions it may be beneficial to consider only or mostly nonpolar amino acids such as alanine, valine, isoleucine, leucine, phenylalanine, tyrosine, tryptophan, and methionine. Hydrophilic or polar amino acids typically reside on the exterior or surface of proteins, which have a significant degree of solvent accessibility. Thus at variable surface positions it may be beneficial to consider only or mostly polar amino acids such as alanine, serine, threonine, aspartic acid, asparagine, glutamine, glutamic acid, arginine, lysine and histidine. Some positions are partly exposed and partly buried, and are not clearly protein core or surface positions, in a sense serving as boundary residues between core and surface residues. Thus at such variable boundary positions it may be beneficial to consider both nonpolar and polar amino acids such as alanine, serine, threonine, aspartic acid, asparagine, glutamine, glutamic acid, arginine, lysine histidine, valine, isoleucine, leucine, phenylalanine, tyrosine, tryptophan, and methionine. Determination of the degree of solvent exposure at variable positions may be by subjective evaluation or visual inspection of the template structure by one skilled in the art of protein structural biology, or by using a variety of algorithms that are known in the art. Selection of amino acid types to be considered at variable positions may be aided or determined wholly by computational methods, such as calculation of solvent accessible surface area, or using algorithms that assess the orientation of the C□-C□ vectors relative to a solvent accessible surface, as outlined in US 6,188,965; 6,269,312; US 6,403,312; USSN 09/782,004; USSN 09/927,790; USSN 10/218,102; PCT WO 98/07254; PCT WO 01/40091; and PCT WO 02/25588. In one embodiment, each variable position may be classified explicitly as a core, surface, or boundary position or a classification substantially similar to core, surface, or boundary.

[141] In an alternate embodiment, selection of the set of amino acids allowed at variable positions may be hypothesis-driven. Hypotheses for which amino acid types should be considered at variable positions may be derived by a subjective evaluation or visual inspection of the template structure by one skilled in the art of protein structural biology. For example, if it is suspected that a hydrogen bonding interaction may be favorable at a variable position, polar residues that have the capacity to form hydrogen bonds may be considered, even if the position is in the core. Likewise, if it is suspected that a hydrophobic packing interaction may be favorable at a variable position, nonpolar residues that have the capacity to form favorable packing interactions may be considered, even if the position is on the surface. Other examples of hypothesis-driven approaches may involve issues of backbone flexibility or protein fold. As is known in the art, certain residues, for example proline, glycine, and cysteine, play important roles in protein structure and stability. Glycine enables greater backbone flexibility than all other amino acids, proline constrains the backbone more than all other

Samsung Bioepis Exhibit No. 1002
Page 11137

amino acids, and cysteines may form disulfide bonds. It may therefore be beneficial to include one or more of these amino acid types to achieve a desired design goal. Alternatively, it may be beneficial to exclude one or more of these amino acid types from the list of considered amino acids.

[142] In an alternate embodiment, subsets of amino acids may be chosen to maximize coverage. In this case, additional amino acids with properties similar to that in the template structure may be considered at variable positions. For example, if the residue at a variable position in the template structure is a large hydrophobic residue, additional large hydrophobic amino acids may be considered at that position. Alternatively, subsets of amino acids may be chosen to maximize diversity. In this case, amino acids with properties dissimilar to those in the template structure may be considered at variable positions. For example, if the residue at a variable position in the template is a large hydrophobic residue, amino acids that are small, polar, etc. may be considered.

[143] As is known in the art, some computational screening methods require only the identity of considered amino acids to be determined during design calculations. That is, no information is required concerning the conformations or possible conformations of the amino acid side chains. Other preferred methods utilize a set of discrete side chain conformations, called rotamers, which are considered for each amino acid. Thus, a set of rotamers may be considered at each variable and floated position. Rotamers may be obtained from published rotamer libraries (see for example, Lovel *et al.*, 2000, *Proteins: Structure Function and Genetics* 40:389-408; Dunbrack & Cohen, 1997, *Protein Science* 6:1661-1681; DeMaeyer *et al.*, 1997, *Folding and Design* 2:53-66; Tuffery *et al.*, 1991, *J Biomol Struct Dyn* 8:1267-1289, Ponder & Richards, 1987, *J Mol Biol* 193:775-791). As is known in the art, rotamer libraries may be backbone-independent or backbone-dependent. Rotamers may also be obtained from molecular mechanics or *ab initio* calculations, and using other methods. In a preferred embodiment, a flexible rotamer model is used (see Mendes *et al.*, 1999, *Proteins: Structure, Function, and Genetics* 37:530-543). Similarly, artificially generated rotamers may be used, or augment the set chosen for each amino acid and/or variable position. In one embodiment, at least one conformation that is not low in energy is included in the list of rotamers. In an alternate embodiment, the rotamer of the variable position residue in the template structure is included in the list of rotamers allowed for that variable position. In an alternate embodiment, only the identity of each amino acid considered at variable positions is provided, and no specific conformational states of each amino acid are used during design calculations. That is, use of rotamers is not essential for computational screening.

[144] Experimental information may be used to guide the choice of variable positions and/or the choice of considered amino acids at variable positions. As is known in the art, mutagenesis experiments are often carried out to determine the role of certain residues in protein structure and function, for example, which protein residues play a role in determining stability, or which residues

Samsung Bioepis Exhibit No. 1002
Page 11138

make up the interface of a protein-protein interaction. Data obtained from such experiments are useful in the present invention. For example, variable positions for Fc/FcγR affinity enhancement could involve varying all positions at which mutation has been shown to affect binding. Similarly, the results from such an experiment may be used to guide the choice of allowed amino acid types at variable positions. For example, if certain types of amino acid substitutions are found to be favorable, similar types of those amino acids may be considered. In one embodiment, additional amino acids with properties similar to those that were found to be favorable experimentally may be considered at variable positions. For example, if experimental mutation of a variable position at an Fc/FcγR interface to a large hydrophobic residue was found to be favorable, the user may choose to include additional large hydrophobic amino acids at that position in the computational screen. As is known in the art, display and other selection technologies may be coupled with random mutagenesis to generate a list or lists of amino acid substitutions that are favorable for the selected property. Such a list or lists obtained from such experimental work find use in the present invention. For example, positions that are found to be invariable in such an experiment may be excluded as variable positions in computational screening calculations, whereas positions that are found to be more acceptable to mutation or respond favorably to mutation may be chosen as variable positions. Similarly, the results from such experiments may be used to guide the choice of allowed amino acid types at variable positions. For example, if certain types of amino acids arise more frequently in an experimental selection, similar types of those amino acids may be considered. In one embodiment, additional amino acids with properties similar to those that were found to be favorable experimentally may be considered at variable positions. For example, if selected mutations at a variable position that resides at an Fc/FcγR interface are found to be uncharged polar amino acids, the user may choose to include additional uncharged polar amino acids, or perhaps charged polar amino acids, at that position.

[145] Sequence information may also be used to guide choice of variable positions and/or the choice of amino acids considered at variable positions. As is known in the art, some proteins share a common structural scaffold and are homologous in sequence. This information may be used to gain insight into particular positions in the protein family. As is known in the art, sequence alignments are often carried out to determine which protein residues are conserved and which are not conserved. That is to say, by comparing and contrasting alignments of protein sequences, the degree of variability at a position may be observed, and the types of amino acids that occur naturally at positions may be observed. Data obtained from such analyses are useful in the present invention. The benefit of using sequence information to choose variable positions and considered amino acids at variable positions are several fold. For choice of variable positions, the primary advantage of using sequence information is that insight may be gained into which positions are more tolerant and which are less tolerant to mutation. Thus sequence information may aid in ensuring that quality diversity, i.e. mutations that are not deleterious to protein structure, stability, etc., is sampled computationally. The same advantage applies to use of sequence information to select amino acid types considered at variable positions. That is, the set of amino acids that occur in a protein sequence alignment may be

Samsung Bioepis Exhibit No. 1002
Page 11139

thought of as being pre-screened by evolution to have a higher chance than random for being compatible with a protein's structure, stability, solubility, function, etc. Thus higher quality diversity is sampled computationally. A second benefit of using sequence information to select amino acid types considered at variable positions is that certain alignments may represent sequences that may be less immunogenic than random sequences. For example, if the amino acids considered at a given variable position are the set of amino acids which occur at that position in an alignment of human protein sequences, those amino acids may be thought of as being pre-screened by nature for generating no or low immune response if the optimized protein is used as a human therapeutic.

[146] The source of the sequences may vary widely, and include one or more of the known databases, including but not limited to the Kabat database (Johnson & Wu, 2001, *Nucleic Acids Res* 29:205-206; Johnson & Wu, 2000, *Nucleic Acids Res* 28:214-218), the IMGT database (IMGT, the international ImMunoGeneTics information system®; Lefranc *et al.*, 1999, *Nucleic Acids Res* 27:209-212; Ruiz *et al.*, 2000 *Nucleic Acids Re.* 28:219-221; Lefranc *et al.*, 2001, *Nucleic Acids Res* 29:207-209; Lefranc *et al.*, 2003, *Nucleic Acids Res* 31:307-310), and VBASE, SwissProt, GenBank and Entrez, and EMBL Nucleotide Sequence Database. Protein sequence information can be obtained, compiled, and/or generated from sequence alignments of naturally occurring proteins from any organism, including but not limited to mammals. Protein sequence information can be obtained from a database that is compiled privately. There are numerous sequence-based alignment programs and methods known in the art, and all of these find use in the present invention for generation of sequence alignments of proteins that comprise Fc and Fc ligands.

[147] Once alignments are made, sequence information can be used to guide choice of variable positions. Such sequence information can relate the variability, natural or otherwise, of a given position. Variability herein should be distinguished from variable position. Variability refers to the degree to which a given position in a sequence alignment shows variation in the types of amino acids that occur there. Variable position, to reiterate, is a position chosen by the user to vary in amino acid identity during a computational screening calculation. Variability may be determined qualitatively by one skilled in the art of bioinformatics. There are also methods known in the art to quantitatively determine variability that may find use in the present invention. The most preferred embodiment measures Information Entropy or Shannon Entropy. Variable positions can be chosen based on sequence information obtained from closely related protein sequences, or sequences that are less closely related.

[148] The use of sequence information to choose variable positions finds broad use in the present invention. For example, if an Fc/FcγR interface position in the template structure is tryptophan, and tryptophan is observed at that position in greater than 90% of the sequences in an alignment, it may be beneficial to leave that position fixed. In contrast, if another interface position is found to have a

Samsung Bioepis Exhibit No. 1002
Page 11140

greater level of variability, for example if five different amino acids are observed at that position with frequencies of approximately 20% each, that position may be chosen as a variable position. In another embodiment, visual inspection of aligned protein sequences may substitute for or aid visual inspection of a protein structure. Sequence information can also be used to guide the choice of amino acids considered at variable positions. Such sequence information can relate to how frequently an amino acid, amino acids, or amino acid types (for example polar or nonpolar, charged or uncharged) occur, naturally or otherwise, at a given position. In one embodiment, the set of amino acids considered at a variable position may comprise the set of amino acids that is observed at that position in the alignment. Thus, the position-specific alignment information is used directly to generate the list of considered amino acids at a variable position in a computational screening calculation. Such a strategy is well known in the art; see for example Lehmann & Wyss, 2001, *Curr Opin Biotechnol* 12(4):371-5; Lehmann *et al.*, 2000, *Biochim Biophys Acta* 1543(2):408-415; Rath & Davidson, 2000, *Protein Sci*, 9(12):2457-69; Lehmann *et al.*, 2000, *Protein Eng* 13(1):49-57; Desjarlais & Berg, 1993, *Proc Natl Acad Sci USA* 90(6):2256-60; Desjarlais & Berg, 1992, *Proteins* 12(2):101-4; Henikoff & Henikoff, 2000, *Adv Protein Chem* 54:73-97; Henikoff & Henikoff, 1994, *J Mol Biol* 243(4):574-8. In an alternate embodiment, the set of amino acids considered at a variable position or positions may comprise a set of amino acids that is observed most frequently in the alignment. Thus, a certain criteria is applied to determine whether the frequency of an amino acid or amino acid type warrants its inclusion in the set of amino acids that are considered at a variable position. As is known in the art, sequence alignments may be analyzed using statistical methods to calculate the sequence diversity at any position in the alignment and the occurrence frequency or probability of each amino acid at a position. Such data may then be used to determine which amino acids types to consider. In the simplest embodiment, these occurrence frequencies are calculated by counting the number of times an amino acid is observed at an alignment position, then dividing by the total number of sequences in the alignment. In other embodiments, the contribution of each sequence, position or amino acid to the counting procedure is weighted by a variety of possible mechanisms. In a preferred embodiment, the contribution of each aligned sequence to the frequency statistics is weighted according to its diversity weighting relative to other sequences in the alignment. A common strategy for accomplishing this is the sequence weighting system recommended by Henikoff and Henikoff (Henikoff & Henikoff, 2000, *Adv Protein Chem* 54:73-97; Henikoff & Henikoff, 1994, *J Mol Biol* 243:574-8. In a preferred embodiment, the contribution of each sequence to the statistics is dependent on its extent of similarity to the target sequence, i.e. the template structure used, such that sequences with higher similarity to the target sequence are weighted more highly. Examples of similarity measures include, but are not limited to, sequence identity, BLOSUM similarity score, PAM matrix similarity score, and BLAST score. In an alternate embodiment, the contribution of each sequence to the statistics is dependent on its known physical or functional properties. These properties include, but are not limited to, thermal and chemical stability, contribution to activity, and solubility. For example, when optimizing aglycosylated Fc for solubility, those sequences in an alignment that are known to be most soluble (for example see Ewert *et al.*, 2003, *J Mol Biol* 325:531-553), will contribute more heavily to the calculated frequencies.

Samsung Bioepis Exhibit No. 1002
Page 11141

[149] Regardless of what criteria are applied for choosing the set of amino acids in a sequence alignment to be considered at variable positions, use of sequence information to choose considered amino acids finds broad use in the present invention. For example, to optimize Fc solubility by replacing exposed nonpolar surface residues, considered amino acids may be chosen as the set of amino acids, or a subset of those amino acids which meet some criteria, that are observed at that position in an alignment of protein sequences. As another example, one or more amino acids may be added or subtracted subjectively from a list of amino acids derived from a sequence alignment in order to maximize coverage. For example, additional amino acids with properties similar to those that are found in a sequence alignment may be considered at variable positions. For example, if an Fc position that is known to or hypothesized to bind an FcγR is observed to have uncharged polar amino acids in a sequence alignment, the user may choose to include additional uncharged polar amino acids in a computational screening calculation, or perhaps charged polar amino acids, at that position.

[150] In one embodiment, sequence alignment information is combined with energy calculation, as discussed below. For example, pseudo energies can be derived from sequence information to generate a scoring function. The use of a sequence-based scoring function may assist in significantly reducing the complexity of a calculation. However, as is appreciated by those skilled in the art, the use of a sequence-based scoring function alone may be inadequate because sequence information can often indicate misleading correlations between mutations that may in reality be structurally conflicting. Thus, in a preferred embodiment, a structure-based method of energy calculation is used, either alone or in combination with a sequence-based scoring function. That is, preferred embodiments do not rely on sequence alignment information alone as the analysis step.

[151] Energy calculation refers to the process by which amino acid modifications are scored. The energies of interaction are measured by one or more scoring functions. A variety of scoring functions find use in the present invention for calculating energies. Scoring functions may include any number of potentials, herein referred to as the energy terms of a scoring function, including but not limited to a van der Waals potential, a hydrogen bond potential, an atomic solvation potential or other solvation models, a secondary structure propensity potential, an electrostatic potential, a torsional potential, and an entropy potential. At least one energy term is used to score each variable or floated position, although the energy terms may differ depending on the position, considered amino acids, and other considerations. In one embodiment, a scoring function using one energy term is used. In the most preferred embodiment, energies are calculated using a scoring function that contains more than one energy term, for example describing van der Waals, solvation, electrostatic, and hydrogen bond interactions, and combinations thereof. In additional embodiments, additional energy terms include but are not limited to entropic terms, torsional energies, and knowledge-based energies.

Samsung Bioepis Exhibit No. 1002
Page 11142

[152] A variety of scoring functions are described in US 6,188,965; US 6,269,312; US 6,403,312; USSN 09/782,004; USSN 09/927,790; USSN 09/877,695; USSN 10/071,859, USSN 10/218,102; PCT WO 98/07254; PCT WO 01/40091; and PCT WO 02/25588. As will be appreciated by those skilled in the art, scoring functions need not be limited to physico-chemical energy terms. For example, knowledge-based potentials may find use in the computational screening methodology of the present invention. Such knowledge-based potentials may be derived from protein sequence and/or structure statistics including but not limited to threading potentials, reference energies, pseudo energies, homology-based energies, and sequence biases derived from sequence alignments. In a preferred embodiment, a scoring function is modified to include models for immunogenicity, such as functions derived from data on binding of peptides to MHC (Major Htocompatability Complex), that may be used to identify potentially immunogenic sequences (see for example USSN 09/903,378; USSN 10/039,170; USSN 60/222,697; USSN 10/339788; PCT WO 01/21823; and PCT WO 02/00165). In one embodiment, sequence alignment information can be used to score amino acid substitutions. For example, comparison of protein sequences, regardless of whether the source of said proteins is human, monkey, mouse, or otherwise, may be used to suggest or score amino acid mutations in the computational screening methodology of the present invention. In one embodiment, as is known in the art, one or more scoring functions may be optimized or "trained" during the computational analysis, and then the analysis re-run using the optimized system. Such altered scoring functions may be obtained for example, by training a scoring function using experimental data. As will be appreciated by those skilled in the art, a number of force fields, which are comprised of one or more energy terms, may serve as scoring functions. Force fields include but are not limited to *ab initio* or quantum mechanical force fields, semi-empirical force fields, and molecular mechanics force fields. Scoring functions that are knowledge-based or that use statistical methods may find use in the present invention. These methods may be used to assess the match between a sequence and a three-dimensional protein structure, and hence may be used to score amino acid substitutions for fidelity to the protein structure. In one embodiment, molecular dynamics calculations may be used to computationally screen sequences by individually calculating mutant sequence scores.

[153] There are a variety of ways to represent amino acids in order to enable efficient energy calculation. In a preferred embodiment, considered amino acids are represented as rotamers, as described previously, and the energy (or score) of interaction of each possible rotamer at each variable and floated position with the other variable and floated rotamers, with fixed position residues, and with the backbone structure and any non-protein atoms, is calculated. In a preferred embodiment, two sets of interaction energies are calculated for each side chain rotamer at every variable and floated position: the interaction energy between the rotamer and the fixed atoms (the "singles" energy), and the interaction energy between the variable and floated positions rotamer and all other possible rotamers at every other variable and floated position (the "doubles" energy). In an alternate embodiment, singles and doubles energies are calculated for fixed positions as well as for variable and floated positions. In an alternate embodiment, considered amino acids are not represented as rotamers.

60

Samsung Bioepis Exhibit No. 1002
Page 11143

[154] An important component of computational screening is the identification of one or more sequences that have a favorable score, i.e. are low in energy. Determining a set of low energy sequences from an extremely large number of possibilities is nontrivial, and to solve this problem a combinatorial optimization algorithm is employed. The need for a combinatorial optimization algorithm is illustrated by examining the number of possibilities that are considered in a typical computational screening calculation. The discrete nature of rotamer sets allows a simple calculation of the number of possible rotameric sequences for a given design problem. A backbone of length n with m possible rotamers per position will have m^n possible rotamer sequences, a number that grows exponentially with sequence length. For very simple calculations, it is possible to examine each possible sequence in order to identify the optimal sequence and/or one or more favorable sequences. However, for a typical design problem, the number of possible sequences (up to 10^{80} or more) is sufficiently large that examination of each possible sequence is intractable. A variety of combinatorial optimization algorithms may then be used to identify the optimum sequence and/or one or more favorable sequences. Combinatorial optimization algorithms may be divided into two classes: (1) those that are guaranteed to return the global minimum energy configuration if they converge, and (2) those that are not guaranteed to return the global minimum energy configuration, but which will always return a solution. Examples of the first class of algorithms include but are not limited to Dead-End Elimination (DEE) and Branch & Bound (B&B) (including Branch and Terminate) (Gordon & Mayo, 1999, *Structure Fold Des* 7:1089-98). Examples of the second class of algorithms include, but are not limited to, Monte Carlo (MC), self-consistent mean field (SCMF), Boltzmann sampling (Metropolis *et al.*, 1953, *J Chem Phys* 21:1087), simulated annealing (Kirkpatrick *et al.*, 1983, *Science*, 220:671-680), genetic algorithm (GA), and Fast and Accurate Side-Chain Topology and Energy Refinement (FASTER) (Desmet, et al., 2002, Proteins, 48:31-43). A combinatorial optimization algorithm may be used alone or in conjunction with another combinatorial optimization algorithm.

[155] In one embodiment of the present invention, the strategy for applying a combinatorial optimization algorithm is to find the global minimum energy configuration. In an alternate embodiment, the strategy is to find one or more low energy or favorable sequences. In an alternate embodiment, the strategy is to find the global minimum energy configuration and then find one or more low energy or favorable sequences. For example, as outlined in USSN 6,269,312, preferred embodiments utilize a Dead End Elimination (DEE) step and a Monte Carlo step. In other embodiments, tabu search algorithms are used or combined with DEE and/or Monte Carlo, among other search methods (see Modern Heuristic Search Methods, edited by V.J. Rayward-Smith *et al.*, 1996, John Wiley & Sons Ltd.; USSN 10/218,102; and PCT WO 02/25588). In another preferred embodiment, a genetic algorithm may be used; see for example USSN 09/877,695 and USSN 10/071,859. As another example, as is more fully described in US 6,188,965; US 6,269,312; US 6,403,312; USSN 09/782,004; USSN 09/927,790; USSN 10/218,102; PCT WO 98/07254; PCT WO 01/40091; and PCT WO 02/25588, the global optimum may be reached, and then further

Samsung Bioepis Exhibit No. 1002
Page 11144

computational processing may occur, which generates additional optimized sequences. In the simplest embodiment, design calculations are not combinatorial. That is, energy calculations are used to evaluate amino acid substitutions individually at single variable positions. For other calculations it is preferred to evaluate amino acid substitutions at more than one variable position. In a preferred embodiment, all possible interaction energies are calculated prior to combinatorial optimization. In an alternatively preferred embodiment, energies may be calculated as needed during combinatorial optimization.

Library generation

[156] The present invention provides methods for generating libraries that may subsequently be screened experimentally to single out optimized Fc variants. By "library" as used herein is meant a set of one or more Fc variants. Library may refer to the set of variants in any form. In one embodiment, the library is a list of nucleic acid or amino acid sequences, or a list of nucleic acid or amino acid substitutions at variable positions. For example, the examples used to illustrate the present invention below provide libraries as amino acid substitutions at variable positions. In one embodiment, a library is a list of at least one sequence that are Fc variants optimized for a desired property. For example see, Filikov *et al.*, 2002, *Protein Sci* 11:1452-1461 and Luo *et al.*, 2002, *Protein Sci* 11:1218-1226. In an alternate embodiment, a library may be defined as a combinatorial list, meaning that a list of amino acid substitutions is generated for each variable position, with the implication that each substitution is to be combined with all other designed substitutions at all other variable positions. In this case, expansion of the combination of all possibilities at all variable positions results in a large explicitly defined library. A library may refer to a physical composition of polypeptides that comprise the Fc region or some domain or fragment of the Fc region. Thus a library may refer to a physical composition of antibodies or Fc fusions, either in purified or unpurified form. A library may refer to a physical composition of nucleic acids that encode the library sequences. Said nucleic acids may be the genes encoding the library members, the genes encoding the library members with any operably linked nucleic acids, or expression vectors encoding the library members together with any other operably linked regulatory sequences, selectable markers, fusion constructs, and/or other elements. For example, the library may be a set of mammalian expression vectors that encode Fc library members, the protein products of which may be subsequently expressed, purified, and screened experimentally. As another example, the library may be a display library. Such a library could, for example, comprise a set of expression vectors that encode library members operably linked to some fusion partner that enables phage display, ribosome display, yeast display, bacterial surface display, and the like.

[157] The library may be generated using the output sequence or sequences from computational screening. As discussed above, computationally generated libraries are significantly enriched in stable, properly folded, and functional sequences relative to randomly generated libraries. As a result, computational screening increases the chances of identifying proteins that are optimized for the

design goal. The set of sequences in a library is generally, but not always, significantly different from the parent sequence, although in some cases the library preferably contains the parent sequence. As is known in the art, there are a variety of ways that a library may be derived from the output of computational screening calculations. For example, methods of library generation described in US 6,403,312; USSN 09/782,004; USSN 09/927,790; USSN 10/218,102; PCT WO 01/40091; and PCT WO 02/25588 find use in the present invention. In one embodiment, sequences scoring within a certain range of the global optimum sequence may be included in the library. For example, all sequences within 10 kcal/mol of the lowest energy sequence could be used as the library. In an alternate embodiment, sequences scoring within a certain range of one or more local minima sequences may be used. In a preferred embodiment, the library sequences are obtained from a filtered set. Such a list or set may be generated by a variety of methods, as is known in the art, for example using an algorithm such as Monte Carlo, B&B, or SCMF. For example, the top 10^3 or the top 10^5 sequences in the filtered set may comprise the library. Alternatively, the total number of sequences defined by the combination of all mutations may be used as a cutoff criterion for the library. Preferred values for the total number of recombined sequences range from 10 to 10^{20}, particularly preferred values range from 100 to 10^9. Alternatively, a cutoff may be enforced when a predetermined number of mutations per position is reached. In some embodiments, sequences that do not make the cutoff are included in the library. This may be desirable in some situations, for instance to evaluate the approach to library generation, to provide controls or comparisons, or to sample additional sequence space. For example, the parent sequence may be included in the library, even if it does not make the cutoff.

[158] Clustering algorithms may be useful for classifying sequences derived by computational screening methods into representative groups. For example, the methods of clustering and their application described in USSN 10/218,102 and PCT WO 02/25588, find use in the present invention. Representative groups may be defined, for example, by similarity. Measures of similarity include, but are not limited to sequence similarity and energetic similarity. Thus the output sequences from computational screening may be clustered around local minima, referred to herein as clustered sets of sequences. For example, sets of sequences that are close in sequence space may be distinguished from other sets. In one embodiment, coverage within one or a subset of clustered sets may be maximized by including in the library some, most, or all of the sequences that make up one or more clustered sets of sequences. For example, it may be advantageous to maximize coverage within the one, two, or three lowest energy clustered sets by including the majority of sequences within these sets in the library. In an alternate embodiment, diversity across clustered sets of sequences may be sampled by including within a library only a subset of sequences within each clustered set. For example, all or most of the clustered sets could be broadly sampled by including the lowest energy sequence from each clustered set in the library.

Samsung Bioepis Exhibit No. 1002
Page 11146

[159] Sequence information may be used to guide or filter computationally screening results for generation of a library. As discussed, by comparing and contrasting alignments of protein sequences, the degree of variability at a position and the types of amino acids which occur naturally at that position may be observed. Data obtained from such analyses are useful in the present invention. The benefits of using sequence information have been discussed, and those benefits apply equally to use of sequence information to guide library generation. The set of amino acids that occur in a sequence alignment may be thought of as being pre-screened by evolution to have a higher chance than random at being compatible with a protein's structure, stability, solubility, function, and immunogenicity. The variety of sequence sources, as well as the methods for generating sequence alignments that have been discussed, find use in the application of sequence information to guiding library generation. Likewise, as discussed above, various criteria may be applied to determine the importance or weight of certain residues in an alignment. These methods also find use in the application of sequence information to guide library generation. Using sequence information to guide library generation from the results of computational screening finds broad use in the present invention. In one embodiment, sequence information is used to filter sequences from computational screening output. That is to say, some substitutions are subtracted from the computational output to generate the library. For example the resulting output of a computational screening calculation or calculations may be filtered so that the library includes only those amino acids, or a subset of those amino acids that meet some criteria, for example that are observed at that position in an alignment of sequences. In an alternate embodiment, sequence information is used to add sequences to the computational screening output. That is to say, sequence information is used to guide the choice of additional amino acids that are added to the computational output to generate the library. For example, the output set of amino acids for a given position from a computational screening calculation may be augmented to include one or more amino acids that are observed at that position in an alignment of protein sequences. In an alternate embodiment, based on sequence alignment information, one or more amino acids may be added to or subtracted from the computational screening sequence output in order to maximize coverage or diversity. For example, additional amino acids with properties similar to those that are found in a sequence alignment may be added to the library. For example, if a position is observed to have uncharged polar amino acids in a sequence alignment, additional uncharged polar amino acids may be included in the library at that position.

[160] Libraries may be processed further to generate subsequent libraries. In this way, the output from a computational screening calculation or calculations may be thought of as a primary library. This primary library may be combined with other primary libraries from other calculations or other libraries, processed using subsequent calculations, sequence information, or other analyses, or processed experimentally to generate a subsequent library, herein referred to as a secondary library. As will be appreciated from this description, the use of sequence information to guide or filter libraries, discussed above, is itself one method of generating secondary libraries from primary libraries. Generation of secondary libraries gives the user greater control of the parameters within a library.

Samsung Bioepis Exhibit No. 1002
Page 11147

This enables more efficient experimental screening, and may allow feedback from experimental results to be interpreted more easily, providing a more efficient design/experimentation cycle.

[161] There are a wide variety of methods to generate secondary libraries from primary libraries. For example, USSN 10/218,102 and PCT WO 02/25588, describes methods for secondary library generation that find use in the present invention. Typically some selection step occurs in which a primary library is processed in some way. For example, in one embodiment a selection step occurs wherein some set of primary sequences are chosen to form the secondary library. In an alternate embodiment, a selection step is a computational step, again generally including a selection step, wherein some subset of the primary library is chosen and then subjected to further computational analysis, including both further computational screening as well as techniques such as "*in silico*" shuffling or recombination (see, for example US 5,830,721; US 5,811,238; US 5,605,793; and US 5,837,458, error-prone PCR, for example using modified nucleotides; known mutagenesis techniques including the use of multi-cassettes; and DNA shuffling (Crameri *et al.*, 1998, *Nature* 391:288-291; Coco *et al.*, 2001, *Nat Biotechnol* 19:354-9; Coco *et al.*, 2002, *Nat Biotechnol*, 20:1246-50), heterogeneous DNA samples (US 5,939,250); ITCHY (Ostermeier *et al.*, 1999, *Nat Biotechnol* 17:1205-1209); StEP (Zhao *et al.*, 1998, *Nat Biotechnol* 16:258-261), GSSM (US 6,171,820 and US 5,965,408); *in vivo* homologous recombination, ligase assisted gene assembly, end-complementary PCR, profusion (Roberts & Szostak, 1997, *Proc Natl Acad Sci USA* 94:12297-12302); yeast/bacteria surface display (Lu *et al.*, 1995, *Biotechnology* 13:366-372); Seed & Aruffo, 1987, *Proc Natl Acad Sci USA* 84(10):3365-3369; Boder & Wittrup, 1997, *Nat Biotechnol* 15:553-557). In an alternate embodiment, a selection step occurs that is an experimental step, for example any of the library screening steps below, wherein some subset of the primary library is chosen and then recombined experimentally, for example using one of the directed evolution methods discussed below, to form a secondary library. In a preferred embodiment, the primary library is generated and processed as outlined in US 6,403,312.

[162] Generation of secondary and subsequent libraries finds broad use in the present invention. In one embodiment, different primary libraries may be combined to generate a secondary or subsequent library. In another embodiment, secondary libraries may be generated by sampling sequence diversity at highly mutatable or highly conserved positions. The primary library may be analyzed to determine which amino acid positions in the template protein have high mutational frequency, and which positions have low mutational frequency. For example, positions in a protein that show a great deal of mutational diversity in computational screening may be fixed in a subsequent round of design calculations. A filtered set of the same size as the first would now show diversity at positions that were largely conserved in the first library. Alternatively, the secondary library may be generated by varying the amino acids at the positions that have high numbers of mutations, while keeping constant the positions that do not have mutations above a certain frequency.

Samsung Bioepis Exhibit No. 1002
Page 11148

[163] This discussion is not meant to constrain generation of libraries subsequent to primary libraries to secondary libraries. As will be appreciated, primary and secondary libraries may be processed further to generate tertiary libraries, quaternary libraries, and so on. In this way, library generation is an iterative process. For example, tertiary libraries may be constructed using a variety of additional steps applied to one or more secondary libraries; for example, further computational processing may occur, secondary libraries may be recombined, or subsets of different secondary libraries may be combined. In a preferred embodiment, a tertiary library may be generated by combining secondary libraries. For example, primary and/or secondary libraries that analyzed different parts of a protein may be combined to generate a tertiary library that treats the combined parts of the protein. In an alternate embodiment, the variants from a primary library may be combined with the variants from another primary library to provide a combined tertiary library at lower computational cost than creating a very long filtered set. These combinations may be used, for example, to analyze large proteins, especially large multi-domain proteins, of which Fc is an example. Thus the above description of secondary library generation applies to generating any library subsequent to a primary library, the end result being a final library that may screened experimentally to obtain protein variants optimized for a design goal. These examples are not meant to constrain generation of secondary libraries to any particular application or theory of operation for the present invention. Rather, these examples are meant to illustrate that generation of secondary libraries, and subsequent libraries such as tertiary libraries and so on, is broadly useful in computational screening methodology for library generation.

Experimental Production and Screening

[164] The present invention provides methods for producing and screening libraries of Fc variants. The described methods are not meant to constrain the present invention to any particular application or theory of operation. Rather, the provided methods are meant to illustrate generally that one or more Fc variants or one or more libraries of Fc variants may be produced and screened experimentally to obtain optimized Fc variants. Fc variants may be produced and screened in any context, whether as an Fc region as precisely defined herein, a domain or fragment thereof, or a larger polypeptide that comprises Fc such as an antibody or Fc fusion. General methods for antibody molecular biology, expression, purification, and screening are described in Antibody Engineering, edited by Duebel & Kontermann, Springer-Verlag, Heidelberg, 2001; and Hayhurst & Georgiou, 2001, *Curr Opin Chem Biol* 5:683-689; Maynard & Georgiou, 2000, *Annu Rev Biomed Eng* 2:339-76.

[165] In one embodiment of the present invention, the library sequences are used to create nucleic acids that encode the member sequences, and that may then be cloned into host cells, expressed and assayed, if desired. Thus, nucleic acids, and particularly DNA, may be made that encode each member protein sequence. These practices are carried out using well-known procedures. For example, a variety of methods that may find use in the present invention are described in Molecular Cloning - A Laboratory Manual, 3rd Ed. (Maniatis, Cold Spring Harbor Laboratory Press, New York,

Samsung Bioepis Exhibit No. 1002
Page 11149

2001), and Current Protocols in Molecular Biology (John Wiley & Sons). As will be appreciated by those skilled in the art, the generation of exact sequences for a library comprising a large number of sequences is potentially expensive and time consuming. Accordingly, there are a variety of techniques that may be used to efficiently generate libraries of the present invention. Such methods that may find use in the present invention are described or referenced in US 6,403,312; USSN 09/782,004; USSN 09/927,790; USSN 10/218,102; PCT WO 01/40091; and PCT WO 02/25588. Such methods include but are not limited to gene assembly methods, PCR-based method and methods which use variations of PCR, ligase chain reaction-based methods, pooled oligo methods such as those used in synthetic shuffling, error-prone amplification methods and methods which use oligos with random mutations, classical site-directed mutagenesis methods, cassette mutagenesis, and other amplification and gene synthesis methods. As is known in the art, there are a variety of commercially available kits and methods for gene assembly, mutagenesis, vector subcloning, and the like, and such commercial products find use in the present invention for generating nucleic acids that encode Fc variant members of a library.

[166] The Fc variants of the present invention may be produced by culturing a host cell transformed with nucleic acid, preferably an expression vector, containing nucleic acid encoding the Fc variants, under the appropriate conditions to induce or cause expression of the protein. The conditions appropriate for expression will vary with the choice of the expression vector and the host cell, and will be easily ascertained by one skilled in the art through routine experimentation. A wide variety of appropriate host cells may be used, including but not limited to mammalian cells, bacteria, insect cells, and yeast. For example, a variety of cell lines that may find use in the present invention are described in the ATCC® cell line catalog, available from the American Type Culture Collection.

[167] In a preferred embodiment, the Fc variants are expressed in mammalian expression systems, including systems in which the expression constructs are introduced into the mammalian cells using virus such as retrovirus or adenovirus. Any mammalian cells may be used, with human, mouse, rat, hamster, and primate cells being particularly preferred. Suitable cells also include known research cells, including but not limited to Jurkat T cells, NIH3T3, CHO, COS, and 293 cells. In an alternately preferred embodiment, library proteins are expressed in bacterial cells. Bacterial expression systems are well known in the art, and include *Escherichia coli* (*E. coli*), *Bacillus subtilis*, *Streptococcus cremoris*, and *Streptococcus lividans*. In alternate embodiments, Fc variants are produced in insect cells or yeast cells. In an alternate embodiment, Fc variants are expressed *in vitro* using cell free translation systems. In vitro translation systems derived from both prokaryotic (e.g. *E. coli*) and eukaryotic (e.g. wheat germ, rabbit reticulocytes) cells are available and may be chosen based on the expression levels and functional properties of the protein of interest. For example, as appreciated by those skilled in the art, *in vitro* translation is required for some display technologies, for example ribosome display. In addition, the Fc variants may be produced by chemical synthesis methods.

Samsung Bioepis Exhibit No. 1002
Page 11150

[168] The nucleic acids that encode the Fc variants of the present invention may be incorporated into an expression vector in order to express the protein. A variety of expression vectors may be utilized for protein expression. Expression vectors may comprise self-replicating extra-chromosomal vectors or vectors which integrate into a host genome. Expression vectors are constructed to be compatible with the host cell type. Thus expression vectors which find use in the present invention include but are not limited to those which enable protein expression in mammalian cells, bacteria, insect cells, yeast, and in *in vitro* systems. As is known in the art, a variety of expression vectors are available, commercially or otherwise, that may find use in the present invention for expressing Fc variant proteins.

[169] Expression vectors typically comprise a protein operably linked with control or regulatory sequences, selectable markers, any fusion partners, and/or additional elements. By "operably linked" herein is meant that the nucleic acid is placed into a functional relationship with another nucleic acid sequence. Generally, these expression vectors include transcriptional and translational regulatory nucleic acid operably linked to the nucleic acid encoding the Fc variant, and are typically appropriate to the host cell used to express the protein. In general, the transcriptional and translational regulatory sequences may include promoter sequences, ribosomal binding sites, transcriptional start and stop sequences, translational start and stop sequences, and enhancer or activator sequences. As is also known in the art, expression vectors typically contain a selection gene or marker to allow the selection of transformed host cells containing the expression vector. Selection genes are well known in the art and will vary with the host cell used.

[170] Fc variants may be operably linked to a fusion partner to enable targeting of the expressed protein, purification, screening, display, and the like. Fusion partners may be linked to the Fc variant sequence via a linker sequences. The linker sequence will generally comprise a small number of amino acids, typically less than ten, although longer linkers may also be used. Typically, linker sequences are selected to be flexible and resistant to degradation. As will be appreciated by those skilled in the art, any of a wide variety of sequences may be used as linkers. For example, a common linker sequence comprises the amino acid sequence GGGGS. A fusion partner may be a targeting or signal sequence that directs Fc variant protein and any associated fusion partners to a desired cellular location or to the extracellular media. As is known in the art, certain signaling sequences may target a protein to be either secreted into the growth media, or into the periplasmic space, located between the inner and outer membrane of the cell. A fusion partner may also be a sequence that encodes a peptide or protein that enables purification and/or screening. Such fusion partners include but are not limited to polyhistidine tags (His-tags) (for example H_6 and H_{10} or other tags for use with Immobilized Metal Affinity Chromatography (IMAC) systems (e.g. Ni^{+2} affinity columns)), GST fusions, MBP fusions, Strep-tag, the BSP biotinylation target sequence of the bacterial enzyme BirA, and epitope tags which are targeted by antibodies (for example c-myc tags, flag-tags, and the like). As will be appreciated by those skilled in the art, such tags may be useful for purification, for screening, or both.

Samsung Bioepis Exhibit No. 1002
Page 11151

For example, an Fc variant may be purified using a His-tag by immobilizing it to a Ni^{+2} affinity column, and then after purification the same His-tag may be used to immobilize the antibody to a Ni^{+2} coated plate to perform an ELISA or other binding assay (as described below). A fusion partner may enable the use of a selection method to screen Fc variants (see below). Fusion partners that enable a variety of selection methods are well-known in the art, and all of these find use in the present invention. For example, by fusing the members of an Fc variant library to the gene III protein, phage display can be employed (Kay *et al.*, Phage display of peptides and proteins: a laboratory manual, Academic Press, San Diego, CA, 1996; Lowman *et al.*, 1991, *Biochemistry* 30:10832-10838; Smith, 1985, *Science* 228:1315-1317). Fusion partners may enable Fc variants to be labeled. Alternatively, a fusion partner may bind to a specific sequence on the expression vector, enabling the fusion partner and associated Fc variant to be linked covalently or noncovalently with the nucleic acid that encodes them. For example, USSN 09/642,574; USSN 10/080,376; USSN 09/792,630; USSN 10/023,208; USSN 09/792,626; USSN 10/082,671; USSN 09/953,351; USSN 10/097,100; USSN 60/366,658; PCT WO 00/22906; PCT WO 01/49058; PCT WO 02/04852; PCT WO 02/04853; PCT WO 02/08023; PCT WO 01/28702; and PCT WO 02/07466 describe such a fusion partner and technique that may find use in the present invention.

[171] The methods of introducing exogenous nucleic acid into host cells are well known in the art, and will vary with the host cell used. Techniques include but are not limited to dextran-mediated transfection, calcium phosphate precipitation, calcium chloride treatment, polybrene mediated transfection, protoplast fusion, electroporation, viral or phage infection, encapsulation of the polynucleotide(s) in liposomes, and direct microinjection of the DNA into nuclei. In the case of mammalian cells, transfection may be either transient or stable.

[172] In a preferred embodiment, Fc variant proteins are purified or isolated after expression. Proteins may be isolated or purified in a variety of ways known to those skilled in the art. Standard purification methods include chromatographic techniques, including ion exchange, hydrophobic interaction, affinity, sizing or gel filtration, and reversed-phase, carried out at atmospheric pressure or at high pressure using systems such as FPLC and HPLC. Purification methods also include electrophoretic, immunological, precipitation, dialysis, and chromatofocusing techniques. Ultrafiltration and diafiltration techniques, in conjunction with protein concentration, are also useful. As is well known in the art, a variety of natural proteins bind Fc and antibodies, and these proteins can find use in the present invention for purification of Fc variants. For example, the bacterial proteins A and G bind to the Fc region. Likewise, the bacterial protein L binds to the Fab region of some antibodies, as of course does the antibody's target antigen. Purification can often be enabled by a particular fusion partner. For example, Fc variant proteins may be purified using glutathione resin if a GST fusion is employed, Ni^{+2} affinity chromatography if a His-tag is employed, or immobilized anti-flag antibody if a flag-tag is used. For general guidance in suitable purification techniques, see Protein Purification: Principles and Practice, 3rd Ed., Scopes, Springer-Verlag, NY, 1994. The degree of

purification necessary will vary depending on the screen or use of the Fc variants. In some instances no purification is necessary. For example in one embodiment, if the Fc variants are secreted, screening may take place directly from the media. As is well known in the art, some methods of selection do not involve purification of proteins. Thus, for example, if a library of Fc variants is made into a phage display library, protein purification may not be performed.

[173] Fc variants may be screened using a variety of methods, including but not limited to those that use *in vitro* assays, *in vivo* and cell-based assays, and selection technologies. Automation and high-throughput screening technologies may be utilized in the screening procedures. Screening may employ the use of a fusion partner or label. The use of fusion partners has been discussed above. By "labeled" herein is meant that the Fc variants of the invention have one or more elements, isotopes, or chemical compounds attached to enable the detection in a screen. In general, labels fall into three classes: a) immune labels, which may be an epitope incorporated as a fusion partner that is recognized by an antibody, b) isotopic labels, which may be radioactive or heavy isotopes, and c) small molecule labels, which may include fluorescent and colorimetric dyes, or molecules such as biotin that enable other labeling methods. Labels may be incorporated into the compound at any position and may be incorporated *in vitro* or *in vivo* during protein expression.

[174] In a preferred embodiment, the functional and/or biophysical properties of Fc variants are screened in an *in vitro* assay. *In vitro* assays may allow a broad dynamic range for screening properties of interest. Properties of Fc variants that may be screened include but are not limited to stability, solubility, and affinity for Fc ligands, for example Fc□Rs. Multiple properties may be screened simultaneously or individually. Proteins may be purified or unpurified, depending on the requirements of the assay. In one embodiment, the screen is a qualitative or quantitative binding assay for binding of Fc variants to a protein or nonprotein molecule that is known or thought to bind the Fc variant. In a preferred embodiment, the screen is a binding assay for measuring binding to the antibody's or Fc fusions' target antigen. In an alternately preferred embodiment, the screen is an assay for binding of Fc variants to an Fc ligand, including but are not limited to the family of Fc□Rs, the neonatal receptor FcRn, the complement protein C1q, and the bacterial proteins A and G. Said Fc ligands may be from any organism, with humans, mice, rats, rabbits, and monkeys preferred. Binding assays can be carried out using a variety of methods known in the art, including but not limited to FRET (Fluorescence Resonance Energy Transfer) and BRET (Bioluminescence Resonance Energy Transfer) -based assays, AlphaScreen™ (Amplified Luminescent Proximity Homogeneous Assay), Scintillation Proximity Assay, ELISA (Enzyme-Linked Immunosorbent Assay), SPR (Surface Plasmon Resonance, also known as BIACORE®), isothermal titration calorimetry, differential scanning calorimetry, gel electrophoresis, and chromatography including gel filtration. These and other methods may take advantage of some fusion partner or label of the Fc variant. Assays may employ a variety of detection methods including but not limited to chromogenic, fluorescent, luminescent, or isotopic labels.

Samsung Bioepis Exhibit No. 1002
Page 11153

[175] The biophysical properties of Fc variant proteins, for example stability and solubility, may be screened using a variety of methods known in the art. Protein stability may be determined by measuring the thermodynamic equilibrium between folded and unfolded states. For example, Fc variant proteins of the present invention may be unfolded using chemical denaturant, heat, or pH, and this transition may be monitored using methods including but not limited to circular dichroism spectroscopy, fluorescence spectroscopy, absorbance spectroscopy, NMR spectroscopy, calorimetry, and proteolysis. As will be appreciated by those skilled in the art, the kinetic parameters of the folding and unfolding transitions may also be monitored using these and other techniques. The solubility and overall structural integrity of an Fc variant protein may be quantitatively or qualitatively determined using a wide range of methods that are known in the art. Methods which may find use in the present invention for characterizing the biophysical properties of Fc variant proteins include gel electrophoresis, chromatography such as size exclusion chromatography and reversed-phase high performance liquid chromatography, mass spectrometry, ultraviolet absorbance spectroscopy, fluorescence spectroscopy, circular dichroism spectroscopy, isothermal titration calorimetry, differential scanning calorimetry, analytical ultra-centrifugation, dynamic light scattering, proteolysis, and cross-linking, turbidity measurement, filter retardation assays, immunological assays, fluorescent dye binding assays, protein-staining assays, microscopy, and detection of aggregates via ELISA or other binding assay. Structural analysis employing X-ray crystallographic techniques and NMR spectroscopy may also find use. In one embodiment, stability and/or solubility may be measured by determining the amount of protein solution after some defined period of time. In this assay, the protein may or may not be exposed to some extreme condition, for example elevated temperature, low pH, or the presence of denaturant. Because function typically requires a stable, soluble, and/or well-folded/structured protein, the aforementioned functional and binding assays also provide ways to perform such a measurement. For example, a solution comprising an Fc variant could be assayed for its ability to bind target antigen, then exposed to elevated temperature for one or more defined periods of time, then assayed for antigen binding again. Because unfolded and aggregated protein is not expected to be capable of binding antigen, the amount of activity remaining provides a measure of the Fc variant's stability and solubility.

[176] In a preferred embodiment, the library is screened using one or more cell-based or *in vivo* assays. For such assays, Fc variant proteins, purified or unpurified, are typically added exogenously such that cells are exposed to individual variants or pools of variants belonging to a library. These assays are typically, but not always, based on the function of an antibody or Fc fusion that comprises the Fc variant; that is, the ability of the antibody or Fc fusion to bind a target antigen and mediate some biochemical event, for example effector function, ligand/receptor binding inhibition, apoptosis, and the like. Such assays often involve monitoring the response of cells to antibody or Fc fusion, for example cell survival, cell death, change in cellular morphology, or transcriptional activation such as cellular expression of a natural gene or reporter gene. For example, such assays may measure the

Samsung Bioepis Exhibit No. 1002
Page 11154

ability of Fc variants to elicit ADCC, ADCP, or CDC. For some assays additional cells or components, that is in addition to the target cells, may need to be added, for example example serum complement, or effector cells such as peripheral blood monocytes (PBMCs), NK cells, macrophages, and the like. Such additional cells may be from any organism, preferably humans, mice, rat, rabbit, and monkey. Antibodies and Fc fusions may cause apoptosis of certain cell lines expressing the antibody's target antigen, or they may mediate attack on target cells by immune cells which have been added to the assay. Methods for monitoring cell death or viability are known in the art, and include the use of dyes, immunochemical, cytochemical, and radioactive reagents. For example, caspase staining assays may enable apoptosis to be measured, and uptake or release of radioactive substrates or fluorescent dyes such as alamar blue may enable cell growth or activation to be monitored. In a preferred embodiment, the DELFIA® EuTDA-based cytotoxicity assay (Perkin Elmer, MA) is used. Alternatively, dead or damaged target cells may be monitoried by measuring the release of one or more natural intracellular proteins, for example lactate dehydrogenase. Transcriptional activation may also serve as a method for assaying function in cell-based assays. In this case, response may be monitored by assaying for natural genes or proteins which may be upregulated, for example the release of certain interleukins may be measured, or alternatively readout may be via a reporter construct. Cell-based assays may also involve the measure of morphological changes of cells as a response to the presence of an Fc variant. Cell types for such assays may be prokaryotic or eukaryotic, and a variety of cell lines that are known in the art may be employed.

[177] Alternatively, cell-based screens are performed using cells that have been transformed or transfected with nucleic acids encoding the Fc variants. That is, Fc variant proteins are not added exogenously to the cells. For example, in one embodiment, the cell-based screen utilizes cell surface display. A fusion partner can be employed that enables display of Fc variants on the surface of cells (Witrrup, 2001, *Curr Opin Biotechnol*, 12:395-399). Cell surface display methods that may find use in the present invention include but are not limited to display on bacteria (Georgiou *et al.*, 1997, *Nat Biotechnol* 15:29-34; Georgiou *et al.*, 1993, *Trends Biotechnol* 11:6-10; Lee *et al.*, 2000, *Nat Biotechnol* 18:645-648; Jun *et al.*, 1998, *Nat Biotechnol* 16:576-80), yeast (Boder & Wittrup, 2000, *Methods Enzymol* 328:430-44; Boder & Wittrup, 1997, *Nat Biotechnol* 15:553-557), and mammalian cells (Whitehorn *et al.*, 1995, *Bio/technology* 13:1215-1219). In an alternate embodiment, Fc variant proteins are not displayed on the surface of cells, but rather are screened intracellularly or in some other cellular compartment. For example, periplasmic expression and cytometric screening (Chen *et al.*, 2001, *Nat Biotechnol* 19: 537-542), the protein fragment complementation assay (Johnsson & Varshavsky, 1994, *Proc Natl Acad Sci USA* 91:10340-10344.; Pelletier *et al.*, 1998, *Proc Natl Acad Sci USA* 95:12141-12146), and the yeast two hybrid screen (Fields & Song, 1989, Nature 340:245-246) may find use in the present invention. Alternatively, if a polypeptide that comprises the Fc variants, for example an antibody or Fc fusion, imparts some selectable growth advantage to a cell, this property may be used to screen or select for Fc variants.

Samsung Bioepis Exhibit No. 1002
Page 11155

[178] As is known in the art, a subset of screening methods are those that select for favorable members of a library. Said methods are herein referred to as "selection methods", and these methods find use in the present invention for screening Fc variant libraries. When libraries are screened using a selection method, only those members of a library that are favorable, that is which meet some selection criteria, are propagated, isolated, and/or observed. As will be appreciated, because only the most fit variants are observed, such methods enable the screening of libraries that are larger than those screenable by methods that assay the fitness of library members individually. Selection is enabled by any method, technique, or fusion partner that links, covalently or noncovalently, the phenotype of an Fc variant with its genotype, that is the function of an Fc variant with the nucleic acid that encodes it. For example the use of phage display as a selection method is enabled by the fusion of library members to the gene III protein. In this way, selection or isolation of variant proteins that meet some criteria, for example binding affinity for an FcγR, also selects for or isolates the nucleic acid that encodes it. Once isolated, the gene or genes encoding Fc variants may then be amplified. This process of isolation and amplification, referred to as panning, may be repeated, allowing favorable Fc variants in the library to be enriched. Nucleic acid sequencing of the attached nucleic acid ultimately allows for gene identification.

[179] A variety of selection methods are known in the art that may find use in the present invention for screening Fc variant libraries. These include but are not limited to phage display (Phage display of peptides and proteins: a laboratory manual, Kay *et al.*, 1996, Academic Press, San Diego, CA, 1996; Lowman *et al.*, 1991, *Biochemistry* 30:10832-10838; Smith, 1985, *Science* 228:1315-1317) and its derivatives such as selective phage infection (Malmborg *et al.*, 1997, J Mol Biol 273:544-551), selectively infective phage (Krebber *et al.*, 1997, *J Mol Biol* 268:619-630), and delayed infectivity panning (Benhar *et al.*, 2000, *J Mol Biol* 301:893-904), cell surface display (Witrrup, 2001, *Curr Opin Biotechnol*, 12:395-399) such as display on bacteria (Georgiou *et al.*, 1997, *Nat Biotechnol* 15:29-34; Georgiou *et al.*, 1993, *Trends Biotechnol* 11:6-10; Lee *et al.*, 2000, *Nat Biotechnol* 18:645-648; Jun *et al.*, 1998, *Nat Biotechnol* 16:576-80), yeast (Boder & Wittrup, 2000, *Methods Enzymol* 328:430-44; Boder & Wittrup, 1997, *Nat Biotechnol* 15:553-557), and mammalian cells (Whitehorn *et al.*, 1995, *Bio/technology* 13:1215-1219), as well as *in vitro* display technologies (Amstutz *et al.*, 2001, *Curr Opin Biotechnol* 12:400-405) such as polysome display (Mattheakis *et al.*, 1994, *Proc Natl Acad Sci USA* 91:9022-9026), ribosome display (Hanes *et al.*, 1997, *Proc Nati Acad Sci USA* 94:4937-4942), mRNA display (Roberts & Szostak, 1997, *Proc Natl Acad Sci USA 94*:12297-12302; Nemoto *et al.*, 1997, *FEBS Lett* 414:405-408), and ribosome-inactivation display system (Zhou *et al.*, 2002, *J Am Chem Soc* 124, 538-543)

[180] Other selection methods that may find use in the present invention include methods that do not rely on display, such as *in vivo* methods including but not limited to periplasmic expression and cytometric screening (Chen *et al.*, 2001, *Nat Biotechnol* 19:537-542), the protein fragment complementation assay (Johnsson & Varshavsky, 1994, *Proc Natl Acad Sci USA* 91:10340-10344;

Pelletier *et al.*, 1998, *Proc Natl Acad Sci USA* 95:12141-12146), and the yeast two hybrid screen (Fields & Song, 1989, *Nature* 340:245-246) used in selection mode (Visintin *et al.*, 1999, *Proc Natl Acad Sci USA* 96:11723-11728). In an alternate embodiment, selection is enabled by a fusion partner that binds to a specific sequence on the expression vector, thus linking covalently or noncovalently the fusion partner and associated Fc variant library member with the nucleic acid that encodes them. For example, USSN 09/642,574; USSN 10/080,376; USSN 09/792,630; USSN 10/023,208; USSN 09/792,626; USSN 10/082,671; USSN 09/953,351; USSN 10/097,100; USSN 60/366,658; PCT WO 00/22906; PCT WO 01/49058; PCT WO 02/04852; PCT WO 02/04853; PCT WO 02/08023; PCT WO 01/28702; and PCT WO 02/07466 describe such a fusion partner and technique that may find use in the present invention. In an alternative embodiment, *in vivo* selection can occur if expression of a polypeptide that comprises the Fc variant, such as an antibody or Fc fusion, imparts some growth, reproduction, or survival advantage to the cell.

[181] A subset of selection methods referred to as "directed evolution" methods are those that include the mating or breading of favorable sequences during selection, sometimes with the incorporation of new mutations. As will be appreciated by those skilled in the art, directed evolution methods can facilitate identification of the most favorable sequences in a library, and can increase the diversity of sequences that are screened. A variety of directed evolution methods are known in the art that may find use in the present invention for screening Fc variant libraries, including but not limited to DNA shuffling (PCT WO 00/42561 A3; PCT WO 01/70947 A3), exon shuffling (US 6,365,377; Kolkman & Stemmer, 2001, *Nat Biotechnol* 19:423-428), family shuffling (Crameri *et al.*, 1998, *Nature* 391:288-291; US 6,376,246), RACHITT™ (Coco *et al.*, 2001, *Nat Biotechnol* 19:354- 359; PCT WO 02/06469), STEP and random priming of *in vitro* recombination (Zhao *et al.*, 1998, *Nat Biotechnol* 16:258-261; Shao *et al.*, 1998, *Nucleic Acids Res* 26:681-683), exonuclease mediated gene assembly (US 6,352,842; US 6,361,974), Gene Site Saturation Mutagenesis™ (US 6,358,709), Gene Reassembly™ (US 6,358,709), SCRATCHY (Lutz et al., 2001, *Proc Natl Acad Sci USA* 98:11248-11253), DNA fragmentation methods (Kikuchi *et al.*, *Gene* 236:159-167), single-stranded DNA shuffling (Kikuchi *et al.*, 2000, *Gene* 243:133-137), and AMEsystem™ directed evolution protein engineering technology (Applied Molecular Evolution) (US US 5,824,514; US 5,817,483; US 5,814,476; US 5,763,192; US 5,723,323).

[182] The biological properties of the antibodies and Fc fusions that comprise the Fc variants of the present invention may be characterized in cell, tissue, and whole organism experiments. As is know in the art, drugs are often tested in animals, including but not limited to mice, rats, rabbits, dogs, cats, pigs, and monkeys, in order to measure a drug's efficacy for treatment against a disease or disease model, or to measure a drug's pharmacokinetics, toxicity, and other properties. Said animals may be referred to as disease models. Therapeutics are often tested in mice, including but not limited to nude mice, SCID mice, xenograft mice, and transgenic mice (including knockins and knockouts). For example, an antibody or Fc fusion of the present invention that is intended as an anti-cancer

Samsung Bioepis Exhibit No. 1002
Page 11157

therapeutic may be tested in a mouse cancer model, for example a xenograft mouse. In this method, a tumor or tumor cell line is grafted onto or injected into a mouse, and subsequently the mouse is treated with the therapeutic to determine the ability of the antibody or Fc fusion to reduce or inhibit cancer growth. Such experimentation may provide meaningful data for determination of the potential of said antibody or Fc fusion to be used as a therapeutic. Any organism, preferably mammals, may be used for testing. For example because of their genetic similarity to humans, monkeys can be suitable therapeutic models, and thus may be used to test the efficacy, toxicity, pharmacokinetics, or other property of the antibodies and Fc fusions of the present invention. Tests of the antibodies and Fc fusions of the present invention in humans are ultimately required for approval as drugs, and thus of course these experiments are contemplated. Thus the antibodies and Fc fusions of the present invention may be tested in humans to determine their therapeutic efficacy, toxicity, pharmacokinetics, and/or other clinical properties.

EXAMPLES

[183] Examples are provided below to illustrate the present invention. These examples are not meant to constrain the present invention to any particular application or theory of operation.

[184] For all positions discussed in the present invention, numbering is according to the EU index as in Kabat (Kabat *et al.*, 1991, *Sequences of Proteins of Immunological Interest,* 5th Ed., United States Public Health Svice, National Institutes of Health, Bethesda). Those skilled in the art of antibodies will appreciate that this convention consists of nonsequential numbering in specific regions of an immunoglobulin sequence, enabling a normalized reference to conserved positions in immunoglobulin families. Accordingly, the positions of any given immunoglobulin as defined by the EU index will not necessarily correspond to its sequential sequence. Figure 3 shows the sequential and EU index numbering schemes for the antibody alemtuzumab in order to illustrate this principal more clearly. It should also be noted that polymorphisms have been observed at a number of Fc positions, including but not limited to Kabat 270, 272, 312, 315, 356, and 358, and thus slight differences between the presented sequence and sequences in the scientific literature may exist.

[185] Example 1. Computational Screening and Design of Fc Libraries

Computational screening calculations were carried out to design optimized Fc variants. Fc variants were computationally screened, constructed, and experimentally investigated over several computation/experimention cycles. For each successive cycle, experimental data provided feedback into the next set of computational screening calculations and library design. All computational screening calculations and library design are presented in Example 1. For each set of calculations, a table is provided that presents the results and provides relevant information and parameters.

Samsung Bioepis Exhibit No. 1002
Page 11158

[186] Several different structures of Fc bound bound to the extracellular domain of Fc□Rs served as template structures for the computational screening calculations. Publicly available Fc/FcγR complex structures included pdb accession code 1E4K (Sondermann *et al.*, 2000, *Nature* 406:267-273.), and pdb accession codes 1IIS and 1IIX (Radaev *et al.*, 2001, *J Biol Chem* 276:16469-16477). The extracellular regions of Fc□RIIIb and FcγRIIIa are 96% identical, and therefore the use of the Fc/FcγRIIIb structure is essentially equivalent to use of FcγRIIIa. Nonetheless, for some calculations, a more precise Fc/Fc□RIIIa template structure was constructed by modeling a D129G mutation in the 1IIS and 1E4K structures (referred to as D129G 1IIS and D129G 1E4K template structures). In addition, the structures for human Fc bound to the extracellular domains of human FcγRIIb, human F158 Fc□RIIIa, and mouse FcγRIII were modeled using standard methods, the available Fc□R sequence information, the aforementioned Fc/FcγR structures, as well as structural information for unbound complexes (pdb accession code 1H9V)(Sondermann *et al.*, 2001, *J Mol Biol* 309:737-749) (pdb accession code 1FCG)(Maxwell *et al.*, 1999, *Nat Struct Biol* 6:437-442), Fc□RIIb (pdb accession code 2FCB)(Sondermann *et al.*, 1999, *Embo J* 18:1095-1103), and Fc□RIIIb (pdb accession code 1E4J)(Sondermann *et al.*, 2000, *Nature* 406:267-273.).

[187] Variable positions and amino acids to be considered at those positions were chosen by visual inspection of the aforementioned Fc/FcγR and FcγR structures, and using solvent accessibility information and sequence information. Sequence information of Fcs and FcγRs was particularly useful for determining variable positions at which substitutions may provide distinguishing affinities between activating and inhibitory receptors. Virtually all Cγ2 positions were screened computationally. The Fc structure is a homodimer of two heavy chains (labeled chains A and B in the 1IIS, 1IIX, and 1E4K structures) that each include the hinge and C□2-C□3 domains (shown in Figure 2). Because the Fc□R (labeled chain C in the 1IIS, 1IIX, and 1E4K structures) binds asymmetrically to the Fc homodimer, each chain was often considered separately in design calculations. For some calculations, Fc and/or Fc□R residues proximal to variable position residues were floated, that is the amino acid conformation but not the amino acid identity was allowed to vary in a protein design calculation to allow for conformational adjustments. These are indicated below the table for each set of calculations when relevant. Considered amino acids typically belonged to either the Core, Core XM, Surface, Boundary, Boundary XM, or All 20 classifications, unless noted otherwise. These classifications are defined as follows: Core = alanine, valine, isoleucine, leucine, phenylalanine, tyrosine, tryptophan, and methionine; Core XM = alanine, valine, isoleucine, leucine, phenylalanine, tyrosine, and tryptophan; Surface = alanine, serine, threonine, aspartic acid, asparagine, glutamine, glutamic acid, arginine, lysine and histidine; Boundary = alanine, serine, threonine, aspartic acid, asparagine, glutamine, glutamic acid, arginine, lysine, histidine, valine, isoleucine, leucine, phenylalanine, tyrosine, tryptophan, and methionine; Boundary XM = Boundary = alanine, serine, threonine, aspartic acid, asparagine, glutamine, glutamic acid, arginine, lysine, histidine, valine, isoleucine, leucine, phenylalanine, tyrosine, and tryptophan; All 20 = all 20 naturally occurring amino acids.

Samsung Bioepis Exhibit No. 1002
Page 11159

[188] The majority of calculations followed one of two general types of computational screening methods. In one method, the conformations of amino acids at variable positions were represented as a set of backbone-independent side chain rotamers derived from the rotamer library of Dunbrack & Cohen (Dunbrack *et al.*, 1997, *Protein Sci* 6:1661-1681). The energies of all possible combinations of the considered amino acids at the chosen variable positions were calculated using a force field containing terms describing van der Waals, solvation, electrostatic, and hydrogen bond interactions, and the optimal (ground state) sequence was determined using a Dead End Elimination (DEE) algorithm. As will be appreciated by those in the art, the predicted lowest energy sequence is not necessarily the true lowest energy sequence because of errors primarily in the scoring function, coupled with the fact that subtle conformational differences in proteins can result in dramatic differences in stability. However, the predicted ground state sequence is likely to be close to the true ground state, and thus additional favorable diversity can be explored by evaluating the energy of sequences that are close in sequence space and energy around the predicted ground state. To accomplish this, as well as to generate a diversity of sequences for a library, a Monte Carlo (MC) algorithm was used to evaluate the energies of 1000 similar sequences around the predicted ground state. The number of sequences out of the 1000 sequence set that contain that amino acid at that variable position is referred to as the occupancy for that substitution, and this value may reflect how favorable that substitution is. This computational screening method is substantially similar to Protein Design Automation® (PDA®) technology, as described in US 6,188,965; US 6,269,312; US 6,403,312; USSN 09/782,004; USSN 09/927,790; USSN 10/218,102; PCT WO 98/07254; PCT WO 01/40091; and PCT WO 02/25588, and for ease of description, is referred to as PDA® technology throughout the examples. Tables that present the results of these calculations provide for each variable position on the designated chain (column 1) the amino acids considered at each variable position (column 2), the WT Fc amino acid identity at each variable position (column 3), the amino acid identity at each variable position in the DEE ground state sequence (column 4), and the set of amino acids and corresponding occupancy that are observed in the Monte Carlo output (column 5).

[189] Other calculations utilized a genetic algorithm (GA) to screen for low energy sequences, with energies being calculated during each round of "evolution" for those sequences being sampled. The conformations of amino acids at variable and floated positions were represented as a set of side chain rotamers derived from a backbone-independent rotamer library using a flexible rotamer model (Mendes *et al.*, 1999, *Proteins* 37:530-543). Energies were calculated using a force field containing terms describing van der Waals, solvation, electrostatic, and hydrogen bond interactions. This calculation generated a list of 300 sequences which are predicted to be low in energy. To facilitate analysis of the results and library generation, the 300 output sequences were clustered computationally into 10 groups of similar sequences using a nearest neighbor single linkage hierarchical clustering algorithm to assign sequences to related groups based on similarity scores (Diamond, 1995, *Acta Cryst* D51:127-135). That is, all sequences within a group are most similar to

Samsung Bioepis Exhibit No. 1002
Page 11160

all other sequences within the same group and less similar to sequences in other groups. The lowest energy sequence from each of these ten clusters are used as a representative of each group, and are presented as results. This computational screening method is substantially similar to Sequence Prediction Algorithm™ (SPA™) technology, as described in (Raha *et al.*, 2000, *Protein Sci* 9:1106-1119); USSN 09/877,695; and USSN 10/071,859, and for ease of description, is referred to as SPA™ technology throughout the examples.

[190] Computational screening was applied to design energetically favorable interactions at the Fc/Fc□R interface at groups of variable positions that mediate or potentially mediate binding with Fc□R. Because the binding interface involves a large number of Fc residues on the two different chains, and because Fc□Rs bind asymmetrically to Fc, residues were grouped in different sets of interacting variable positions, and designed in separate sets of calculations. In many cases these sets were chosen as groups of residues that were deemed to be coupled, that is the energy of one or more residues is dependent on the identity of one or more other residues. Various template structures were used, and in many cases calculations explored substitutions on both chains. For many of the variable position sets, calculations were carried out using both the PDA® and SPA™ technology computational screening methods described. The results of these calculations and relevant parameters and information are presented in Tables 1 – 30 below.

[191] Tables that present the results of these calculations provide for each variable position on the designated chain (column 1) the amino acids considered at each variable position (column 2), the WT Fc amino acid identity at each variable position (column 3), and the amino acid identity at the variable positions for the lowest energy sequence from each cluster group (columns 4-13). Tables 1-59 are broken down into two sets, as labeled below, PDA® and SPA™ technology. Column 4 of the PDA® tables show the frequency of each residue that occurs in the top 1000 sequences during that PDA® run. Thus, in the first row of Table 1, at position 328, when run using boundary amino acids as the set of variable residues for that position, L occurred 330 times in the top 1000 sequence, M occurred 302 times, etc.

[192] In addition, included within the compositions of the invention are antibodies that have any of the listed amino acid residues in the listed positions, either alone or in any combination (note preferred combinations are listed in the claims, the summary and the figures). One preferred combination is the listed amino acids residues in the listed positions in a ground state (sometimes referred to herein as the "global solution", as distinguished from the wild-type). Similarly, residue positions and particular amino acids at those residue positions may be combined between tables.

[193] For SPA™ technology tables, such as Table 4, column 4 is a SPA™ run that results in a protein with the six listed amino acids at the six listed positions (e.g. column 4 is a single protein with

Samsung Bioepis Exhibit No. 1002
Page 11161

a wild-type sequence except for 239E, 265G, 267S, 269Y, 270T and 299S. Thus, each of these individual proteins are included within the invention. In addition, combinations between SPA™ proteins, both within tables and between tables, are also included.

[194] In addition, each table shows the presence or absence of carbohydrate, but specifically included are the reverse sequences; e.g. Table 1 is listed for an aglycosylated variant, but these same amino acid changes can be done on a glycosylated variant.

[195] Furthermore, each table lists the template structure used, as well as "floated" residues; for example, Table 2 used a PDA® run that floated C120, C132 and C134.

Table 1

Position	Considered Amino Acids	WT	Ground State	Sequences Around Ground State
328 A	Boundary	L	L	L:330 M:302 E:111 K:62 A:45 Q:39 D:36 S:30 T:28 N:10 R:7
332 A	Surface	I	R	R:247 K:209 Q:130 H:95 E:92 T:59 D:51 N:51 S:42 A:24
328 B	Boundary	L	L	L:321 M:237 T:166 K:73 R:72 S:55 Q:20 D:17 E:13 A:12 V:10 N:4
332 B	Surface	I	E	E:269 Q:180 R:145 K:111 D:97 T:78 N:65 S:28 A:14 H:13

PDA® technology, 1IIS template structure; - carbohydrate

Table 2

Position	Considered Amino Acids	WT	Ground State	Sequences Around Ground State
239 A	Surface	S	K	E:349 D:203 K:196 A:95 Q:83 S:63 N:10 R:1
265 A	Boundary XM	D	D	D:616 N:113 L:110 E:104 S:25 A:23 Q:9
299 A	Boundary XM	T	I	I:669 H:196 V:135
327 A	Boundary XM	A	S	A:518 S:389 N:67 D:26
265 B	Boundary XM	D	Q	Q:314 R:247 N:118 I:115 A:63 E:55 D:34 S:22 K:21 V:11

PDA® technology; 1IIS template structure; + carbohydrate; floated 120 C, 132 C, 134 C

Table 3

Position	Considered Amino Acids	WT	Ground State	Sequences Around Ground State
239 A	Surface	S	E	E:872 Q:69 D:39 K:16 A:4
265 A	Boundary XM	D	Y	Y:693 H:111 E:69 D:62 F:29 K:19 R:14 W:2 Q:1
267 A	Boundary XM	S	S	S:991 A:9
269 A	Core XM	E	F	F:938 E:59 Y:3
270 A	Surface	D	E	E:267 T:218 K:186 D:89 Q:88 R:46 S:34 N:29 H:23 A:20
299 A	Boundary XM	T	H	H:486 T:245 K:130 E:40 S:39 D:27 Q:27 A:4 N:2

PDA® technology; 1IIS template structure; - carbohydrate; floated 120 C, 122 C, 132 C, 133 C, 134 C

Table 4

Position	Considered Amino Acids	WT	1	2	3	4	5	6	7	8	9	10
239 A	Surface	S	E	Q	Q	Q	E	E	E	Q	E	E
265 A	All 20	D	G	G	G	G	G	G	G	G	G	G
267 A	All 20	S	S	S	S	S	S	S	S	S	S	S
269 A	Core	E	Y	Y	A	A	V	Y	A	A	A	A
270 A	Surface	D	T	S	A	S	T	T	T	A	A	A
299 A	All 20	T	S	S	S	S	S	S	S	S	S	S

SPA™ technology; 1IIS template structure; + carbohydrate; floated 120 C, 122 C, 132 C, 133 C, 134 C

Table 5

Position	Considered Amino Acids	WT	Ground State	Sequences Around Ground State
235 A	Boundary XM	L	T	T:195 V:131 L:112 W:107 K:85 F:66 Y:56 E:52 Q:38 S:37 I:34 R:29 H:26 N:23 D:9
296 A	Surface	Y	N	N:322 D:181 R:172 K:76 Y:70 Q:59 E:48 S:40 H:20 T:11 A:1
298 A	Surface	S	T	T:370 R:343 K:193 A:55 S:39
235 B	Boundary XM	L	L	L:922 I:78

PDA® technology; 1IIS template structure; - carbohydrate; floated 119 C, 128 C, 157 C

Table 6

Position	Considered Amino Acids	WT	1	2	3	4	5	6	7	8	9	10
235 A	All 20	L	S	S	P	S	S	S	S	S	S	S
296 A	Surface	Y	Q	Q	Q	E	E	Q	E	Q	Q	N
298 A	Surface	S	S	K	K	K	K	S	S	S	K	S
235 B	All 20	L	K	K	K	L	L	L	L	L	L	K

SPA™ technology; 1IIS template structure; + carbohydrate; floated 119 C, 128 C, 157 C

Table 7

Position	Considered Amino Acids	WT	Ground State	Sequences Around Ground State
239 B	Surface	S	E	K:402 E:282 H:116 T:67 R:47 Q:39 D:26 A:11 S:7 N:3
265 B	Boundary XM	D	W	Y:341 W:283 I:236 V:77 F:36 H:9 T:7 E:4 K:4 A:2 D:1
327 B	Boundary XM	A	R	R:838 K: 86 H:35 E:12 T:10 Q:7 A:6 D:3 N:3
328 B	Core XM	L	L	L:1000
329 B	Core XM	P	P	P:801 A:199
330 B	Core XM	A	Y	Y:918 F:42 L:22 A:18
332 B	Surface	I	I	I:792 E:202 Q:5 K:1

PDA® technology; 1IIS template structure; - carbohydrate; floated 88 C, 90 C, 113 C, 114 C, 116 C, 160 C, 161 C

Table 8

Position	Considered Amino Acids	WT	1	2	3	4	5	6	7	8	9	10
239 B	Surface	S	D	T	E	E	E	E	E	E	E	E
265 B	All 20	D	G	G	K	G	K	G	G	K	K	G
327 B	All 20	A	K	M	L	L	N	L	K	L	L	L
328 B	Core	L	M	M	M	L	A	M	L	M	L	L
329 B	Core	P	P	P	P	P	P	P	P	P	P	P
330 B	Core	A	L	A	A	A	A	A	A	A	A	A
332 B	Surface	I	I	Q	I	I	Q	Q	E	D	I	I

SPA™ technology; 1IIS template structure; + carbohydrate; floated 88 C, 90 C, 113 C, 114 C, 116 C, 160 C, 161 C

Table 9

Position	Considered Amino Acids	WT	1	2	3	4	5	6	7	8	9	10
239 A	Surface	S	Q	Q	Q	E	Q	E	Q	E	Q	Q
265 A	All 20	D	G	G	G	G	G	G	G	G	G	G
299 A	All 20	T	S	S	A	S	S	S	S	S	S	S
327 A	All 20	A	A	S	S	S	S	S	S	S	A	S
265 B	All 20	D	N	G	G	G	G	G	G	G	G	G

SPA™ technology; 1IIS template structure; - carbohydrate; floated 120 C, 132 C, 134 C

Table 10

Position	Considered Amino Acids	WT	Ground State	Sequences Around Ground State
234 A	Boundary XM	L	K	Y:401 L:260 F:151 I:82 K:63 H:17 Q:11 W:7 R:3 T:2 E:2 V:1
235 A	Boundary XM	L	L	W:777 L:200 K:12 Y:5 I:3 F:2 V:1
234 B	Boundary XM	L	W	W:427 Y:203 L:143 F:74 I:59 E:32 K:23 V:14 D:10 T:7 H:4 R:4
235 B	Boundary XM	L	W	W:380 Y:380 F:135 K:38 L:26 E:15 Q:12 H:8 R:4 T:2

PDA® technology; D129G 1E4K template structure; - carbohydrate; floated 113 C, 116 C, 132 C, 155 C, 157 C

Table 11

Position	Considered Amino Acids	WT	1	2	3	4	5	6	7	8	9	10
234 A	All 20	L	G	G	G	G	G	G	G	G	G	G
235 A	All 20	L	T	L	L	L	L	L	L	L	T	L
234 B	All 20	L	G	G	G	G	G	G	G	G	G	G
235 B	All 20	L	S	A	S	A	A	S	S	S	A	A

SPA™ technology; D129G 1E4K template structure; + carbohydrate; floated 113 C, 116 C, 132 C, 155 C, 157 C

Table 12

Position	Considered Amino Acids	WT	Ground State	Sequences Around Ground State
239 A	Boundary XM	S	E	E:235 S:122 D:94 Q:93 A:74 K:70 L:67 T:63 N:57 R:51 I:29 V:18 W:15 H:12
328 A	Boundary XM	L	L	L:688 E:121 K:43 Q:41 A:33 D:26 S:14 T:14 N:12 R:8
332 A	Boundary XM	I	W	I:155 W:95 L:82 K:79 E:74 Q:69 H:67 V:63 R:57 T:57 D:45 S:43 N:42 A:35 F:19 Y:18

PDA® technology; D129G 1IIS template structure; - carbohydrate; floated 120 C

Table 13

Position	Considered Amino Acids	WT	1	2	3	4	5	6	7	8	9	10
239 A	All 20	S	L	E	E	Q	E	E	K	K	K	K
328 A	All 20	L	L	Q	L	Q	K	L	L	Q	K	L
332 A	All 20	I	K	K	L	Q	A	K	L	Q	A	Q

SPA™ technology; D129G 1IIS template structure; + carbohydrate; floated 120 C

Table 14

Position	Considered Amino Acids	WT	Ground State	Sequences Around Ground State
239 B	Boundary XM	S	I	R:195 I:169 L:126 V:91 K:89 E:61 H:52 T:50 Q:42 N:35 S:34 D:30 A:26
328 B	Boundary XM	L	L	L:671 T:165 K:40 S:38 E:28 R:17 Q:17 V:11 A:8 D:5
332 B	Boundary XM	I	I	I:387 E:157 L:151 V:78 Q:63 K:50 R:33 T:29 D:25 A:12 N:8 S:6 W:1

PDA® technology; D129G 1IIS template structure; - carbohydrate; floated 90 C, 160 C, 161 C

Table 15

Position	Considered Amino Acids	WT	1	2	3	4	5	6	7	8	9	10
239 B	All 20	S	T	L	L	L	L	L	L	L	L	L
328 B	All 20	L	M	R	M	D	T	M	L	Q	D	L
332 B	All 20	I	I	D	Q	Q	Q	L	L	T	Q	L

SPA™ technology; D129G 1IIS template structure; + carbohydrate; floated 90 C, 160 C, 161 C

Table 16

Position	Considered Amino Acids	WT	Ground State	Sequences Around Ground State
239 B	Boundary XM	S	T	T:164 S:159 L:156 E:86 W:76 K:71 D:65 A:52 R:43 H:38 Q:38 N:31 I:14 V:7
328 B	Boundary XM	L	L	L:556 E:114 T:84 K:80 S:69 Q:36 A:31 D:15 R:11 N:4
332 B	Boundary XM	I	W	I:188 W:177 E:97 L:94 T:59 Q:57 V:54 K:52 F:51 D:34 H:33 S:27 R:26 N:18 A:17 Y:16

PDA® technology; D129G 1E4K template structure; - carbohydrate; floated 117 C

Table 17

Position	Considered Amino Acids	WT	1	2	3	4	5	6	7	8	9	10
239 B	All 20	S	P	S	P	E	L	L	L	L	L	L
328 B	All 20	L	K	K	K	K	K	L	K	K	K	L
332 B	All 20	I	S	S	E	L	L	L	E	L	L	L

SPA™ technology; D129G 1E4K template structure; + carbohydrate; floated 117 C

Table 18

Position	Considered Amino Acids	WT	Ground State	Sequences Around Ground State
239 A	Boundary XM	S	L	K:196 L:171 I:146 E:88 V:76 R:75 T:50 H:45 D:43 Q:39 S:30 N:22 A:19
328 A	Boundary XM	L	W	L:517 F:230 W:164 H:40 K:29 E:11 R:5 T:4
332 A	Boundary XM	I	E	I:283 L:217 E:178 Q:81 V:64 D:47 T:35 K:27 W:18 R:12 A:10 Y:7 N:7 F:6 S:5 H:3

PDA® technology; D129G 1E4K template structure; - carbohydrate; floated 87 C, 157 C, 158 C

Table 19

Position	Considered Amino Acids	WT	1	2	3	4	5	6	7	8	9	10
239 A	All 20	S	F	Q	E	T	P	P	T	P	P	P
328 A	All 20	L	K	R	R	K	K	M	R	K	M	R
332 A	All 20	I	L	L	I	I	E	I	E	E	I	I

SPA™ technology; D129G 1E4K template structure; + carbohydrate atoms; floated 87 C, 157 C, 158 C

Table 20

Position	Considered Amino Acids	WT	Ground State	Sequences Around Ground State
240 A	Core + Thr	V	V	V:698 M:162 T:140
263 A	Core + Thr	V	V	V:966 T:34
266 A	Core + Thr	V	V	V:983 T:17
325 A	Boundary	N	N	N:943 T:40 A:17
328 A	Boundary	L	L	L:610 M:363 K:27
332 A	Glu	I	E	E:1000

PDA® technology; D129G 1IIS template structure; - carbohydrate; floated 273 A, 275 A, 302 A, 323 A, 134 C

Table 21

Position	Considered Amino Acids	WT	1	2	3	4	5	6	7	8	9	10
240 A	All 20	V	V	A	V	V	V	V	V	V	V	V
263 A	All 20	V	V	V	V	V	V	V	V	V	V	V
266 A	All 20	V	I	V	I	I	T	V	V	V	V	I
325 A	All 20	N	A	N	N	N	Q	T	T	Q	N	T

Samsung Bioepis Exhibit No. 1002
Page 11166

328 A	All 20	L	K	K	L	K	L	K	L	L	L	L
332 A	Glu	I	D	D	D	D	D	D	D	D	D	D

SPA™ technology; D129G 1IIS template structure; + carbohydrate; floated 273 A, 275 A, 302 A, 323 A, 134 C

Table 22

Position	Considered Amino Acids	WT	Ground State	Sequences Around Ground State
240 B	Core + Thr	V	V	V:713 T:287
263 B	Core + Thr	V	V	V:992 T:8
266 B	Core + Thr	V	V	V:976 T:24
325 B	Boundary	N	N	N:453 T:296 A:116 D:96 S:30 V:9
328 B	Boundary	L	L	L:623 M:194 T:100 R:72 K:11
332 B	Glu	I	E	E:1000

PDA® technology; D129G 1IIS template structure; - carbohydrate; floated 273 B, 275 B, 302 B, 323 B, 161 C

Table 23

Position	Considered Amino Acids	WT	1	2	3	4	5	6	7	8	9	10
240 B	All 20	V	A	T	A	T	T	A	A	T	T	T
263 B	All 20	V	V	A	A	T	T	V	V	T	A	T
266 B	All 20	V	V	V	V	V	V	V	V	V	I	V
325 B	All 20	N	N	K	K	N	K	K	N	N	N	N
328 B	All 20	L	R	L	L	L	L	L	L	L	L	L
332 A	Glu	I	D	D	D	D	D	D	D	D	D	D

SPA™ technology; D129G 1IIS template structure; + carbohydrate; floated 273 B, 275 B, 302 B, 323 B, 161 C

Table 24

Position	Considered Amino Acids	WT	Ground State	Sequences Around Ground State
240 B	Core + Thr	V	M	V:715 M:271 T:12 I:2
263 B	Core + Thr	V	V	V:992 T:8
266 B	Core + Thr	V	V	V:996 T:4
325 B	Boundary	N	N	N:651 T:232 D:64 A:53
328 B	Boundary	L	M	M:556 L:407 K:37
332 B	Glu	I	E	E:1000

PDA® technology; D129G 1E4K template structure; - carbohydrate; floated 273 B, 275 B, 302 B, 323 B, 131 C

Table 25

Position	Considered Amino Acids	WT	1	2	3	4	5	6	7	8	9	10
240 B	All 20	V	T	A	T	A	A	A	A	T	A	A
263 B	All 20	V	T	W	T	T	A	T	T	T	L	L
266 B	All 20	V	L	A	T	T	V	L	T	T	L	V
325 B	All 20	N	A	N	A	A	N	A	A	A	A	A
328 B	All 20	L	L	K	L	L	L	L	L	L	L	L

332 A	Glu	I	D	D	D	D	D	D	D	D	D	D

SPA™ technology; D129G 1E4K template structure; + carbohydrate; floated 273 B, 275 B, 302 B, 323 B, 131 C

Table 26

Position	Considered Amino Acids	WT	Ground State	Sequences Around Ground State
240 A	Core + Thr	V	V	V:876 T:109 M:15
263 A	Core + Thr	V	V	V:913 T:87
266 A	Core + Thr	V	V	V:969 T:31
325 A	Boundary	N	V	V:491 N:236 T:187 A:35 D:32 S:19
328 A	Boundary	L	L	L:321 W:290 M:271 F:49 K:46 R:23
332 A	Glu	I	E	E:1000

PDA® technology; D129G 1E4K template structure; - carbohydrate; floated 273 A, 275 A, 302 A, 323 A, 158 C

Table 27

Position	Considered Amino Acids	WT	1	2	3	4	5	6	7	8	9	10
240 A	All 20	V	A	T	A	A	T	T	A	A	A	T
263 A	All 20	V	T	T	V	V	T	V	L	L	V	T
266 A	All 20	V	V	V	V	V	V	V	V	V	V	V
325 A	All 20	N	Q	N	Q	Q	Q	Q	Q	Q	N	N
328 A	All 20	L	K	M	K	K	K	K	K	K	K	K
332 A	Glu	I	D	D	D	D	D	D	D	D	D	D

SPA™ technology; D129G 1E4K template structure; + carbohydrate; floated 273 A, 275 A, 302 A, 323 A, 158 C

[196] Computational screening calculations were aimed at designing Fc variants to optimize the conformation of the N297 carbohydrate and the Cγ2 domain. By exploring energetically favorable substitutions at positions that interact with carbohydrate, variants can be engineered that sample new, potentially favorable carbohydrate conformations. Fc residues F241, F243, V262, and V264 mediate the Fc/carbohydrate interaction and thus are target positions. The results of these design calculations are presented in Table 28.

Table 28

Position	Considered Amino Acids	WT	Ground State	Sequences Around Ground State
241 A	Core	F	Y	Y:172 M:162 L:144 F:140 W:110 I:97 A:91 V:84
243 A	Core	F	Y	Y:211 L:204 W:199 F:160 M:141 A:85
262 A	Core	V	M	M:302 I:253 V:243 A:202
264 A	Core	V	F	I:159 M:152 V:142 L:140 W:136 F:120 Y:104 A:47

PDA® technology, 1IIS template structure; - carbohydrate

[197] Computational screening calculations were aimed at designing Fc variants to optimize the angle between the Cγ3 and Cγ2 domains. Residues P244, P245, P247, and W313, which reside at the Cγ2/Cγ3 interface, appear to play a key role in determining the Cγ2-Cγ3 angle and the flexibility of the domains relative to one another. By exploring energetically favorable substitutions at these positions, variants can be designed that sample new, potentially favorable angles and levels of flexibility. The results of these design calculations are presented in Table 29.

Table 29

Position	Considered Amino Acids	WT	Ground State	Sequences Around Ground State
244 A	Boundary	P	H	K:164 H:152 R:110 M:100 S:92 N:57 A:54 D:50 Q:49 T:46 E:37 V:30 L:27 W:23 F:9
245 A	Boundary	P	A	A:491 S:378 N:131
247 A	Boundary	P	V	V:156 T:125 K:101 E:87 Q:79 R:78 S:76 A:72 D:72 H:60 M:47 N:47
313 A	Boundary	W	W	W:359 F:255 Y:128 M:114 H:48 K:29 T:24 A:11 E:10 V:10 S:9 Q:3

PDA® technology; 1IIS template structure; - carbohydrate

[198] In addition to the above calculations using PDA® and SPA™ computational screening methods, additional calculations using solely an electrostatic potential were used to computationally screen Fc variants. Calculations with Coulomb's law and Debye-Huckel scaling highlighted a number of positions in the Fc for which amino acid substitutions would favorably affect binding to one or more FcγRs, including positions for which replacement of a neutral amino acid with a negatively charged amino acid may enhance binding to FcγRIIIa, and for which replacement of a positively charged amino acid with a neutral or negatively charged amino acid may enhance binding to FcγRIIIa. These results are presented in Table 30.

Table 30

Replacement of a + residue with a - residue	Replacement of a neutral residue with a - residue
H268	S239
K326	Y296
K334	A327
	I332

Coulomb's law and Debye-Huckel scaling; 1IIS template structure; + carbohydrate

[199] Computational screening calculations were carried out to optimize aglycosylated Fc, that is to optimize Fc structure, stability, solubility, and Fc/FcγR affinity in the absence of the N297 carbohydrate. Design calculations were aimed at designing favorable substitutions in the context of

the aglycosylated Fc template structure at residue 297, residues proximal to it, residues at the Fc/FcγR interface, and residues at the Fc/carbohydrate interface. Variable positions were grouped in different sets of interacting variable positions and designed in separate sets of calculations, and various template structures were used. For many of the variable position sets, calculations were carried out using both the PDA® and SPA™ computational screening methods. The results of these calculations and relevant information are presented in Tables 31 - 53 below.

Table 31

Position	Considered Amino Acids	WT	Ground State	Sequences Around Ground State
265 A	Boundary XM	D	Y	Y:531 F:226 W:105 H:92 K:21 D:16 E:6 T:3
297 A	Boundary XM	N	D	A:235 S:229 D:166 E:114 N:92 Y:57 F:55 Q:25 H:10 T:7 K:6 L:3 R:1
299 A	Boundary XM	T	L	L:482 Y:186 F:131 T:55 S:51 K:31 H:22 A:18 E:14 Q:10
297 B	Boundary XM	N	I	I:299 K:147 V:85 R:82 W:71 N:65 D:35 E:35 Q:34 S:32 L:31 H:30 T:28 A:26

PDA® technology; 1IIS template structure; - carbohydrate; floated 122 C, 129 C, 132 C, 155 C

Table 32

Position	Considered Amino Acids	WT	1	2	3	4	5	6	7	8	9	10
265 A	All 20	D	G	G	G	G	G	G	G	G	G	G
297 A	All 20	N	A	T	A	E	K	K	A	A	N	N
299 A	All 20	T	S	K	S	K	F	F	F	F	F	S
297 B	All 20	N	K	K	K	K	K	K	K	K	K	K

SPA™ technology; 1IIS template structure; - carbohydrate; floated 122 C, 129 C, 132 C, 155 C

Table 33

Position	Considered Amino Acids	WT	Ground State	Sequences Around Ground State
239 A	Surface	S	E	E:928 Q:65 D:7
265 A	Boundary XM	D	W	W:709 Y:248 F:43
296 A	Surface	Y	H	H:449 Y:146 E:137 D:89 K:64 N:32 T:30 R:25 Q:23 S:5
297 A	Surface	N	E	E:471 H:189 D:102 T:97 K:96 R:22 Q:15 S:8
298 A	Boundary XM	S	R	R:353 T:275 K:269 A:56 S:38 E:5 Q:2 H:2
299 A	Boundary XM	T	F	Y:398 F:366 L:217 H:15 K:4

PDA® technology; D129G 1IIS template structure; - carbohydrate; floated 120 C, 122 C, 128 C, 132 C, 155 C

Table 34

Position	Considered Amino Acids	WT	1	2	3	4	5	6	7	8	9	10
239 A	All 20	S	E	Q	Q	E	Q	Q	Q	Q	Q	Q
265 A	All 20	D	G	G	G	G	G	G	G	G	G	G
296 A	All 20	Y	D	Q	N	N	Q	N	N	N	Q	N

Samsung Bioepis Exhibit No. 1002
Page 11170

297 A	All 20	N	A	A	N	A	D	D	E	N	N	E
298 A	All 20	S	K	K	K	S	K	K	K	K	S	K
299 A	All 20	T	S	Y	F	S	Y	F	K	F	S	K

SPA™ technology; D129G 1IIS template structure; - carbohydrate; floated 120 C, 122 C, 128 C, 132 C, 155 C

Table 35

Position	Considered Amino Acids	WT	Ground State	Sequences Around Ground State
239 B	Surface	S	E	E:417 T:122 D:117 Q:94 R:84 S:63 K:47 H:29 N:19 A:8
265 B	Boundary XM	D	W	W:865 Y:79 F:55 K:1
296 B	Surface	Y	Y	Y:549 H:97 D:80 S:75 N:48 E:45 K:32 R:30 Q:28 A:16
297 B	Surface	N	R	R:265 H:224 E:157 K:154 Q:75 D:47 T:34 N:24 S:13 A:7
298 B	Boundary XM	S	V	V:966 D:10 T:8 A:8 N:4 S:4
299 B	Boundary XM	T	Y	Y:667 F:330 H:3

PDA® technology; D129G 1E4K template structure; - carbohydrate; floated 117 C, 119 C, 125 C, 129 C, 152 C

Table 36

Position	Considered Amino Acids	WT	1	2	3	4	5	6	7	8	9	10
239 B	All 20	S	S	R	E	K	S	S	E	E	E	K
265 B	All 20	D	A	D	K	Y	A	A	F	F	K	Y
296 B	All 20	Y	A	A	A	A	A	A	A	A	A	A
297 B	All 20	N	T	S	T	T	E	E	E	S	E	E
298 B	All 20	S	G	G	G	G	G	G	G	G	G	G
299 B	All 20	T	L	F	E	E	Y	F	Y	F	Y	Y

SPA™ technology; D129G 1E4K template structure; - carbohydrate; floated 117 C, 119 C, 125 C, 129 C, 152 C

Table 37

Position	Considered Amino Acids	WT	Ground State	Sequences Around Ground State
239 A	Surface	S	E	E:868 Q:92 D:38 K:1 N:1
265 A	Boundary XM	D	W	W:575 Y:343 F:66 H:15 K:1
296 A	Surface	Y	H	H:489 Y:103 R:98 K:97 Q:64 D:63 T:41 N:38 E:7
297 A	Asp	N	D	D:1000
298 A	Boundary XM	S	R	R:340 K:262 T:255 A:59 S:57 E:11 Q:10 H:6
299 A	Boundary XM	T	F	Y:375 F:323 L:260 H:24 K:18

PDA® technology; D129G 1IIS template structure; - carbohydrate; floated 120 C, 122 C, 128 C, 132 C, 155 C

Table 38

Position	Considered Amino Acids	WT	1	2	3	4	5	6	7	8	9	10
239 A	All 20	S	E	Q	E	E	E	E	E	E	Q	E

265 A	All 20	D	G	G	G	G	G	G	G	G	G	G
296 A	All 20	Y	E	N	Q	E	N	Q	Q	Q	Q	N
297 A	Asp	N	D	D	D	D	D	D	D	D	D	D
298 A	All 20	S	K	S	K	S	K	K	K	S	K	K
299 A	All 20	T	S	K	Y	S	F	F	F	F	F	K

SPA™ technology; D129G 1IIS template structure; - carbohydrate; floated 120 C, 122 C, 128 C, 132 C, 155 C

Table 39

Position	Considered Amino Acids	WT	Ground State	Sequences Around Ground State
239 B	Surface	S	E	E:318 Q:123 T:109 D:108 R:93 S:89 K:69 N:40 H:38 A:13
265 B	Boundary XM	D	W	W:745 Y:158 F:85 K:9 E:1 R:1 H:1
296 B	Surface	Y	Y	Y:390 H:127 S:83 R:81 K:78 N:65 D:55 E:49 Q:44 A:26 T:2
297 B	Asp	N	D	D:1000
298 B	Boundary XM	S	V	V:890 T:35 A:29 D:19 S:16 N:10 E:1
299 B	Boundary XM	T	Y	Y:627 F:363 H:10

PDA® technology; D129G 1E4K template structure; - carbohydrate; floated 117 C, 119 C, 125 C, 129 C, 152 C

Table 40

Position	Considered Amino Acids	WT	1	2	3	4	5	6	7	8	9	10
239 B	All 20	S	K	E	E	Q	E	K	Q	E	K	Q
265 B	All 20	D	F	K	K	A	K	Y	W	K	L	F
296 B	All 20	Y	A	A	A	A	A	A	A	A	A	A
297 B	Asp	N	D	D	D	D	D	D	D	D	D	D
298 B	All 20	S	G	G	G	G	G	G	G	G	G	G
299 B	All 20	T	Y	Y	Y	Y	Y	Y	F	F	Y	Y

SPA™ technology; D129G 1E4K template structure; - carbohydrate; floated 117 C, 119 C, 125 C, 129 C, 152 C

Table 41

Position	Considered Amino Acids	WT	Ground State	Sequences Around Ground State
239 A	Boundary XM	S	E	E:312 L:148 D:102 Q:98 K:64 I:61 S:57 A:44 T:39 N:29 R:23 V:18 W:5
265 A	Boundary XM	D	W	W:363 Y:352 F:139 H:77 K:39 R:14 D:11 E:4 Q:1
297 A	Asp	N	D	D:1000
299 A	Boundary XM	T	Y	Y:309 F:224 L:212 H:96 K:92 E:28 Q:20 R:16 T:2 S:1

PDA® technology; D129G 1IIS template structure; - carbohydrate; floated 120 C, 122 C, 132 C, 155 C

Table 42

Position	Considered	WT	1	2	3	4	5	6	7	8	9	10

	Amino Acids											
239 A	All 20	S	E	L	L	L	E	E	E	Q	L	E
265 A	All 20	D	G	G	G	G	G	G	G	G	G	G
297 B	Asp	N	D	D	D	D	D	D	D	D	D	D
299 A	All 20	T	S	K	K	F	F	F	K	F	K	F

SPA™ technology; D129G 1IIS template structure; - carbohydrate; floated 120 C, 122 C, 132 C, 155 C

Table 43

Position	Considered Amino Acids	WT	Ground State	Sequences Around Ground State
239 B	Boundary XM	S	L	L:194 T:122 S:120 E:111 D:79 K:71 A:62 Q:57 R:43 H:43 N:37 I:24 W:24 V:13
265 B	Boundary XM	D	W	Y:248 W:233 F:198 K:84 D:57 E:55 H:42 R:28 Q:20 A:10 T:10 N:8 S:7
297 B	Asp	N	D	D:1000
299 B	Boundary XM	T	Y	Y:493 F:380 H:76 T:31 E:10 D:4 A:3 S:3

PDA® technology; D129G 1E4K template structure; - carbohydrate; floated 117 C, 119 C, 129 C, 152 C

Table 44

Position	Considered Amino Acids	WT	1	2	3	4	5	6	7	8	9	10
239 B	All 20	S	R	E	P	L	L	F	P	P	L	L
265 B	All 20	D	D	K	S	F	S	Y	A	M	A	D
297 B	Asp	N	D	D	D	D	D	D	D	D	D	D
299 B	All 20	T	Y	Y	Y	Y	E	Y	Y	Y	Y	Y

SPA™ technology; D129G 1E4K template structure; - carbohydrate; floated 117 C, 119 C, 129 C, 152 C

Table 45

Position	Considered Amino Acids	WT	Ground State	Sequences Around Ground State
239 A	Boundary XM	S	E	E:251 L:125 D:120 Q:112 S:73 K:65 I:61 A:58 T:45 N:35 R:28 V:23 W:4
265 A	Boundary XM	D	Y	Y:216 H:153 K:135 D:109 W:104 F:86 R:54 T:38 E:29 Q:22 A:21 N:17 S:13 L:3
297 A	Asp	N	D	D:1000

PDA® technology; D129G 1IIS template structure; - carbohydrate; floated 299 A, 120 C, 122 C, 132 C, 155 C

Table 46

Position	Considered Amino Acids	WT	1	2	3	4	5	6	7	8	9	10
239 A	All 20	S	S	L	E	L	Q	Q	E	Q	Q	E
265 A	All 20	D	G	G	G	G	G	G	G	G	G	G
297 A	Asp	N	D	D	D	D	D	D	D	D	D	D

SPA™ technology; D129G 1IIS template structure; - carbohydrate; floated 299 A, 120 C, 122 C, 132 C, 155 C

Table 47

Position	Considered Amino Acids	WT	Ground State	Sequences Around Ground State
239 B	Boundary XM	S	L	L:158 S:137 T:125 E:115 D:86 K:75 A:62 Q:56 H:43 R:39 N:35 W:30 I:24 V:15
265 B	Boundary XM	D	Y	Y:188 W:159 F:156 D:122 K:77 E:71 H:61 Q:44 R:39 A:24 S:22 N:19 T:18
297 B	Asp	N	D	D:1000

PDA® technology; D129G 1E4K template structure; - carbohydrate; floated 299 B, 117 C, 119 C, 129 C, 152 C

Table 48

Position	Considered Amino Acids	WT	1	2	3	4	5	6	7	8	9	10
239 B	All 20	S	S	E	P	P	E	S	P	L	F	L
265 B	All 20	D	A	K	A	M	K	F	Y	D	F	F
297 B	Asp	N	D	D	D	D	D	D	D	D	D	D

SPA™ technology; D129G 1E4K template structure; - carbohydrate; floated 299 B, 117 C, 119 C, 129 C, 152 C

Table 49

Position	Considered Amino Acids	WT	Ground State	Sequences Around Ground State
297 A	Asp	N	D	D:1000
299 A	Boundary XM	T	Y	T:123 Y:64 H:64 K:64 Q:64 F:64 R:63 D:63 E:63 S:63 L:63 N:62 I:57 A:54 V:52 W:17

PDA® technology; D129G 1IIS template structure; - carbohydrate; floated 239 A, 265 A, 120 C, 122 C, 132 C, 155 C

Table 50

Position	Considered Amino Acids	WT	1	2	3	4	5	6	7	8	9	10
297 A	Asp	N	D	D	D	D	D	D	D	D	D	D
299 A	All 20	T	K	K	K	K	F	F	K	K	K	K

SPA™ technology; D129G 1IIS template structure; - carbohydrate; floated 239 A, 265 A, 120 C, 122 C, 132 C, 155 C

Table 51

Position	Considered Amino Acids	WT	Ground State	Sequences Around Ground State
297 B	Asp	N	D	D:1000
299 B	Boundary XM	T	Y	T:123 F:64 Y:64 H:64 S:63 N:61 Q:61 D:61 E:60 K:58 V:57 A:57 R:54 I:52 L:51 W:50

PDA® technology; D129G 1E4K template structure; - carbohydrate; floated 239 B, 265 B, 117 C, 119 C, 129 C, 152 C

Samsung Bioepis Exhibit No. 1002
Page 11174

Table 52

Position	Considered Amino Acids	WT	1	2	3	4	5	6	7	8	9	10
297 B	Asp	N	D	D	D	D	D	D	D	D	D	D
299 B	All 20	T	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y

SPA™ technology; D129G 1E4K template structure; - carbohydrate; floated 239 B, 265 B, 117 C, 119 C, 129 C, 152 C

[200] Computational screening calculations were carried out to optimize aglycosylated Fc by designing favorable substitutions at residues that are exposed to solvent in the absence of glycosylation such that they are stable, maintain Fc structure, and have no tendency to aggregate. The N297 carbohydrate covers up the exposed hydrophobic patch that would normally be the interface for a protein-protein interaction with another Ig domain, maintaining the stability and structural integrity of Fc and keeping the Cγ2 domains from aggregating across the central axis. Key residues for design are F241, F243, V262, and V264, which reside behind the carbohydrate on Cγ2, in addition to residues such as L328, I332, and I336, which are exposed nonpolar residues facing inward towards the opposed Cγ2 domain, that were considered in previously presented calculations. The importance of these Cγ2 residues is supported by noting that the corresponding residues in the Cγ3 domain by sequence alignment either mediate the nonpolar interaction between the two Cγ3 domains or are buried in the Cγ3 core. The results of these design calculations are presented in Table 53.

Table 53

Position	Considered Amino Acids	WT	Ground State	Sequences Around Ground State
241 A	Surface	F	E	E:190 R:172 K:138 H:117 T:93 Q:91 D:85 S:49 N:49 A:16
243 A	Surface	F	R	R:190 H:164 Q:152 E:149 K:92 T:71 D:64 N:58 S:42 A:18
262 A	Surface	V	D	D:416 E:164 N:138 Q:87 T:83 R:44 S:32 K:24 A:11 H:1
264 A	Surface	V	H	R:368 H:196 K:147 E:108 Q:68 T:34 N:33 D:25 S:15 A:6

PDA® technology; 1IIS template structure; - carbohydrate

[201] In a final set of calculations, a SPA™ computational screening method was applied to evaluate the replacement of all chosen variable positions with all 20 amino acids. The lowest energy rotamer conformation for all 20 amino acids was determined, and this energy was defined as the energy of substitution for that amino acid at that variable position. These calculations thus provided an energy of substitution for each of the 20 amino acids at each variable position. These data were

useful for a variety of design goals aimed at both glycosylated and aglycosylated Fc, including optimization of Fc/FcγR affinity, Fc stability, Fc solubility, carbohydrate conformation, and hinge conformation. Furthermore, because these calculations provide energies for both favorable and unfavorable substitutions, they guide substitutions that may enable differential binding to activating versus inhibitory FcγRs. Various template structures were used, and calculations explored substitutions on both chains. The results of these calculations and relevant parameters and information are presented in Tables 54 - 59 below. Column 1 lists the variable positions on chain A and B of the 1IIS template structure. Column 2 lists the wild-type amino acid identity at each variable position. The remaining 20 columns provide the energy for each of the natural 20 amino acids (shown in the top row). All substitutions were normalized with respect to the lowest energy substitution, which was set to 0 energy. For example in Table 54, for L235 on chain A, serine is the lowest energy substitution, and L235A is 0.9 kcal/mol less stable than L235S. Extremely high energies were set to 20 kcal/mol for energies between 20 – 50 kcal/mol, and 50 kcal/mold for energies greater than 50 kcal/mol. Favorable substitutions may be considered to be the lowest energy substitution for each position, and substitutions that have small energy differences from the lowest energy substitution, for example substitutions within 1-2, 1-3, 1-5, or 1-10 kcal/mol.

Samsung Bioepis Exhibit No. 1002
Page 11176

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Samsung Bioepis Exhibit No. 1002
Page 11177

Table 54

Pos	WT	A	C	D	E	F	G	H	I	K	L	M	N	P	Q	R	S	T	V	W	Y
235 A	L	0.9	2.8	2.8	1.5	3.2	3.2	3.4	4.9	1.6	2.1	3.2	0.9	0.3	1.3	0.7	0.0	1.7	4.3	6.5	3.2
236 A	G	0.0	1.9	5.1	6.7	10.0	2.3	4.3	17.2	5.7	20.0	4.6	3.2	12.6	5.6	6.1	0.6	6.2	12.0	6.7	20.0
237 A	G	20.0	20.0	20.0	50.0	50.0	0.0	50.0	50.0	20.0	50.0	20.0	20.0	50.0	50.0	50.0	20.0	20.0	50.0	50.0	50.0
239 A	S	0.2	4.3	2.6	0.0	12.8	4.5	6.9	11.3	1.7	0.1	2.1	1.7	7.9	1.2	2.6	0.3	5.7	11.0	20.0	20.0
265 A	D	9.0	8.1	6.3	7.8	5.1	0.0	7.3	50.0	8.2	9.9	7.7	6.0	50.0	9.0	8.5	7.8	20.0	50.0	20.0	5.8
267 A	S	2.1	3.3	7.3	1.4	50.0	7.3	20.0	20.0	0.9	2.2	5.0	4.8	0.0	2.2	3.1	2.9	20.0	20.0	50.0	50.0
269 A	E	0.5	2.1	1.3	0.6	1.6	3.9	2.0	1.2	1.1	1.3	2.7	0.0	50.0	0.6	1.1	0.3	0.8	1.0	5.6	1.2
270 A	D	0.3	2.8	2.3	2.0	4.0	4.0	3.4	2.4	1.2	0.0	2.3	2.1	20.0	2.0	2.3	1.4	1.8	4.2	5.4	6.0
296 A	Y	2.7	2.0	1.4	0.0	50.0	0.0	50.0	4.6	2.1	2.4	3.3	1.2	50.0	0.2	1.5	1.3	4.6	4.4	16.3	18.2
298 A	S	0.7	2.4	6.7	3.4	20.0	3.9	20.0	6.7	0.0	4.1	1.4	4.1	50.0	1.8	1.1	0.2	2.2	6.3	17.8	20.0
299 A	T	0.6	2.8	11.5	10.1	20.0	6.1	20.0	10.7	7.1	20.0	4.3	6.8	50.0	6.3	12.0	0.0	3.0	7.1	14.8	20.0
234 B	L	2.1	3.2	4.1	4.2	1.6	5.3	0.1	0.7	0.6	1.0	2.0	1.7	50.0	2.8	0.3	2.3	1.7	2.6	13.0	0.0
235 B	L	0.6	2.3	2.5	0.7	5.4	4.8	1.4	3.6	0.1	0.0	2.0	1.7	16.6	0.5	1.2	0.7	0.7	5.3	6.8	5.5
236 B	G	3.1	1.3	4.4	8.2	5.2	0.0	1.9	20.0	3.1	20.0	4.1	2.7	50.0	3.7	16.0	1.2	20.0	20.0	20.0	11.3
237 B	G	20.0	50.0	50.0	50.0	50.0	0.0	50.0	50.0	50.0	50.0	50.0	50.0	50.0	50.0	50.0	50.0	50.0	50.0	50.0	50.0
239 B	S	0.9	2.4	3.4	1.8	5.4	5.6	2.7	3.0	0.9	0.0	2.0	1.6	50.0	1.8	1.8	1.4	1.4	5.1	20.0	5.3
265 B	D	4.5	5.1	4.6	4.6	4.9	0.0	3.8	9.0	2.0	2.5	4.1	2.1	50.0	4.5	5.1	4.4	5.9	9.2	11.4	5.8
327 B	A	1.8	3.4	4.7	3.9	20.	7.0	20.	20.	0.8	0.0	1.9	1.5	20.	3.0	2.6	3.2	20.	20.	20.	20.

Samsung Bioepis Exhibit No. 1002
Page 11178

						0		0	0					0				0	0	0	0
328 B	L	3.7	3.6	4.0	3.7	50.0	8.4	6.8	50.0	3.8	0.0	2.1	4.1	50.0	3.6	8.1	4.9	3.0	12.5	50.0	50.0
329 B	P	3.4	8.6	20.0	20.0	50.0	8.0	16.8	50.0	20.0	20.0	16.9	20.0	0.0	20.0	20.0	1.3	17.1	16.5	50.0	50.0
330 B	A	0.5	2.0	2.6	0.5	2.4	3.8	1.4	4.2	0.0	2.0	2.2	0.8	20.0	0.1	0.6	0.9	0.3	5.1	8.0	2.7
332 B	I	1.5	2.7	1.2	1.6	11.9	6.8	12.9	1.2	2.9	0.0	1.4	1.7	50.0	1.3	4.9	1.8	1.7	3.0	20.0	20.0

SPA™ technology; 1IIS template structure; + carbohydrate atoms, no floated positions

Samsung Bioepis Exhibit No. 1002
Page 11179

Table 55

Pos	WT	A	C	D	E	F	G	H	I	K	L	M	N	P	Q	R	S	T	V	W	Y
235 A	L	0.9	2.8	2.6	1.7	3.3	3.3	3.4	5.0	1.6	2.1	3.3	1.0	0.3	1.4	1.8	0.0	1.9	3.6	6.6	3.3
236 A	G	0.0	1.7	5.2	6.0	11.3	2.3	4.4	17.2	5.8	19.0	4.9	3.3	8.2	5.6	6.0	0.8	5.6	11.8	6.6	20.0
237 A	G	20.0	20.0	20.0	50.0	50.0	0.0	50.0	50.0	20.0	50.0	20.0	20.0	50.0	50.0	50.0	20.0	20.0	50.0	50.0	50.0
238 A	P	8.6	8.0	10.5	13.4	6.4	0.0	5.0	50.0	12.4	11.3	9.7	9.3	3.2	12.4	20.0	8.6	50.0	50.0	20.0	8.4
239 A	S	0.1	4.2	2.5	0.0	20.0	4.5	9.0	10.8	1.8	0.2	2.1	1.8	9.1	1.3	2.5	0.3	5.7	10.7	20.0	19.7
240 A	V	1.3	2.4	2.3	6.3	20.0	7.2	20.0	5.1	10.8	6.2	5.7	2.0	1.1	9.5	13.1	2.5	0.5	0.0	20.0	20.0
241 A	F	0.1	1.6	1.2	0.3	0.2	4.1	1.2	10.0	1.3	0.1	2.1	0.4	14.7	0.5	1.1	0.1	0.0	8.3	3.6	0.4
242 A	L	3.0	3.4	5.5	8.3	14.4	8.5	11.1	3.3	13.9	2.2	2.7	5.5	0.9	7.9	17.1	3.8	2.3	0.0	20.0	17.5
243 A	F	1.6	2.2	2.7	0.2	1.4	5.6	2.5	0.0	2.2	2.0	3.0	2.3	10.2	0.5	1.6	1.3	0.9	1.2	5.3	1.6
244 A	P	1.2	1.8	3.8	0.8	10.2	3.8	4.6	20.0	0.2	2.9	2.0	2.8	2.0	0.9	1.7	0.0	19.3	20.0	7.6	12.2
245 A	P	3.9	20.0	20.0	20.0	20.0	9.1	20.0	20.0	20.0	20.0	20.0	20.0	0.0	20.0	20.0	8.0	20.0	50.0	20.0	20.0
246 A	K	1.3	2.7	2.0	2.0	2.9	5.7	2.9	1.4	1.4	1.5	3.1	0.2	0.0	1.2	1.5	1.7	1.4	1.2	5.4	3.0
247 A	P	1.2	2.1	0.3	0.7	4.0	3.9	3.7	1.8	1.6	1.7	3.3	0.0	0.5	0.9	1.5	0.7	1.1	1.3	6.9	3.7
248 A	K	0.9	2.7	1.5	0.8	3.1	4.7	3.4	3.3	2.0	1.9	2.6	1.2	3.6	1.5	2.3	0.7	0.0	2.5	5.6	2.7
249 A	D	1.2	3.7	1.6	0.0	20.0	7.3	19.7	50.0	1.7	20.0	2.2	1.4	20.0	1.5	3.4	2.5	18.3	50.0	20.0	20.0
250 A	T	0.0	1.8	3.8	5.8	50.0	6.0	20.0	4.5	6.3	6.3	0.3	3.2	50.0	8.7	9.3	1.8	1.3	1.9	20.0	50.0
251 A	L	1.1	1.9	1.2	0.5	5.8	5.1	1.9	5.6	0.9	0.7	2.4	1.4	50.0	0.0	1.4	0.5	0.8	6.9	8.9	5.8
252	M	0.3	1.2	0.6	0.0	3.0	3.8	3.4	3.9	1.0	0.3	2.2	0.3	17.	0.1	1.1	0.1	0.2	4.6	4.2	3.3

Samsung Bioepis Exhibit No. 1002
Page 11180

A														4						
253A	I	0.7	1.7	1.1	0.2	1.8	3.5	2.2	2.0	0.3	1.2	0.8	0.8	0.3	0.0	1.1	0.3	0.5	2.8	2.4	1.9
254A	S	0.7	1.7	0.4	0.7	2.2	3.6	2.0	0.3	1.2	1.9	2.4	0.0	20.0	0.3	1.2	0.3	0.8	0.7	3.8	1.9
255A	R	1.4	2.8	2.4	2.5	0.2	5.4	1.1	17.0	1.0	2.2	1.5	1.7	50.0	2.1	0.0	2.3	50.0	17.2	4.0	0.5
256A	T	0.6	1.8	1.2	1.1	2.7	3.4	2.1	1.4	0.7	1.5	2.4	0.0	0.4	0.1	0.2	0.4	0.9	1.2	5.6	2.7
257A	P	0.0	7.8	20.0	12.9	50.0	6.2	50.0	20.0	12.3	12.8	14.4	20.0	0.1	13.1	20.0	2.9	16.0	20.0	50.0	50.0
258A	E	0.0	1.6	4.8	2.6	1.0	4.3	2.2	14.8	4.4	6.2	3.2	2.9	10.4	7.4	6.0	1.0	6.2	17.6	20.0	1.0
259A	V	3.9	4.3	5.1	8.7	20.0	10.3	6.8	2.3	9.6	2.8	6.2	4.1	50.0	9.2	20.0	5.2	2.1	0.0	20.0	20.0
260A	T	1.7	2.3	3.3	1.1	20.0	6.6	8.6	0.0	0.2	1.8	2.8	1.8	1.1	0.8	0.9	1.7	0.4	1.9	7.1	20.0
261A	C	0.0	20.0	20.0	20.0	20.0	3.9	20.0	20.0	20.0	20.0	20.0	20.0	50.0	20.0	20.0	3.6	20.0	20.0	20.0	20.0
262A	V	1.9	3.2	0.0	3.3	20.0	7.2	20.0	8.3	2.9	2.9	2.2	0.6	50.0	3.8	5.2	3.4	3.0	1.7	20.0	20.0
263A	V	2.2	2.7	6.0	17.4	20.0	8.8	20.0	10.0	7.1	7.6	16.9	5.2	50.0	19.8	17.7	2.8	1.4	0.0	20.0	20.0
264A	V	1.9	3.3	2.8	2.2	0.0	6.4	2.1	0.7	2.6	0.9	2.7	2.1	2.3	2.6	2.7	2.2	1.1	0.6	3.9	0.1
265A	D	9.0	8.1	5.9	8.6	5.3	0.0	7.3	50.0	7.9	9.7	7.5	5.5	50.0	10.2	8.6	7.9	20.0	50.0	20.0	5.7
266A	V	4.9	5.3	7.1	12.1	20.0	11.2	20.0	0.4	12.2	20.0	8.8	7.1	50.0	12.2	20.0	6.1	3.8	0.0	20.0	20.0
267A	S	2.3	3.5	7.2	1.3	50.0	7.4	20.0	20.0	0.7	1.4	3.9	4.7	0.0	2.3	3.1	3.0	20.0	20.0	50.0	50.0
268A	H	1.2	1.9	2.2	1.5	3.7	5.0	4.9	0.4	0.5	3.7	2.7	1.7	0.0	1.4	1.7	1.1	0.2	0.9	6.1	3.7
269A	E	0.3	1.9	1.3	0.5	1.3	3.7	1.9	1.1	0.8	1.2	2.5	0.0	50.0	0.6	0.8	0.2	0.6	0.7	4.0	1.0
270A	D	0.2	2.6	2.1	1.9	5.2	3.9	3.1	2.1	1.2	0.0	2.2	1.9	20.0	1.9	1.8	1.2	1.7	4.1	5.1	7.0

Samsung Bioepis Exhibit No. 1002
Page 11181

Table 55 (continued)

Pos	WT	A	C	D	E	F	G	H	I	K	L	M	N	P	Q	R	S	T	V	W	Y
271 A	P	0.0	5.3	8.1	9.3	20.0	3.1	9.1	20.0	6.0	9.5	5.3	7.3	5.9	5.9	5.9	1.6	4.1	15.2	20.0	20.0
272 A	Q	0.8	1.9	0.9	1.2	3.0	3.2	3.7	3.7	1.6	1.8	3.2	0.3	50.0	1.1	1.6	0.0	1.0	3.5	4.0	3.4
273 A	V	1.2	2.9	1.8	20.0	20.0	7.1	20.0	6.8	20.0	20.0	20.0	0.0	2.8	20.0	20.0	2.1	1.4	1.7	20.0	20.0
274 A	K	0.4	1.8	1.4	0.8	1.9	3.9	2.4	1.4	0.7	1.1	2.9	0.9	20.0	0.0	0.1	0.0	0.4	0.7	3.3	2.3
275 A	F	8.0	9.5	10.3	9.5	0.0	13.5	5.1	10.1	6.2	6.3	6.0	9.1	6.1	9.1	15.1	9.6	7.2	6.1	13.5	4.3
276 A	N	1.3	2.4	2.4	2.2	0.8	5.1	0.8	1.2	0.6	2.3	2.5	1.8	50.0	1.6	2.5	1.2	0.0	0.3	4.2	3.6
277 A	W	5.5	7.4	8.4	6.4	15.4	11.2	3.2	8.2	1.9	3.9	3.6	6.6	3.5	5.5	15.4	6.9	6.1	14.1	0.0	20.0
278 A	Y	1.6	2.7	3.9	1.6	1.0	7.3	3.4	17.7	1.4	7.5	2.1	0.0	50.0	1.9	2.2	2.6	9.9	20.0	15.8	1.4
279 A	V	3.1	4.1	4.0	2.2	20.0	8.1	9.7	8.5	0.0	1.4	3.1	3.3	20.0	1.9	4.6	4.3	3.4	4.2	20.0	20.0
280 A	D	1.8	2.6	2.7	0.2	11.5	2.9	8.8	20.0	3.4	3.2	2.8	3.8	50.0	0.0	3.7	0.6	6.8	12.7	11.9	11.4
281 A	G	50.0	50.0	50.0	50.0	50.0	0.0	50.0	50.0	50.0	50.0	50.0	50.0	50.0	50.0	50.0	50.0	50.0	50.0	50.0	50.0
282 A	V	0.9	2.1	1.6	1.1	2.9	4.2	3.5	1.4	1.5	1.8	3.6	0.4	18.9	0.5	1.0	0.0	0.6	0.9	4.7	3.1
283 A	E	0.7	1.6	0.7	0.5	1.0	4.4	1.4	0.4	1.2	1.8	1.9	0.0	0.4	0.6	1.5	0.4	0.3	1.2	4.1	0.9
284 A	V	0.0	2.2	3.1	1.2	20.0	5.0	20.0	4.0	0.7	2.6	0.8	2.6	50.0	0.8	0.7	0.8	0.1	1.5	20.0	20.0
285 A	H	0.2	1.4	3.1	1.3	3.0	2.0	2.4	3.6	1.1	2.6	3.0	0.7	2.2	0.2	0.8	0.0	1.1	4.7	4.9	4.0
286 A	N	0.8	2.5	1.2	1.1	2.4	4.7	2.7	2.1	0.0	0.7	1.8	0.6	20.0	1.2	0.7	0.9	1.7	2.1	5.2	2.7
287 A	A	0.6	2.6	5.8	3.3	10.4	5.4	9.1	11.3	0.0	4.4	1.3	3.6	50.0	2.6	2.3	1.0	1.9	12.5	9.1	10.4
288	K	0.8	2.6	2.0	1.3	3.0	3.4	3.8	2.3	1.4	1.7	2.5	0.3	50.	0.5	1.3	0.0	0.4	2.0	4.5	3.6

Samsung Bioepis Exhibit No. 1002
Page 11182

A														0							
289 A	T	0.3	1.9	4.7	1.1	3.1	3.6	2.9	10.5	0.4	2.7	1.6	2.1	8.2	1.2	2.0	0.0	0.4	12.0	3.9	3.2
290 A	K	1.7	2.2	0.5	0.6	3.0	1.3	3.0	3.7	1.7	2.1	3.2	0.0	50.0	0.7	2.0	0.3	1.3	3.3	5.6	3.3
291 A	P	1.6	3.1	1.8	0.5	1.9	5.5	1.8	0.1	0.5	1.5	1.2	1.2	0.7	0.0	2.9	2.2	0.9	1.3	2.6	0.9
292 A	R	1.1	2.2	3.1	0.8	5.9	4.4	8.0	5.0	0.0	1.6	2.1	1.1	8.4	0.2	0.4	1.0	1.3	4.7	8.3	5.7
293 A	E	2.2	6.5	9.0	17.9	16.3	0.0	13.2	50.0	12.8	10.3	10.3	7.2	5.5	15.1	14.5	3.5	20.0	50.0	14.5	17.1
294 A	E	1.5	2.1	2.1	0.7	8.1	2.8	3.3	2.0	2.6	1.8	2.8	1.0	50.0	1.3	1.3	0.5	0.0	3.4	11.2	10.2
295 A	Q	50.0	50.0	50.0	50.0	50.0	0.0	50.0	50.0	50.0	50.0	50.0	50.0	50.0	50.0	50.0	50.0	50.0	50.0	50.0	50.0
296 A	Y	2.8	2.3	1.1	0.4	50.0	0.0	50.0	4.6	2.2	2.3	3.1	0.9	50.0	0.2	1.8	1.3	4.7	4.8	18.2	20.0
297 A	N	0.0	6.5	8.4	5.3	20.0	3.4	20.0	13.8	2.7	20.0	4.8	9.3	50.0	4.4	4.4	1.5	1.6	15.5	20.0	20.0
298 A	S	0.8	2.4	5.7	2.2	20.0	3.7	20.0	6.2	0.9	9.2	1.8	3.3	50.0	1.7	2.1	0.0	2.2	7.3	15.6	20.0
299 A	T	1.9	3.4	6.0	3.1	1.0	7.1	2.9	3.1	0.0	2.7	2.6	3.6	50.0	2.2	2.5	1.1	2.2	5.4	3.6	1.4
300 A	Y	2.8	2.9	2.7	4.5	20.0	4.0	7.5	13.1	1.2	0.0	2.2	2.3	50.0	3.3	4.0	2.6	1.1	1.1	11.0	2.4
301 A	R	3.0	3.5	3.8	2.8	0.8	3.4	1.8	0.0	1.3	0.7	2.6	2.5	50.0	2.6	2.3	2.9	1.8	0.9	9.8	1.8
302 A	V	2.7	4.6	6.7	3.9	2.8	8.9	1.2	6.9	2.7	2.0	2.2	4.8	50.0	4.7	3.2	4.3	7.7	3.8	0.0	8.4
303 A	V	0.0	2.2	3.3	1.0	6.7	4.5	5.3	1.4	2.5	3.1	2.0	3.1	1.0	2.1	2.9	0.4	0.4	2.9	10.9	6.2
304 A	S	0.0	12.1	10.8	20.0	20.0	6.2	20.0	20.0	17.2	20.0	11.9	16.6	50.0	20.0	16.6	2.2	14.2	17.9	20.0	20.0
305 A	V	1.1	2.3	3.3	1.2	0.3	5.4	1.2	0.0	0.9	1.1	2.8	1.1	3.9	1.1	1.4	1.2	0.9	0.0	0.8	0.8

307 100

Table 55 (continued)

Pos	WT	A	C	D	E	F	G	H	I	K	L	M	N	P	Q	R	S	T	V	W	Y
306 A	L	4.3	6.2	7.1	5.9	2.8	10.4	3.4	13.7	3.0	0.0	3.5	6.0	50.0	5.9	9.9	6.2	5.3	11.4	9.6	10.3
307 A	T	1.4	3.2	3.8	2.2	6.5	5.5	4.2	0.5	0.3	4.2	3.0	2.2	0.0	1.9	1.3	1.4	0.9	1.2	6.2	6.5
308 A	V	1.8	5.5	6.5	8.0	50.0	7.9	20.0	4.5	20.0	5.5	19.4	7.6	50.0	7.7	15.5	0.0	0.7	5.9	50.0	50.0
309 A	L	1.1	2.7	0.7	0.7	1.3	4.6	2.7	0.7	1.7	1.0	2.8	0.0	1.6	0.7	1.3	1.0	0.6	0.5	5.0	2.1
310 A	H	2.0	2.6	0.9	4.1	50.0	5.6	0.2	6.8	4.0	7.1	4.0	0.0	0.2	4.9	10.0	2.0	2.5	6.4	50.0	50.0
311 A	Q	0.6	2.5	1.6	1.6	2.5	4.3	1.6	1.4	0.6	0.9	2.9	0.9	1.7	0.8	0.9	0.0	0.3	2.2	4.6	2.0
312 A	N	5.4	5.1	5.9	1.3	20.0	0.0	20.0	10.0	3.4	4.8	3.3	7.1	50.0	2.7	3.9	4.1	3.2	11.9	20.0	20.0
313 A	W	4.6	6.4	5.5	5.6	1.1	10.8	5.0	11.0	5.8	5.2	7.6	5.4	50.0	4.8	12.9	6.0	3.8	6.6	0.0	2.6
314 A	L	2.1	2.9	4.3	2.2	5.7	6.1	7.9	5.4	0.7	0.0	1.7	2.3	50.0	1.6	1.6	3.0	4.7	6.3	8.0	6.0
315 A	D	0.3	1.4	1.5	0.1	3.3	4.2	1.9	1.8	0.8	0.5	1.8	0.6	50.0	0.0	0.7	0.0	0.9	2.4	6.2	3.7
316 A	G	50.0	50.0	50.0	50.0	50.0	0.0	50.0	50.0	50.0	50.0	50.0	50.0	50.0	50.0	50.0	50.0	50.0	50.0	50.0	50.0
317 A	K	0.0	14.0	18.4	17.9	50.0	5.0	50.0	20.0	8.5	12.5	12.7	20.0	15.9	17.2	13.5	2.8	9.2	20.0	50.0	50.0
318 A	E	2.0	3.0	2.7	1.7	2.7	6.7	2.6	0.0	1.1	1.6	1.3	1.7	20.0	1.4	2.6	2.2	1.3	0.0	6.1	9.5
319 A	Y	2.9	4.4	3.9	3.4	0.0	8.8	1.8	20.0	0.5	5.2	0.7	3.2	50.0	3.1	5.6	3.4	3.6	20.0	20.0	0.2
320 A	K	2.3	3.1	3.0	2.7	20.0	7.8	20.0	9.4	0.0	0.6	2.7	1.3	50.0	2.4	1.9	3.3	3.3	7.2	20.0	20.0
321 A	C	0.0	3.2	20.0	18.8	20.0	6.9	20.0	20.0	20.0	20.0	10.4	20.0	50.0	19.6	20.0	1.5	8.7	18.3	20.0	20.0
322 A	K	2.0	2.5	3.5	2.8	2.7	6.4	2.1	0.2	0.1	1.2	2.7	2.7	50.0	2.1	0.0	2.3	1.6	0.9	14.5	2.8
323	V	1.5	2.8	7.3	11.	20.	8.1	20.	6.0	9.6	20.	4.9	8.5	50.	13.	20.	2.8	1.6	0.0	20.	20.

A					9	0		0			0			0	6	0				0	0
324 A	S	2.0	2.1	0.6	0.0	1.9	4.9	3.9	1.5	2.8	0.7	1.9	0.9	50.0	0.8	2.9	2.7	1.9	2.1	3.8	2.5
325 A	N	2.8	3.9	8.4	3.0	20.0	8.3	20.0	0.0	7.7	20.0	6.2	1.6	13.4	0.5	20.0	3.1	0.1	1.3	20.0	20.0
326 A	K	1.0	2.7	3.0	1.6	3.7	4.1	3.1	3.2	1.7	2.4	3.7	1.2	0.0	0.6	1.4	1.0	1.9	2.6	5.6	3.6
327 A	A	0.9	2.8	5.8	3.1	20.0	6.3	16.7	14.7	2.8	20.0	2.5	5.3	20.0	1.3	4.1	0.0	5.2	13.7	20.0	20.0
328 A	L	6.0	6.3	7.0	4.1	50.0	8.6	20.0	50.0	5.7	0.0	7.1	6.0	50.0	3.7	8.2	6.6	50.0	50.0	20.0	50.0
329 A	P	1.0	2.5	0.9	0.6	4.0	3.4	3.3	1.7	1.9	2.5	3.6	0.0	0.3	0.7	1.5	0.1	1.1	1.1	6.2	3.6
330 A	A	0.9	2.0	1.3	0.7	3.4	3.8	3.0	2.0	1.4	2.0	3.4	0.0	20.0	0.6	1.2	0.2	0.6	1.9	7.0	3.4
331 A	P	50.0	50.0	50.0	50.0	50.0	0.0	50.0	50.0	50.0	50.0	50.0	50.0	50.0	50.0	50.0	50.0	50.0	50.0	50.0	50.0
332 A	I	1.9	3.7	4.6	1.7	5.0	7.0	1.9	3.8	1.8	0.0	2.5	3.9	20.0	0.8	2.4	2.3	2.6	4.4	20.0	5.9
333 A	E	0.0	3.1	3.2	0.8	4.1	4.4	4.2	16.9	3.6	2.8	2.8	2.5	1.6	1.3	3.2	1.3	1.4	7.7	4.0	4.8
334 A	K	1.7	2.9	2.5	0.0	1.0	6.1	3.3	1.0	1.5	0.5	3.5	1.5	4.4	0.1	2.7	2.2	0.9	1.3	4.9	1.8
335 A	T	0.5	3.2	4.5	2.7	4.2	4.9	4.1	20.0	2.1	3.1	3.0	1.2	0.0	2.3	2.8	1.4	1.4	7.3	5.1	4.5
336 A	I	1.2	1.6	5.0	1.5	20.0	6.1	16.8	0.7	3.4	7.8	2.5	3.2	20.0	2.8	1.4	0.7	0.6	0.0	20.0	20.0
337 A	S	4.8	4.8	7.5	11.5	10.1	0.0	5.5	50.0	9.9	7.0	7.9	5.0	50.0	11.4	12.7	4.5	2.3	50.0	19.3	10.6
338 A	K	1.0	2.7	2.3	2.2	4.6	5.9	2.4	50.0	0.0	2.1	1.9	1.0	50.0	1.5	0.9	0.7	10.3	50.0	5.4	4.9
339 A	A	1.0	2.5	0.8	1.1	4.4	3.7	3.7	2.1	1.8	2.6	3.6	0.0	0.8	0.6	1.6	0.6	0.9	2.4	6.8	3.8
340 A	K	1.3	2.4	2.3	2.0	1.7	4.1	2.3	1.9	0.0	2.3	1.8	1.0	1.9	0.9	1.3	0.5	0.8	1.7	4.9	2.4

Table 55 (continued)

Pos	WT	A	C	D	E	F	G	H	I	K	L	M	N	P	Q	R	S	T	V	W	Y
232 B	P	1.3	3.2	2.2	2.2	4.1	2.9	3.6	1.8	2.1	2.8	3.9	1.1	0.0	1.1	1.6	0.7	1.4	3.0	6.2	4.1
233 B	E	0.5	2.2	1.7	0.5	2.6	3.7	2.9	4.4	1.4	1.1	3.2	0.6	2.7	0.4	1.6	0.0	1.2	6.9	5.5	2.6
234 B	L	2.9	4.0	4.8	4.9	2.0	6.1	0.8	1.5	0.0	1.9	2.7	2.6	20.0	3.6	1.2	3.1	2.5	3.4	13.4	0.5
235 B	L	0.6	2.3	2.4	0.9	5.7	4.9	1.4	3.7	0.0	0.0	1.9	1.9	17.3	0.6	1.4	0.8	0.7	5.2	7.8	5.3
236 B	G	3.6	2.5	5.1	11.8	6.8	0.0	2.8	20.0	5.0	20.0	4.5	3.5	50.0	5.5	19.9	2.6	20.0	20.0	20.0	14.1
237 B	G	20.0	50.0	50.0	50.0	50.0	0.0	50.0	50.0	50.0	50.0	50.0	50.0	50.0	50.0	50.0	50.0	50.0	50.0	50.0	50.0
238 B	P	3.5	4.7	8.5	4.2	20.0	9.8	20.0	0.0	5.6	9.6	4.6	8.1	1.3	5.8	20.0	4.9	4.4	1.3	20.0	20.0
239 B	S	1.0	2.5	3.4	2.0	7.2	5.7	3.1	3.1	0.6	0.0	2.0	1.9	50.0	1.7	1.1	1.5	1.5	5.2	20.0	5.2
240 B	V	0.1	2.3	7.0	11.9	20.0	6.5	20.0	8.1	12.7	20.0	12.0	7.6	0.0	11.6	20.0	1.2	1.9	0.8	20.0	20.0
241 B	F	0.0	2.0	1.4	0.8	1.0	4.0	2.0	6.5	1.1	0.6	2.3	0.2	50.0	0.3	1.5	0.1	0.9	5.7	4.1	1.1
242 B	L	2.2	3.3	6.5	6.6	6.9	7.9	4.3	0.0	8.7	3.9	4.8	5.3	0.0	9.1	6.8	2.9	1.1	0.5	20.0	8.7
243 B	F	0.8	2.6	1.9	1.7	0.8	4.9	2.0	3.6	1.2	0.8	2.5	0.0	50.0	1.6	2.7	0.1	1.8	3.9	4.3	1.0
244 B	P	1.1	2.1	4.0	1.1	11.9	3.5	5.4	20.0	1.4	3.2	3.0	2.0	1.8	1.2	1.3	0.0	19.6	20.0	9.1	11.0
245 B	P	3.2	20.0	20.0	20.0	20.0	8.6	20.0	20.0	20.0	20.0	20.0	20.0	0.0	20.0	20.0	6.0	20.0	50.0	20.0	20.0
246 B	K	0.5	2.6	1.4	1.2	2.1	4.4	1.6	0.6	0.9	1.4	2.5	0.2	0.3	0.2	0.3	0.1	0.0	2.0	4.9	2.4
247 B	P	0.8	2.5	0.7	1.0	3.6	3.9	2.6	6.2	1.8	2.1	2.9	0.3	0.0	0.8	1.5	0.3	0.7	9.5	6.6	3.4
248 B	K	0.2	2.2	0.2	0.6	2.2	4.1	2.5	2.4	1.7	1.0	2.2	0.0	1.3	0.8	1.7	0.5	0.7	2.8	4.7	2.3
249	D	2.8	3.3	0.0	4.6	10.	8.2	6.5	50.	4.6	6.2	4.4	0.5	50.	4.7	6.3	3.5	6.1	50.	20.	7.2

Samsung Bioepis Exhibit No. 1002
Page 11186

B						1			0					0					0	0	
250 B	T	0.0	2.2	4.9	2.8	20.0	6.3	20.0	2.2	4.3	3.2	3.0	9.2	50.0	3.4	4.9	1.3	2.3	3.1	20.0	20.0
251 B	L	0.0	2.4	1.6	1.2	5.6	3.6	2.2	7.4	1.2	0.6	2.3	0.5	50.0	0.6	1.8	0.4	2.5	8.7	8.2	5.9
252 B	M	1.3	2.4	0.8	0.0	1.8	5.7	2.3	0.6	1.6	0.6	2.5	1.0	50.0	1.0	1.6	1.5	1.3	0.8	5.1	1.6
253 B	I	1.6	3.0	2.0	1.2	3.7	4.5	3.5	2.9	0.8	2.4	2.4	1.1	1.0	0.0	1.5	1.2	1.4	3.4	4.4	3.6
254 B	S	1.0	1.5	0.8	0.6	3.8	3.8	3.2	0.5	1.9	2.5	3.1	0.3	6.2	0.5	1.7	0.0	0.1	1.1	5.5	3.7
255 B	R	0.9	2.0	2.0	1.7	0.0	5.4	1.4	20.0	1.0	1.6	1.3	0.8	50.0	1.4	1.1	1.5	20.0	20.0	3.7	0.8
256 B	T	0.6	2.0	1.8	1.1	2.5	3.7	1.9	1.6	1.0	1.4	2.2	0.0	1.2	0.5	0.1	0.8	1.2	1.2	5.5	2.4
257 B	P	2.5	20.0	20.0	20.0	50.0	9.0	50.0	20.0	20.0	20.0	20.0	20.0	0.0	20.0	20.0	4.8	20.0	20.0	50.0	50.0
258 B	E	1.5	2.4	2.7	1.4	2.7	6.4	4.2	0.0	0.2	5.4	2.4	1.1	50.0	1.3	2.5	2.2	1.1	1.0	19.1	3.0
259 B	V	2.9	4.2	6.3	5.2	20.0	9.3	20.0	0.0	8.1	8.9	5.5	5.6	50.0	6.2	20.0	4.5	2.5	0.0	20.0	20.0
260 B	T	0.0	1.6	5.3	1.9	20.0	4.9	20.0	0.6	1.1	2.8	1.4	3.9	0.2	2.3	2.6	0.4	0.1	2.7	20.0	20.0
261 B	C	0.0	10.0	20.0	20.0	20.0	2.6	20.0	20.0	20.0	20.0	20.0	20.0	20.0	20.0	20.0	2.0	16.6	20.0	20.0	20.0
262 B	V	2.1	2.4	2.7	2.4	8.1	7.2	3.8	1.8	3.5	8.6	3.4	2.7	50.0	3.2	4.8	2.9	1.9	0.0	14.7	9.1
263 B	V	2.2	3.7	4.7	11.2	20.0	9.1	20.0	15.0	13.7	2.8	20.0	5.4	50.0	13.0	20.0	3.6	2.1	0.0	20.0	20.0
264 B	V	2.1	3.0	4.6	2.7	8.6	6.8	6.6	0.0	1.8	1.8	3.7	3.6	10.1	3.0	2.2	2.6	2.2	1.0	12.7	20.0
265 B	D	4.5	5.2	4.8	4.7	5.0	0.0	3.8	8.5	1.8	2.6	4.1	1.8	50.0	4.5	5.3	4.5	6.0	9.2	12.2	5.6
266 B	V	5.3	5.5	7.2	12.7	20.0	12.0	20.0	2.1	20.0	20.0	20.0	5.7	50.0	18.3	20.0	5.9	4.7	0.0	50.0	50.0
267 B	S	2.8	4.3	6.2	3.8	0.0	7.4	1.0	50.0	1.0	0.3	3.2	3.2	0.5	1.5	0.8	3.3	11.6	50.0	6.3	50.0

104

311

Table 55 (continued)

Pos	WT	A	C	D	E	F	G	H	I	K	L	M	N	P	Q	R	S	T	V	W	Y
268 B	H	2.6	3.7	5.1	4.1	4.9	6.0	1.8	2.6	0.0	2.5	3.8	2.6	3.4	2.1	1.8	2.5	3.8	2.7	7.8	5.5
269 B	E	0.4	2.4	1.7	0.8	2.8	3.7	2.6	1.0	1.0	1.6	3.0	0.0	12.8	0.5	0.7	0.3	0.7	0.6	5.1	2.7
270 B	D	0.0	1.6	1.1	7.3	4.8	4.3	2.6	20.0	3.8	14.5	3.8	1.2	5.9	6.3	2.1	0.3	1.9	5.4	16.3	5.6
271 B	P	1.1	3.3	5.6	3.4	4.1	5.5	4.2	20.0	1.9	3.6	3.9	3.3	7.4	2.7	0.0	1.5	2.2	5.2	4.8	4.4
272 B	Q	0.9	1.9	1.0	0.6	3.0	3.9	2.9	1.5	1.7	2.2	3.5	0.6	4.9	0.0	1.4	0.2	0.6	1.4	3.9	3.2
273 B	V	3.5	4.8	6.2	8.3	20.0	9.2	20.0	4.6	8.4	3.1	3.5	7.4	50.0	10.6	20.0	2.0	0.0	4.8	20.0	20.0
274 B	K	0.1	1.6	0.4	0.9	1.7	3.8	1.8	1.9	0.4	0.5	2.4	0.3	15.6	0.1	0.0	0.0	0.2	1.6	2.2	1.9
275 B	F	5.7	7.0	8.4	9.2	0.0	11.2	3.5	9.2	7.9	5.7	5.1	7.0	4.1	9.7	12.3	6.9	4.5	3.3	10.3	5.0
276 B	N	0.0	6.2	6.9	6.4	20.0	4.7	12.1	20.0	9.3	10.0	7.4	3.8	50.0	6.4	9.2	2.8	20.0	20.0	20.0	20.0
277 B	W	8.3	10.0	10.6	9.2	2.6	14.2	7.4	12.7	6.7	7.4	6.4	10.8	6.8	9.3	11.9	9.7	8.0	14.4	0.0	15.9
278 B	Y	0.0	2.3	17.4	4.0	50.0	5.1	50.0	20.0	2.8	20.0	2.1	12.6	11.0	4.4	2.0	0.8	2.5	19.8	20.0	4.2
279 B	V	3.1	3.5	4.2	2.9	20.0	8.5	13.9	0.4	0.0	2.9	2.0	3.4	20.0	1.4	4.0	4.2	2.4	1.2	20.0	20.0
280 B	D	0.5	3.0	2.1	1.5	6.7	3.1	4.7	12.6	2.9	1.6	2.9	1.6	20.0	1.4	3.1	0.0	2.7	5.5	8.1	7.3
281 B	G	5.6	5.8	5.5	4.8	7.9	0.0	7.2	6.5	5.3	5.7	7.1	3.4	50.0	4.0	5.3	3.6	3.2	6.4	10.3	7.6
282 B	V	0.4	1.9	1.1	0.6	2.9	4.1	2.1	1.3	1.0	1.4	2.9	0.2	50.0	0.0	0.7	0.0	0.4	0.7	6.1	2.8
283 B	E	0.6	1.9	4.3	1.7	6.7	4.2	5.2	2.9	0.5	4.4	0.3	2.5	0.0	1.5	1.6	1.0	1.5	3.9	7.9	6.7
284 B	V	0.4	2.4	2.5	1.1	20.0	5.9	20.0	1.1	1.2	6.2	0.8	2.4	50.0	1.5	3.3	0.0	1.5	1.8	20.0	20.0
285	H	1.3	2.4	2.1	1.7	2.4	3.4	1.2	1.8	0.7	2.3	2.7	0.0	1.6	0.9	0.8	0.5	0.4	2.0	5.8	2.4

B																				
286 B	N	1.2	2.7	1.0	1.1	3.0	3.1	2.6	0.8	2.0	1.9	2.9	0.0	50.0	0.4	1.6	1.1	0.5	2.9	4.9	3.0
287 B	A	2.5	4.4	6.1	7.5	0.0	8.2	3.0	10.2	5.1	16.5	4.5	0.3	12.3	8.1	9.1	4.1	3.3	7.1	3.4	0.8
288 B	K	0.4	1.9	1.9	0.0	2.9	3.5	2.9	2.5	1.8	2.1	2.5	0.9	15.4	0.6	1.1	0.2	0.9	3.8	5.9	2.7
289 B	T	0.1	1.5	3.7	1.4	2.7	3.9	2.6	1.8	0.0	2.2	1.6	1.5	1.8	1.1	1.7	0.0	0.4	2.3	3.4	2.5
290 B	K	0.9	1.8	0.8	0.5	2.4	0.8	2.7	3.0	1.3	1.3	2.6	0.2	50.0	0.7	1.5	0.0	0.6	2.9	5.0	2.7
291 B	P	1.2	2.1	2.5	0.5	3.9	4.6	3.4	0.7	0.0	3.4	1.5	1.1	0.6	0.1	1.1	1.1	0.9	1.5	3.2	2.6
292 B	R	0.8	2.6	3.3	1.2	4.9	3.6	6.8	3.1	2.0	2.4	2.2	2.2	16.6	1.5	1.8	0.1	0.0	3.2	7.6	5.2
293 B	E	0.0	3.0	4.1	2.8	7.3	3.6	5.8	5.8	2.6	4.5	3.2	2.2	1.3	2.2	2.5	0.0	1.2	7.8	7.0	6.9
294 B	E	2.5	3.3	3.9	2.3	8.3	6.8	4.4	5.6	3.6	2.3	3.7	4.1	0.0	3.3	5.0	2.1	2.9	5.0	6.7	11.9
295 B	Q	1.1	2.2	1.9	0.6	3.8	2.8	3.1	8.0	1.4	2.2	3.4	1.0	0.4	0.4	1.1	0.0	3.9	6.6	6.1	3.5
296 B	Y	1.5	2.7	1.2	1.2	4.1	4.1	3.5	1.1	1.8	2.7	3.5	0.0	20.0	0.6	1.9	1.2	1.4	1.3	6.4	4.0
297 B	N	3.9	4.5	10.1	6.0	15.5	7.3	16.7	6.6	0.0	5.1	4.6	7.3	20.0	4.4	4.2	3.6	4.1	7.9	18.0	15.0
298 B	S	1.7	2.5	3.5	2.5	2.5	3.7	2.4	3.0	0.0	1.8	2.3	0.4	50.0	1.2	1.0	0.9	2.2	3.3	5.5	2.0
299 B	T	0.0	2.7	7.2	11.1	20.0	4.8	20.0	7.5	6.9	20.0	7.1	4.8	50.0	9.8	17.9	0.3	1.3	5.8	20.0	20.0
300 B	Y	3.8	5.2	8.0	4.3	20.0	8.6	20.0	12.2	0.0	4.3	3.2	6.5	50.0	4.0	3.8	4.3	3.6	9.1	20.0	6.4
301 B	R	1.2	1.8	2.3	1.1	20.0	5.8	11.3	5.2	0.3	5.0	2.0	1.6	14.1	0.6	0.4	1.8	1.1	0.0	17.9	20.0
302 B	V	3.5	4.8	5.5	3.7	0.2	9.6	1.1	0.5	2.6	3.5	2.5	4.7	9.6	4.1	0.6	4.3	2.0	0.0	20.0	0.2
303 B	V	0.2	0.0	0.1	1.0	20.0	5.0	13.3	5.1	1.7	10.4	1.9	2.0	8.6	2.0	4.7	0.6	0.5	1.3	20.0	20.0
304	S	1.5	2.3	8.2	20.	20.	7.6	20.	7.6	20.	20.	20.	6.3	50.	20.	20.	0.0	2.7	3.8	20.	20.

106

313



Samsung Bioepis Exhibit No. 1002
Page 11190

Table 55 (continued)

Pos	WT	A	C	D	E	F	G	H	I	K	L	M	N	P	Q	R	S	T	V	W	Y
304 B	S	1.5	2.3	8.2	20.0	20.0	7.6	20.0	7.6	20.0	20.0	20.0	6.3	50.0	20.0	20.0	0.0	2.7	3.8	20.0	20.0
305 B	V	0.1	1.2	3.3	1.1	20.0	4.6	20.0	3.2	1.1	11.0	1.5	1.8	50.0	0.6	2.0	0.6	0.0	0.7	20.0	20.0
306 B	L	4.7	6.8	6.3	4.3	10.4	11.1	7.8	4.2	3.0	0.0	3.8	5.7	13.4	4.4	14.1	5.5	4.3	6.0	20.0	12.1
307 B	T	1.5	3.0	2.7	1.7	4.1	5.2	3.0	1.6	1.9	3.1	3.4	1.7	0.0	1.7	1.9	1.5	1.4	2.0	4.4	4.3
308 B	V	0.0	0.6	7.6	20.0	20.0	6.6	20.0	20.0	16.1	15.1	20.0	12.4	50.0	20.0	20.0	1.2	3.6	4.3	20.0	20.0
309 B	L	1.4	3.0	2.2	1.1	3.0	6.0	3.5	20.0	2.4	1.7	3.6	0.2	0.0	1.6	2.3	1.8	14.3	20.0	5.1	3.3
310 B	H	2.4	2.9	2.7	4.9	20.0	6.8	4.4	4.8	3.1	15.0	3.4	0.0	2.3	4.6	7.0	1.8	1.6	3.8	20.0	20.0
311 B	Q	0.0	2.2	1.3	0.7	2.1	3.3	2.4	12.6	0.6	0.9	2.3	0.6	3.2	0.4	0.8	0.2	1.6	18.8	4.6	2.0
312 B	N	0.0	1.0	0.2	0.3	6.0	5.4	2.3	12.0	2.1	2.9	1.6	0.9	50.0	1.3	5.7	0.1	5.6	3.8	8.0	7.8
313 B	W	5.3	6.6	7.3	5.4	0.0	11.4	6.2	20.0	4.0	5.2	4.3	8.0	50.0	6.5	8.9	6.6	17.2	20.0	2.1	0.9
314 B	L	1.7	2.2	3.1	0.0	6.4	5.6	1.5	2.1	0.6	0.2	1.1	1.9	50.0	0.8	1.0	1.7	0.9	3.1	3.7	11.3
315 B	D	1.4	2.3	2.4	0.7	6.0	5.5	2.3	4.8	2.2	1.0	2.9	1.8	50.0	1.0	2.2	0.2	0.0	4.5	8.5	6.8
316 B	G	50.0	50.0	50.0	50.0	50.0	0.0	50.0	50.0	50.0	50.0	50.0	50.0	50.0	50.0	50.0	50.0	50.0	50.0	50.0	50.0
317 B	K	0.9	2.3	4.3	2.8	1.2	4.0	0.6	13.9	0.0	4.8	1.6	1.3	50.0	4.2	0.9	0.4	13.8	10.1	20.0	1.7
318 B	E	0.7	1.2	3.1	1.0	7.0	5.1	8.2	0.4	1.0	5.7	1.7	2.3	3.8	1.0	1.6	0.4	0.0	1.0	3.8	7.7
319 B	Y	6.5	7.1	8.5	8.8	0.0	12.5	3.9	3.1	5.2	5.4	8.4	7.2	50.0	9.0	13.7	7.2	5.8	3.9	20.0	1.7
320 B	K	3.1	4.3	7.3	4.3	20.0	8.6	15.0	1.4	0.0	11.6	3.6	6.6	50.0	2.9	2.4	4.0	3.3	2.0	20.0	20.0
321	C	0.0	6.5	20.	20.	20.	6.6	20.	20.	20.	20.	20.	20.	19.	20.	20.	3.1	11.	20.	20.	20.

B				0	0	0		0	0	0	0	0	0	7	0	0		2	0	0	0
322 B	K	2.3	3.2	3.5	1.8	20.0	7.9	20.0	1.1	0.6	4.9	3.7	2.2	50.0	0.9	0.3	3.3	1.6	0.0	20.0	20.0
323 B	V	4.0	4.6	6.9	8.1	20.0	10.6	20.0	9.0	17.1	7.9	8.1	10.5	50.0	8.7	20.0	5.6	4.6	0.0	20.0	20.0
324 B	S	1.3	3.0	1.4	0.0	2.1	6.0	4.4	1.3	2.4	0.6	2.7	2.2	50.0	1.3	3.6	1.5	1.6	1.8	3.6	2.4
325 B	N	3.4	5.1	9.0	4.7	20.0	8.2	20.0	16.6	16.6	20.0	20.0	0.0	50.0	6.3	20.0	4.6	8.8	17.8	20.0	20.0
326 B	K	0.3	2.1	2.0	0.9	1.0	3.5	2.0	2.9	0.9	2.9	2.8	0.1	4.4	0.0	1.1	0.1	3.2	2.1	5.2	0.7
327 B	A	1.9	3.3	4.7	3.5	20.0	7.0	20.0	20.0	0.3	0.0	1.9	1.9	20.0	3.0	2.3	3.3	20.0	20.0	20.0	20.0
328 B	L	3.7	3.6	3.8	4.4	50.0	8.4	7.0	50.0	3.8	0.0	2.6	4.0	50.0	4.2	8.7	4.8	2.9	12.3	50.0	50.0
329 B	P	3.3	8.5	20.0	20.0	50.0	8.0	16.5	50.0	18.5	20.0	14.7	20.0	0.0	20.0	20.0	1.4	17.1	16.4	50.0	50.0
330 B	A	0.5	2.0	2.8	0.5	2.4	3.9	1.2	4.0	0.0	2.0	2.1	0.8	20.0	0.0	0.5	0.8	0.2	4.6	8.2	2.6
331 B	P	1.7	3.8	6.4	10.1	20.0	4.7	11.0	10.1	7.5	20.0	5.5	5.0	0.0	7.6	7.4	2.6	20.0	10.1	17.6	20.0
332 B	I	1.7	2.9	1.3	1.7	14.8	7.0	13.9	1.7	3.1	0.0	1.7	1.7	50.0	1.8	5.3	2.0	1.9	3.4	20.0	20.0
333 B	E	1.9	2.5	1.9	0.0	8.9	5.9	8.2	1.2	3.0	6.4	3.4	2.0	3.1	1.1	2.3	1.8	1.6	1.6	8.9	9.3
334 B	K	2.9	3.9	3.7	2.6	20.0	8.3	12.1	1.5	2.6	5.3	3.7	4.3	50.0	1.9	0.0	3.4	1.8	1.4	9.9	20.0
335 B	T	0.0	2.1	7.2	7.0	4.2	0.4	3.3	17.3	6.5	7.7	5.2	5.5	3.5	7.0	5.7	0.2	5.5	11.5	5.2	3.1
336 B	I	0.5	1.6	2.1	0.7	20.0	5.0	6.1	0.0	1.3	5.3	2.1	1.8	20.0	0.6	3.1	1.1	0.8	0.7	19.4	20.0
337 B	S	1.1	2.1	4.0	2.0	3.1	3.2	2.0	50.0	0.0	1.6	0.9	1.9	15.8	1.1	2.2	1.4	50.0	50.0	5.5	3.9
338 B	K	0.6	2.3	3.0	3.0	9.4	5.3	10.6	2.2	1.1	0.0	3.2	1.5	16.2	2.7	2.7	1.1	2.8	3.5	8.1	11.0
339 B	A	1.1	2.4	1.2	0.8	4.3	3.6	3.7	2.6	1.8	2.6	3.5	0.0	2.3	0.5	1.3	0.2	0.8	2.0	6.7	3.8
340	K	0.9	2.0	1.4	0.8	3.0	3.4	2.9	2.1	0.8	2.5	2.3	0.2	1.0	0.1	1.2	0.0	0.5	2.0	5.5	3.2

316 109

B

SPA™ technology; 1IIS template structure; - carbohydrate, no floated positions

Samsung Bioepis Exhibit No. 1002
Page 11193

Table 56

Pos	WT	A	C	D	E	F	G	H	I	K	L	M	N	P	Q	R	S	T	V	W	Y
239 A	S	0.2	4.6	2.7	0.0	20.0	4.6	14.5	11.0	1.9	0.3	2.0	1.9	8.1	1.4	2.6	0.4	5.7	11.6	20.0	20.0
240 A	V	1.5	2.4	2.4	6.9	20.0	7.4	20.0	5.1	9.9	5.9	5.5	2.4	1.1	12.3	13.1	2.6	0.5	0.0	20.0	20.0
263 A	V	2.3	2.8	6.3	16.5	20.0	8.8	20.0	9.6	7.3	7.3	15.3	4.8	50.0	16.4	17.4	2.8	1.4	0.0	20.0	20.0
264 A	V	1.8	3.1	2.6	1.8	0.0	6.3	1.9	0.6	2.4	0.8	2.7	2.1	1.6	2.3	2.7	2.3	1.1	0.5	3.5	0.0
266 A	V	4.9	5.2	6.9	12.3	20.0	11.1	20.0	0.8	11.9	20.0	8.5	6.6	50.0	12.5	20.0	6.1	3.7	0.0	20.0	20.0
296 A	Y	3.4	2.7	1.1	0.0	50.0	0.7	50.0	5.0	3.6	3.5	4.2	0.9	50.0	0.9	2.9	2.2	5.3	5.5	16.1	18.4
299 A	T	0.7	3.2	9.9	10.4	20.0	6.2	20.0	10.7	6.7	20.0	4.1	12.9	50.0	5.9	11.8	0.0	2.5	8.2	13.3	20.0
325 A	N	2.5	3.5	7.7	2.5	20.0	8.0	20.0	0.0	6.1	20.0	7.8	1.2	12.8	0.8	20.0	2.7	0.0	1.0	20.0	20.0
328 A	L	6.1	6.3	7.1	4.2	50.0	8.8	20.0	50.0	4.6	0.0	7.2	6.1	50.0	4.0	8.3	6.7	50.0	50.0	20.0	50.0
330 A	A	0.9	1.8	1.2	0.0	2.5	4.0	2.9	1.7	1.2	1.6	2.8	0.0	20.0	0.4	1.0	0.2	0.5	1.7	6.2	2.9
332 A	I	1.9	3.8	4.6	1.3	5.1	7.1	1.8	3.4	0.2	0.0	2.6	3.8	20.0	0.6	2.4	2.3	2.5	4.2	20.0	5.6
239 B	S	1.0	2.4	3.5	2.0	6.7	5.6	2.9	3.1	0.3	0.0	1.9	2.1	50.0	1.5	1.8	1.4	1.4	5.2	20.0	4.2
240 B	V	0.3	2.4	6.9	11.7	20.0	6.6	20.0	8.3	12.3	20.0	14.2	7.4	0.0	13.4	20.0	1.3	1.9	0.9	20.0	20.0
263 B	V	2.4	3.9	4.5	12.5	20.0	9.3	20.0	15.8	17.1	2.1	20.0	5.3	50.0	13.8	20.0	3.9	2.2	0.0	20.0	20.0
264 B	V	2.2	3.2	4.8	2.7	7.4	6.9	6.0	0.0	1.9	1.9	3.8	3.7	9.9	3.1	2.2	2.7	2.4	0.9	14.7	18.2
266 B	V	5.4	5.5	7.5	13.2	20.0	12.1	20.0	2.6	20.0	20.0	20.0	5.4	50.0	16.1	20.0	6.0	4.7	0.0	50.0	50.0
296 B	Y	1.5	2.7	1.3	1.2	4.0	4.1	3.6	1.1	1.9	2.6	3.5	0.0	20.0	0.7	1.8	1.1	1.4	1.3	6.5	4.2
299	T	0.0	2.2	7.5	10.	20.	4.8	20.	7.7	5.8	20.	10.	5.1	50.	10.	18.	0.3	1.1	5.4	20.	20.

Samsung Bioepis Exhibit No. 1002
Page 11194

B					2	0		0			0	3		0	2	4				0	0
325 B	N	3.4	5.1	8.6	5.0	20.0	8.2	20.0	16.7	20.0	20.0	20.0	0.0	19.7	6.3	20.0	4.6	8.6	18.2	20.0	20.0
328 B	L	3.6	3.5	3.8	3.9	50.0	8.3	7.0	50.0	2.9	0.0	1.9	3.8	50.0	3.4	8.4	4.7	2.9	12.5	50.0	50.0
330 B	A	0.7	2.1	2.9	0.7	2.7	4.0	1.4	4.8	0.0	2.2	2.3	0.8	20.0	0.2	0.8	1.1	0.2	4.7	7.8	3.2
332 B	I	1.8	2.9	1.2	1.8	13.5	7.0	9.9	1.7	3.2	0.0	1.7	1.9	50.0	1.2	5.4	2.0	2.0	3.3	20.0	20.0

SPA™ technology; D129G 1IIS template structure; + carbohydrate

Table 57

Pos	WT	A	C	D	E	F	G	H	I	K	L	M	N	P	Q	R	S	T	V	W	Y
239 A	S	1.2	3.5	1.7	0.0	20.0	5.8	11.0	6.6	2.9	3.9	3.9	2.7	8.5	1.3	2.7	0.6	3.5	5.4	20.0	20.0
240 A	V	1.2	2.4	6.0	14.0	20.0	7.1	20.0	6.7	9.4	10.1	7.5	4.4	1.8	14.8	20.0	2.0	0.4	0.0	20.0	20.0
263 A	V	0.0	0.4	1.0	8.7	20.0	6.9	4.4	11.7	4.9	16.0	19.2	0.8	50.0	11.7	20.0	1.4	0.1	1.0	20.0	20.0
264 A	V	2.9	3.7	6.3	2.8	11.6	7.6	13.2	0.0	3.2	3.4	4.1	4.2	7.1	2.9	3.4	3.1	1.9	0.8	12.8	16.3
266 A	V	4.8	5.9	6.8	9.5	50.0	10.3	20.0	3.5	12.7	12.2	12.7	4.1	50.0	11.9	11.9	5.2	2.9	0.0	50.0	50.0
296 A	Y	0.8	2.0	1.5	0.1	0.2	3.4	1.5	6.6	1.7	0.6	1.8	1.2	2.6	0.0	1.6	0.2	2.5	5.6	3.8	0.0
299 A	T	1.9	3.7	7.5	0.0	20.0	7.9	14.2	2.9	0.8	3.4	4.4	2.3	50.0	1.9	3.0	3.5	4.1	3.3	20.0	20.0
325 A	N	1.0	1.4	3.1	2.8	20.0	7.4	20.0	8.5	7.7	10.4	6.1	2.8	15.4	5.4	20.0	0.0	0.1	3.8	20.0	20.0
328 A	L	2.5	5.3	4.0	1.9	50.0	7.5	20.0	20.0	1.6	0.2	0.0	2.9	50.0	0.4	4.8	3.2	2.9	7.0	50.0	50.0
330 A	A	0.9	2.1	1.8	1.2	2.4	2.7	3.1	3.1	1.4	2.1	3.5	0.5	20.0	0.8	1.0	0.0	0.5	2.9	5.2	2.9
332 A	I	2.9	3.7	3.9	0.9	6.1	7.8	2.5	0.0	2.7	0.8	2.8	3.5	50.0	0.7	3.7	2.9	2.5	1.0	8.1	6.9
239 B	S	1.9	3.1	3.0	1.9	1.5	6.2	2.3	14.1	1.8	1.4	2.9	1.8	0.0	1.9	3.2	1.9	2.3	7.7	6.6	15.8
240 B	V	0.5	1.7	5.0	13.3	20.0	6.6	20.0	1.2	12.4	12.1	8.8	4.6	6.3	20.0	20.0	1.0	0.2	0.0	20.0	20.0
263 B	V	2.9	3.2	6.4	18.2	10.1	9.2	6.9	12.8	6.0	20.0	10.3	5.7	50.0	17.5	20.0	3.2	2.2	0.0	20.0	20.0
264 B	V	2.9	3.6	4.4	3.0	8.8	7.1	6.2	0.0	2.3	1.9	4.5	3.4	1.7	3.2	3.5	3.5	2.0	0.9	12.0	16.4
266 B	V	4.4	4.6	2.6	6.6	20.0	10.7	20.0	0.0	4.9	1.7	8.5	5.6	50.0	6.0	12.4	5.3	4.6	1.5	20.0	50.0
296 B	Y	0.0	7.1	6.7	7.2	20.0	0.1	18.6	50.0	7.0	2.7	6.6	6.8	50.0	7.2	9.3	2.3	50.0	50.0	20.0	14.1
299	T	0.0	3.2	10.	6.0	20.	5.5	20.	15.	3.2	5.9	4.4	6.4	50.	5.7	9.4	1.2	1.4	13.	20.	20.

113

320

B				4		0		0	9					0					7	0	0
325 B	N	1.4	2.5	5.0	0.0	20.0	7.0	20.0	20.0	1.0	2.2	1.0	0.3	1.9	1.1	20.0	2.6	5.1	20.0	20.0	20.0
328 B	L	0.4	1.3	5.6	0.0	50.0	4.5	50.0	50.0	1.9	2.4	2.4	8.3	50.0	0.8	16.4	1.0	1.2	50.0	50.0	50.0
330 B	A	0.6	1.4	2.5	0.9	3.1	2.5	1.2	20.0	0.0	2.4	2.1	0.3	20.0	0.4	0.6	0.0	4.0	20.0	13.5	3.4
332 B	I	4.3	5.3	5.7	0.0	11.4	9.3	4.3	2.5	5.8	2.0	4.0	6.5	17.9	3.7	5.9	4.6	4.2	3.7	20.0	11.6

SPA™ technology; D129G 1IIX template structure; + carbohydrate

Table 58

Pos	WT	A	C	D	E	F	G	H	I	K	L	M	N	P	Q	R	S	T	V	W	Y
239 A	S	1.2	2.3	2.2	1.8	7.9	5.5	7.6	0.5	0.2	1.8	2.6	1.4	0.9	1.3	1.9	1.5	0.8	0.0	8.6	9.6
240 A	V	0.7	2.9	6.8	4.3	20.0	6.5	20.0	0.0	10.7	20.0	3.1	9.1	2.1	7.7	20.0	1.4	1.1	2.4	20.0	20.0
263 A	V	1.7	2.9	4.6	18.8	20.0	8.4	5.8	15.1	2.3	14.5	2.1	3.2	50.0	20.0	15.0	3.6	1.2	0.0	20.0	20.0
264 A	V	2.7	3.3	3.6	1.5	13.9	6.7	5.9	0.0	2.3	4.9	3.7	3.2	1.9	2.5	3.0	3.0	2.5	0.7	19.9	19.0
266 A	V	3.5	3.5	5.7	12.4	20.0	10.0	20.0	5.7	6.3	7.8	7.4	5.2	50.0	16.6	20.0	4.2	1.7	0.0	20.0	50.0
296 A	Y	2.6	50.0	50.0	50.0	50.0	0.0	50.0	50.0	18.5	18.0	50.0	50.0	50.0	50.0	50.0	50.0	50.0	50.0	50.0	13.6
299 A	T	0.2	0.7	6.6	1.2	20.0	5.6	9.6	1.6	0.8	1.5	1.8	4.8	50.0	1.0	9.2	0.0	0.0	1.6	20.0	20.0
325 A	N	3.1	3.6	7.3	2.4	20.0	7.7	20.0	20.0	20.0	10.0	13.1	3.6	50.0	0.0	20.0	4.0	9.7	20.0	20.0	20.0
328 A	L	0.6	0.0	1.5	5.4	50.0	1.6	50.0	50.0	3.1	4.2	9.6	1.4	50.0	6.9	9.6	0.6	0.1	50.0	50.0	50.0
330 A	A	1.9	2.5	4.1	2.8	4.5	4.1	3.0	3.2	1.0	2.7	3.5	2.1	20.0	2.4	2.6	1.3	0.0	3.9	7.6	5.3
332 A	I	2.3	3.5	2.2	0.8	20.0	6.8	9.6	0.0	3.4	0.2	2.6	2.8	14.5	3.3	4.6	2.6	1.3	0.9	10.5	20.0
239 B	S	1.4	3.6	2.5	1.4	16.8	5.8	6.2	5.0	2.5	1.4	2.0	3.8	0.3	0.5	2.4	0.0	1.6	5.3	20.0	19.5
240 B	V	0.0	2.6	12.8	18.6	20.0	5.7	20.0	12.7	10.4	20.0	8.5	15.1	3.1	20.0	20.0	1.0	0.2	2.4	20.0	20.0
263 B	V	1.1	2.4	3.6	20.0	20.0	7.8	17.7	11.8	4.5	20.0	6.3	3.3	50.0	20.0	20.0	3.2	1.2	0.0	20.0	20.0
264 B	V	3.3	4.0	5.0	2.9	14.2	7.5	4.8	0.0	2.6	3.6	4.6	3.5	1.7	3.1	4.1	3.9	2.9	1.3	6.9	20.0
266 B	V	2.9	3.3	4.9	11.3	50.0	9.5	20.0	20.0	20.0	7.9	15.0	4.5	50.0	4.9	20.0	1.9	0.0	3.6	50.0	50.0
296 B	Y	2.8	50.0	50.0	50.0	50.0	0.0	50.0	50.0	17.7	18.7	50.0	50.0	50.0	50.0	50.0	50.0	50.0	50.0	50.0	11.3
299	T	0.0	3.8	12.	9.2	20.	5.9	20.	7.3	4.8	3.2	4.3	8.0	50.	12.	8.8	0.2	2.1	4.4	20.	20.

115

322

B				6		0		0						0	3				0	0
325 B	N	0.3	2.0	5.5	2.2	50.0	6.1	20.0	0.0	10.5	15.5	14.6	1.3	10.0	2.4	20.0	2.3	2.0	1.0	20.0	50.0
328 B	L	5.4	5.7	7.3	4.4	50.0	9.8	20.0	50.0	2.5	0.0	5.1	5.9	50.0	2.8	7.4	6.1	6.4	50.0	50.0	50.0
330 B	A	0.6	1.4	3.2	1.3	3.9	3.2	2.7	4.0	1.3	3.7	3.1	0.7	20.0	0.6	1.3	0.0	0.4	4.2	8.2	3.6
332 B	I	1.9	3.1	2.7	1.7	5.2	6.9	3.1	0.4	1.3	0.0	1.9	2.6	7.7	1.3	2.2	2.3	1.6	2.0	10.4	5.6

SPA™ technology; D129G 1E4K template structure; + carbohydrate

Table 59

Pos	WT	A	C	D	E	F	G	H	I	K	L	M	N	P	Q	R	S	T	V	W	Y
239 A	S	1.4	2.6	3.1	1.0	20.0	5.7	4.8	3.4	2.0	1.2	2.6	1.6	4.8	0.0	2.1	1.3	2.1	3.3	13.8	19.6
240 A	V	2.9	3.5	3.7	4.6	20.0	8.2	10.8	0.0	9.1	3.2	5.4	3.1	4.8	5.5	17.5	4.0	1.8	1.2	20.0	20.0
263 A	V	3.6	4.9	6.2	8.7	20.0	9.9	20.0	3.7	4.2	0.5	6.7	6.1	50.0	9.5	20.0	5.1	3.6	0.0	20.0	20.0
264 A	V	1.8	2.8	3.3	2.0	2.9	6.2	3.1	0.0	2.4	0.8	3.0	2.4	6.1	1.4	2.8	2.4	1.9	0.8	10.2	2.2
266 A	V	4.4	5.2	4.9	7.1	20.0	10.6	20.0	1.0	12.1	4.8	9.1	4.6	50.0	7.9	12.6	5.8	3.5	0.0	20.0	20.0
296 A	Y	1.2	2.9	0.7	1.4	3.1	3.9	2.7	2.4	2.3	1.9	2.2	0.0	1.6	1.4	3.0	0.9	1.0	3.5	6.0	2.6
299 A	T	0.0	2.6	6.0	11.5	20.0	5.3	20.0	20.0	6.0	20.0	4.4	3.0	50.0	14.1	13.2	0.9	3.8	15.1	15.0	20.0
325 A	N	5.2	7.0	6.6	6.9	50.0	11.3	20.0	1.3	14.3	13.5	13.9	0.0	5.0	6.0	20.0	6.0	4.6	3.2	20.0	50.0
328 A	L	4.8	5.5	7.0	3.2	20.0	10.5	20.0	50.0	5.1	0.0	8.5	5.5	50.0	3.5	8.2	5.5	13.4	50.0	20.0	50.0
330 A	A	0.9	1.8	1.1	0.9	3.5	4.0	3.0	2.3	1.2	1.6	2.8	0.0	14.5	0.9	1.1	0.1	0.4	2.0	6.4	3.2
332 A	I	5.3	6.4	6.7	4.8	8.2	9.9	5.2	3.1	0.0	3.6	5.2	6.8	20.0	3.5	4.6	5.5	4.8	4.0	11.2	7.1
239 B	S	0.7	2.3	2.6	2.0	5.3	5.1	3.3	1.7	0.0	0.0	2.0	0.8	15.5	0.9	0.8	0.7	0.7	3.3	8.2	6.0
240 B	V	2.3	3.0	4.1	7.3	20.0	8.1	20.0	5.1	20.0	11.8	10.9	3.8	2.0	17.0	20.0	3.6	1.3	0.0	20.0	20.0
263 B	V	3.2	4.3	7.3	8.3	20.0	9.6	20.0	13.3	8.5	0.6	20.0	6.0	50.0	8.5	20.0	4.6	4.0	0.0	20.0	20.0
264 B	V	2.1	3.2	3.7	2.7	17.8	6.6	11.5	0.0	2.0	0.8	3.5	3.0	7.8	2.0	1.5	2.5	1.3	1.0	13.9	20.0
266 B	V	5.0	5.0	5.2	16.3	20.0	11.2	20.0	2.3	20.0	14.3	17.3	2.5	50.0	11.6	20.0	5.4	3.9	0.0	20.0	20.0
296 B	Y	0.9	2.3	1.0	0.5	2.7	3.7	2.5	1.2	1.3	2.1	3.0	0.0	7.0	0.4	1.1	0.3	0.8	1.8	6.0	2.4
299	T	1.1	2.2	7.6	5.4	20.	6.4	12.	1.8	3.9	17.	6.9	3.9	20.	4.6	10.	0.8	0.0	1.9	20.	20.

Samsung Bioepis Exhibit No. 1002
Page 11200

B						0		8			5			0		3				0	0
325 B	N	10.1	11.5	13.1	11.2	20.0	15.7	20.0	8.6	14.3	17.1	20.0	0.0	16.1	10.6	20.0	11.1	10.9	10.5	20.0	20.0
328 B	L	2.9	4.1	4.8	3.5	50.0	8.5	1.7	9.6	1.5	0.0	1.5	3.5	50.0	3.3	2.0	3.3	1.9	5.2	50.0	50.0
330 B	A	0.1	2.0	1.4	1.8	1.6	4.0	3.0	2.0	0.5	0.5	2.6	0.0	20.0	0.7	2.0	0.3	0.6	2.1	4.4	2.4
332 B	I	3.4	4.4	3.5	3.1	6.1	8.2	4.1	0.0	3.3	1.3	3.3	4.0	15.7	0.8	2.1	3.9	2.7	1.1	20.0	6.1

SPA™ technology; Fc/Fc□RIIb model template structure; - carbohydrate

118

325

[202] The results of the design calculations presented above in Tables 1 – 59 were used to construct a series of Fc variant libraries for experimental production and screening. Experimental libraries were designed in successive rounds of computational and experimental screening. Design of subsequent Fc libraries benefitted from feedback from prior libraries, and thus typically comprised combinations of Fc variants that showed favorable properties in the previous screen. The entire set of Fc variants that were constructed and experimentally tested is shown in Table 60. In this table, row 1 lists the variable positions, and the rows that follow indicate the amino acids at those variable positions for WT and the Fc variants. For example, variant 18 has the following four mutations: F241E, F243Y, V262T, and V264R. The variable position residues that compose this set of Fc variants are illustrated structurally in Figure 3, and are presented in the context of the human IgG1 Fc sequence in Figure 4.

Samsung Bioepis Exhibit No. 1002
Page 11202

Table 60

Position	234	235	239	240	241	243	244	245	247	262	263	264	265	266	267	269	296	297	298	299	313	325	326	327	328	329	330	332	333	334
WT	L	L	S	V	F	F	P	P	P	V	V	V	D	V	S	E	Y	N	S	T	W	N	K	A	L	P	A	I	E	K
1												A																		
2												L																		
3												I																		
4					W																									
5					L																									
6						W																								
7						L																								
8					L	L				I		I																		
9					W	W																								
10					W	W				A		A																		
11					L					I																				
12						L						I																		
13						L				I		W																		
14					Y	Y				T		T																		
15					E	R				E		R																		
16					E	Q				T		E																		
17					R	Q				T		R																		
18					E	Y				T		R																		
19																									M					
20																									E					
21																									F					
22																												E		
23																									M			E		
24							H																							
25								A																						
26									V																					
27																					F									
28							H	A	V																					
29									G																					
30												I																E		

Table 60 (continued)

Position	234	235	239	240	241	243	244	245	247	262	263	264	265	266	267	269	296	297	298	299	313	325	326	327	328	329	330	332	333	334
WT	L	L	S	V	F	F	P	P	P	V	V	V	D	V	S	E	Y	N	S	T	W	N	K	A	L	P	A	I	E	K
31					E	R				E		R																E		
32					E	Q				T		E																E		
33					R	Q				T		R																E		
34					E	Y				T		R																E		
35																			A											
36																			A									E		
37																			A										A	A
41			E																									E		
42			Q																									E		
43			E																											
44													G																	
45													N																	
46			E										G																	
47			E										N																	
48			E										Q																	
49																	E													
50																	Q													
51																			T											
52																			N											
53																				I										
54																								S						
55																								N						
56															Q									S						
57															L									S						
58																								L						
59																										F				
60																											L			
61																											Y			
62																												D		

121

328

Table 60 (continued)

Position	234	235	239	240	241	243	244	245	247	262	263	264	265	266	267	269	296	297	298	299	313	325	326	327	328	329	330	332	333	334
WT	L	L	S	V	F	F	P	P	P	V	V	V	D	V	S	E	Y	N	S	T	W	N	K	A	L	P	A	I	E	K
62																												D		
63																		S												
64																		D												
65																		S										E		
66																		D										E		
67																		E										E		
68													Y					D										E		
69													Y					D										E		
70													F					E										E		
71																									I			E		
72																									Q			E		
73																												N		
74																												Q		
75												T																		
76												F																		
77				I																										
78											I																			
79														I																
80																				A										
81																				S										
82																				V										
83																						Q								
84																						L								
85																						I								
86			D																											
87			N																											
88			F																											
89			D																									D		
90			D																									E		
91			D																									N		
92			D																									Q		

122

329

Table 60 (continued)

Position	234	235	239	240	241	243	244	245	247	262	263	264	265	266	267	269	296	297	298	299	313	325	326	327	328	329	330	332	333	334
WT	L	L	S	V	F	F	P	P	P	V	V	V	D	V	S	E	Y	N	S	T	W	N	K	A	L	P	A	I	E	K
93			E																									D		
94			E																									N		
95			E																									Q		
96			N																									D		
97			N																									E		
98			N																									N		
99			N																									Q		
100			Q																									D		
101			Q																									N		
102			Q																									Q		
103																							E							
104																	D													
105																	N													
106					Y	Y				T		T						D										E		
107																											Y	E		
108												I															Y	E		
109																											L	E		
110												I															L	E		
111	D																													
112	E																													
112	N																													
114	Q																													
115	T																													
116	H																													
117	Y																													
118	I																													
119	V																													
120	F																													
121		D																												
122		S																												

123

330

Table 60 (continued)

Position	234	235	239	240	241	243	244	245	247	262	263	264	265	266	267	269	296	297	298	299	313	325	326	327	328	329	330	332	333	334
WT	L	L	S	V	F	F	P	P	P	V	V	V	D	V	S	E	Y	N	S	T	W	N	K	A	L	P	A	I	E	K
123		N																												
124		Q																												
125		T																												
126		H																												
127		Y																												
128		I																												
129		V																												
130		F																												
131			T																											
132			H																											
133			Y																											
134				A																										
135				T																										
136				M																										
137											A																			
138											T																			
139											M																			
140												M																		
141												Y																		
142														A																
143														T																
144														M																
145																H														
146																Y														
147																F														
148																R														
149																	S													
150																	T													
151																	L													
152																	I													

124

331

Table 60 (continued)

Position	234	235	239	240	241	243	244	245	247	262	263	264	265	266	267	269	296	297	298	299	313	325	326	327	328	329	330	332	333	334
WT	L	L	S	V	F	F	P	P	P	V	V	V	D	V	S	E	Y	N	S	T	W	N	K	A	L	P	A	I	E	K
153																			H											
154																				H										
155																											V			
156																											I			
157																											F			
158																											R			
159																											H			
160																						D								
161																						E								
162																						A								
163																						T								
164																						V								
165																						H								
166																									D			E		
167																									E			E		
168																									N			E		
169																									Q			E		
170																									V			E		
171																									T			E		
172																									H			E		
173																									I			E		
174																									A					
175																												T		
176																												H		
177																												Y		
178																												A		
179			E									I																E		
180			Q									I																E		
181			E									I															Y	E		
182			E									I							A								Y	E		

332

Table 60 (continued)

Position	234	235	239	240	241	243	244	245	247	262	263	264	265	266	267	269	296	297	298	299	313	325	326	327	328	329	330	332	333	334
WT	L	L	S	V	F	F	P	P	P	V	V	V	D	V	S	E	Y	N	S	T	W	N	K	A	L	P	A	I	E	K
183			D															D										E		
184			E															D										E		
185			D										V					D										E		
186			D										I					D										E		
187			D										L					D										E		
188			D										F					D										E		
189			D										Y					D										E		
190			D										H					D										E		
191			D										T					D										E		
192												E						D										E		
193																	D	D										E		
194																	E	D										E		
195																	N	D										E		
196																	Q	D										E		
197																	H	D										E		
198																	T	D										E		
199																		D		V								E		
200																		D		I								E		
201																		D		L								E		
202																		D		F								E		
203																		D		H								E		
204																		D		E								E		
205																		D									Y	E		
206																		D	A								Y	E		
207			D																								Y	E		
208			N																								Y	E		
209			D																								L	E		
210			N																								L	E		
211												I							A									E		
212			D																A									E		

126

333

Table 60 (continued)

Position	234	235	239	240	241	243	244	245	247	262	263	264	265	266	267	269	296	297	298	299	313	325	326	327	328	329	330	332	333	334
WT	L	L	S	V	F	F	P	P	P	V	V	V	D	V	S	E	Y	N	S	T	W	N	K	A	L	P	A	I	E	K
213			N																A									E		
214			D									I																E		
215			D									I							A									E		
216			D									I															L	E		

[203] Example 2: Experimental production and screening of Fc libraries

The majority of experimentation on the Fc variants was carried out in the context of the anti-cancer antibody alemtuzumab (Campath®, a registered trademark of Ilex Pharmaceuticals LP). Alemtuzumab binds a short linear epitope within its target antigen CD52 (Hale *et al.*, 1990, *Tissue Antigens* 35:118-127; Hale, 1995, *Immunotechnology* 1:175-187). Alemtuzumab has been chosen as the primary engineering template because its efficacy is due in part to its ability to recruit effector cells (Dyer *et al.*, 1989, *Blood* 73:1431-1439; Friend *et al.*, 1991, *Transplant Proc* 23:2253-2254; Hale *et al.*, 1998, *Blood* 92:4581-4590; Glennie *et al.*, 2000, *Immunol Today* 21:403-410), and because production and use of its antigen in binding assays are relatively straightforward. In order to evaluate the optimized Fc variants of the present invention in the context of other antibodies, select Fc variants were evaluated in the anti-CD20 antibody rituximab (Rituxan®, a registered trademark of IDEC Pharmaceuticals Corporation), and the anti-Her2 antibody trastuzumab (Herceptin®, a registered trademark of Genentech). The use of alemtuzumab, rituximab, and trastuzumab for screening purposes is not meant to constrain the present invention to any particular antibody.

[204] The IgG1 full length light (V_L-C_L) and heavy (V_H-Cγ1-Cγ2-Cγ3) chain antibody genes for alemtuzumab, rituximab, and trastuzumab were constructed with convenient end restriction sites to facilitate subcloning. The genes were ligated into the mammalian expression vector pcDNA3.1Zeo (Invitrogen). The V_H-Cγ1-Cγ2-Cγ3 clone in pcDNA3.1zeo was used as a template for mutagenesis of the Fc region. Mutations were introduced into this clone using PCR-based mutagenesis techniques. Fc variants were sequenced to confirm the fidelity of the sequence. Plasmids containing heavy chain gene (V_H-Cγ1-Cγ2-Cγ3) (wild-type or variants) were co-transfected with plasmid containing light chain gene (V_L-C_L) into 293T cells. Media were harvested 5 days after transfection. Expression of immunoglobulin was monitored by screening the culture supernatant of transfectomas by western using peroxidase-conjugated goat-anti human IgG (Jackson ImmunoResearch, catalog # 109-035-088). Figure 6 shows expression of wild-type alemtuzumab and variants 1 through 10 in 293T cells. Antibodies were purified from the supernatant using protein A affinity chromatography (Pierce, Catalog # 20334. Figure 7 shows results of the protein purification for WT alemtuzumab. Antibody Fc variants showed similar expression and purification results to WT. Some Fc variants were deglycosylated in order to determine their solution and functional properties in the absence of carbohydrate. To obtain deglycosylated antibodies, purified alemtuzumab antibodies were incubated with peptide-N-glycosidase (PNGase F) at 37°C for 24h. Figure 8 presents an SDS PAGE gel confirming deglycosylation for several Fc variants and WT alemtuzumab.

[205] In order to confirm the functional fidelity of alemtuzumab produced under these conditions, the antigenic CD52 peptide, fused to GST, was expressed in E.coli BL21 (DE3) under IPTG induction. Both un-induced and induced samples were run on a SDS PAGE gel, and transferred to PVDF membrane. For western analysis, either alemtuzumab from Sotec (final concentration 2.5ng/ul) or

Samsung Bioepis Exhibit No. 1002
Page 11211

media of transfected 293T cells (final alemtuzumab concentration about 0.1-0.2ng/ul) were used as primary antibody, and peroxidase-conjugated goat-anti human IgG was used as secondary antibody. Figure 9 presents these results. The ability to bind target antigen confirms the structural and functional fidelity of the expressed alemtuzumab. Fc variants that have the same variable region as WT alemtuzumab are anticipated to maintain a comparable binding affinity for antigen.

[206] In order to screen for Fc/FcγR binding, the extracellular regions of human V158 FcγRIIIa, human F158 FcγRIIIa, human FcγRIIb, human FcγRIIa, and mouse FcγRIII, were expressed and purified. Figure 10 presents an SDS PAGE gel that shows the results of expression and purification of human V158 FcγRIIIa. The extracellular region of this receptor was obtained by PCR from a clone obtained from the Mammalian Gene Collection (MGC:22630). The receptor was fused with glutathione S-Transferase (GST) to enable screening. Tagged Fc□RIIIa was transfected in 293T cells, and media containing secreted Fc□RIIIa were harvested 3 days later and purified. For western analysis, membrane was probed with anti-GST antibody.

[207] Binding affinity to Fc□RIIIa and FcγRIIb was measured for all designed Fc variants using an AlphaScreen™ assay (Amplified Luminescent Proximity Homogeneous Assay (ALPHA), PerkinElmer, Wellesley, MA), a bead-based non-radioactive luminescent proximity assay. Laser excitation of a donor bead excites oxygen, which if sufficiently close to the acceptor bead generates a cascade of chemiluminescent events, ultimately leading to fluorescence emission at 520-620 nm. The AlphaScreen™ assay was applied as a competition assay for screening Fc variants. WT alemtuzumab antibody was biotinylated by standard methods for attachment to streptavidin donor beads, and GST-tagged FcγR was bound to glutathione chelate acceptor beads. In the absence of competing Fc variants, WT antibody and FcγR interact and produce a signal at 520-620 nm. Addition of untagged Fc variant competes with the WT Fc/FcγR interaction, reducing fluorescence quantitatively to enable determination of relative binding affinities. All Fc variants were screened for V158 FcγRIIIa binding using the AlphaScreen™ assay. Select Fc variants were subsequently screened for binding to FcγRIIb, as well as other FcγRs and Fc ligands.

[208] Figure 11 shows AlphaScreen™ data for binding to human V158 FcγRIIIa by select Fc variants. The binding data were normalized to the maximum and minimum luminescence signal provided by the baselines at low and high concentrations of competitor antibody respectively. The data were fit to a one site competition model using nonlinear regression, and these fits are represented by the curves in the figure. These fits provide the inhibitory concentration 50% (IC50) (i.e. the concentration required for 50% inhibition) for each antibody, illustrated by the dotted lines in Figure 11, thus enabling the relative binding affinities of Fc variants to be quantitatively determined. Here, WT alemtuzumab has an IC50 of $(4.63 \times 10^{-9}) \times (2) = 9.2$ nM, whereas S239D has an IC50 of $(3.98 \times 10^{-10}) \times (2) = 0.8$ nM. Thus S239D alemtuzumab binds 9.2 nM / 0.8 nM = 11.64-fold more tightly

Samsung Bioepis Exhibit No. 1002
Page 11212

than WT alemtuzumab to human V158 FcγRIIIa. Similar calculations were performed for the binding of all Fc variants to human V158 FcγRIIIa. Select Fc variants were also screened for binding to human Fc□RIIb, and examples of these AlphaScreen™ binding data are shown in Figure 12. Table 61 presents the fold-enhancement or fold-reduction relative to the parent antibody for binding of Fc variants to human V158 FcγRIIIa (column 3) and human FcγRIIb (column 4), as determined by the AlphaScreen™ assay. For these data, a fold above 1 indicates an enhancement in binding affinity, and a fold below 1 indicates a reduction in binding affinity relative to WT Fc. All data were obtained in the context of alemtuzumab, except for those indicated with an asterix (*), which were tested in the context of trastuzumab.

Samsung Bioepis Exhibit No. 1002
Page 11213

Table 61

Variant	Substitution(s)	FcγRIIIa Fold	FcγRIIb Fold	FcγIIIa-fold : FcγIIb-fold
1	V264A	0.53		
2	V264L	0.56		
3	V264I	1.43		
4	F241W	0.29		
5	F241L	0.26		
6	F243W	0.51		
7	F243L	0.51		
8	F241L/F243L/V262I/V264I	0.09		
9	F241W/F243W	0.07		
10	F241W/F243W/V262A/V264A	0.04		
11	F241L/V262I	0.06		
12	F243L/V264I	1.23		
13	F243L/V262I/V264W	0.02		
14	F241Y/F243Y/V262T/V264T	0.05		
15	F241E/F243R/V262E/V264R	0.05		
16	F241E/F243Q/V262T/V264E	0.07		
17	F241R/F243Q/V262T/V264R	0.02		
18	F241E/F243Y/V262T/V264R	0.05		
19	L328M	0.21		
20	L328E	0.12		
21	L328F	0.24		
22	I332E	6.72	3.93	1.71
23	L328M/I332E	2.60		
24	P244H	0.83		
25	P245A	0.25		
26	P247V	0.53		
27	W313F	0.88		
28	P244H/P245A/P247V	0.93		
29	P247G	0.54		
30	V264I/I332E	12.49	1.57*	7.96
31	F241E/F243R/V262E/V264R/I332E	0.19		
32	F241E/F243Q/V262T/V264E/I332E			
33	F241R/F243Q/V262T/V264R/I332E			
34	F241E/F243Y/V262T/V264R/I332E	0.10		
35	S298A	2.21		
36	S298A/I332E	21.73		
37	S298A/E333A/K334A	2.56		
41	S239E/I332E	5.80	3.49	1.66
42	S239Q/I332E	6.60	4.68	1.41
43	S239E	10.16		
44	D265G	<0.02		
45	D265N	<0.02		
46	S239E/D265G	<0.02		
47	S239E/D265N	0.02		
48	S239E/D265Q	0.05		
49	Y296E	0.73	1.11	0.66
50	Y296Q	0.52	0.43	1.21

Samsung Bioepis Exhibit No. 1002
Page 11214

Table 61 (continued)

Variant	Substitution(s)	FcγRIIIa Fold	FcγRIIb Fold	FcγIIIa-fold : FcγIIb-fold
51	S298T	0.94	<0.02	
52	S298N	0.41	<0.02	
53	T299I	<0.02		
54	A327S	0.23	0.39	0.59
55	A327N	0.19	1.15	0.17
56	S267Q/A327S	0.03		
57	S267L/A327S	<0.02		
58	A327L	0.05		
59	P329F	<0.02		
60	A330L	0.73	0.38	1.92
61	A330Y	1.64	0.75	2.19
62	I332D	17.80	3.34	5.33
63	N297S	<0.02		
64	N297D	<0.02		
65	N297S/I332E	<0.02		
66	N297D/I332E	0.08	<0.02	
67	N297E/I332E	<0.02		
68	D265Y/N297D/I332E	<0.02		
69	D265Y/N297D/T299L/I332E	<0.02		
70	D265F/N297E/I332E	<0.02		
71	L328I/I332E	7.03		
72	L328Q/I332E	1.54		
73	I332N	0.39		
74	I332Q	0.37		
75	V264T	2.73		
76	V264F	0.16		
77	V240I	3.25		
78	V263I	0.10		
79	V266I	1.86		
80	T299A	0.03		
81	T299S	0.15		
82	T299V	<0.02		
83	N325Q	<0.02		
84	N325L	<0.02		
85	N325I	<0.02		
86	S239D	11.64	4.47*	2.60
87	S239N	<0.02		
88	S239F	0.22	<0.02	
89	S239D/I332D	14.10		
90	S239D/I332E	56.10	19.71*	2.85
91	S239D/I332N	7.19		
92	S239D/I332Q	9.28		
93	S239E/I332D	9.33		
94	S239E/I332N	11.93		
95	S239E/I332Q	3.80		
96	S239N/I332D	3.08		
97	S239N/I332E	14.21		
98	S239N/I332N	0.43		

Samsung Bioepis Exhibit No. 1002
Page 11215

Table 61 (continued)

Variant	Substitution(s)	FcγRIIIa Fold	FcγRIIb Fold	FcγIIIa-fold : FcγIIb-fold
99	S239N/I332Q	0.56		
100	S239Q/I332D	5.05		
101	S239Q/I332N	0.39		
102	S239Q/I332Q	0.59		
103	K326E	3.85		
104	Y296D	0.62		
105	Y296N	0.29		
106	F241Y/F243Y/V262T/V264T/N297D/I332E	0.15		
107	A330Y/I332E	12.02	4.40	2.73
108	V264I/A330Y/I332E	12.00	3.54	3.39
109	A330L/I332E	10.34	2.03	5.09
110	V264I/A330L/I332E	11.15	1.79	6.23
111	L234D	0.21		
112	L234E	1.34	2.21	0.61
113	L234N	0.56	1.39	0.40
114	L234Q	0.37		
115	L234T	0.35		
116	L234H	0.33		
117	L234Y	1.42	1.08	1.31
118	L234I	1.55	1.14	1.36
119	L234V	0.38		
120	L234F	0.30		
121	L235D	1.66	3.63	0.46
122	L235S	1.25		
123	L235N	0.40		
124	L235Q	0.51		
125	L235T	0.52		
126	L235H	0.41		
127	L235Y	1.19	10.15	0.12
128	L235I	1.10	0.94	1.17
129	L235V	0.48		
130	L235F	0.73	3.53	0.21
131	S239T	1.34		
132	S239H	0.20		
133	S239Y	0.21		
134	V240A	0.70	0.14	5.00
135	V240T			
136	V240M	2.06	1.38	1.49
137	V263A			
138	V263T	0.43		
139	V263M	0.05		
140	V264M	0.26		
141	V264Y	1.02	0.27	3.78
142	V266A	<0.02		
143	V266T	0.45		
144	V266M	0.62		
145	E269H	<0.02		
146	E269Y	0.12		

Samsung Bioepis Exhibit No. 1002
Page 11216

Table 61 (continued)

Variant	Substitution(s)	FcγRIIIa Fold	FcγRIIb Fold	FcγIIIa-fold : FcγIIb-fold
147	E269F	0.16		
148	E269R	0.05		
149	Y296S	0.12		
150	Y296T	<0.02		
151	Y296L	0.22		
152	Y296I	0.09		
153	A298H	0.27		
154	T299H	<0.02		
155	A330V	0.43		
156	A330I	1.71	0.02	85.5
157	A330F	0.60		
158	A330R	<0.02		
159	A330H	0.52		
160	N325D	0.41		
161	N325E	<0.02		
162	N325A	0.11		
163	N325T	1.10		
164	N325V	0.48		
165	N325H	0.73		
166	L328D/I332E	1.34		
167	L328E/I332E	0.20		
168	L328N/I332E	<0.02		
169	L328Q/I332E	0.70		
170	L328V/I332E	2.06		
171	L328T/I332E	1.10		
172	L328H/I332E	<0.02		
173	L328I/I332E	3.49		
174	L328A	0.20		
175	I332T	0.72		
176	I332H	0.46		
177	I332Y	0.76		
178	I332A	0.89		
179	S239E/V264I/I332E	15.46		
180	S239Q/V264I/I332E	2.14		
181	S239E/V264I/A330Y/I332E	8.53		
182	S239E/V264I/S298A/A330Y/I332E			
183	S239D/N297D/I332E	0.28		
184	S239E/N297D/I332E	0.06		
185	S239D/D265V/N297D/I332E			
186	S239D/D265I/N297D/I332E			
187	S239D/D265L/N297D/I332E	<0.02		
188	S239D/D265F/N297D/I332E	<0.02		
189	S239D/D265Y/N297D/I332E	0.02		
190	S239D/D265H/N297D/I332E	0.04		
191	S239D/D265T/N297D/I332E	<0.02		
192	V264I/N297D/I332E	0.05		
193	Y296D/N297D/I332E			
194	Y296E/N297D/I332E	<0.02		

Samsung Bioepis Exhibit No. 1002
Page 11217

Table 61 (continued)

Variant	Substitution(s)	FcγRIIIa Fold	FcγRIIb Fold	FcγIIIa-fold : FcγIIb-fold
195	Y296N/N297D/I332E	0.04		
196	Y296Q/N297D/I332E	<0.02		
197	Y296H/N297D/I332E	<0.02		
198	Y296T/N297D/I332E	<0.02		
199	N297D/T299V/I332E	<0.02		
200	N297D/T299I/I332E	<0.02		
201	N297D/T299L/I332E	<0.02		
202	N297D/T299F/I332E	<0.02		
203	N297D/T299H/I332E	<0.02		
204	N297D/T299E/I332E	<0.02		
205	N297D/A330Y/I332E	0.43		
206	N297D/S298A/A330Y/I332E			
207*	S239D/A330Y/I332E	129.58		
208*	S239N/A330Y/I332E	14.22		
209*	S239D/A330L/I332E	138.63	7.50	18.48
210*	S239N/A330L/I332E	12.95		
211*	V264I/S298A/I332E	16.50		
212*	S239D/S298A/I332E	295.16	6.16	47.92
213*	S239N/S298A/I332E	32.14	5.15	6.24
214*	S239D/V264I/I332E	36.58	14.39	2.54
215*	S239D/V264I/S298A/I332E			
216*	S239D/V264I/A330L/I332E			

Samsung Bioepis Exhibit No. 1002
Page 11218

[209] Example 3: Selectively enhanced binding to FcγRs

A number of promising Fc variants with optimized properties were obtained from the FcγRIIIa and FcγRIIb screen. Table 61 provides Fc variants that bind more tightly to FcγRIIIa, and thus are candidates for improving the effector function of antibodies and Fc fusions. These include a number of variants that comprise substitutions at 239, 264, 330, and 332. Figure 13 shows AlphaScreen™ binding data for some of these Fc variants. The majority of these Fc variants provide substantially greater FcγRIIIa binding enhancements over S298A/E333A/K334A.

[210] Although the majority of Fc variants were screened in the context of the antibody alemtuzumab, select Fc variants were also screened in the context of rituximab and trastuzumab. AlphaScreen™ data for binding of select Fc variants to human V158 FcγRIIIa in the context of rituximab and trastuzumab are shown in Figures 14 and 15 respectively. The results indicate that the Fc variants display consistent binding enhancements regardless of the antibody context, and thus the Fc variants of the present invention are broadly applicable to antibodies and Fc fusions.

[211] Fc variants have been obtained that show differentially enhanced binding to FcγRIIIa over FcγRIIb. As discussed, optimal effector function may result from Fc variants wherein affinity for activating FcγRs is greater than affinity for the inhibitory FcγRIIb. AlphaScreen™ data directly comparing binding to FcγRIIIa and FcγRIIb for two Fc variants with this specificity profile are shown in Figures 16a and 16b. This concept can be defined quantitatively as the fold-enhancement or -reduction of the activating FγR (Table 61, column 3) divided by the fold-enhancement or -reduction of the inhibitory FcγR (Table 61, column 4), herein referred to as the FcγRIIIa-fold:FcγRIIb-fold ratio. This value provided in Column 5 in Table 61. Table 61 shows that Fc variants provide this specificity profile, with a FcγRIIIa-fold:FcγRIIb-fold ratio as high as 86:1.

[212] Some of the most promising Fc variants of the present invention for enhancing effector function have both substantial increases in affinity for FcγRIIIa and favorable FcγRIIIa-fold:FcγRIIb-fold ratios. These include, for example, S239D/I332E (FcγRIIIa-fold = 56, FcγRIIIa-fold:FcγRIIb-fold = 3), S239D/A330Y/I332E (FcγRIIIa-fold = 130), S239D/A330L/I332E (FcγRIIIa-fold = 139, FcγRIIIa-fold:FcγRIIb-fold = 18), and S239D/S298A/I332E (FcγRIIIa-fold = 295, FcγRIIIa-fold:FcγRIIb-fold = 48). Figure 17 shows AlphaScreen™ binding data for these and other Fc variants to human V158 FcγRIIIa.

[213] Because there are a number of FcγRs that contribute to effector function, it may be worthwhile to additionally screen Fc variants against other receptors. Figure 18 shows AlphaScreen™ data for binding of select Fc variants to human R131 FcγRIIa. As can be seen, those aforementioned variants

Samsung Bioepis Exhibit No. 1002
Page 11219

with favorable binding enhancements and specificity profiles also show enhanced binding to this activating receptor. The use of FcγRIIIa, FcγRIIb, and FcγRIIc for screening is not meant to constrain experimental testing to these particular FcγRs; other FcγRs are contemplated for screening, including but not limited to the myriad isoforms and allotypes of FcγRI, FcγRII, and FcγRIII from humans, mice, rats, monkeys, and the like, as previously described.

[214] Taken together, the FcγR binding data provided in Figures 11 – 18 and Table 61 indicate that a number of substitions at positions 234, 235, 239, 240, 243, 264, 266, 325, 328, 330, and 332 are promising candidates for improving the effector function of antibodies and Fc fusions. Because combinations of some of these substitutions have typically resulted in additive or synergistic binding improvements, it is anticipated that as yet unexplored combinations of the Fc variants provided in Table 61 will also provide favorable results. Thus all combinations of the Fc variants in Table 61 are contemplated. Likewise, combinations of any of the Fc variants in Table 61 with other discovered or undiscovered Fc variants may also provide favorable properties, and these combinations are also contemplated. Furthermore, it is anticipated from these results that other substitutions at positions 234, 235, 239, 240, 243, 264, 266, 325, 328, 330, and 332 may also provide favorable binding enhancements and specificities, and thus substitutions at these positions other than those presented in Table 61 are contemplated.

[215] Example 4: Reduced binding to FcγRs

As discussed, although there is a need for greater effector function, for some antibody therapeutics, reduced or eliminated effector function may be desired. Several Fc variants in Table 61 substantially reduce or ablate FcγR binding, and thus may find use in antibodies and Fc fusions wherein effector function is undesirable. AlphaScreen™ binding data for some examples of such variants are shown in Figures 19a and 19b. These Fc variants, as well as their use in combination, may find use for eliminating effector function when desired, for example in antibodies and Fc fusions whose mechanism of action involves blocking or antagonism but not killing of the cells bearing target antigen.

[216] Example 5: Aglycosylated Fc variants

As discussed, one goal of the current experiments was to obtain optimized aglycosylated Fc variants. Several Fc variants provide significant progress towards this goal. Because it is the site of glycosylation, substitution at N297 results in an aglycosylated Fc. Whereas all other Fc variants that comprise a substitution at N297 completely ablate FcγR binding, N297D/I332E has significant binding affinity for FcγRIIIa, shown in Table 61 and illustrated in Figure 20. The exact reason for this result is uncertain in the absence of a high-resolution structure for this variant, although the computational screening predictions suggest that it is potentially due to a combination of new favorable Fc/FcγR interactions and favorable electrostatic properties. Indeed other electrostatic substitutions are

Samsung Bioepis Exhibit No. 1002
Page 11220

envisioned for further optimization of aglycosylated Fc. Table 61 shows that other aglycosylated Fc variants such as S239D/N297D/I332E and N297D/A330Y/I332E provide binding enhancements that bring affinity for FcγRIIIa within 0.28- and 0.43-fold respectively of glycosylated WT alemtuzumab. Combinations of these variants with other Fc variants that enhance FcγR binding are contemplated, with the goal of obtaining aglycosylated Fc variants that bind one or more FcγRs with affinity that is approximately the same as or even better than glycosylated parent Fc. An additional set of promising Fc variants provide stability and solubility enhancements in the absence of carbohydrate. Fc variants that comprise substitutions at positions 241, 243, 262, and 264, positions that do not mediate FγR binding but do determine the interface between the carbohydrate and Fc, ablate FγR binding, presumably because they perturb the conformation of the carbohydrate. In deglycosylated form, however, Fc variants F241E/F243R/V262E/V264R, F241E/F243Q/V262T/V264E, F241R/F243Q/V262T/V264R, and F241E/F243Y/V262T/V264R show stronger binding to FcγRIIIa than in glycosylated form, as shown by the AlphaScreen™ data in Figure 21. This result indicates that these are key positions for optimization of the structure, stability, solubility, and function of aglycosylated Fc. Together these results suggests that protein engineering can be used to restore the favorable functional and solution properties of antibodies and Fc fusions in the absence of carbohydrate, and pave the way for aglycosylated antibodies and Fc fusions with favorable solution properties and full functionality that comprise substitutions at these and other Fc positions.

[217] Example 6. Affinity of Fc variants for polymorphic forms of FcγRIIIa

As discussed above, an important parameter of Fc-mediated effector function is the affinity of Fc for both V158 and F158 polymorphic forms of FcγRIIIa. AlphaScreen™ data comparing binding of select variants to the two receptor allotypes are shown in Figure 22a (V158 FcγRIIIa) and Figure 22b (F158 FcγRIIIa). As can be seen, all variants improve binding to both FcγRIIIa allotypes. These data indicate that those Fc variants of the present invention with enhanced effector function will be broadly applicable to the entire patient population, and that enhancement to clinical efficacy will potentially be greatest for the low responsive patient population who need it most.

[218] The FcγR binding affinities of these Fc variants were further investigated using Surface Plasmon Resonance (SPR) (Biacore, Uppsala, Sweden). SPR is a sensitive and extremely quantitative method that allows for the measurement of binding affinities of protein-protein interactions, and has been used to effectively measure Fc/FcγR binding (Radaev *et al.*, 2001, *J Biol Chem* 276:16478-16483). SPR thus provides an excellent complementary binding assay to the AlphaScreen™ assay. His-tagged V158 FcγRIIIa was immobilized to an SPR chip, and WT and Fc variant alemtuzumab antibodies were flowed over the chip at a range of concentrations. Binding constants were obtained from fitting the data using standard curve-fitting methods. Table 62 presents dissociation constants (Kd) for binding of select Fc variants to V158 FcγRIIIa and F158 FcγRIIIa obtained using SPR, and compares these with IC50s obtained from the AlphaScreen™ assay. By

Samsung Bioepis Exhibit No. 1002
Page 11221

dividing the Kd and IC50 for each variant by that of WT alemtuzumab, the fold-improvements over WT (Fold) are obtained.

Samsung Bioepis Exhibit No. 1002
Page 11222

Table 62

	SPR V158 FcγRIIIa		SPR F158 FcγRIIIa		AlphaScreen™ V158 FcγRIIIa		AlphaScreen™ F158 FcγRIIIa	
	Kd (nM)	Fold	Kd (nM)	Fold	IC50 (nM)	Fold	IC50 (nM)	Fold
WT	68		730		6.4		17.2	
V264I	64	1.1	550	1.3	4.5	1.4	11.5	1.5
I332E	31	2.2	72	10.1	1.0	6.4	2.5	6.9
V264I/I332E	17	4.0	52	14.0	0.5	12.8	1.1	15.6
S298A	52	1.3	285	2.6	2.9	2.2	12.0	1.4
S298A/E333A/ K334A	39	1.7	156	4.7	2.5	2.6	7.5	2.3

[219] The SPR data corroborate the improvements to FcγRIIIa affinity observed by AlphaScreen™ assay. Table 62 further indicates the superiority of V264I/I332E and I332E over S298A and S298A/E333A/K334A; whereas S298A/E333A/K334A improves Fc binding to V158 and F158 FcγRIIIa by 1.7-fold and 4.7-fold respectively, I332E shows binding enhancements of 2.2-fold and 10.1-fold respectively, and V264I/I332E shows binding enhancements of 4.0-fold and 14-fold respectively. Also worth noting is that the affinity of V264I/I332E for F158 FcγRIIIa (52 nM) is better than that of WT for the V158 allotype (68 nM), suggesting that this Fc variant, as well as those with even greater improvements in binding, may enable the clinical efficacy of antibodies for the low responsive patient population to achieve that currently possible for high responders. The correlation between the SPR and AlphaScreen™ binding measurements are shown in Figures 23a – 23d. Figures 23a and 23b show the Kd - IC50 correlations for binding to V158 FcγRIIIa and F158 FcγRIIIa respectively, and Figures 23c and 23d show the fold-improvement correlations for binding to V158 FcγRIIIa and F158 FcγRIIIa respectively. The good fits of these data to straight lines (r^2 = 0.9, r^2 = 0.84, r^2 = 0.98, and r^2 = 0.90) support the accuracy the AlphaScreen™ measurements, and validate its use for determining the relative Fc□R binding affinities of Fc variants.

[220] Example 7. ADCC of Fc variants

In order to determine the effect on effector function, cell-based ADCC assays were performed on select Fc variants. ADCC was measured using the DELFIA® EuTDA-based cytotoxicity assay (Perkin Elmer, MA) with purified human peripheral blood monocytes (PBMCs) as effector cells. Target cells were loaded with BATDA at $1x10^6$ cells/ml, washed 4 times and seeded into 96-well plate at 10,000 cells/well. The target cells were then opsonized using Fc variant or WT antibodies at the indicated final concentration. Human PBMCs were added at the indicated fold-excess of target cells and the plate was incubated at 37°C for 4 hrs. The co-cultured cells were centrifuged at 500xg, supernatants were transferred to a separate plate and incubated with Eu solution, and relative fluorescence units were measured using a Packard Fusion™ reader (Packard Biosciences, IL). Samples were run in triplicate to provide error estimates (n=3, +/- S.D.). PBMCs were allotyped for the V158 or F158 FcγRIIIa allotype using PCR.

Samsung Bioepis Exhibit No. 1002
Page 11223

[221] ADCC assays were run on Fc variant and WT alemtuzumab using DoHH-2 lymphoma target cells. Figure 24a is a bar graph showing the ADCC of these proteins at 10 ng/ml antibody. Results show that alemtuzumab Fc variants I332E, V264I, and I332E/V264I have substantially enhanced ADCC compared to WT alemtuzumab, with the relative ADCC enhancements proportional to their binding improvements to FcγRIIIa as indicated by AlphaScreen™ assay and SPR. The dose dependence of ADCC on antibody concentration is shown in Figure 24b. These data were normalized to the minimum and maximum fluorescence signal provided by the baselines at low and high concentrations of antibody respectively. The data were fit to a sigmoidal dose-response model using nonlinear regression, represented by the curve in the figure. The fits enable determination of the effective concentration 50% (EC50) (i.e. the concentration required for 50% effectiveness), which provides the relative enhancements to ADCC for each Fc variant. The EC50s for these binding data are analogous to the IC50s obtained from the AlphaScreen™ competition data, and derivation of these values is thus analogous to that described in Example 2 and Figure 11. In Figure 24b, the log(EC50)s, obtained from the fits to the data, for WT, V264I/I332E, and S239D/I332E alemtuzumab are 0.99, 0.60, and 0.49 respectively, and therefore their respective EC50s are 9.9, 4.0, and 3.0. Thus V264I/I332E and S239E/I332E provide a 2.5-fold and 3.3-fold enhancement respectively in ADCC over WT alemtuzumab using PBMCs expressing heterozygous V158/F158 FcγRIIIa. These data are summarized in Table 63 below.

Table 63

	log(EC50)	EC50 (ng/ml)	Fold Improvement Over WT
WT	0.99	9.9	
V264I/I332E	0.60	4.0	2.5
S239D/I332E	0.49	3.0	3.3

[222] In order to determine whether these ADCC enhancements are broadly applicable to antibodies, select Fc variants were evaluated in the context of rituximab and trastuzumab. ADCC assays were run on V264I/I332E, WT, and S298A/D333A/K334A rituximab using WIL2-S lymphoma target cells. Figure 25a presents a bar graph showing the ADCC of these proteins at 1 ng/ml antibody. Results indicate that V264I/I332E rituximab provides substantially enhanced ADCC relative to WT rituximab, as well as superior ADCC to S298A/D333A/K334A, consistent with the FcγRIIIa binding improvements observed by AlphaScreen™ assay and SPR. Figure 25b shows the dose dependence of ADCC on antibody concentration. The EC50s obtained from the fits of these data and the relative fold-improvements in ADCC are provided in Table 64 below. As can be seen V264I/I332E rituximab provides an 11.3-fold enhancement in EC50 over WT for PBMCs expressing homozygous F158/F158 FcγRIIIa. The greater improvements observed for rituximab versus alemtuzumab are

Samsung Bioepis Exhibit No. 1002
Page 11224

likely due to the use of homozygous F158/F158 FcγRIIIa rather than heterozygous V158/F158 FcγRIIIa PBMCs, as well as potentially the use of different antibodies and target cell lines.

Table 64

	log(EC50)	EC50 (ng/ml)	Fold Improvement Over WT
WT	0.23	1.7	
S298A/E333A/K334A	-0.44	0.37	4.6
V264I/I332E	-0.83	0.15	11.3

[223] ADCC assays were run on Fc variant and WT trastuzumab using two breast carcinoma target cell lines BT474 and Sk-Br-3. Figure 26a shows a bar graph illustrating ADCC at 1 ng/ml antibody. Results indicate that V264I and V264I/I332E trastuzumab provide substantially enhanced ADCC compared to WT trastuzumab, with the relative ADCC enhancements proportional to their binding improvements to FcγRIIIa as indicated by AlphaScreen™ assay and SPR. Figure 26b shows the dose dependence of ADCC on antibody concentration. The EC50s obtained from the fits of these data and the relative fold-improvements in ADCC are provided in Table 65 below. Significant ADCC improvements are observed for I332E trastuzumab when combined with A330L and A330Y.

Table 65

	log(EC50)	EC50 (ng/ml)	Fold Improvement Over WT
WT	1.1	11.5	
I332E	0.34	2.2	5.2
A330Y/I332E	-0.04	0.9	12.8
A330L/I332E	0.04	1.1	10.5

[224] Figure 26c shows another set of dose response ADCC data at variable antibody concentrations for trastuzumab variants. The EC50s obtained from the fits of these data and the relative fold-improvements in ADCC are provided in Table 66 below. Results show that trastuzumab Fc variants S239D/I332E, S239D/S298A/I332E, S239D/A330Y/I332E, and S239D/A330L/I332E/ provide substantial ADCC enhancements relative to WT trastuzumab and S298A/E333A/K334A; consistent with the FcγR binding data observed by the AlphaScreen™ assay and SPR. S239D/A330L/I332E trastuzumab shows the largest increase in effector function observed thus far, providing an approximate 50-fold enhancement in EC50 over WT for PBMCs expressing homozygous F158/F158 FcγRIIIa.

Samsung Bioepis Exhibit No. 1002
Page 11225

Table 66

	log(EC50)	EC50 (ng/ml)	Fold Improvement Over WT
WT	0.45	2.83	
S298A/E333A/K334A	-0.17	0.67	4.2
S239D/I332E	-0.18	0.66	4.3
S239D/A330Y/I332E	-0.29	0.51	5.5
S239D/S298A/I332E	-0.52	0.30	9.4
S239D/A330L/I332E	-1.22	0.06	47.2

[225] Example 8. Complement binding and activation by Fc variants

Complement protein C1q binds to a site on Fc that is proximal to the FcγR binding site, and therefore it was prudent to determine whether the Fc variants have maintained their capacity to recruit and activate complement. The AlphaScreen™ assay was used to measure binding of select Fc variants to the complement protein C1q. The assay was carried out with biotinylated WT alemtuzumab antibody attached to streptavidin donor beads as described in Example 2, and using C1q coupled directly to acceptor beads. Binding data of select Fc variants shown in Figure 27a indicate that C1q binding is uncompromised. Cell-based CDC assays were also performed on select Fc variants to investigate whether Fc variants maintain the capacity to activate complement. Amar Blue was used to monitor lysis of Fc variant and WT rituximab-opsonized WIL2-S lymphoma cells by human serum complement (Quidel, San Diego, CA). The results shown in Figure 27b for select Fc variants indicate that CDC is uncompromised.

[226] Example 9. Protein A binding by Fc variants

As discussed, bacterial protein A binds to the Fc region between the C□2 and C□3 domains, and is frequently employed for antibody purification. The AlphaScreen™ assay was used to measure binding of select Fc variants to the protein A using biotinylated WT alemtuzumab antibody attached to streptavidin donor beads as described in Example 2, and using protein A coupled directly to acceptor beads. The binding data shown in Figure 28 for select Fc variants indicate that the capacity of the Fc variants to bind protein A is uncompromised. These results suggest that affinity of the Fc variants for other Fc ligands that bind the same site on Fc as protein A, such as the neonatal Fc receptor FcRn and protein G, are also unaffected.

[227] Example 10. Capacity of Fc variants to bind mouse Fc□Rs

Optimization of Fc to nonhuman Fc□Rs may be useful for experimentally testing Fc variants in animal models. For example, when tested in mice (for example nude mice, SCID mice, xenograft mice, and/or transgenic mice), antibodies and Fc fusions that comprise Fc variants that are optimized for

Samsung Bioepis Exhibit No. 1002
Page 11226

one or more mouse Fc□Rs may provide valuable information with regard to efficacy, mechanism of action, and the like. In order to evaluate whether the Fc variants of the present invention may be useful in such experiments, affinity of select Fc variants for mouse FcγRIII was measured using the AlphaScreen™ assay. The AlphaScreen™ assay was carried out using biotinylated WT alemtuzumab attached to streptavidin donor beads as described in Example 2, and GST-tagged mouse FcγRIII bound to glutathione chelate acceptor beads, expressed and purified as described in Example 2. These binding data are shown in Figure 29. Results show that some Fc variants that enhance binding to human FcγRIIIa also enhance binding to mouse FcγRIII. This result indicates that the Fc variants of the present invention, or other Fc variants that are optimized for nonhuman FcγRs, may find use in experiments that use animal models.

[228] Example 11. Validation of Fc variants expressed in CHO cells

Whereas the Fc variants of the present invention were expressed in 293T cells for screening purposes, large scale production of antibodies is typically carried out by expression in Chinese Hamster Ovary (CHO) cell lines. In order to evaluate the properties of CHO-expressed Fc variants, select Fc variants and WT alemtuzumab were expressed in CHO cells and purified as described in Example 2. Figure 30 shows AlphaScreen™ data comparing binding of CHO- and 293T- expressed Fc variant and WT alemtuzumab to human V158 FcγRIIIa. The results indicate that the Fc variants of the present invention show comparable FcγR binding enhancements whether expressed in 293T or CHO.

[229] Example 12. Therapeutic application of Fc variants

A number of Fc variants described in the present invention have significant potential for improving the therapeutic efficacy of anticancer antibodies. For illustration purposes, a number of Fc variants of the present invention have been incorporated into the sequence of the antibody rituximab. The WT rituximab light chain and heavy chain, described in US 5,736,137, are provided in Figures 31a and 32b. The improved anti-CD20 antibody sequences are provided in Figure 31c. The improved anti-CD20 antibody sequences comprise at least non-WT amino acid selected from the group consisting of X_1, X_2, X_3, X_4, X_5, and X_6. These improved anti-CD20 antibody sequences may also comprise a substitution Z_1. The use of rituximab here is solely an example, and is not meant to constrain application of the Fc variants to this antibody or any other particular antibody or Fc fusion.

[230] All references are herein expressly incorporated by reference.

Samsung Bioepis Exhibit No. 1002
Page 11227

[231] Whereas particular embodiments of the invention have been described above for purposes of illustration, it will be appreciated by those skilled in the art that numerous variations of the details may be made without departing from the invention as described in the appended claims.

Samsung Bioepis Exhibit No. 1002
Page 11228

CLAIMS

We claim:

1. An antibody comprising an Fc variant portion comprising at least one amino acid modification in the Fc region of said parent Fc polypeptide, wherein said Fc variant modulates binding to an FcγR as compared to the parent Fc polypeptide.

2. An antibody according to claim 1 wherein said modulation is an increase in affinity of said antibody to said FcγR.

3. An antibody according to claim 1 wherein said Fc variant portion comprises at least one substitution at a position corresponding to a position of the human sequence selected from the group consisting of: 234, 235, 239, 240, 241, 243, 244, 245, 247, 262, 263, 264, 265, 266, 267, 269, 296, 297, 298, 299, 313, 325, 326, 327, 328, 329, 330, 332, 333, and 334.

4. An antibody according to claim 1, wherein said Fc variant comprises at least one substitution at a position corresponding to a position of the human sequence selected from the group consisting of: 240, 244, 245, 247, 262, 263, 266, 299, 313, 325, 328, and 332.

5. An antibody according to claim 1, wherein said Fc variant comprises a substitution at position 332.

6. An antibody according to claim 1, wherein at least one substitution is at a position selected from the group consisting of: 239, 264, 297, and 330, with the proviso that if said sequence is substantially human, said substitution is not S239A, V264A, N297A, N297Q, A330D, A330Q, A330K, or A330S.

7. An antibody according to claim 1, wherein said Fc variant comprises at least one substitution selected from the group consisting of 234D, 234E, 234N, 234Q, 234T, 234H, 234Y, 234I, 234V, 234F, 235D, 235S, 235N, 235Q, 235T, 235H, 235Y, 235I, 235V, 235F, 239D, 239E, 239N, 239Q, 239F, 239T, 239H, 239Y, 240I, 240A, 240T, 240M, 241W, 241L, 241Y, 241E, 241R, 243W, 243L 243Y, 243R, 243Q, 244H, 245A, 247V, 247G, 262I, 262A, 262T, 262E, 263I, 263A, 263T, 263M, 264L, 264I, 264W, 264T, 264R, 264F, 264M, 264Y, 264E, 265G, 265N, 265Q, 265Y, 265F, 265V, 265I, 265L, 265H, 265T, 266I, 266A, 266T, 266M, 267Q, 267L, 269H, 269Y, 269F, 269R, 296E, 296Q, 296D, 296N, 296S, 296T, 296L, 296I, 296H,

Samsung Bioepis Exhibit No. 1002
Page 11229

297S, 297D, 297E, 298H, 299I, 299L, 299A, 299S, 299V, 299H, 299F, 299E, 313F, 325Q, 325L, 325I, 325D, 325E, 325A, 325T, 325V, 325H, 327N, 327L, 328M, 328D, 328E, 328N, 328Q, 328F, 328I, 328V, 328T, 328H, 328A, 329F, 330L, 330Y, 330V, 330I, 330F, 330R, 330H, 332D, 332E, 332N, 332Q, 332T, 332H, 332Y, and 332A.

8. An antibody according to claim 1, wherein said Fc variant is selected from the group consisting of 264L, 264I, 241W, 241L, 243W, 243L, 241L/243L/262I/264I, 241W/243W, 241W/243W/262A/264A, 241L/262I, 243L/264I, 243L/262I/264W, 241Y/243Y/262T/264T, 241E/243R/262E/264R, 241E/243Q/262T/264E, 241R/243Q/262T/264R, 241E/243Y/262T/264R, 328M, 328E, 328F, 332E, 328M/332E, 244H, 245A, 247V, 313F, 244H/245A/247V, 247G, 264I/332E, 241E/243R/262E/264R/332E, 241E/243Q/262T/264E/332E, 241R/243Q/262T/264R/332E, 241E/243Y/262T/264R/332E, 298A/332E, 239EI332E, 239Q/332E, 239E, 265G, 265N, 239E/265G, 239E/265N, 239E/265Q, 296E, 296Q, 299I, 327N, 267Q/327S, 267L/327S , 327L, 329F, 330L, 330Y, 332D, 297S, 297D, 297S/332E, 297D/332E, 297E/332E, 265Y/297D/332E, 265Y/297D/299L/332E, 265F/297E/332E, 328I/332E, 328Q/332E, 332N, 332Q, 264T, 264F, 240I, 263I, 266I, 299A, 299S, 299V, 325Q, 325L, 325I, 239D, 239N, 239F, 239D/332D, 239D/332E, 239D/332N, 239D/332Q, 239E/332D, 239E/332N, 239E/332Q, 239N/332D, 239N/332E, 239N/332N, 239NI332Q, 239Q/332D, 239Q/332N, 239Q/332Q, 296D, 296N, 241Y/243Y/262T/264T/297D/332E, 330Y/332E, 264I/330Y/332E, 330L/332E, 264I/330L/332E, 234D, 234E, 234N, 234Q, 234T, 234H, 234Y, 234I, 234V, 234F, 235D, 235S, 235N, 235Q, 235T, 235H, 235Y, 235I, 235V, 235F, 239T, 239H, 239Y, 240A, 240T, 240M, 263A, 263T, 263M, 264M, 264Y, 266A, 266T, 266M, 269H, 269Y, 269F, 269R, 296S, 296T, 296L, 296I, 298H, 299H, 330V, 330I, 330F, 330R, 330H, 325D, 325E, 325A, 325T, 325V, 325H, 328D/332E, 328E/332E, 328N/332E, 328Q/332E, 328V/332E, 328T/332E, 328H/332E, 328I/332E, 328A, 332T, 332H, 332Y, 332A, 239E/264I/332E, 239Q/264I/332E, 239E/264I/330Y/332E, 239E/264I/298A/330Y/332E, 239D/297D/332E, 239E/297D/332E, 239D/265V/297D/332E, 239D/265I/297D/332E, 239D/265L/297D/332E, 239D/265F/297D/332E, 239D/265Y/297D/332E, 239D/265H/297D/332E, 239D/265T/297D/332E, 264E/297D/332E, 296D/297D/332E, 296E/297D/332E, 296N/297D/332E, 296Q/297D/332E, 296H/297D/332E, 296T/297D/332E, 297D/299V/332E, 297D/299I/332E, 297D/299L/332E, 297D/299F/332E, 297D/299H/332E, 297D/299E/332E, 297D/330Y/332E, 297D/298A/330YI332E, 239D/330Y/332E, 239N/330Y/332E, 239D/330L/332E, 239N/330L/332E, 264I/298A/332E, 239D/298A/332E, 239N/298A/332E, 239D/264I/332E, 239D/264I/298A/332E, and 239D/264I/330L/332E.

9. An antibody according to claim 7, wherein said Fc variant portion further comprises at least one substitution at a position corresponding to a position of the human sequence selected from the group consisting of: 256, 270, 290, 298, 312, 322, 326, 329, 331, 333, 334, and 339.

Samsung Bioepis Exhibit No. 1002
Page 11230

10. An antibody according to claim 1, wherein said FcγR is FcγRIIIa.

11. An antibody according to claim 10, wherein said FcγRIIIa is a V158 or F158 allotype of FcγRIIIa.

12. An Fc variant according to claim 2, wherein said parent Fc polypeptide is substantially human, and said affinity is approximately 5-fold greater than that of said parent Fc polypeptide.

13. An antibody according to claim 12, wherein said parent Fc polypeptide is substantially human, and said affinity is between about 5-fold and about 300-fold greater than that of said parent Fc polypeptide.

14. An antibody according to claim 12, wherein said Fc variant portion comprises at least one substitution at a position corresponding to a position of the human sequence selected from the group consisting 234, 235, 239, 240, 243, 264, 266, 328, 330, 332, and 325.

15. An antibody according to claim 14, wherein said Fc variant comprises at least one substitution selected from the group consisting of 234E, 234Y, 234I, 235D, 235S, 235Y, 235I, 239D, 239E, 239N, 239Q, 239T, 240I, 240M, 243L, 264I, 264T, 264Y, 266I, 328M, 328I, 328Q, 328D, 328V, 328T, 330Y, 330L, 330I, 332D, 332E, 332N, 332Q, and 325T.

16. An antibody according to claim 15, wherein said Fc variant is selected from the group consisting of 264I, 243L/264I, 328M, 332E, 328M/332E, 264I/332E, 298A/332E, 239E/332E, 239Q/332E, 239E, 330Y, 332D, 328I/332E, 328Q/332E, 264T, 240I, 266I, 239D, 239D/332D, 239D/332E, 239D/332N, 239D/332Q, 239E/332D, 239E/332N, 239E/332Q, 239N/332D, 239N/332E, 239Q/332D, 330Y/332E, 264I/330Y/332E, 330L/332E, 264I/330L/332E, 234E, 234Y, 234I, 235D, 235S, 235Y, 235I, 239T, 240M, 264Y, 330I, 325T, 328D/332E, 328V/332E, 328T/332E, 328I/332E, 239E/264I/332E, 239Q/264I/332E, 239E/264I/330Y/332E, 239D/330Y/332E, 239N/330Y/332E, 239D/330L/332E, 239N/330L/332E, 264I/298A/332E, 239D/298A/332E, 239N/298A/332E, 239D/264I/332E, 239D/264I/298A/332E, and 239D/264I/330L/332E.

Samsung Bioepis Exhibit No. 1002
Page 11231

17. An antibody according to claim 15, wherein said Fc variant further comprises at least one substitution at a position selected from the group consisting of 256, 270, 290, 298, 312, 322, 326, 329, 331, 333, 334, and 339.

18. An antibody according to claim 1 or 2, wherein said parent Fc polypeptide is substantially human, substantially mouse, substantially rat, or substantially monkey.

19. An antibody according to claim 1 or 2, wherein binding to one or more Fc ligands is unaltered.

20. An antibody according to claim 19, wherein said Fc ligand is selected from the group consisting of C1q, FcRn, protein A, and protein G.

21. An antibody according to claim 1 or 2, wherein CDC is unaffected.

22. An antibody according to claim 1 or 2, wherein binding to one or more Fc ligands is altered.

23. An antibody according to claim 1, wherein said Fc variant has a FcγRIIIa-fold:FcγRIIb-fold ratio greater than 1.

24. An antibody according to claim 23, wherein said Fc variant has a FcγRIIIa-fold:FcγRIIb-fold ratio greater than approximately 11:1.

25. An antibody according to claim 24, wherein said Fc variant has a FcγRIIIa-fold:FcγRIIb-fold ratio between approximately 11:1 and approximately 86:1.

26. An antibody according to claim 23, wherein said Fc variant portion comprises at least one substitution at a position corresponding to a position of the human sequence selected from the group consisting of: 234, 235, 239, 240, 264, 296, 330, and I332.

27. An antibody according to claim 26, wherein said Fc variant comprises at least one substitution selected from the group consisting of: 234Y, 234I, 235I, 239D, 239E, 239N, 239Q, 240A, 240M, 264I, 264Y, 296Q, 330L, 330Y, 330I, 332D, and 332E.

Samsung Bioepis Exhibit No. 1002
Page 11232

28. An antibody according to claim 27, wherein said Fc variant is selected from the group consisting of 332E, 264I/332E, 239E/332E, 239Q/332E, 296Q, 330L, 330Y, 332D, 239D, 239D/332E, 330Y/332E, 264I/330Y/332E, 330L/332E, 264I/330L/332E, 234Y, 234I, 235I, 240A, 240M, 264Y, 330I, 239D/330L/332E, 239D/298A/332E, 239N/298A/332E, 239D/264I/332E, 239D/264I/298A/332E, and 239D/264I/330L/332E.

29. An antibody according to claim 26, wherein said Fc variant further comprises one or more substitutions at a position selected from the group consisting of 256, 270, 290, 298, 312, 322, 326, 329, 331, 333, 334, and 339.

30. An antibody according to claim 1, wherein said Fc variant binds to at least one FcγR with reduced affinity relative to the parent Fc polypeptide.

31. An antibody according to claim 30, wherein said FcγR is FcγRIIIa.

32. An antibody according to claim 31, wherein said Fc variant comprises at least one substitution selected from the group consisting of 234D, 234N, 234Q, 234T, 234H, 234V, 234F, 235N, 235Q, 235T, 235H, 235V, 235F, 239E, 239N, 239Q, 239F, 239H, 239Y, 240A, 240T, 241W, 241L, 241Y, 241E, 241R, 243W, 243L 243Y, 243R, 243Q, 244H, 245A, 247V, 247G, 262I, 262A, 262T, 262E, 263I, 263A, 263T, 263M, 264L, 264I, 264W, 264T, 264R, 264F, 264M, 264E, 265G, 265N, 265Q, 265Y, 265F, 265V, 265I, 265L, 265H, 265T, 266A, 266T, 266M, 267Q, 267L, 269H, 269Y, 269F, 269R, 296E, 296Q, 296D, 296N, 296S, 296T, 296L, 296I, 296H, 297S, 297D, 297E, 298H, 299I, 299L, 299A, 299S, 299V, 299H, 299F, 299E, 313F, 325Q, 325L, 325I, 325D, 325E, 325A, 325V, 325H, 327N, 327L, 328M, 328E, 328N, 328Q, 328F, 328H, 328A, 329F, 330L, 330V, 330F, 330R, 330H, 332N, 332Q, 332T, 332H, 332Y, and 332A

33. An antibody according to claim 31, wherein said Fc variant is selected from the group consisting of 264L, 241W, 241L, 243W, 243L, 241L/243L/262I/264I, 241W/243W, 241W/243W/262A/264A, 241L/262I, 243L/262I/264W, 241Y/243Y/262T/264T, 241E/243R/262E/264R, 241E/243Q/262T/264E, 241R/243Q/262T/264R, 241E/243Y/262T/264R, 328M, 328E, 328F, 244H, 245A, 247V, 313F, 244H/245A/247V, 247G, 241E/243R/262E/264R/332E, 241E/243Y/262T/264R/332E, 265G, 265N, 239E/265G, 239E/265N, 239E/265Q, 296E, 296Q, 299I, 327N, 267Q/327S, 267L/327S , 327L, 329F, 330L, 297S, 297D, 297S/332E, 332N, 332Q, 264F, 263I, 299A, 299S, 299V, 325Q, 325L, 325I, 239N, 239F, 239N/332N, 239N/332Q, 239Q/332N, 239Q/332Q, 296D, 296N, 234D, 234N, 234Q, 234T, 234H, 234V, 234F, 235N, 235Q, 235T, 235H, 235V, 235F, 239H, 239Y,

Samsung Bioepis Exhibit No. 1002
Page 11233

240A, 263T, 263M, 264M, 266A, 266T, 266M, 269H, 269Y, 269F, 269R, 296S, 296T, 296L, 296I, 298H, 299H, 330V, 330F, 330R, 330H, 325D, 325E, 325A, 325V, 325H, 328E/332E, 328N/332E, 328Q/332E, 328H/332E, 328A, 332T, 332H, 332Y, and 332A.

34. An antibody comprising a variant of a parent Fc polypeptide comprising at least one amino acid modification in the Fc region of said parent Fc polypeptide, wherein said Fc variant modulates effector function as compared to the parent Fc polypeptide.

35. An antibody according to claim 34, wherein said effector function is ADCC.

36. An antibody according to claim 35, wherein said Fc variant improves ADCC as compared to said parent Fc polypeptide.

37. An antibody according to claim 36, wherein said ADCC improvement is approximately 5-fold greater than that of said parent Fc polypeptide.

38. An antibody according to claim 37, wherein said ADCC improvement is between approximately 5-fold and 50-fold greater than that of said parent Fc polypeptide.

39. An antibody according to claim 37, wherein said Fc variant portion comprises at least one substitution at a position corresponding to a position of the human sequence selected from the group consisting of: 234, 235, 239, 240, 243, 264, 266, 328, 330, 332, and 325.

40. An antibody according to claim 39, wherein said Fc variant comprises at least one substitution selected from the group consisting of 234E, 234Y, 234I, 235D, 235S, 235Y, 235I, 239D, 239E, 239N, 239Q, 239T, 240I, 240M, 243L, 264I, 264T, 264Y, 266I, 328M, 328I, 328Q, 328D, 328V, 328T, 330Y, 330L, 330I, 332D, 332E, 332N, 332Q, and 325T.

41. An antibody according to claim 39, wherein said Fc variant is selected from the group consisting of 264I, 243L/264I, 328M, 332E, 328M/332E, 264I/332E, 298A/332E, 239E/332E, 239Q/332E, 239E, 330Y, 332D, 328I/332E, 328Q/332E, 264T, 240I, 266I, 239D, 239D/332D, 239D/332E, 239D/332N, 239D/332Q, 239E/332D, 239E/332N, 239E/332Q, 239N/332D, 239N/332E, 239Q/332D, 330Y/332E, 264I/330Y/332E, 330L/332E, 264I/330L/332E, 234E, 234Y, 234I, 235D, 235S, 235Y, 235I, 239T, 240M, 264Y, 330I, 325T, 328D/332E, 328V/332E, 328T/332E, 328I/332E, 239E/264I/332E, 239Q/264I/332E, 239E/264I/330Y/332E,

Samsung Bioepis Exhibit No. 1002
Page 11234

239D/330Y/332E, 239N/330Y/332E, 239D/330L/332E, 239N/330L/332E, 264I/298A/332E, 239D/298A/332E, 239N/298A/332E, 239D/264I/332E, 239D/264I/298A/332E, and 239D/264I/330L/332E.

42. An antibody according to claim 39, wherein said Fc variant further comprises at least one substitution at a position selected from the group consisting of 256, 270, 290, 298, 312, 322, 326, 329, 331, 333, 334, and 339.

43. An antibody according to claim 39, wherein said parent Fc polypeptide is substantially human, substantially mouse, substantially rat, or substantially monkey.

44. An antibody according to claim 35, wherein said Fc variant reduces ADCC as compared to said parent Fc polypeptide.

45. An antibody according to claim 44, wherein said Fc variant comprises at least one substitution selected from the group consisting of 234D, 234N, 234Q, 234T, 234H, 234V, 234F, 235N, 235Q, 235T, 235H, 235V, 235F, 239E, 239N, 239Q, 239F, 239H, 239Y, 240A, 240T, 241W, 241L, 241Y, 241E, 241R, 243W, 243L 243Y, 243R, 243Q, 244H, 245A, 247V, 247G, 262I, 262A, 262T, 262E, 263I, 263A, 263T, 263M, 264L, 264I, 264W, 264T, 264R, 264F, 264M, 264E, 265G, 265N, 265Q, 265Y, 265F, 265V, 265I, 265L, 265H, 265T, 266A, 266T, 266M, 267Q, 267L, 269H, 269Y, 269F, 269R, 296E, 296Q, 296D, 296N, 296S, 296T, 296L, 296I, 296H, 297S, 297D, 297E, 298H, 299I, 299L, 299A, 299S, 299V, 299H, 299F, 299E, 313F, 325Q, 325L, 325I, 325D, 325E, 325A, 325V, 325H, 327N, 327L, 328M, 328E, 328N, 328Q, 328F, 328H, 328A, 329F, 330L, 330V, 330F, 330R, 330H, 332N, 332Q, 332T, 332H, 332Y, and 332A.

46. An antibody according to claim 44, wherein said Fc variant is selected from the group consisting of 264L, 241W, 241L, 243W, 243L, 241L/243L/262I/264I, 241W/243W, 241W/243W/262A/264A, 241L/262I, 243L/262I/264W, 241Y/243Y/262T/264T, 241E/243R/262E/264R, 241E/243Q/262T/264E, 241R/243Q/262T/264R, 241E/243Y/262T/264R, 328M, 328E, 328F, 244H, 245A, 247V, 313F, 244H/245A/247V, 247G, 241E/243R/262E/264R/332E, 241E/243Y/262T/264R/332E, 265G, 265N, 239E/265G, 239E/265N, 239E/265Q, 296E, 296Q, 299I, 327N, 267Q/327S, 267L/327S , 327L, 329F, 330L, 297S, 297D, 297S/332E, 332N, 332Q, 264F, 263I, 299A, 299S, 299V, 325Q, 325L, 325I, 239N, 239F, 239N/332N, 239N/332Q, 239Q/332N, 239Q/332Q, 296D, 296N, 234D, 234N, 234Q, 234T, 234H, 234V, 234F, 235N, 235Q, 235T, 235H, 235V, 235F, 239H, 239Y, 240A, 263T, 263M, 264M, 266A, 266T, 266M, 269H, 269Y, 269F, 269R, 296S, 296T, 296L,

Samsung Bioepis Exhibit No. 1002
Page 11235

296I, 298H, 299H, 330V, 330F, 330R, 330H, 325D, 325E, 325A, 325V, 325H, 328E/332E, 328N/332E, 328Q/332E, 328H/332E, 328A, 332T, 332H, 332Y, and 332A.

47. An antibody comprising an aglycosylated Fc variant of a parent Fc polypeptide comprising at least one amino acid modification in the Fc region of said parent Fc polypeptide, wherein said aglycosylated Fc variant has improved stability, solubility, or binding affinity to an Fc ligand relative to the aglycosylated form of said parent Fc polypeptide.

48. An antibody according to claim 47, wherein said aglycosylated Fc variant has improved binding affinity to an Fc ligand as compared to the aglycosylated form of the parent Fc polypeptide.

49. An antibody according to claim 48, wherein said Fc ligand is an FcγR.

50. An antibody according to claim 49, wherein said FcγR is FcγRIIIa.

51. An antibody according to claim 48, wherein said improved binding affinity is within 0.4-fold of the glycosylated form of the parent Fc polypeptide.

52. An antibody according to claim 47, wherein said Fc variant portion comprises at least one substitution at a position corresponding to a position of the human sequence selected from the group consisting of: 239, 241, 243, 262, 264, 265, 296, 297, 330, and 332.

53. An antibody according to claim 52, wherein said Fc variant comprises one or more substitutions selected from the group consisting of 239D, 239E, 241Y, 243Y, 262T, 264T, 264E, 265Y, 265H, 296N, 297D, 330Y, and 332E.

54. An antibody according to claim 52, wherein said Fc variant is selected from the group consisting of 297D/332E, 241Y/243Y/262T/264T/297D/332E, 239D/297D/332E, 239E/297D/332E, 239D/265Y/297D/332E, 239D/265H/297D/332E, 264E/297D/332E, 296N/297D/332E, and 297D/330Y/332E.

55. An antibody according to claim 53, wherein said aglycosylated Fc variant portion comprises at least one substitution at a position corresponding to a position of the human sequence

Samsung Bioepis Exhibit No. 1002
Page 11236

selected from the group consisting of: 256, 270, 290, 298, 312, 322, 326, 329, 331, 333, 334, and 339.

56. An antibody according to claim 1 comprising a Fc fusion comprising said Fc variant.

57. An antibody according to claim 1 or 56, wherein said antibody further comprises an engineered glycoform.

58. An antibody according to claim 57, wherein said engineered glycoform improves effector function.

59. A pharmaceutical composition comprising an antibody according to claim 1 and a pharmaceutically acceptable carrier.

60. A method of treating a mammal in need of said treatment, comprising administering an antibody of claim 1.

61. An antibody comprising an Fc variant, said Fc variant comprises at least one substitution selected from the group consisting of: 332D, 332E, 332N, or 332Q, wherein said positions corresponding to the human sequence position, wherein said antibody has specificity for a target antigen selected from the group consisting of CD20, CD22, CD33, CD52, Her2/neu, EGFR, EpCAM, MUC1, GD3, CEA, CA 125, HLA-DR, TNFalpha, and VEGF.

62. An antibody comprising an Fc variant, said Fc variant comprises at least one substitution selected from the group consisting of 264I, 264T, or 264Y, wherein said positions corresponding to the human sequence position, wherein said antibody or Fc fusion has specificity for a target antigen selected from the group consisting of CD20, CD22, CD33, CD52, Her2/neu, EGFR, EpCAM, MUC1, GD3, CEA, CA 125, HLA-DR, TNFalpha, and VEGF.

63. An antibody comprising an Fc variant, said Fc variant comprises at least one substitution selected from the group consisting of 239D, 239E, 239N, 239Q, or 239T, wherein said positions corresponding to the human sequence position, wherein said antibody or Fc fusion has specificity for a target antigen selected from the group consisting of CD20, CD22, CD33,

Samsung Bioepis Exhibit No. 1002
Page 11237

CD52, Her2/neu, EGFR, EpCAM, MUC1, GD3, CEA, CA 125, HLA-DR, TNFalpha, and VEGF.

64. An antibody comprising an Fc variant, said Fc variant comprises at least one substitution selected from the group consisting of 330Y, 330L, or 330I, wherein said positions corresponding to the human sequence position, wherein said antibody or Fc fusion has specificity for a target antigen selected from the group consisting of CD20, CD22, CD33, CD52, Her2/neu, EGFR, EpCAM, MUC1, GD3, CEA, CA 125, HLA-DR, TNFalpha, and VEGF.

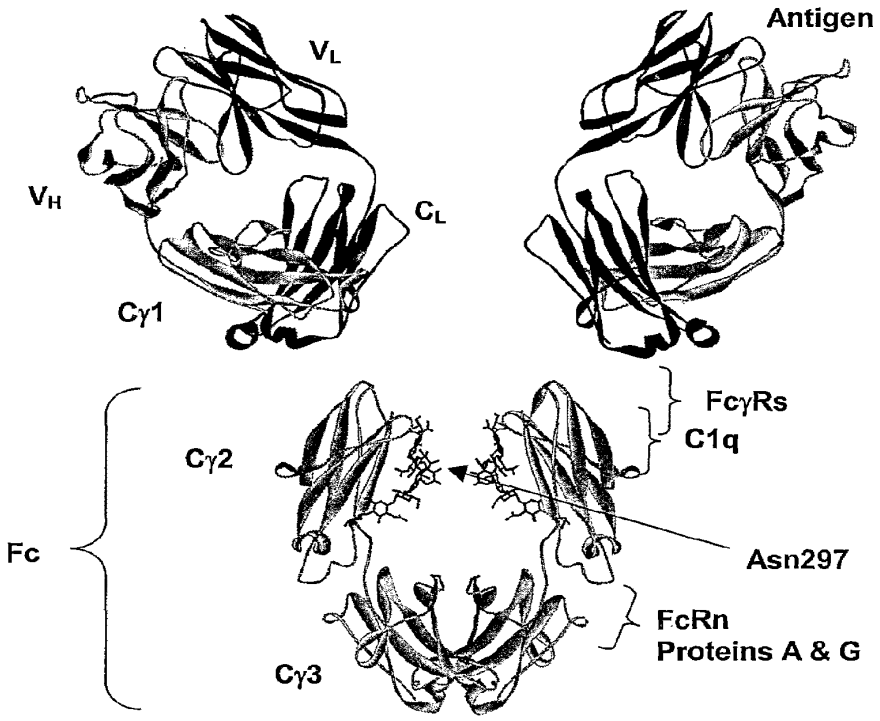
65. An antibody comprising an Fc variant, said Fc variant comprises at least one substitution selected from the group consisting of 240I or 240M, wherein said positions corresponding to the human sequence position, wherein said antibody or Fc fusion has specificity for a target antigen selected from the group consisting of CD20, CD22, CD33, CD52, Her2/neu, EGFR, EpCAM, MUC1, GD3, CEA, CA 125, HLA-DR, TNFalpha, and VEGF.

66. An antibody comprising an Fc variant, said Fc variant comprises a substitution consisting of 297D, wherein said position corresponds to the human sequence position, wherein said antibody or Fc fusion has specificity for a target antigen selected from the group consisting of CD20, CD22, CD33, CD52, Her2/neu, EGFR, EpCAM, MUC1, GD3, CEA, CA 125, HLA-DR, TNFalpha, and VEGF.

67. An antibody according to claims 61, 62, 63, 64, 65 or 66 wherein said Fc variant additionally comprises the substitutions 298A.

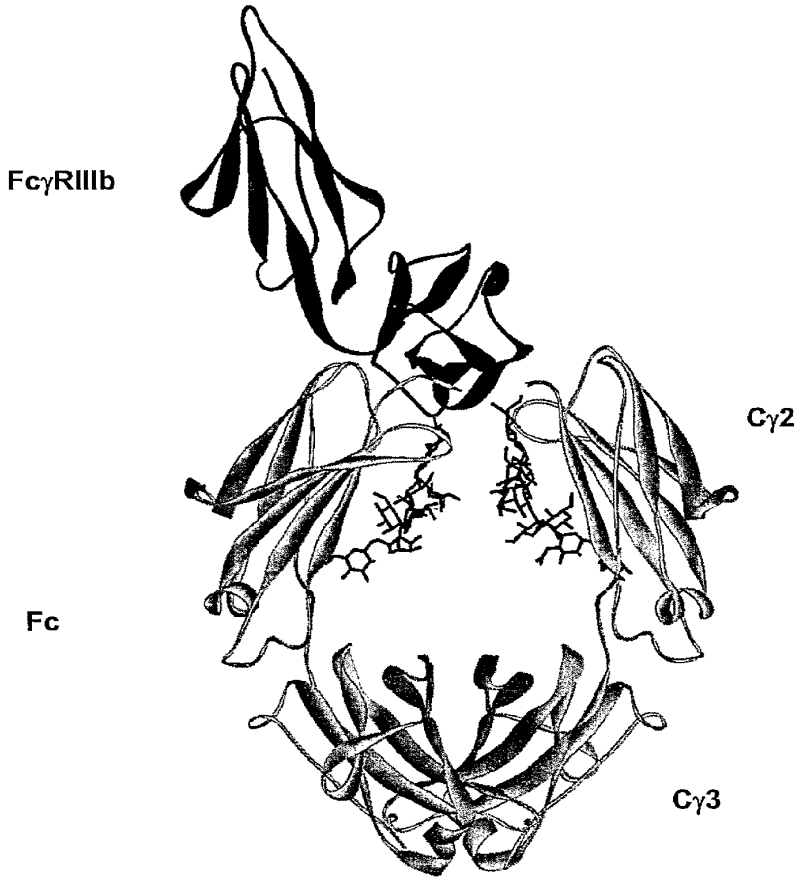
Samsung Bioepis Exhibit No. 1002
Page 11238

Figure 1



Samsung Bioepis Exhibit No. 1002
Page 11239

Figure 2



Samsung Bioepis Exhibit No. 1002
Page 11240

Figure 3

```
VH1->
1        10         20         30         40         50         60
12345678901234567890123456789012345678901234567890123456789012345678901234567890
QVQLQESGPGLVRPSQTLSLTCTVSGFTFTDFYMNWVRQPPGRGLEWIGFIRDKAKGYTT

         70         80         90        100        110        120
12345678901234567890123456789012345678901234567890123456789012345678901234567890
EYNPSVKGRVTMLVDTSKNQFSLRLSSVTAADTAVYYCAREGHTAAPFDYWGQGSLVTVS

  Cγ1->
       130        140        150        160        170        180
12345678901234567890123456789012345678901234567890123456789012345678901234567890
SASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQS

                                                 HINGE->
       190        200        210        220        230        240
12345678901234567890123456789012345678901234567890123456789012345678901234567890
SGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLG
                                                 1234567890123456
                                       KABAT  22        23

Cγ2->
       250        260        270        280        290        300
12345678901234567890123456789012345678901234567890123456789012345678901234567890
GPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQY
78901234567890123456789012345678901234567890123456789012345678901234567890123456
 240        250        260        270        280        290

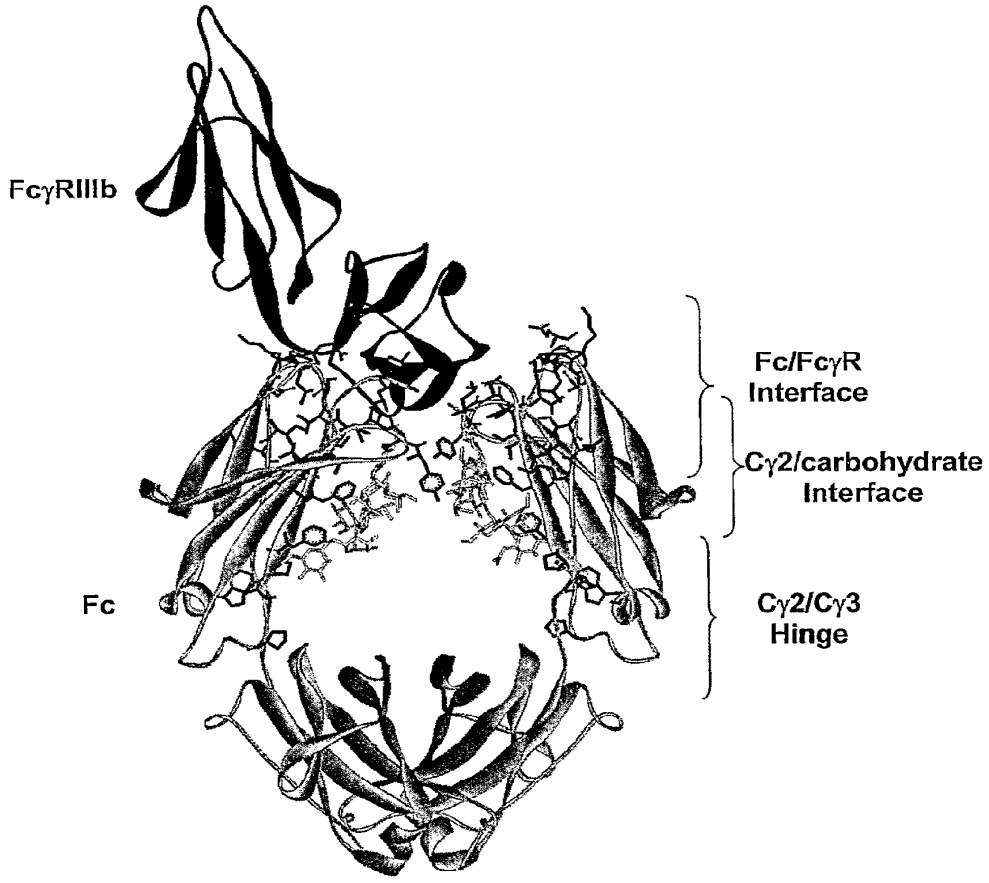
                                                       ?Cγ3?->
       310        320        330        340        350        360
12345678901234567890123456789012345678901234567890123456789012345678901234567890
NSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRD
78901234567890123456789012345678901234567890123456789012345678901234567890123456
 300        310        320        330        340        350

       370        380        390        400        410        420
12345678901234567890123456789012345678901234567890123456789012345678901234567890
ELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSR
78901234567890123456789012345678901234567890123456789012345678901234567890123456
 360        370        380        390        400        410

       430        440        450
123456789012345678901234567890123456789012345678901
WQQGNVFSCSVMHEALHNHYTQKSLSLSPGK
78901234567890123456789012345678901234567890123456
 420        430        440
```


Samsung Bioepis Exhibit No. 1002
Page 11241

Figure 4



Samsung Bioepis Exhibit No. 1002
Page 11242

Figure 5

```
22        23        24        25        26        27        28
 12345678901234567890123456789012345678901234567890123456789012345678
 DKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVD

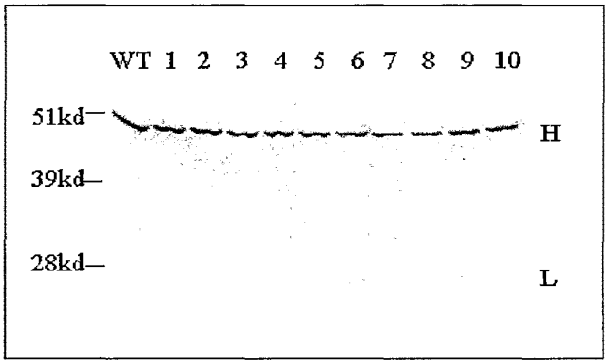
          29        30        31        32        33        34
 12345678901234567890123456789012345678901234567890123456789012345678
 GVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAK

          35        36        37        38        39        40
 12345678901234567890123456789012345678901234567890123456789012345678
 GQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDS

          41        42        43        44
 1234567890123456789012345678901234567890123456
 DGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK
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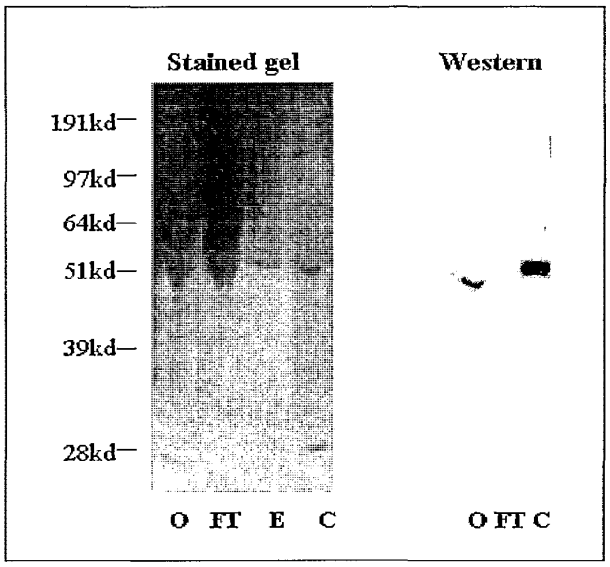

Samsung Bioepis Exhibit No. 1002
Page 11243

Figure 6



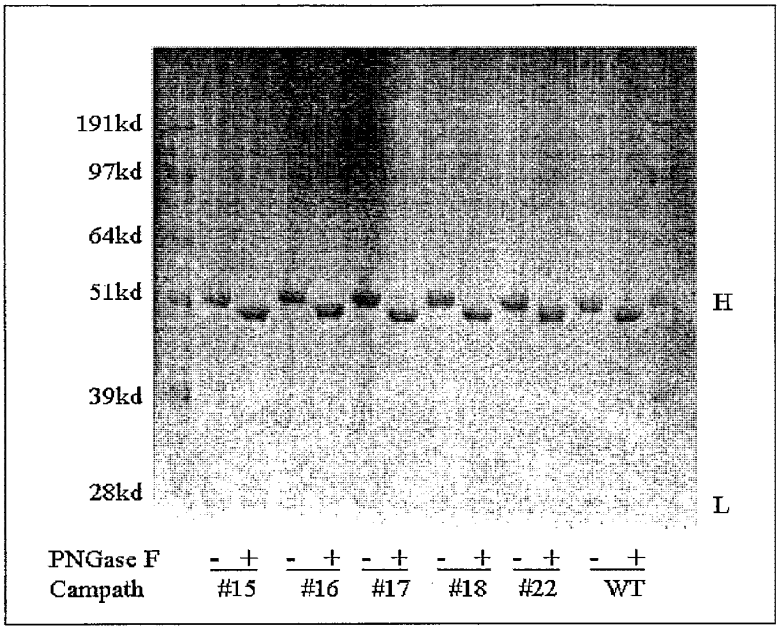
Samsung Bioepis Exhibit No. 1002
Page 11244

Figure 7



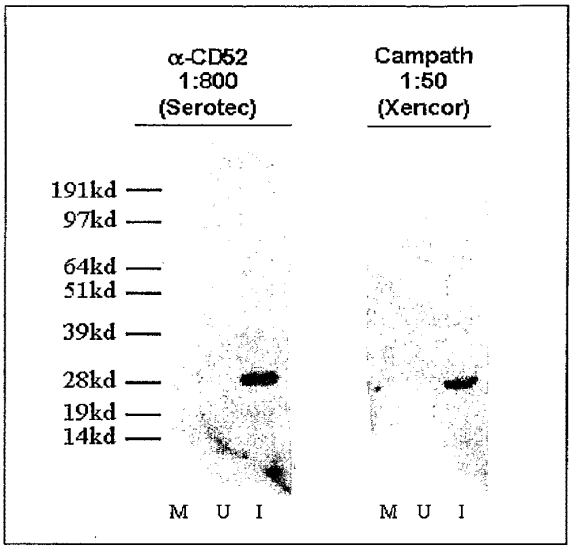
Samsung Bioepis Exhibit No. 1002
Page 11245

Figure 8



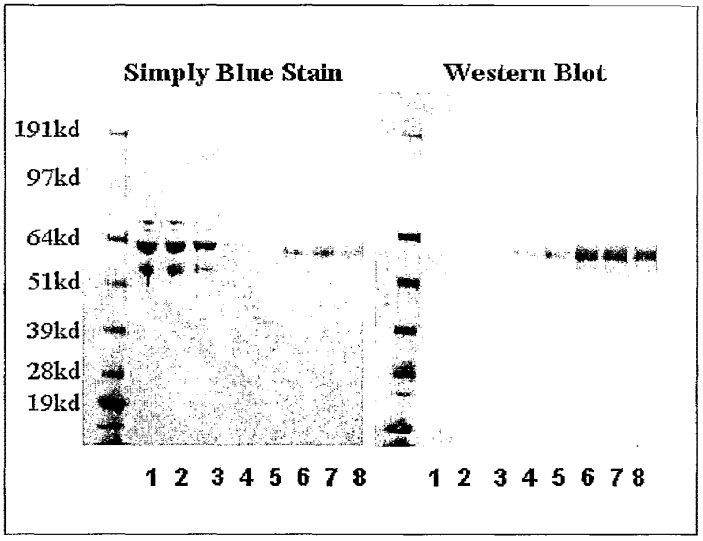
Samsung Bioepis Exhibit No. 1002
Page 11246

Figure 9



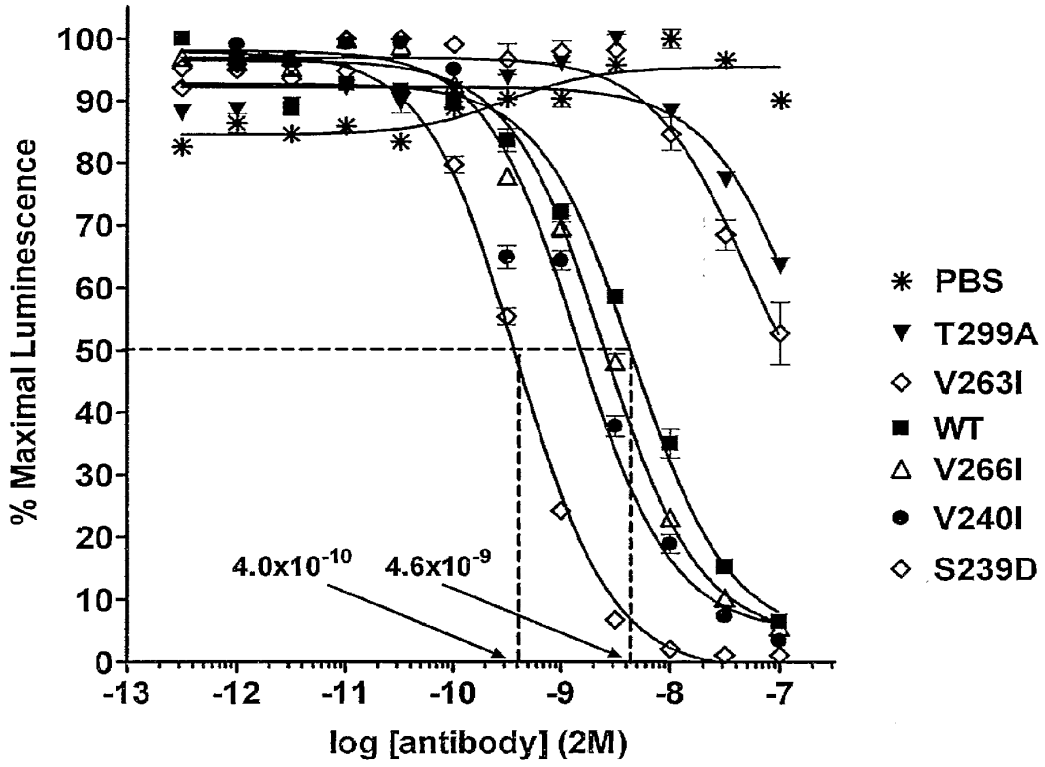
Samsung Bioepis Exhibit No. 1002
Page 11247

Figure 10



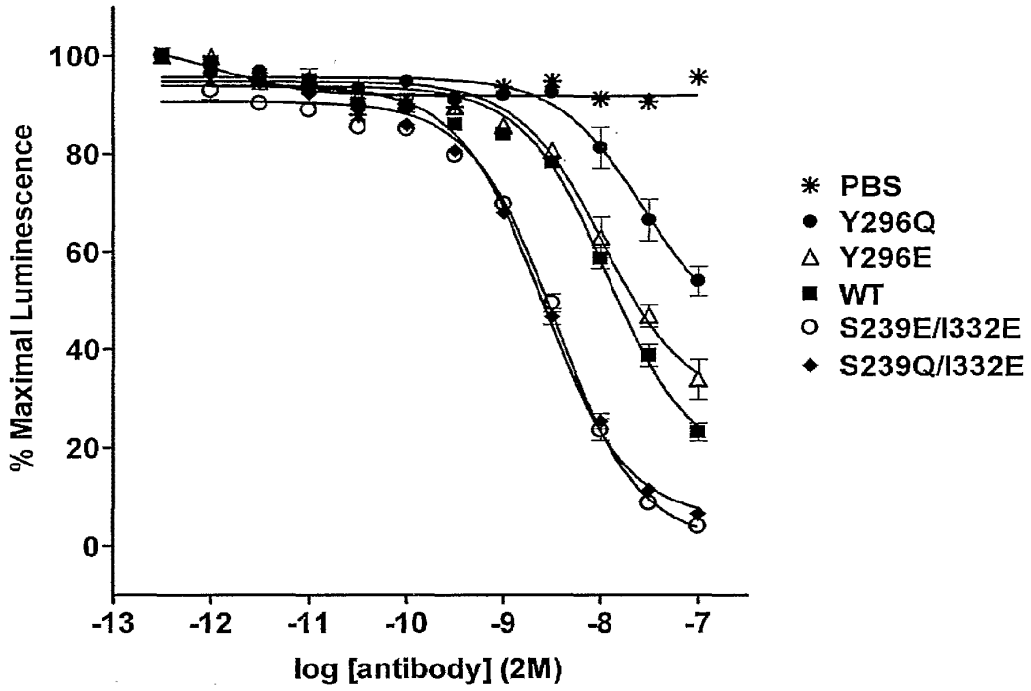
Samsung Bioepis Exhibit No. 1002
Page 11248

Figure 11



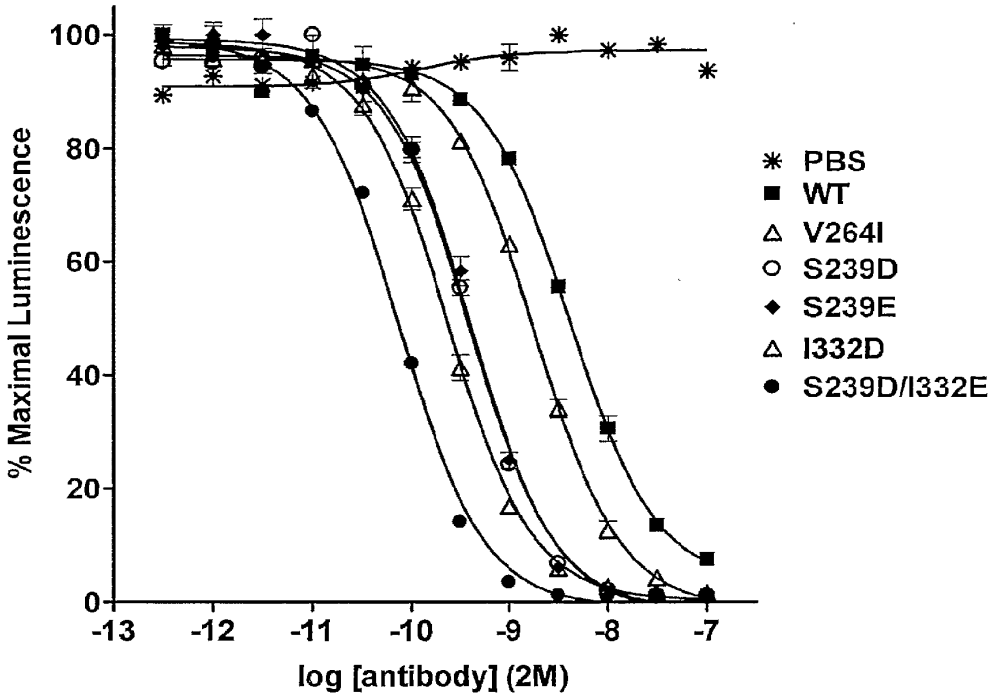
Samsung Bioepis Exhibit No. 1002
Page 11249

Figure 12



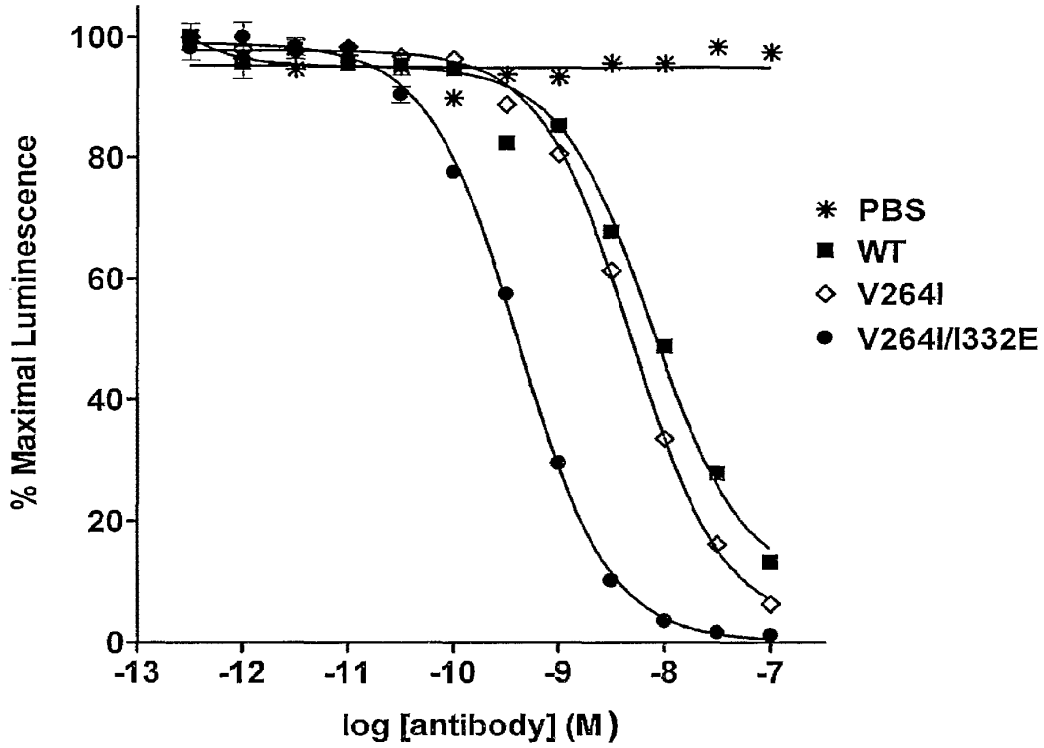
Samsung Bioepis Exhibit No. 1002
Page 11250

Figure 13



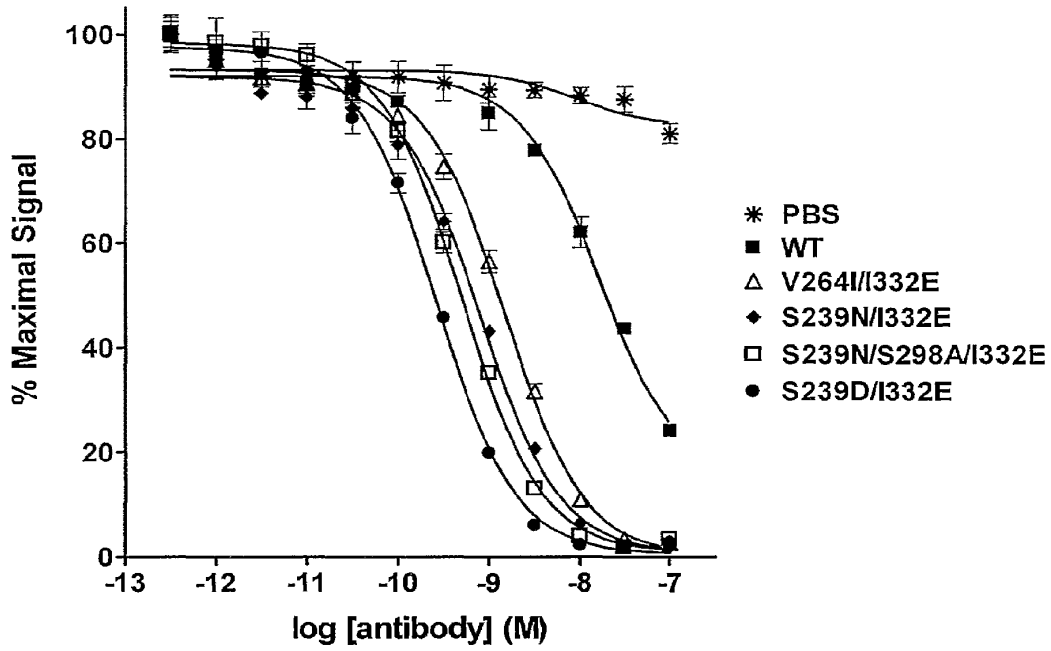
Samsung Bioepis Exhibit No. 1002
Page 11251

Figure 14



Samsung Bioepis Exhibit No. 1002
Page 11252

Figure 15



Samsung Bioepis Exhibit No. 1002
Page 11253

Figure 16a

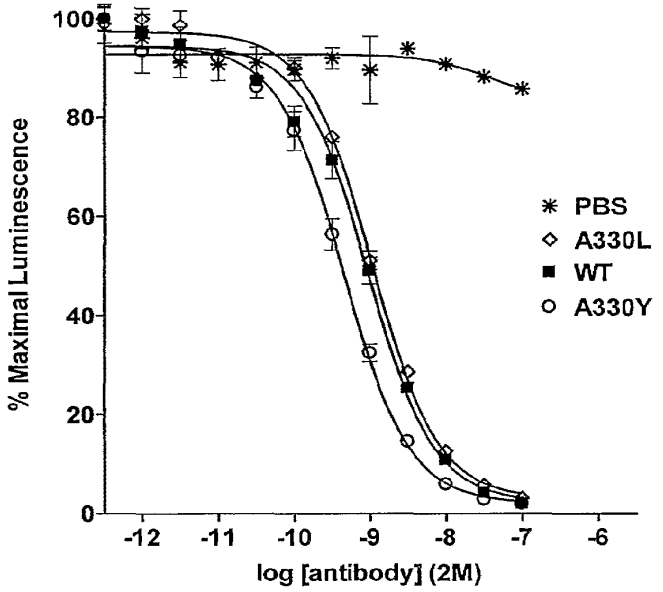
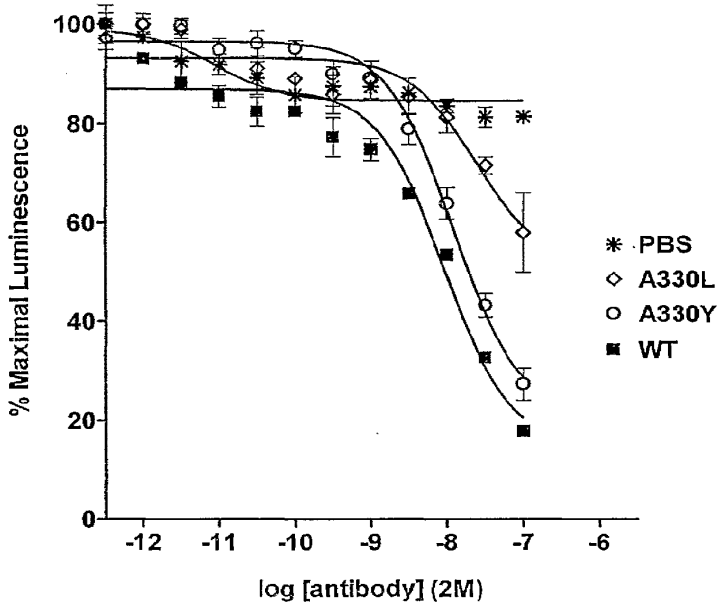
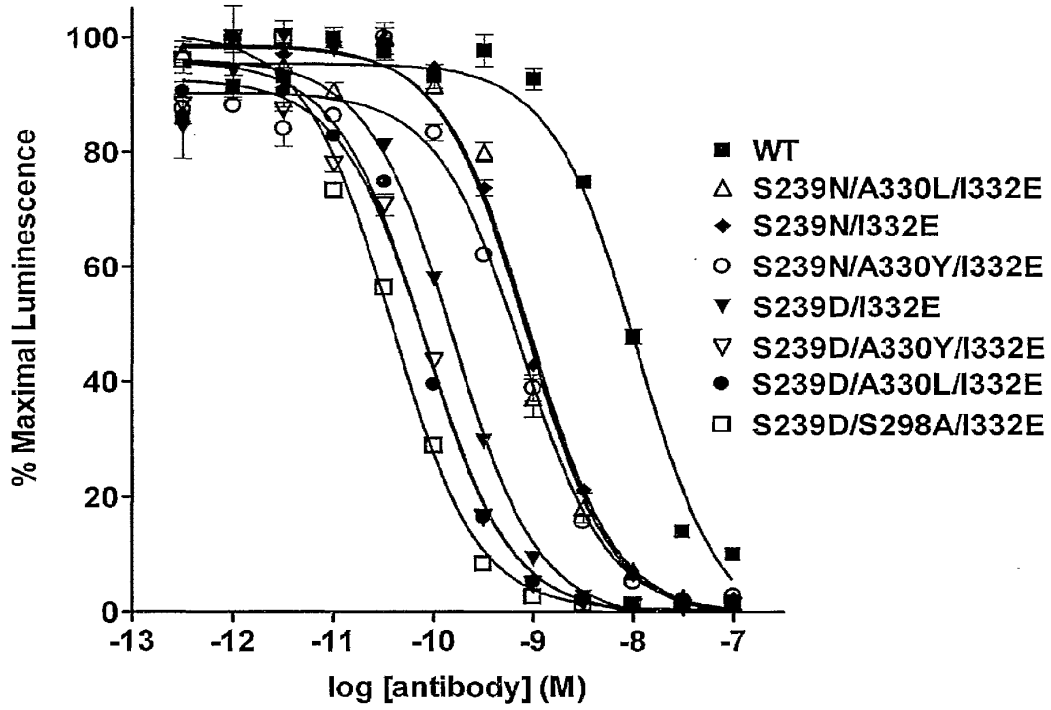


Figure 16b



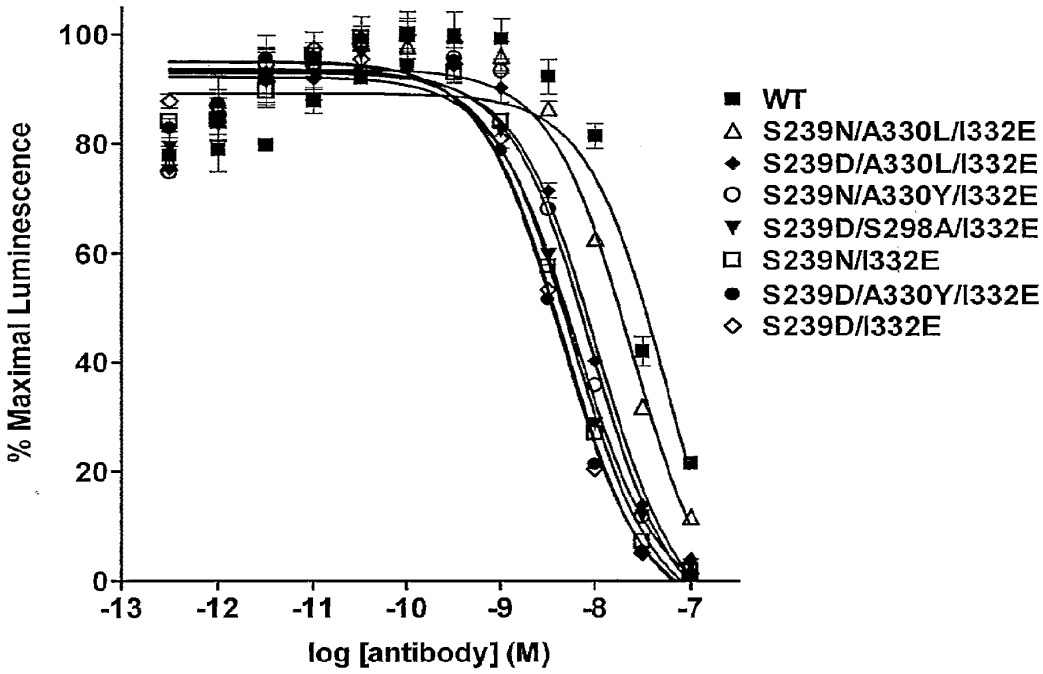
Samsung Bioepis Exhibit No. 1002
Page 11254

Figure 17



Samsung Bioepis Exhibit No. 1002
Page 11255

Figure 18



Samsung Bioepis Exhibit No. 1002
Page 11256

Figure 19a

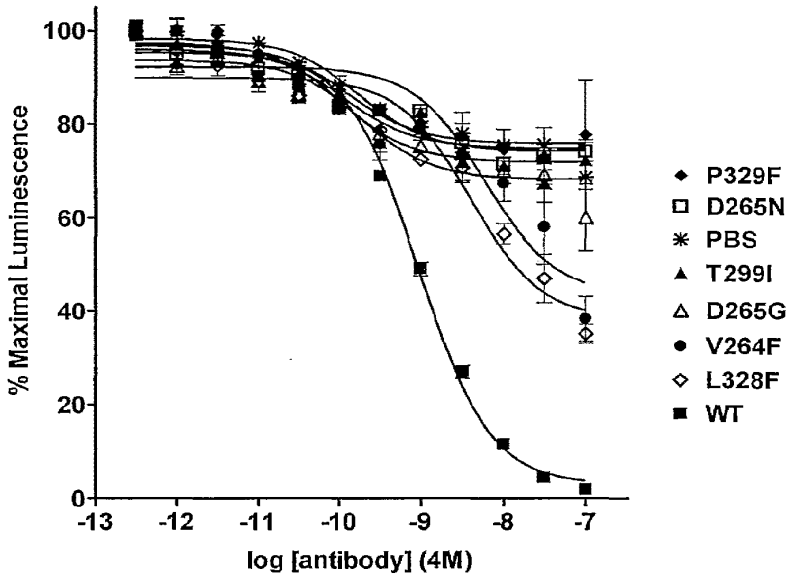
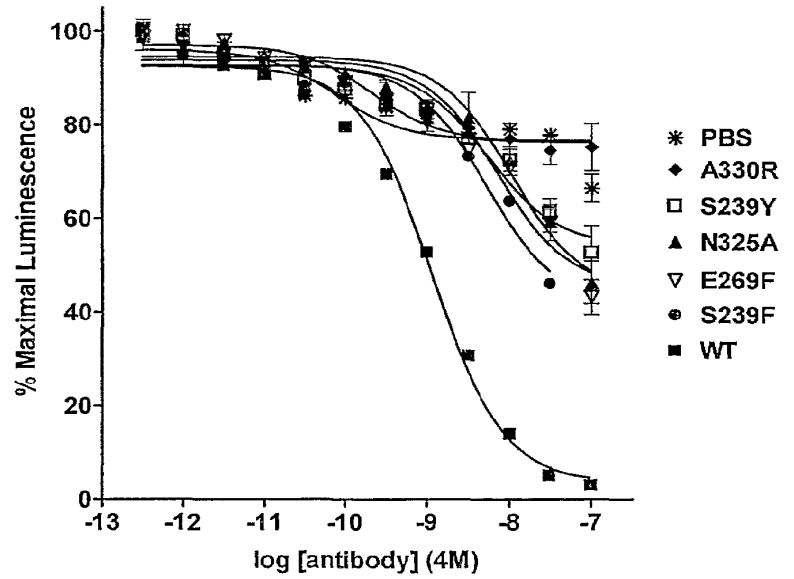
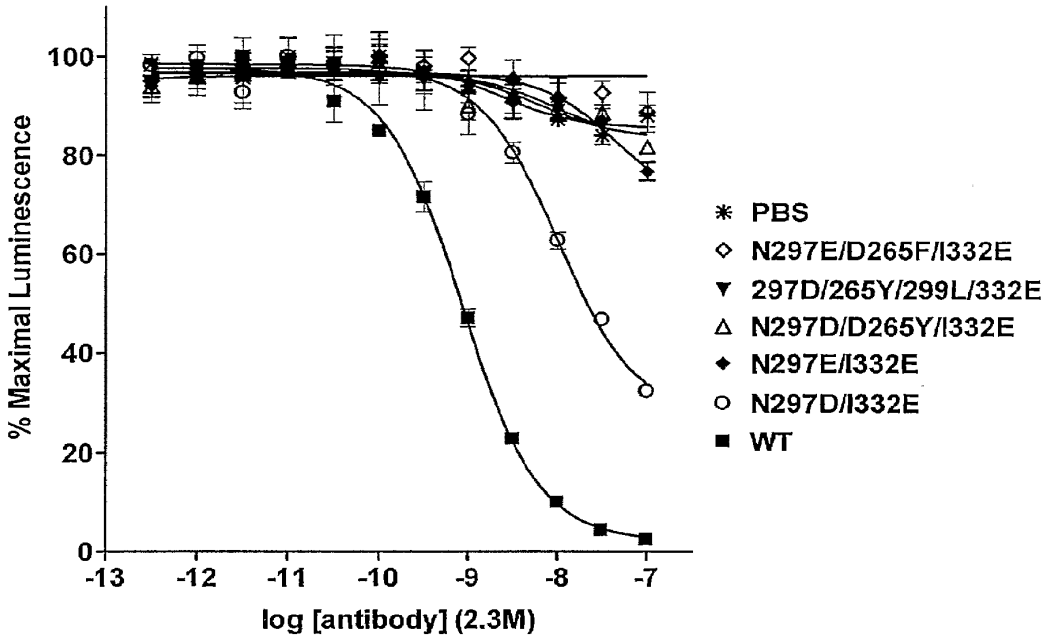


Figure 19b



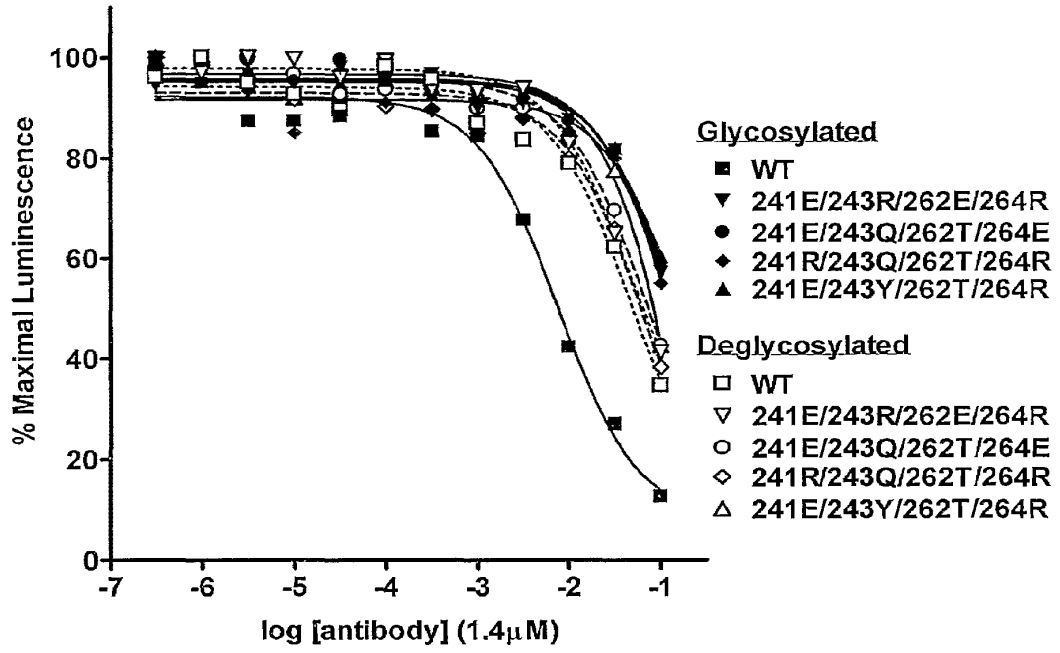
Samsung Bioepis Exhibit No. 1002
Page 11257

Figure 20



Samsung Bioepis Exhibit No. 1002
Page 11258

Figure 21



Samsung Bioepis Exhibit No. 1002
Page 11259

Figure 22a

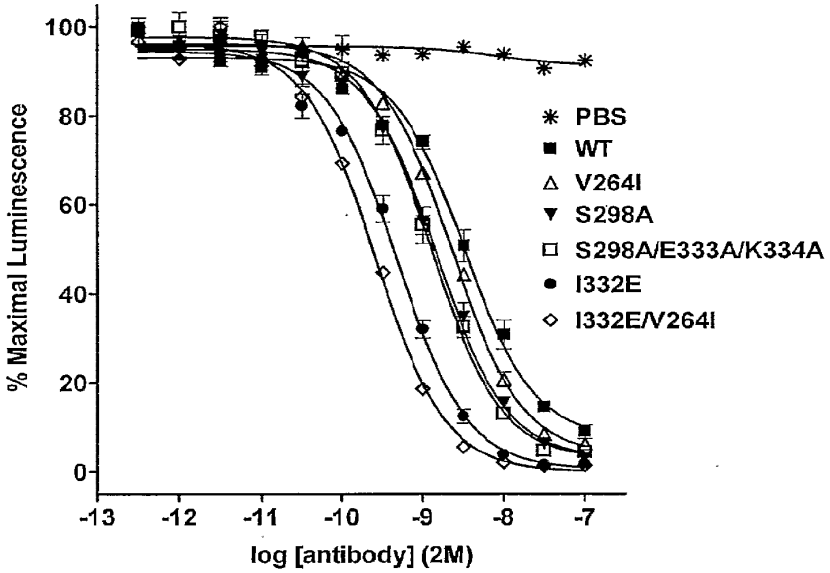
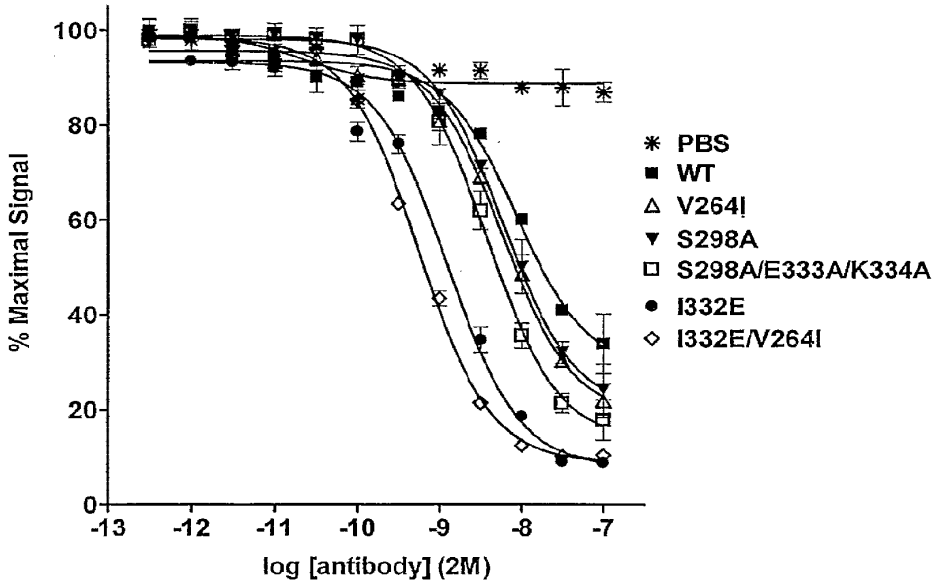


Figure 22b



Samsung Bioepis Exhibit No. 1002
Page 11260

Figure 23a

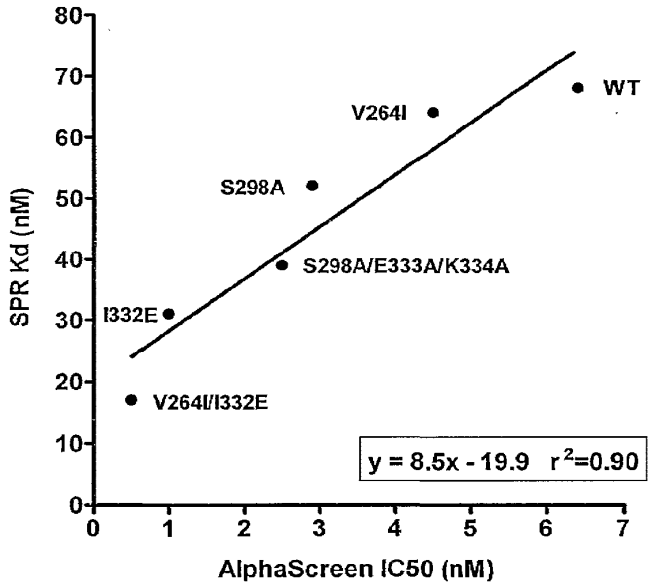
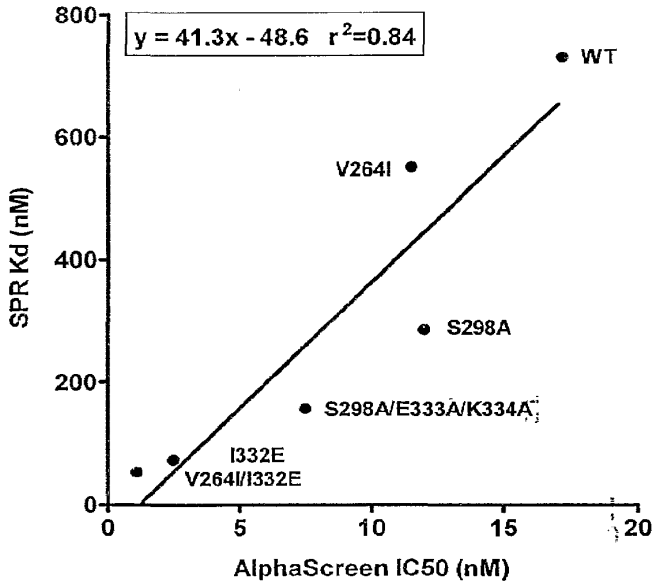


Figure 23b



Samsung Bioepis Exhibit No. 1002
Page 11261

Figure 23c

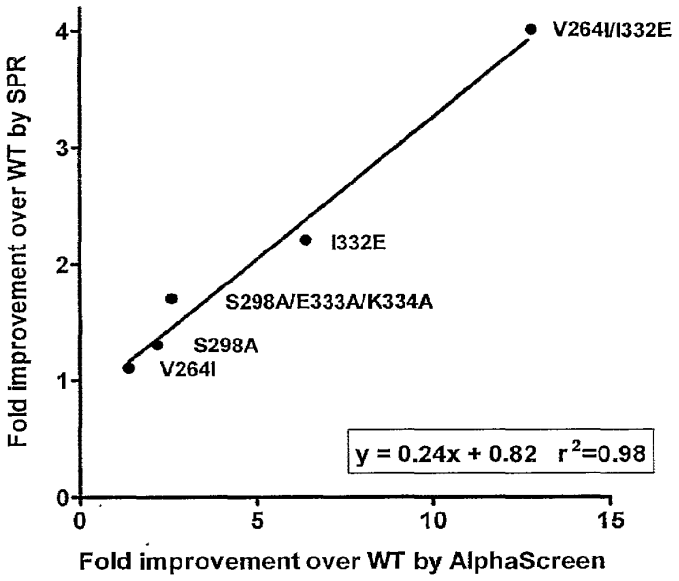
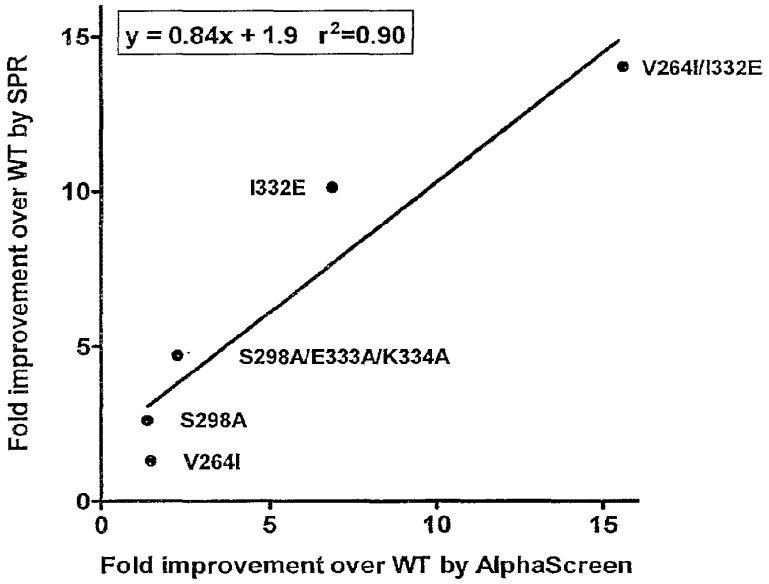
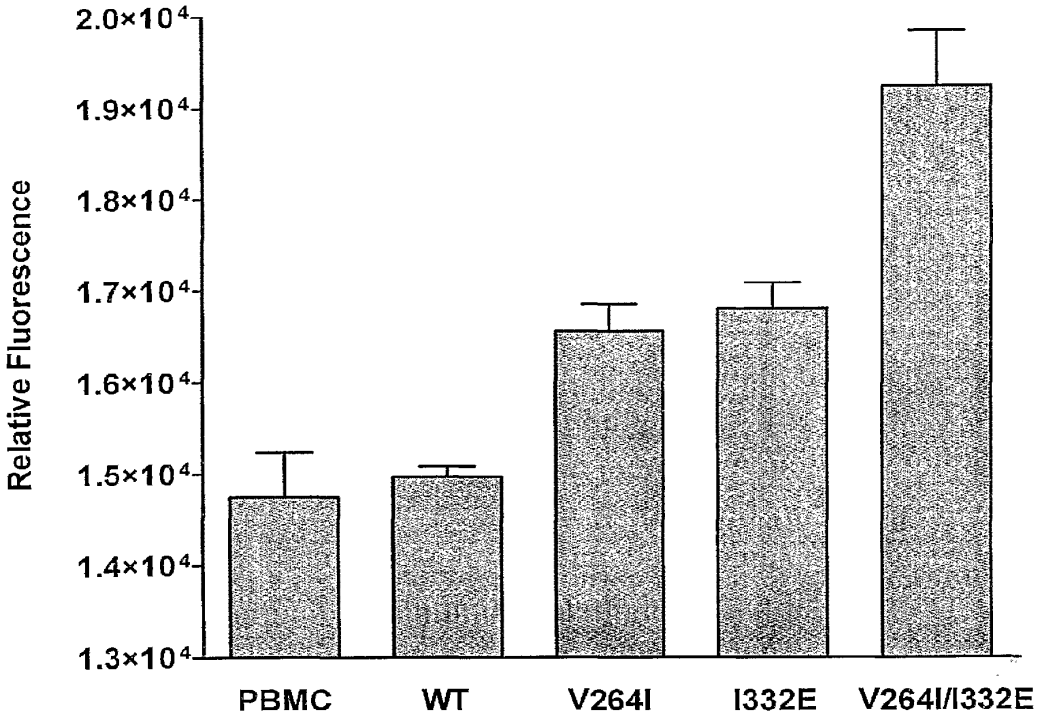


Figure 23d



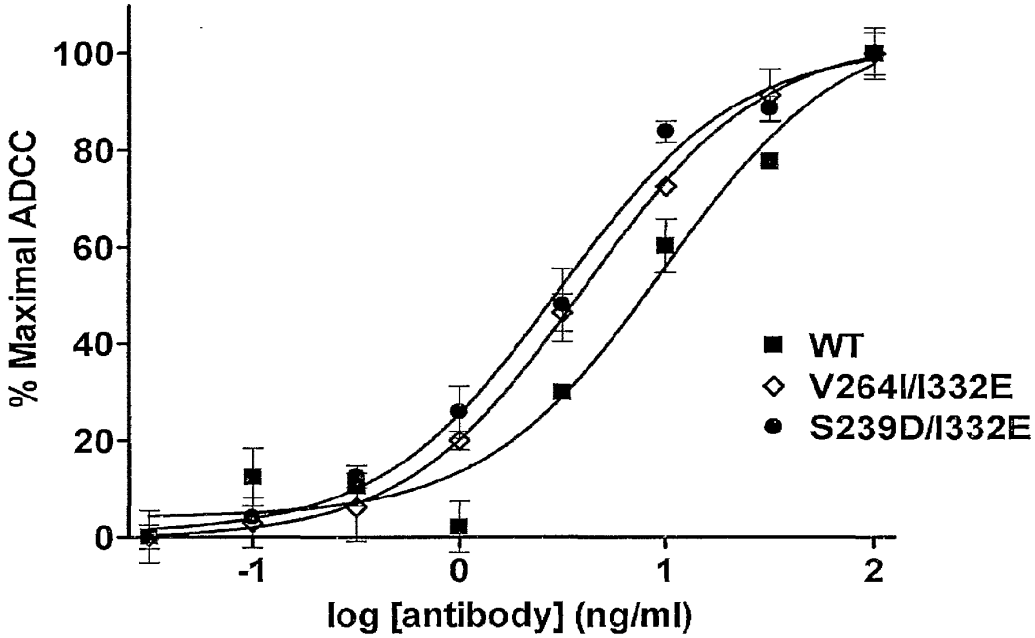
Samsung Bioepis Exhibit No. 1002
Page 11262

Figure 24a



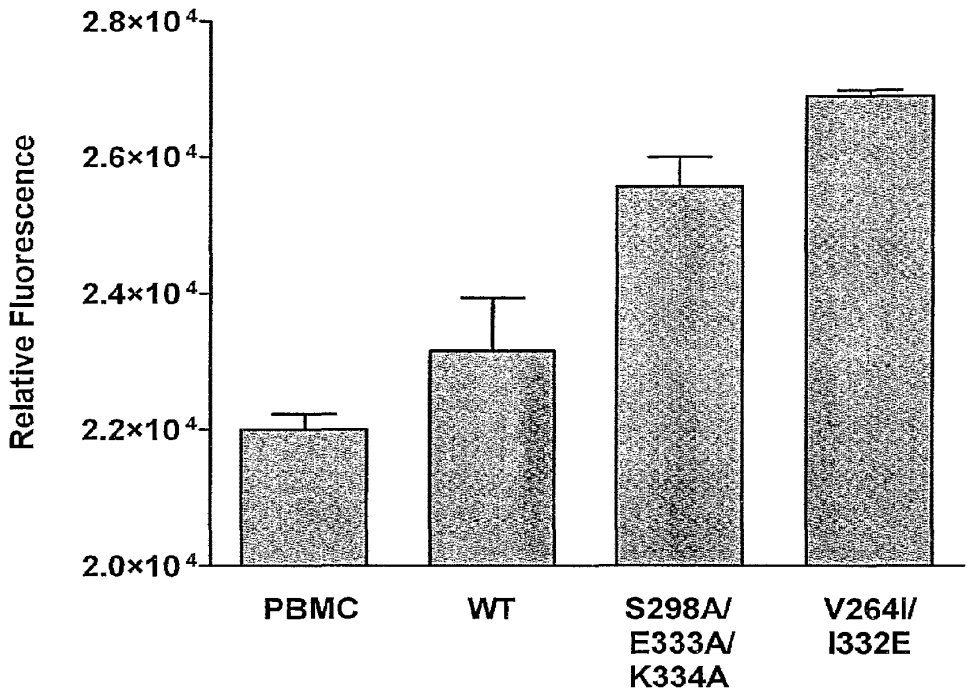
Samsung Bioepis Exhibit No. 1002
Page 11263

Figure 24b



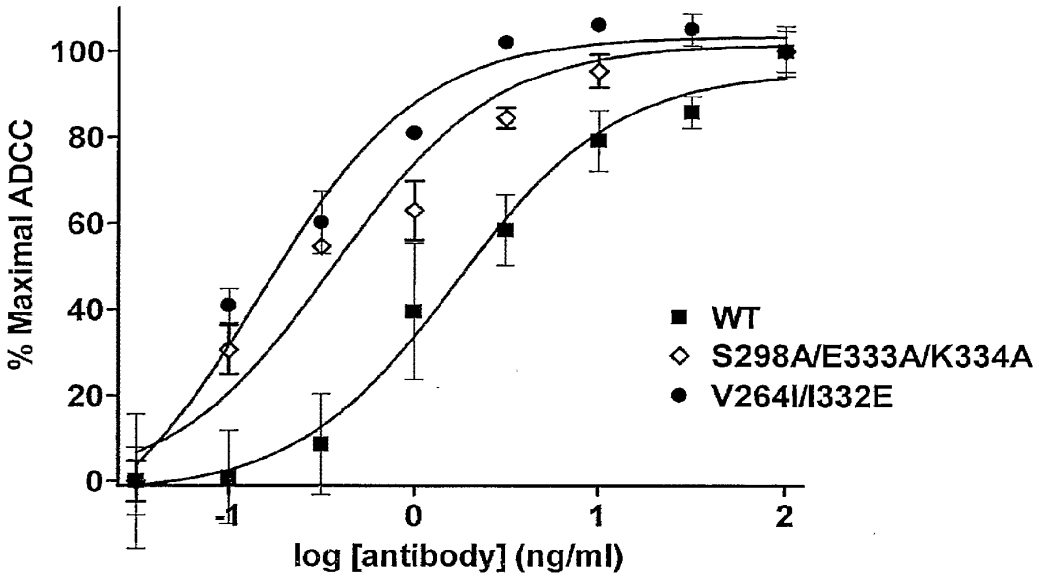
Samsung Bioepis Exhibit No. 1002
Page 11264

Figure 25a



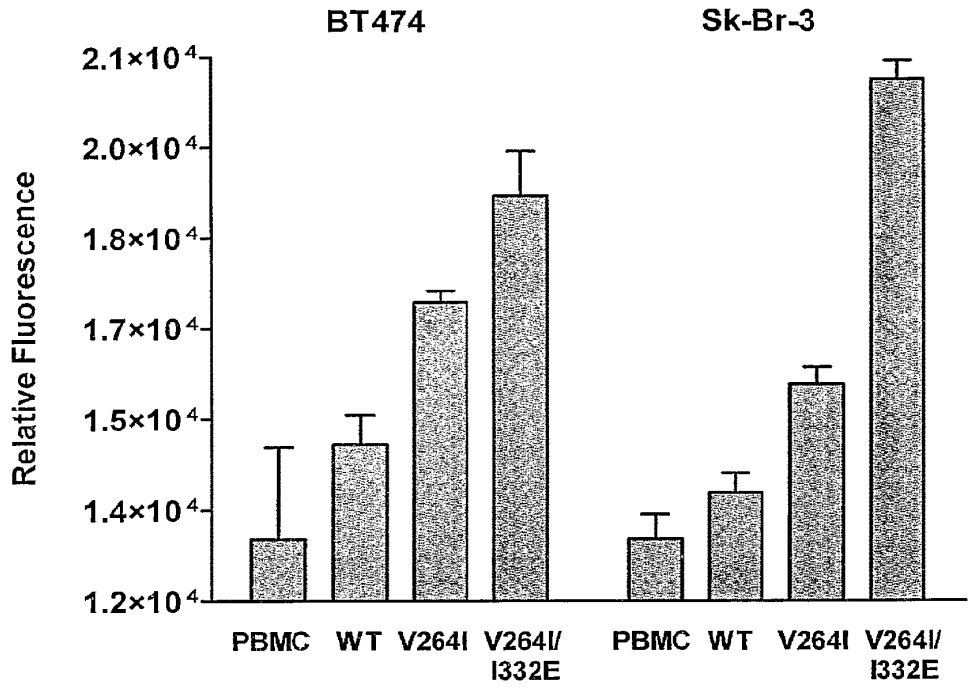
Samsung Bioepis Exhibit No. 1002
Page 11265

Figure 25b



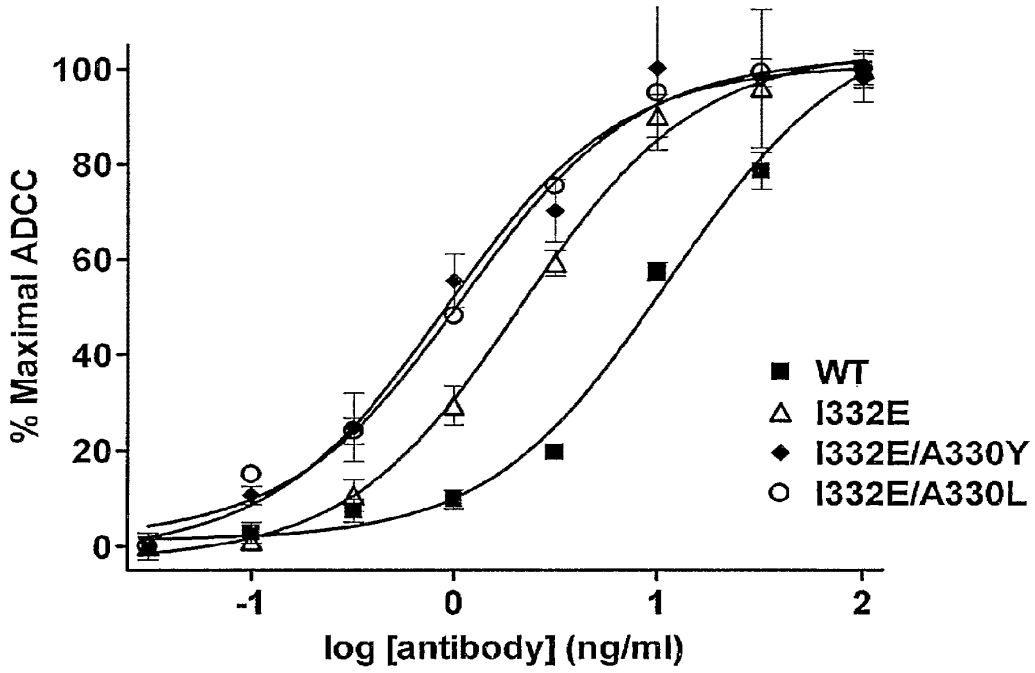
Samsung Bioepis Exhibit No. 1002
Page 11266

Figure 26a



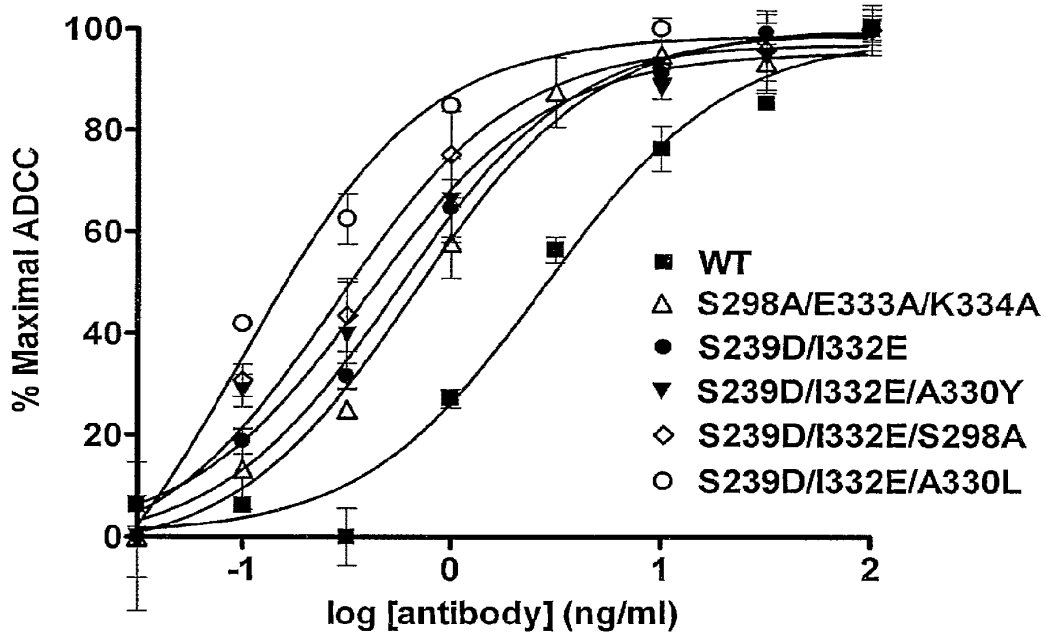
Samsung Bioepis Exhibit No. 1002
Page 11267

Figure 26b



Samsung Bioepis Exhibit No. 1002
Page 11268

Figure 26c



Samsung Bioepis Exhibit No. 1002
Page 11269

Figure 27a

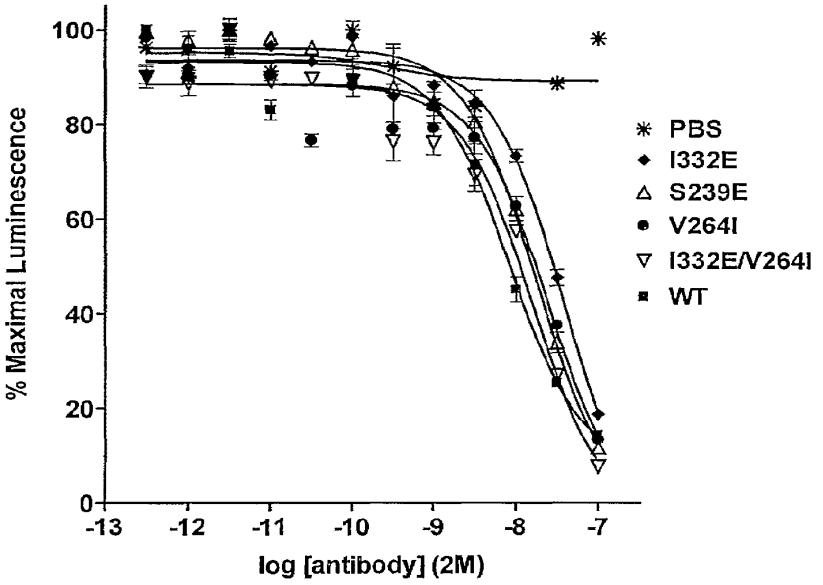
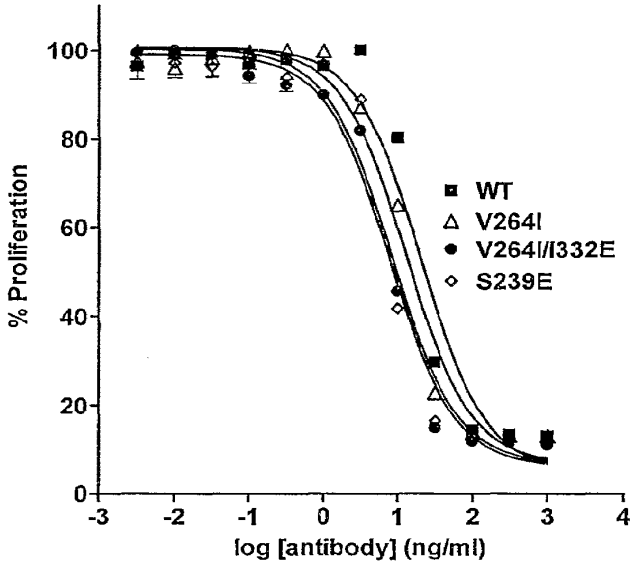
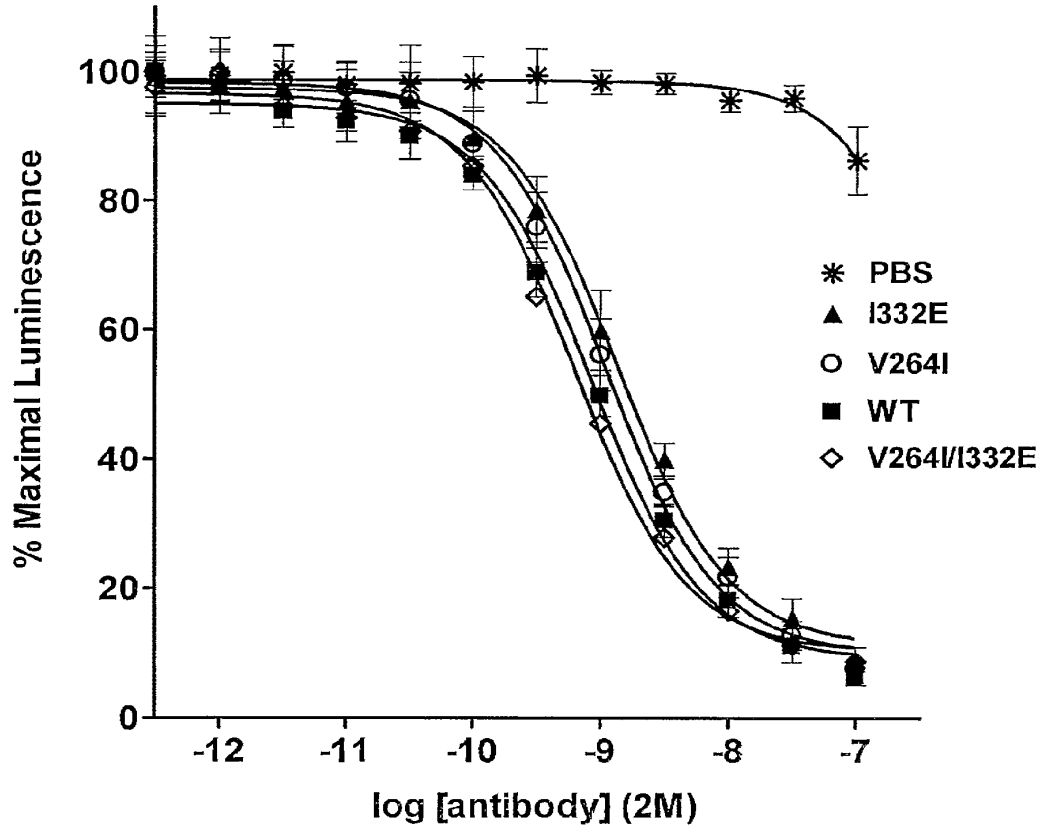


Figure 27b



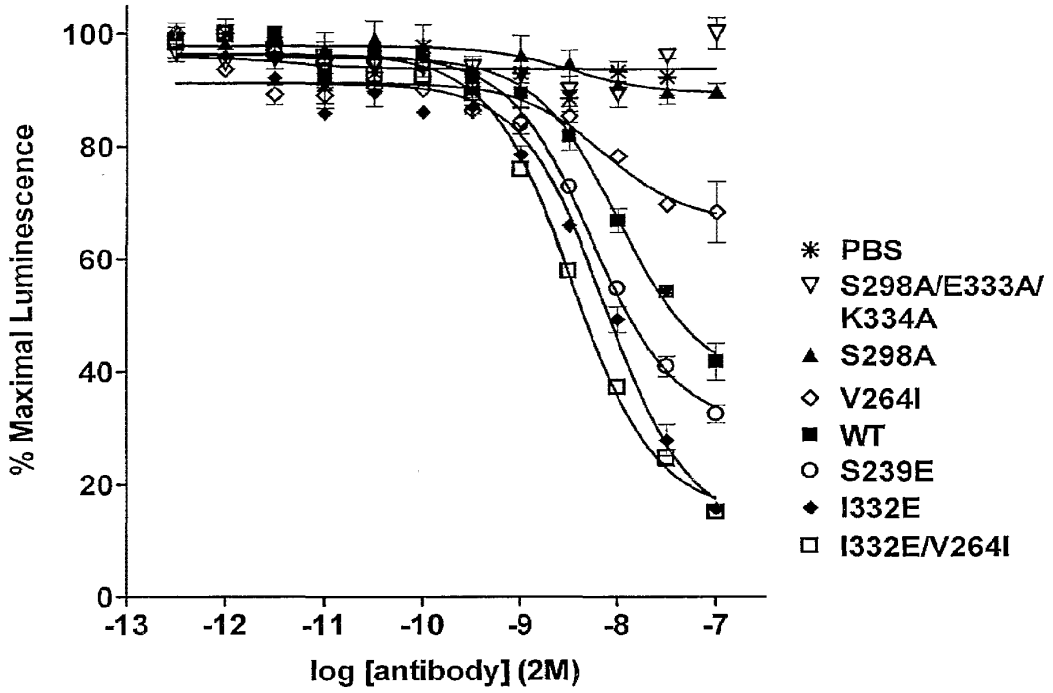
Samsung Bioepis Exhibit No. 1002
Page 11270

Figure 28



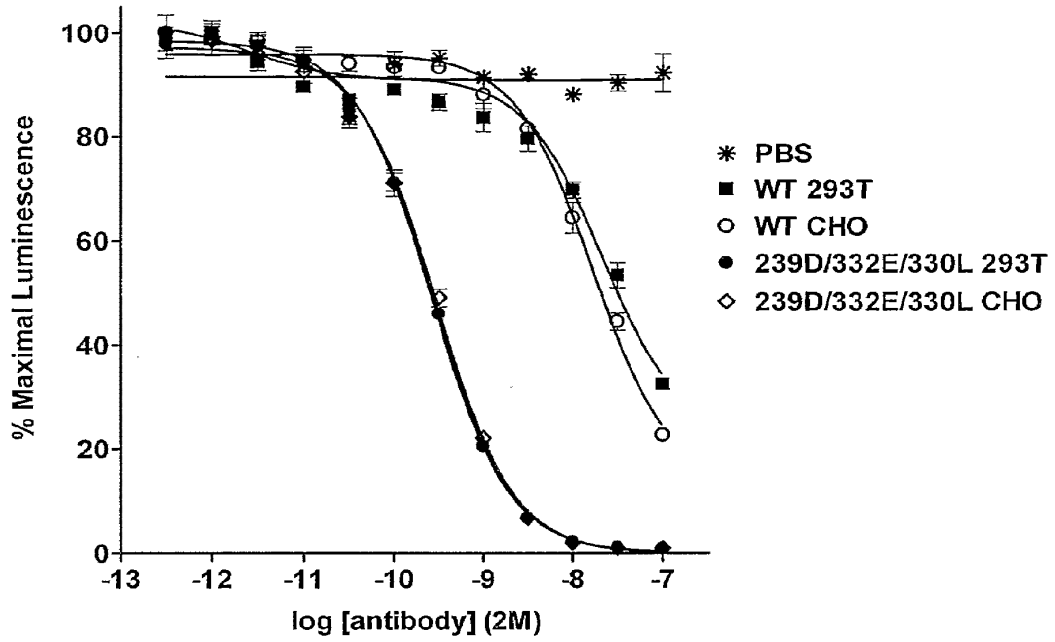
Samsung Bioepis Exhibit No. 1002
Page 11271

Figure 29



Samsung Bioepis Exhibit No. 1002
Page 11272

Figure 30



Samsung Bioepis Exhibit No. 1002
Page 11273

Figure 31a

Anti-CD20 light chain
QIVLSQSPAILSASPGEKVTMTCRASSSVSYIHWFQQKPGSSPKPWIYATSNLASGVPVRFSGSGSG
TSYSLTISRVEAEDAATYYCQQWTSNPPTFGGGTKLEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLL
NNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLS
SPVTKSFNRGEC

Figure 31b

Anti-CD20 heavy chain

QVQLQQPGAELVKPGASVKMSCKASGYTFTSYNMHWVKQTPGRGLEWIGAIYPGNGDTSYNQKFK
GKATLTADKSSSTAYMQLSSLTSEDSAVYYCARSTYYGGDWYFNVWGAGTTVTVSAASTKGPSVFP
LAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLG
TQTYICNVNHKPSNTKVDKKAEPKSCDKTHTCPPCPAPELLGGP**SV**FLFPPKPKDTLMISRTPEVTCV
VVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQY**NS**TYRVVSVLTVLHQDWLNGKEYKCKVSNKA
LP**A**PIEKTISKAKGQPREPQVYTLPP**S**RDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTP
PVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK

Figure 31c

Anti-CD20 heavy chain comprising possible Fc variants
QVQLQQPGAELVKPGA**S**VKMSCKASGYTFTSY**N**MHWVKQTPGRGLEWIGAIYPGNGDTSYNQKFK
GKATLTADKSSSTAYMQLSSLTSEDSAVYYCARSTYYGGDWYF**N**VWGAGTTVTVSAASTKGPSVFP
LAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLG
TQTYICNVNHKPSNTKVDKKAEPKSCDKTHTCPPCPAPELLGGP**X_1X_2**FLFPPKPKDTLMISRTPEVTC
VV**X_3**DVSHEDPEVKFNWYVDGVEVHNAKTKPREEQY**X_4Z_1**TYRVVSVLTVLHQDWLNGKEYKCKVSN
KALP**X_5PX_6**EKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNY
KTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK

Position	WT	Possible Substitutions
X_1	S	D, E, N, Q, T
X_2	V	I, M
X_3	V	I, T, Y
X_4	N	D
X_5	A	Y, L, I
X_6	I	D, E, N, Q
Z_1	S	A

Samsung Bioepis Exhibit No. 1002
Page 11274

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(75) Inventors/Applicants *(for US only)*: **BELL, Leonard** [US/US]; 59 Tumblebrook Road, Woodbridge, CT 06525 (US). **ROTHER, Russell, P.** [US/US]; 25 Blue Trail Drive, Prospect, CT 06712 (US).

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Published:
— *without international search report and to be republished upon receipt of that report*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: METHOD OF TREATING HEMOLYTIC DISEASE

Biochemical Parameters of Hemolysis During Eculizumab Treatment

Biochemical Marker	Normal range	Time of Analysis			p-value[a]
		Pre-study[b]	12 weeks	64 weeks	
LDH (IU/L)	150 - 480	3110.7 +/- 598.4	594.0 +/- 31.7	622.4 +/-41.1	0.002
AST (IU/L)	10 - 40	76.2 +/- 16.0	26.2 +/- 2.3	30.1 +/- 3.2	0.02
Haptoglobin (g/L)	0.5 - 2	<0.06	<0.06	0.14 +/- 0.07[c]	N.S.[d]
Hemoglobin (g/dL)	11.5 - 18	10.0 +/- 0.4	10.3 +/- 0.4	10.4 +/- 0.4	N.S.
Bilirubin	3 - 15	25.9 +/- 4.3	28.2 +/- 4.4	28.7 +/- 4.0	N.S.
Reticulocytes (x10^{-3}/mm^3)	20 - 80	161.4 +/- 25.9	191.2 +/- 23.6	189.6 +/- 21.8	N.S.

[a]from comparisons of mean change from pre-study to 64 weeks
[b]values represent means during 52 week period prior to treatment except for AST which represents the baseline mean
[c]10 of 11 patients were below the detectable limit of haptoglobin (<0.06 g/L); 1 patient had a value of 0.69 g/L.
[d]not significant

(57) Abstract: Paroxysmal nocturnal hemoglobinuria or other hemolytic diseases are treating using a compound which binds to or otherwise blocks the generation and/or the activity of one or more complement components, such as, for example, a complement-inhibiting antibody.

WO 2005/074607 A2

Samsung Bioepis Exhibit No. 1002
Page 11275

METHOD OF TREATING HEMOLYTIC DISEASE

RELATED APPLICATIONS

This application claims priority to, and is a continuation-in-part of, U.S. Patent Application Serial No. 10/771,552, filed February 3, 2004, the entire disclosure of which is incorporated herein by this reference.

BACKGROUND

Technical Field

This disclosure relates to a method of treating a hemolytic disease such as, for example, paroxysmal nocturnal hemoglobinuria ("PNH"), by administering a compound which binds to, or otherwise blocks, the generation and/or activity of one or more complement components.

Background of Related Art

Paroxysmal nocturnal hemoglobinuria ("PNH") is an uncommon blood disorder wherein red blood cells are compromised and are thus destroyed more rapidly than normal red blood cells. PNH results from a mutation of bone marrow cells resulting in the generation of abnormal blood cells. More specifically, PNH is believed to be a disorder of hematopoietic stem cells, which give rise to distinct populations of mature blood cells. The basis of the disease appears to be somatic mutations leading to the inability to synthesize the glycosyl-phosphatidylinositol ("GPI") anchor that is responsible for binding

Samsung Bioepis Exhibit No. 1002
Page 11276

proteins to cell membranes. The mutated gene, PIG-A (phosphatidylinositol glycan class A) resides in the X chromosome and can have several different mutations, varying from deletions to point mutations.

PNH causes a sensitivity to complement proteins and this sensitivity occurs in the cell membrane. PNH cells are deficient in a number of proteins, particularly essential complement-regulating surface proteins. These complement-regulating surface proteins include the decay-accelerating factor ("DAF") or CD55 and membrane inhibitor of reactive lysis ("MIRL") or CD59.

PNH is characterized by hemolytic anemia (a decreased number of red blood cells), hemoglobinuria (the presence of hemoglobin in the urine particularly evident after sleeping), and hemoglobinemia (the presence of hemoglobin in the bloodstream). PNH-afflicted individuals are known to have paroxysms, which are defined here as incidences of dark-colored urine. Hemolytic anemia is due to intravascular destruction of red blood cells by complement components. Other known symptoms include dysphagia, fatigue, erectile dysfunction, thrombosis and recurrent abdominal pain.

Hemolysis resulting from hemolytic diseases causes local and systemic nitric oxide (NO) deficiency through the release of free hemoglobin. Free hemoglobin is a very efficient scavenger of NO, due in part to the accessibility of NO in the non-erythrocyte compartment and a 10^6 times greater affinity of the heme moiety for NO than that for oxygen. The occurrence of intravascular hemolysis often generates sufficient free hemoglobin to completely deplete haptoglobin. Once the capacity of this hemoglobin scavenging protein is exceeded, consumption of endogenous NO ensues. For example, in a setting of intravascular hemolysis such as PNH, where LDH levels can easily exceed

Samsung Bioepis Exhibit No. 1002
Page 11277

2 - 3 times their normal levels, free hemoglobin would likely obtain concentrations of 0.8 – 1.6 g/l. Since haptoglobin can only bind somewhere between 0.7 to 1.5 g/l of hemoglobin depending on the haptoglobin allotype, a large excess of free hemoglobin would be generated. Once the capacity of hemoglobin reabsorption by the kidney proximal tubules is exceeded, hemoglobinuria ensues. The release of free hemoglobin during intravascular hemolysis results in excessive consumption of NO with subsequent enhanced smooth muscle contraction, vasoconstriction and platelet activation and aggregation. PNH-related morbidities associated with NO scavenging by hemoglobin include abdominal pain, erectile dysfunction, esophageal spasm, and thrombosis.

The laboratory evaluation of hemolysis normally includes hematologic, serologic, and urine tests. Hematologic tests include an examination of the blood smear for morphologic abnormalities of RBCs (to determine causation), and the measurement of the reticulocyte count in whole blood (to determine bone marrow compensation for RBC loss). Serologic tests include lactate dehydrogenase (LDH; widely performed), and free hemoglobin (not widely performed) as a direct measure of hemolysis. LDH levels, in the absence of tissue damage in other organs, can be useful in the diagnosis and monitoring of patients with hemolysis. Other serologic tests include bilirubin or haptoglobin, as measures of breakdown products or scavenging reserve, respectively. Urine tests include bilirubin, hemosiderin, and free hemoglobin, and are generally used to measure gross severity of hemolysis and for differentiation of intravascular vs. extravascular etiologies of hemolysis rather than routine monitoring of hemolysis. Further, RBC numbers, RBC (i.e. cell-

Samsung Bioepis Exhibit No. 1002
Page 11278

bound) hemoglobin, and hematocrit are generally performed to determine the extent of any accompanying anemia rather than as a measure of hemolytic activity per se.

Steroids have been employed as a therapy for hemolytic diseases and may be effective in suppressing hemolysis in some patients, although long term use of steroid therapy carries many negative side effects. Afflicted patients may require blood transfusions, which carry risks of infection. Anti-coagulation therapy may also be required to prevent blood clot formation. Bone marrow transplantation has been known to cure PNH, however, bone marrow matches are often very difficult to find and mortality rates are high with such procedure.

It would be advantageous to provide a treatment which safely and reliably eliminates and/or limits hemolytic diseases, such as PNH, and their effects.

Summary

Paroxysmal nocturnal hemoglobinuria ("PNH") and other hemolytic diseases are treated in accordance with this disclosure using a compound which binds to or otherwise blocks the generation and/or activity of one or more complement components. Suitable compounds include, for example, antibodies which bind to or otherwise block the generation and/or activity of one or more complement components, such as, for example, an antibody specific to complement component C5. In particularly useful embodiments, the compound is an anti-C5 antibody selected from the group consisting of h5G1.1-mAb (eculizumab), h5G1.1-scFv (pexelizumab) and other functional

Samsung Bioepis Exhibit No. 1002
Page 11279

fragments of h5G1.1. It has surprisingly been found that the present methods provide improvements in the PNH subject within 24 hours of administration of the compound. For example, hemolysis is significantly reduced within 24 hours of administration of the compound as indicated by resolution of hemoglobinuria.

The complement-inhibiting compound can be administered prophylactically in individuals known to have a hemolytic disease to prevent, or help prevent the onset of symptoms. Alternatively, the complement-inhibiting compound can be administered as a therapeutic regimen to an individual experiencing symptoms of a hemolytic disease.

In another aspect, a method of increasing the proportion of complement sensitive type III red blood cells and therefore the total red blood cell count in a patient afflicted with a hemolytic disease is contemplated. The method comprises administering a compound which binds to or otherwise blocks the generation and/or activity of one or more complement components to a patient afflicted with a hemolytic disease. By increasing type III red blood cell count, symptoms such as fatigue and anemia also can be alleviated in a patient afflicted with a hemolytic disease.

In yet another aspect, the present disclosure contemplates a method of rendering a subject afflicted with a hemolytic disease less dependent on transfusions or transfusion-independent by administering a compound to the subject, the compound being selected from the group consisting of compounds which bind to one or more complement components, compounds which block the generation of one or more complement components and compounds which block the activity of one or more complement components.

Samsung Bioepis Exhibit No. 1002
Page 11280

It has surprisingly been found that patients can be rendered transfusion-independent in accordance with the present methods. Unexpectedly, transfusion-independence can be maintained in some embodiments for twelve months or more, long beyond the 120 day life cycle of red blood cells. In other embodiments, transfusion-independence can be maintained for two years or more. Treatment for six months or more is required for the evaluation of transfusion independence given the long half life of red blood cells.

In another aspect, the present disclosure contemplates a method of treating a nitric oxide (NO) imbalance in a subject by administering a compound to the subject, the compound being selected from the group consisting of compounds which bind to one or more complement components, compounds which block the generation of one or more complement components and compounds which block the activity of one or more complement components. By reducing the lysis of red blood cells, the present methods reduce the amount of free hemoglobin in the bloodstream, thereby increasing serum levels of nitric oxide (NO). In particularly useful embodiments, NO homeostasis is restored wherein there is a resolution of symptoms attributable to NO deficiency.

In another aspect, the present disclosure contemplates a method of treating thrombosis in a subject by administering a compound to the subject, the compound being selected from the group consisting of compounds which bind to one or more complement components, compounds which block the generation of one or more complement components and compounds which block the activity of one or more complement components.

Samsung Bioepis Exhibit No. 1002
Page 11281

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15/642,096	07/05/2017	Leonard BELL	AXJ-114BUSCN5	7606

133485 7590 05/31/2019

Nelson Mullins Riley & Scarborough LLP/Alexion
One Post Office Square
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Boston, MA 02109-2127

EXAMINER	
ROGERS, JAMES L	

ART UNIT	PAPER NUMBER
1644	

NOTIFICATION DATE	DELIVERY MODE
05/31/2019	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

ipboston.docketing@nelsonmullins.com

Office Action Summary	**Application No.** 15/642,096	**Applicant(s)** BELL et al.	
	Examiner JAMES L ROGERS	**Art Unit** 1644	**AIA (FITF) Status** No

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTHS FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☑ Responsive to communication(s) filed on 8/24/2017.

☐ A declaration(s)/affidavit(s) under **37 CFR 1.130(b)** was/were filed on _____.

2a)☐ This action is **FINAL.** 2b) ☑ This action is non-final.

3)☐ An election was made by the applicant in response to a restriction requirement set forth during the interview on _____; the restriction requirement and election have been incorporated into this action.

4)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims*

5) ☑ Claim(s) 52-59 is/are pending in the application.

5a) Of the above claim(s) _____ is/are withdrawn from consideration.

6) ☐ Claim(s) _____ is/are allowed.

7) ☑ Claim(s) 52-59 is/are rejected.

8) ☐ Claim(s) _____ is/are objected to.

9) ☐ Claim(s) _____ are subject to restriction and/or election requirement

* If any claims have been determined allowable, you may be eligible to benefit from the **Patent Prosecution Highway** program at a participating intellectual property office for the corresponding application. For more information, please see http://www.uspto.gov/patents/init_events/pph/index.jsp or send an inquiry to **PPHfeedback@uspto.gov.**

Application Papers

10)☐ The specification is objected to by the Examiner.

11)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

Certified copies:

a)☐ All b)☐ Some** c)☐ None of the:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

** See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)

2) ☑ Information Disclosure Statement(s) (PTO/SB/08a and/or PTO/SB/08b) Paper No(s)/Mail Date _____.

3) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date _____.

4) ☐ Other: _____.

Notice of Pre-AIA or AIA Status

The present application is being examined under the pre-AIA first to invent provisions.

DETAILED ACTION

1. Claims 52-59 pending and under consideration in the instant examination.

2. Applicant's IDSs filed on 8/22/2017, 3/28/2018, 4/27/2018, and 4/29/2019 are acknowledged and have been considered.

Priority

3. Applicant's claim for the benefit of a prior-filed application under 35 U.S.C. 119(e) or under 35 U.S.C. 120, 121, or 365(c) is acknowledged. The priority date of the instant claims of the current application is considered to be 3/15/2007, the filing date of PCT/US2007/006606.

Claim Rejections - 35 USC § 103

4. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained even though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

5. Claim 52 is rejected under 35 U.S.C. 103(a) as being unpatentable over Hillmen et al. (N Engl J Med 2004; 350: 552-9; IDS 8/22/2017), in view of Evans et al. (US 6,355,245 B1, issued 3/12/2002; IDS 8/22/2017), Wang (US 2005/0271660; IDS 8/22/2017), and Bowdish et al. (US 2003/232972; IDS 4/29/2019).

Hillmen teaches a method for treating a human patient that suffers from paroxysmal nocturnal hemoglobinuria (PNH) by administering to the patent an effective amount of eculizumab (p. 552, "methods) which specifically binds to the terminal complement protein C5, inhibiting its cleavage into C5a and C5b (p. 553, 3rd ¶).

Hillmen differs from the claimed invention in the recitation that the pharmaceutical composition comprises a 300 mg single-use formulation of 30 ml of a 10 mg/ml sterile, preservative free solution as in claim 6. Instead, Hillmen teaches that patients received infusion of 600 mg of eculizumab (treatment schedule at p. 554).

Evans teaches the antibody 5G1.1, eculizumab, is effective at doses of 2.2, 3, or 5 mg per kg body weight; this corresponds to 154, 210, or 350 mg of antibody for a 70kg adult human ('245 patent, column 16 lines 10-30). Evans (the '245 patent) also teaches that eculizumab is therapeutically effective when as little as 210 mg are present (column 16 lines 10-15). Evans teaches that the antibodies are particularly advantageous in that they are highly active even when administered in low doses (col 8 lines 25-32), providing a reasonable expectation of success in treating PNH with a dose less than what was disclosed by Hillmen. The reference teaches that it is within the skill of an artisan, particularly a physician, to determine the optimal dose (column 18 lines 15-30). Evans teaches formulations of the anti-C5 antibodies may be formulated in a pharmaceutically effective carrier such saline, which is considered to be a "preservative free solution". (col 18 lines 30-45).

Neither Hillmen nor the '245 patent (Evans) teaches a 300 mg single unit dosage as recited in the claims.

Nevertheless it would have been obvious to one of ordinary skill in the art to modify the teachings of Hillmen to administer 300 mg single unit dosages. Hillmen teaches that both 600 and 900 mg dosages can be used, and since Evans patent teaches that 210 or 350 mg of antibody would be expected to be therapeutically effective, arriving at the 300 mg dosage would be routine, convenient and obvious. One of ordinary skill in the art would have a reasonable expectation of success, as Evans teaches that the antibody exerts its effect at low doses.

It is further noted, [I]t is not inventive to discover the optimum or workable ranges by routine experimentation." In re Aller, 220 F.2d 454, 456 (CCPA 1955); see also In re Peterson, 315 F.3d 1325 (Fed. Cir. 2003). "Only if the 'results of optimizing a variable' are 'unexpectedly good' can a patent be obtained for the claimed critical range." In re Geisler, 116 F.3d 1465, 1469 (Fed. Cir. 1997) (quoting In re Antonie, 559 F.2d 618, 620 (CCPA 1977)). "[Discovery of an optimum value of a result effective variable in a

known process is ordinarily within the skill of the art." In re Boesch, 617 F.2d 272, 276 (CCPA 1980).

Finally, **Wang** teaches that eculizumab is highly soluble, including at up to 30 mg per ml (paragraph 0171, Figure 10). Wang further teaches that pharmaceutically acceptable carriers include pyrogen-free water may be used in formulation of the antibody (¶71) (sterile, preservative free solution). Therefore the artisan of ordinary skill would have had a reasonable expectation of success in making a 10 mg / ml solution of the antibody sterile, preservative free solution.

The combined references still do not precisely teach that the antibody that binds C5 has a heavy chain consisting of SEQ ID NO: 2 and a light chain consisting of SEQ ID NO: 4 as currently claimed.

Bowdish teaches construction of a 5G1.1+peptide antibody (see ¶191 which references Figs. 13A and 13B) having a humanized antibody H chain with an amino acid sequence (SEQ ID NO: 67) which has 96% sequence identity to the currently claimed heavy chain SEQ ID NO: 2. (see sequence alignment below)

```
Query Match             96.0%;  Score 2300.5;  DB 1;  Length 472;\par
  Best Local Similarity   95.4%;  \par
  Matches  437;  Conservative    2;  Mismatches    4;  Indels   15;  Gaps    2;\par
\par
Qy          1 QVQLVQSGAEVKKPGASVKVSCKASGYIFSNYWIQWVRQAPGQGLEWMGEILPGSGSTEY 60\par
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||\par
Db         20 QVQLVQSGAEVKKPGASVKVSCKASGYIFSNYWIQWVRQAPGQGLEWMGEILPGSGSTEY 79\par
\par
Qy         61 TENFKDRVTMTRDTSTSTVYMELSSLRSEDTAVYYCAR----------YFFGSSPNWYFD 110\par
              |||||||||||||||||||||||||||||||||||||||          :    :|     \par
Db         80 TENFKDRVTMTRDTSTSTVYMELSSLRSEDTAVYYCARLPIEGPTLRQWLAARAP----- 134\par
\par
Qy        111 VWGQGTLVTVSSASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTS 170\par
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||\par
Db        135 VWGQGTLVTVSSASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTS 194\par
\par
Qy        171 GVHTFPAVLQSSGLYSLSSVVTVPSSNFGTQTYTCNVDHKPSNTKVDKTVERKCCVECPP 230\par
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||\par
Db        195 GVHTFPAVLQSSGLYSLSSVVTVPSSNFGTQTYTCNVDHKPSNTKVDKTVERKCCVECPP 254\par
\par
Qy        231 CPAPPVAGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQFNWYVDGVEVHNAKT 290\par
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||\par
Db        255 CPAPPVAGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQFNWYVDGVEVHNAKT 314\par
\par
Qy        291 KPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQVY 350\par
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||\par
Db        315 KPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQVY 374\par
\par
Qy        351 TLPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSR 410\par
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||\par
Db        375 TLPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSR 434\par
\par
Qy        411 LTVDKSRWQEGNVFSCSVMHEALHNHYTQKSLSLSLGK 448\par
              |||||||||||||||||||||||||||||||||||||\par
Db        435 LTVDKSRWQEGNVFSCSVMHEALHNHYTQKSLSLSLGK 472\par
```

Bowdish also teaches that the 5G1.1+ peptide has a humanized antibody L chain with an amino acid sequence (SEQ ID NO: 69) which has 100% sequence identity to the currently claimed light chain SEQ ID NO: 4 (see sequence alignment below).

```
Query Match             100.0%;  Score 1110;  DB 4;  Length 236;
  Best Local Similarity   100.0%;
  Matches  214;  Conservative    0;  Mismatches    0;  Indels    0;  Gaps    0;

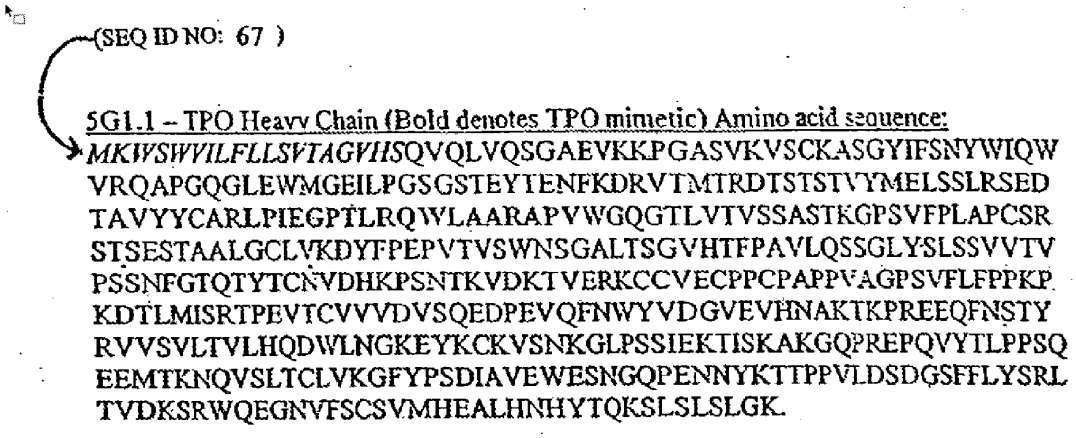
Qy          1 DIQMTQSPSSLSASVGDRVTITCGASENIYGALNWYQQKPGKAPKLLIYGATNLADGVPS 60
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db         23 DIQMTQSPSSLSASVGDRVTITCGASENIYGALNWYQQKPGKAPKLLIYGATNLADGVPS 82

Qy         61 RFSGSGSGTDFTLTISSLQPEDFATYYCQNVLNTPLTFGQGTKVEIKRTVAAPSVFIFPP 120
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db         83 RFSGSGSGTDFTLTISSLQPEDFATYYCQNVLNTPLTFGQGTKVEIKRTVAAPSVFIFPP 142

Qy        121 SDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLT 180
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        143 SDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLT 202

Qy        181 LSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC 214
              |||||||||||||||||||||||||||||||||
Db        203 LSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC 236
```

Bowdish further teaches that the sequence of the above **humanized antibody H chain** SEQ ID NO: 67, which as noted supra has 96% sequence identity to the currently claimed H chain SEQ ID NO: 2, is based on Evan's eculizumab 5G1.1 antibody framework from U.S. Application Ser. No. 06/487,263, which is the USD 6,355,245 Evans Patent supra, with the exception that the CD3 region was replaced with a TPO mimetic peptide sequence (¶191). (see Fig. 13A of Bowdish which depicts the TPO H chain sequence where the CDR3 region that has been substituted with the TPO mimetic is highlighted in bold).



However, Evan's '245 Patent in Fig. 19 provides the missing CD3 sequence for the5G1.1 eculizumab antibody (see Fig. 19 from Evans, which shows framework 5G1.1

antibody with the CDR3 sequence underlined).

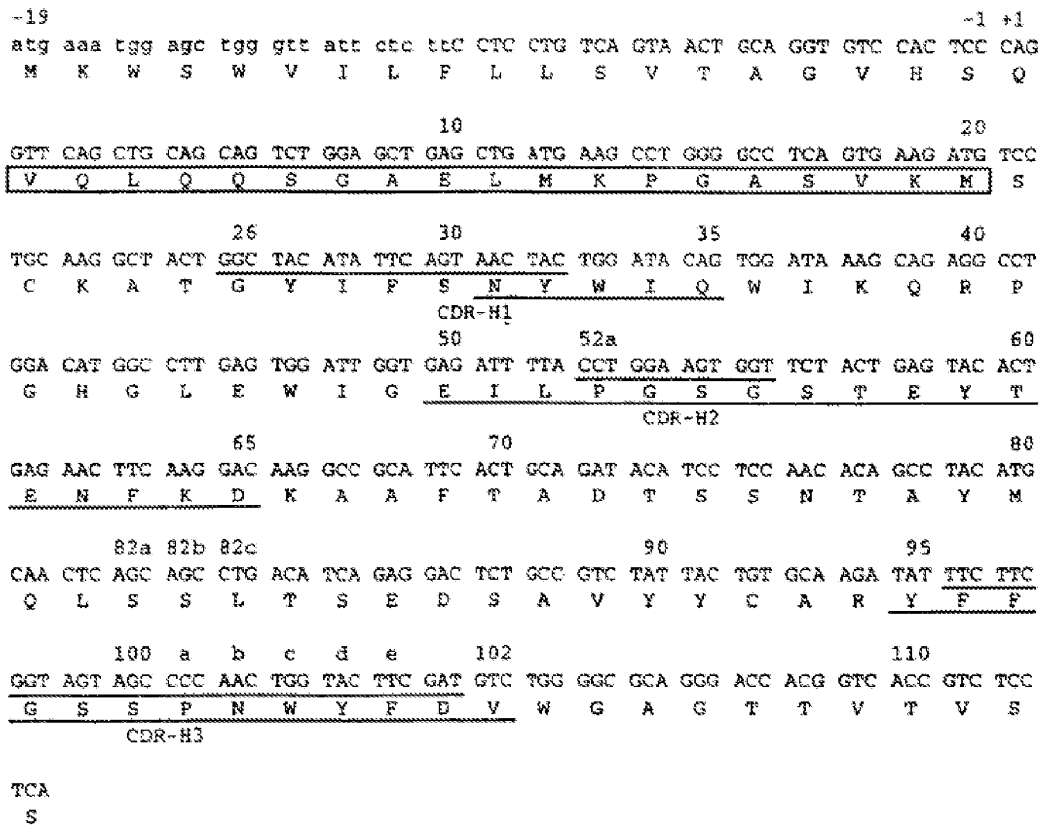


FIG.19

It would have been obvious to one of ordinary skill in the art at the time the invention was made to substitute Bowdish's TPO mimic amino acid sequence in Bowdish's H chain published SEQ ID NO: 67 which is 96% identical with currently claimed H chain SEQ ID NO: 2 with Evan's CDR3 5G1.1 eculizumab amino acid sequence, thereby arriving at a H chain sequence having 100% sequence identity to currently claimed H chain SEQ ID NO: 2 and to have combined that H chain sequence with Bowdish's L chain SEQ ID NO 69 that has 100% sequence identity to currently claimed L chain SEQ ID NO: 4.

One of ordinary skill in the art at the time the invention was made would have been motivated to do so because Bowdish teaches that the 5G1.1+peptide antibody H chain is based on the 5G1.1 antibody framework taught by Evans, with the exception that the

CDR3 was replaced with a TPO mimic sequence. But the substituted CDR3 was taught by Evans. One of skill in the art would accordingly look to the '245 Evans Patent for the native CDR3. Evans Fig. 19 shows the heavy chain variable region as residues 95-102. Substituting the CDR3 from Evans into the heavy chain 5G1.1+ taught by Bowdish would result in a sequence having 100% sequence identity to currently claimed SEQ ID No: 2. Bowdish also teaches that the light chain of 5G1.1" (published SEQ ID NO: 69), which as shown supra has 100% amino acid sequence identity to currently claimed L chain SEQ ID NO:4.

Thus upon reading Bowdish, one of ordinary skill in the art would have found it obvious to substitute CDRH3 from the 5G1.1 of Evans into the H chain SEQ ID NO: 67 which is only 96% identical in sequence identity due to the missing CDR3 region as taught by Bowdish to arrive at 100% sequence identity for the H chain of currently claimed SEQ ID NO: 2 and to pair it with the L chain SEQ ID NO: 69 from Bowdish, thereby producing an antibody identical to currently claimed SEQ ID NO: 2 and 4. The motivation to do so comes directly form the two references, as Bowdish indicates that the 5G1.1 sequence is that of Evans, albeit with an altered CDR3 in the heavy chain.

From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

6. Claims 52-59 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hillmen et al. (N Engl J Med 2004; 350: 552-9; IDS 8/22/2017), in view of Evans et al. (US 6,355,245 B1, issued 3/12/2002; IDS 8/22/2017), Wang (US 2005/0271660; IDS 8/22/2017), and Bowdish et al. (US 2003/232972; IDS 4/29/2019), as applied to claim 52 above, and further in view of Bell et al. (US 2005/0191298; IDS 8/22/2017).

The prior art teachings of Hillmen, Evans, Wang, and Bowdish are discussed supra.

The teachings differs with respect to the characteristics of the patient population. For example, the references differ in the recitation that the patient has received at least four transfusion in the twelve months prior to administration of the antibody (claims 53 and 57), has a platelet count greater than or equal to 100k per microliter prior to administration of the antibody (claims 54 and 58).

The teachings also differ in the recitation that the patient exhibits decreased lactate dehydrogenase levels (claim 56).

The teachings also differ in the recitation that the patient is treated with the antibody for at least 26 weeks as in claims 55 and 59.

However, Hillmen further teaches that the patients in its study had received at least four red-cell transfusions in the preceding 12 months (p. 553, last 2 lines).

Bell also teaches treating PNH using an anti-C5 antibody such as h5G1.1 mAb eculizumab (¶52). Bells teaches that PNH patients were transfusion dependent and hemolytic with a history of four or more transfusion within 12 months (¶81).

Bell further teaches that the patient for treatment has a platelet count preferably in excess of 150k per microliter (¶67).

Bell further teaches that that patients received weekly intravenous infusion of anti-C5 antibody for 64 weeks (¶82).

Bell also teaches that lactate dehydrogenase levels (LDH) are used as an objective indicator of hemolysis and that LDH levels were decreased as a result of the treatment (¶85).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to have continued eculizumab treatment for PNH for a period of at least 26 weeks to a patient population having received at least four transfusion in the twelve months prior to administration of eculizumab and having a platelet count in excess of 100k per microliter prior to administration of the antibody as well as to have also used a decreased LDH as a measure of clinical outcome in a method of treating PNH as taught by Hillmen. Those of skill in the art would have had reason to do so because Hillmen itself teaches that patients for treatment of PNH by administration of eculizumab had received at least 4 transfusion in the preceding 12 months, most preferably having a platelet count in excess of 150k, and Bell teaches that in the treatment of PNH with eculizumab, LDH is a known indicator of efficacy and that treatment can continue for 64 weeks, which is a period of greater than 26 weeks. The combination of familiar elements according to known methods is obvious when it does no more than yield predictable results (see KSR Int'l v. Teleflex Inc., 127 S. Ct. 1727, 1739 (2007).

From the teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

Double Patenting

7. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper time wise extension of the "right to exclude" granted by a patent

and to prevent possible harassment by multiple assignees. A nonstatutory double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on nonstatutory double patenting provided the reference application or patent either is shown to be commonly owned with the examined application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement. See MPEP § 717.02 for applications subject to examination under the first inventor to file provisions of the AIA as explained in MPEP § 2159. See MPEP §§ 706.02(l)(1) - 706.02(l)(3) for applications not subject to examination under the first inventor to file provisions of the AIA. A terminal disclaimer must be signed in compliance with 37 CFR 1.321(b).

The USPTO Internet website contains terminal disclaimer forms which may be used. Please visit www.uspto.gov/patent/patents-forms. The filing date of the application in which the form is filed determines what form (e.g., PTO/SB/25, PTO/SB/26, PTO/AIA/25, or PTO/AIA/26) should be used. A web-based eTerminal Disclaimer may be filled out completely online using web-screens. An eTerminal Disclaimer that meets all requirements is auto-processed and approved immediately upon submission. For more information about eTerminal Disclaimers, refer to www.uspto.gov/patents/process/file/efs/guidance/eTD-info-I.jsp.

8. Claims 52-59 are rejected on the ground of nonstatutory obviousness- type double patenting as being unpatentable over claim 1 of **US Patent 9,732,149,** in view of Bell et al. (US 2005/0191298; IDS 8/22/2017).

Although the conflicting claims are not identical, they are not patentably distinct from each other because both the current application and 149 Patent claim the same antibody having a H chain of SEQ ID NO: 2 and L chain of SEQ ID NO: 4.

While the ‘149 Patent is drawn to a composition whereas the current application is drawn to administering the antibody to a patient suffering from PNH, it is clear from the specification of the ‘149 that the intended use for the antibody is PNH (see abstract) and that said antibody is administered as a single unit dosage form at 300 mg in 30 ml of a 10 mg/ml sterile, preservative free solution (¶ before detailed description). See *Sun Pharmaceuticals Industries, Ltd., v. Eli Lilly and Company*, Fed. Cir. 2010 for the

appropriateness of making an ODP to a product claim where one of the intended uses of the product is for the method as now claimed).

While the '149 does not specifically recite some of the limitations contained in the dependent claims such as that the patient exhibits decreased LDH levels, these limitations would have been obvious in view of Bell as is discussed supra.

9. Claims 52-59 are rejected on the ground of nonstatutory obviousness- type double patenting as being unpatentable over claims 1-3 of **US Patent 9,718,880,** in view of Bell et al. (US 2005/0191298; IDS 8/22/2017).

Although the conflicting claims are not identical, they are not patentably distinct from each other because both the current application and 880 Patent claim the same antibody having a H chain of SEQ ID NO: 2 and L chain of SEQ ID NO: 4, in a sterile, preservative free 300 mg single-use dosage form comprising 30 ml of a 10 mg/ml solution..

While the '880 Patent is drawn to a composition whereas the current application is drawn to administering the antibody to a patient suffering from PNH, it is clear from the specification of the '149 that the intended use for the antibody is PNH (see abstract) and that said antibody is administered as a single unit dosage form at 300 mg in 30 ml of a 10 mg/ml sterile, preservative free solution (¶ before detailed description). See *Sun Pharmaceuticals Industries, Ltd., v. Eli Lilly and Company*, Fed. Cir. 2010 for the appropriateness of making an ODP to a product claim where one of the intended uses of the product is for the method as now claimed).

While the '880 does not specifically recite some of the limitations contained in the dependent claims such as that the patient exhibits decreased LDH levels, these limitations would be obvious in view of Bell as is discussed supra.

10. Claims 52-59 are rejected on the ground of nonstatutory obviousness- type double patenting as being unpatentable over claims 1-10 of **US Patent 9,725,504,** in view of Bell et al. (US 2005/0191298; IDS 8/22/2017).

Although the conflicting claims are not identical, they are not patentably distinct from each other because both the current application and 504 Patent claim the same method of treating PNH using an antibody having a H chain of SEQ ID NO: 2 and L chain of SEQ ID NO: 4, in a sterile, preservative free 300 mg single-use dosage form comprising 30 ml of a 10 mg/ml solution. See in particular claims 1, and 4-6 of the '504 patent.

The '504 also claims a decreased in mean levels of LDH after administration (claim 9).

11. Claims 52-59 are rejected on the ground of nonstatutory obviousness- type double patenting as being unpatentable over claims 1-17 of **US Patent 9,409,980,** in view of Evans et al. (US 6,355,245 B1, issued 3/12/2002; IDS 8/22/2017), Wang (US 2005/0271660; IDS 8/22/2017) and Bell et al. (US 2005/0191298; IDS 8/22/2017).

Although the conflicting claims are not identical, they are not patentably distinct from each other because both the current application and 980 Patent appear to claim the same anti-C5 antibody (see claim 1 of the '980). In addition, the '980 claim using the antibody to treat PNH (see claim 17).

While the '980 does not specifically recite that the antibody is a single-unit dosage form of 300 mg in 30 mL of sterile, preservative free solution or the various limitations contained in the dependent claims, those limitation would be obvious in view of Evans, Wang and Bell as is discussed supra.

12. Claims 52-59 are rejected on the ground of nonstatutory obviousness- type double patenting as being unpatentable over claims 1-15 of **US Patent 9,415,102,** in view of Evans et al. (US 6,355,245 B1, issued 3/12/2002; IDS 8/22/2017), Wang (US 2005/0271660; IDS 8/22/2017) and Bell et al. (US 2005/0191298; IDS 8/22/2017).

Although the conflicting claims are not identical, they are not patentably distinct from each other because both the current application and 102 Patent appear to claim the same anti-C5 antibody (see claims 1-2 of the '102). In addition, the '102 claims using the antibody to treat PNH (see claim 17).

While the '102 Patent is drawn to a composition whereas the current application is drawn to administering the antibody to a patient suffering from PNH, it is clear from the specification of the '102 that the intended use for the antibody is PNH (see methods of treatment in the specification) See *Sun Pharmaceuticals Industries, Ltd., v. Eli Lilly and Company*, Fed. Cir. 2010 for the appropriateness of making an ODP to a product claim where one of the intended uses of the product is for the method as now claimed).

While the '102 does not specifically recite that the antibody is a single-unit dosage form of 300 mg in 30 mL of sterile, preservative free solution or the various limitations contained in the dependent claims, those limitation would be obvious in view of Evans, Wang and Bell as is discussed supra.

13. Claims 52-59 are rejected on the ground of nonstatutory obviousness- type double patenting as being unpatentable over claims 1-14 of **US Patent 9,556,263,** in view of Evans et al. (US 6,355,245 B1, issued 3/12/2002; IDS 8/22/2017), Wang (US 2005/0271660; IDS 8/22/2017) and Bell et al. (US 2005/0191298; IDS 8/22/2017).

Although the conflicting claims are not identical, they are not patentably distinct from each other because both the current application and 256 Patent appear to claim the same eculizumab antibody (see claim 1 of the '263). In addition, the '263 claim using the antibody to treat PNH (see claim 3).

While the '263 does not specifically recite that the antibody is a single-unit dosage form of 300 mg in 30 mL of sterile, preservative free solution or the various limitations contained in the dependent claims, those limitation would be obvious in view of Evans, Wang and Bell as is discussed supra.

14. Claims 52-59 are rejected on the ground of nonstatutory obviousness- type double patenting as being unpatentable over claims 1-12 of **US Patent 9,352,035,** in view of Evans et al. (US 6,355,245 B1, issued 3/12/2002; IDS 8/22/2017), Wang (US 2005/0271660; IDS 8/22/2017) and Bell et al. (US 2005/0191298; IDS 8/22/2017).

Although the conflicting claims are not identical, they are not patentably distinct from each other because both the current application and 035 Patent appear to claim the same eculizumab antibody (see claim 1 of the '035).

While the '035 Patent is drawn to a composition whereas the current application is drawn to administering the antibody to a patient suffering from PNH, it is clear from the specification of the '035 that the intended use for the antibody is PNH (see ¶129 of the '35 which lists PNH as one of the complement associated disorders that can be treated by the composition) See *Sun Pharmaceuticals Industries, Ltd., v. Eli Lilly and Company*, Fed. Cir. 2010 for the appropriateness of making an ODP to a product claim where one of the intended uses of the product is for the method as now claimed).

While the '035 does not specifically recite that the antibody is a single-unit dosage form of 300 mg in 30 mL of sterile, preservative free solution or the various limitations contained in the dependent claims, those limitation would be obvious in view of Evans, Wang and Bell as is discussed supra.

15. Claims 52-59 are rejected on the ground of nonstatutory obviousness- type double patenting as being unpatentable over claims 1-13 of **US Patent 9,925,262,** in view of Evans et al. (US 6,355,245 B1, issued 3/12/2002; IDS 8/22/2017), Wang (US 2005/0271660; IDS 8/22/2017) and Bell et al. (US 2005/0191298; IDS 8/22/2017).

Although the conflicting claims are not identical, they are not patentably distinct from each other because both the current application and 262 Patent claim the same method of treating PNH using an eculizumab antibody. See in particular claims 1, and 4 of the '262 patent.

While the '262 does not specifically recite that the antibody is a single-unit dosage form of 300 mg in 30 mL of sterile, preservative free solution or the various limitations contained in the dependent claims, those limitation would be obvious in view of Evans, Wang and Bell as is discussed supra.

16. Claims 52-59 are rejected on the ground of nonstatutory obviousness- type double patenting as being unpatentable over claims 1-33 of **US Patent 10,239,937,** in view of Evans et al. (US 6,355,245 B1, issued 3/12/2002; IDS 8/22/2017), Wang (US 2005/0271660; IDS 8/22/2017) and Bell et al. (US 2005/0191298; IDS 8/22/2017).

Although the conflicting claims are not identical, they are not patentably distinct from each other because both the current application and 937 Patent claim the same method of treating PNH using an eculizumab antibody. See in particular claims 1, and 11 of the '937 patent.

While the '937 does not specifically recite that the antibody is a single-unit dosage form of 300 mg in 30 mL of sterile, preservative free solution or the various limitations contained in the dependent claims, those limitation would be obvious in view of Evans, Wang and Bell as is discussed supra.

17. No claim is allowed.

18. Any inquiry concerning this communication or earlier communications from the examiner should be directed to James Rogers whose telephone number is (571) 270-5374. The examiner can normally be reached Monday through Friday from 8:00 am to 5:30 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, **Daniel Kolker** can be reached on (571) 272-3181. The fax number for the organization where this application or proceeding is assigned is 571-273-8300.

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May 14, 2019

/JAMES ROGERS/
Art Unit 1644

/DANIEL E KOLKER/
Supervisory Patent Examiner, Art Unit 1644

Search Notes	Application/Control No.	Applicant(s)/Patent Under Reexamination
	15/642,096	BELL et al.
	Examiner	Art Unit
	JAMES L ROGERS	1644

CPC - Searched*		
Symbol	Date	Examiner

CPC Combination Sets - Searched*		
Symbol	Date	Examiner

US Classification - Searched*			
Class	Subclass	Date	Examiner

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Search Notes		
Search Notes	Date	Examiner
STN: DISSABS MEETINGS BIOSCI CAPLUS MEDICINE	05/01/2019	JR
EAST: PGPUB, USPAT, JPO, EPO, DRWNT, INVENTOR SEARCH	05/01/2019	JR

Interference Search			
US Class/CPC Symbol	US Subclass/CPC Group	Date	Examiner

/JAMES L ROGERS/ Examiner, Art Unit 1644	

Bibliographic Data

Application No: 15/642,096

Foreign Priority claimed: ○ Yes ◉ No

35 USC 119 (a-d) conditions met: ☐ Yes ☑ No ☐ Met After Allowance

Verified and Acknowledged: /JAMES L ROGERS/ (Examiner's Signature) | (Initials)

Title: TREATMENT OF PAROXYSMAL NOCTURNAL HEMOGLOBINURIA PATIENTS BY AN INHIBITOR OF COMPLEMENT

FILING or 371(c) DATE	CLASS	GROUP ART UNIT	ATTORNEY DOCKET NO.
07/05/2017	424	1644	AXJ-114BUSCN5
RULE			

APPLICANTS

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INVENTORS

Leonard BELL Woodbridge, CT, UNITED STATES

Russell P. ROTHER Oklahoma City, OK, UNITED STATES

Mark J. EVANS Radnor, PA, UNITED STATES

CONTINUING DATA

This application is a CON of 15284015 10/03/2016 PAT 9732149

15284015 is a CON of 15260888 09/09/2016 PAT 9725504

15260888 is a CON of 15148839 05/06/2016 PAT 9718880

15148839 is a CON of 13426973 03/22/2012ABN

13426973 is a CON of 12225040 05/13/2009ABN

12225040 is a 371 of PCT/US2007/006606 03/15/2007

FOREIGN APPLICATIONS

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07/19/2017

STATE OR COUNTRY

UNITED STATES

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UNITED STATES

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Doc description: Information Disclosure Statement (IDS) Filed

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INFORMATION DISCLOSURE STATEMENT BY APPLICANT (**Not for submission under 37 CFR 1.99**)		
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	First Named Inventor	Leonard BELL
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	1	DATABASE REGISTRY [Online] CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; 14 February 1999 (1999-02-14), retrieved from STN Database accession no. 219685-50-4, 2 pages.	☐
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☐ That each item of information contained in the information disclosure statement was first cited in any communication from a foreign patent office in a counterpart foreign application not more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(1).

OR

☐ That no item of information contained in the information disclosure statement was cited in a communication from a foreign patent office in a counterpart foreign application, and, to the knowledge of the person signing the certification after making reasonable inquiry, no item of information contained in the information disclosure statement was known to any individual designated in 37 CFR 1.56(c) more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(2).

☐ See attached certification statement.

☐ The fee set forth in 37 CFR 1.17 (p) has been submitted herewith.

☒ A certification statement is not submitted herewith.

SIGNATURE

A signature of the applicant or representative is required in accordance with CFR 1.33, 10.18. Please see CFR 1.4(d) for the form of the signature.

Signature	/Jill Gorny Sloper, Esq./	Date (YYYY-MM-DD)	2018-03-28
Name/Print	Jill Gorny Sloper, Esq.	Registration Number	60,760

This collection of information is required by 37 CFR 1.97 and 1.98. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 1 hour to complete, including gathering, preparing and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /J.L.R/

Privacy Act Statement

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9. A record from this system of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.

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I hereby certify that this paper (along with any paper referred to as being attached or enclosed) is being transmitted via the Office electronic filing system in accordance with 37 CFR § 1.6(a)(4).

Dated: August 22, 2017
Electronic Signature for Jill Gorny Sloper, Esq.: /Jill Gorny Sloper, Esq./

Docket No.: AXJ-114BUSCN5
(PATENT)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of:
Leonard Bell *et al.*

Application No.: 15/642,096

Confirmation No.: 7606

Filed: July 5, 2017

Art Unit: 1662

For: TREATMENT OF PAROXYSMAL NOCTURNAL HEMOGLOBINURIA PATIENTS BY AN INHIBITOR OF COMPLEMENT

Examiner: Not Yet Assigned

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

INFORMATION DISCLOSURE STATEMENT (IDS)

Dear Sir:

In compliance with 37 C.F.R. § 1.56, 1.97 and 1.98, the attention of the Patent and Trademark Office is hereby directed to the documents listed on the attached PTO/SB/08. It is respectfully requested that the documents listed on the PTO/SB/08 be expressly considered by the Examiner during the prosecution of this application, and that the documents be made of record therein and appear among the "References Cited" on any patent to issue therefrom.

The present application is a continuation of U.S. Application No. 15/284,015, filed October 3, 2016 (Atty. Docket No. AXJ-114BUSCN4). For the Examiner's convenience in reviewing this continuation application, Applicant submits a consolidated PTO Form SB/08, listing all references cited during the prosecution of the parent applications. In accordance with 37 C.F.R. §1.98(d), copies of the references previously cited by or submitted to the Office in the parent applications are not enclosed, but will be provided upon request.

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /J.L.R/

Additionally, in accordance with 37 C.F.R. § 1.98(a)(2)(i)-(iv), Applicant submits herewith copies of foreign patents and non-patent literature references, but has not included copies of U.S. patents and U.S. patent applications.

Applicant calls to the attention of the Examiner the following Applications and Office Actions cited therein:

Applications				
Examiner's Initials	*Serial No.*	*Filing Date*	*First Named Inventor*	*Docket No.*
	15/284,015	10-03-2016	Leonard Bell	AXJ-114BUSCN4
	15/260,888	09-09-2016	Leonard Bell	AXJ-114BUSCN3
	15/148,839	05-06-2016	Leonard Bell	AXJ-114BUSCN2
	13/426,973	03-22-2012	Leonard Bell	AXJ-114BUSCN
	12/225,040	05-13-2009	Leonard Bell	AXJ-114BUS
	12/621,792	11-19-2009	Leonard Bell	AXJ-114DV
	10/771,552	02-03-2004	Leonard Bell	AXJ-114RCE
	11/050,543	02-03-2005	Leonard Bell	AXJ-114CPRCE
	11/595,118	11-08-2006	Leonard Bell	AXJ-114CP2
	12/902,617	10-12-2010	Leonard Bell	AXJ-114CPCN
	13/335,518	12-22-2011	Leonard Bell	AXJ-114CPCN2RCE

Office Actions (copies enclosed)			
Examiner's Initials	Serial No.	Date Mailed from USPTO	Examiner
	15/284,015	07-03-2017	J. Rogers
	15/284,015	04-11-2017	J. Rogers
	15/284,015	11-01-2017	J. Rogers
	15/260,888	06-28-2017	J. Rogers
	15/260,888	04-11-2017	J. Rogers
	15/260,888	12-22-2016	J. Rogers
	15/260,888	10-27-2016	J. Rogers
	15/148,839	06-07-2017	J. Rogers
	15/148,839	04-04-2017	J. Rogers
	15/148,839	08-16-2016	J. Rogers
	13/426,973	01-27-2014	J. Rogers
	13/426,973	05-31-2013	J. Rogers
	13/426,973	08-20-2012	J. Rogers
	12/225,040	09-22-2011	J. Rogers
	12/225,040	06-01-2011	J. Rogers

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /J.L.R/

	12/225,040	04-11-2011	J. Rogers
	12/621,792	09-30-2010	P. Gambel
	10/771,552	12-22-2008	F. Vandervegt
	10/771,552	03-21-2008	F. Vandervegt
	10/771,552	08-10-2007	F. Vandervegt
	10/771,552	02-26-2007	F. Vandervegt
	10/771,552	09-26-2006	F. Vandervegt
	11/050,543	07-09-2010	P. Gambel
	11/050,543	04-02-2008	F. Vandervegt
	11/050,543	10-10-2007	F. Vandervegt
	11/050,543	06-11-2007	F. Vandervegt
	11/595,118	01-21-2011	P. Gambel
	11/595,118	10-05-2010	P. Gambel
	11/595,118	07-07-2010	P. Gambel
	11/595,118	04-03-2009	F. Vandervegt
	12/902,617	06-23-2011	P. Gambel
	12/902,617	04-04-2011	P. Gambel
	13/335,518	08-22-2016	P. Gambel
	13/335,518	09-12-2014	P. Gambel
	13/335,518	02-06-2014	P. Gambel
	13/335,518	11-07-2013	P. Gambel

/JAMES L ROGERS/ 04/30/2019

The Examiner is requested to review the file histories of these applications, including cited references, Office Actions, Responses, etc., and is asked to contact Applicant's Attorney if the Examiner would like the Applicant to supply copies of any or all of the information included in any of these applications. For any of these applications, if Applicant's Attorney is not contacted by the Examiner with such a request, then it will be concluded that the Examiner has reviewed or will review the file content of these applications.

Applicant respectfully requests that the Examiner initial the blank columns next to the cited Applications and Office Actions, to indicate that the information has been considered by the Examiner. Alternatively, Applicant requests that the Examiner insert the phrase, "All references considered except where lined through," on each page of the Information Disclosure Statement, along with the Examiner's initials.

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /J.L.R/

The filing of this Information Disclosure Statement is not to be interpreted as a representation that the cited documents are material, that an exhaustive search has been conducted, or that no other relevant information exists. Nor shall the citation of any documents herein be construed *per se* as a representation that such document is prior art. Moreover, Applicant understands the Examiner will make an independent evaluation of the cited documents.

This Information Disclosure Statement is filed within three months of the U.S. filing date (37 C.F.R. § 1.97(b)(1)).

Dated: August 22, 2017

Respectfully submitted,

Electronic signature: /Jill Gorny Sloper, Esq./
Jill Gorny Sloper, Esq.
Registration No.: 60,760
NELSON MULLINS RILEY & SCARBOROUGH LLP
One Post Office Square
Boston, Massachusetts 02109-2127
(617) 217-4630
(617) 217-4699 (Fax)
Attorney/Agent For Applicant

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Samsung Bioepis Exhibit No. 1002
Page 11314

Doc code: IDS
Doc description: Information Disclosure Statement (IDS) Filed

PTO/SB/08a (03-15)
Approved for use through 07/31/2016. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it contains a valid OMB control number.

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (**Not for submission under 37 CFR 1.99**)		
	Application Number	15642096
	Filing Date	2017-07-05
	First Named Inventor	Leonard BELL
	Art Unit	1662
	Examiner Name	Not Yet Assigned
	Attorney Docket Number	AXJ-114BUSCN5

U.S.PATENTS Remove

Examiner Initial*	Cite No	Patent Number	Kind Code[1]	Issue Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear
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U.S.PATENT APPLICATION PUBLICATIONS Remove

Examiner Initial*	Cite No	Publication Number	Kind Code[1]	Publication Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear
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Examiner Initial*	Cite No	Foreign Document Number[3]	Country Code[2] i	Kind Code[4]	Publication Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear	T[5]
	1							

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NON-PATENT LITERATURE DOCUMENTS Remove

Examiner Initials*	Cite No	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc), date, pages(s), volume-issue number(s), publisher, city and/or country where published.	T[5]

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	1	PCT/US2007/006606 Certified Copy of Priority document US 60/783,070, March 15, 2006, 43 pages.	
	2	PIERANGELI,S. et al., "Requirement of activation of complement C3 and C5 for antiphospholipid antibody-mediated thrombophilia," Arthritis & Rheumatology, vol. 52, Issue 7: 2120-2124(2005)	
	3	REITER et al., "Cell-free hemoglobin limits nitric oxide bioavailability in sickle-cell disease," Nature Med., vol. 8 (12):1383-1389(2002)	
	4	RICHARDS et al., "Evolution of GPI-Deficient Clones Predicts Clinical Course in Paroxysmal Nocturnal Haemoglobinuria," Blood, vol. 104:Abstract 172 (2004)	
	5	RICKLIN, D. et al., "Complement-targeted therapeutics," Nature Biotechnology, vol. 25(11): 1265-1275 (2007)	
	6	RODARY et al., "Patient preference for either the EORTC QLQ-C30 or the FACIT Quality of Life (QOL) measures: a study performed in patient suffering from carcinoma of an unknown primary site (CUP)," European Journal of Cancer, Vol. 40, pp. 521-528 (2004).	
	7	Rosse et al. "Immune-mediated hemolytic anemia" Hematology Am Soc, 48-62 (2004)	
	8	ROTHER et al., "The clinical sequelae of intravascular hemolysis and extracellular plasma hemoglobin, " JAMA, vol. 293(13):1653-1662 (2005).	
	9	ROTHER et al., Eculizumab, a C5 complement-blocking antibody, abolishes hemolysis and reduces transfusion dependency in patients with paroxysmal nocturnal hemoglobinuria (PNH)," Molecular Immunology, Vol. 40(2-4): page 197, XP009163498, (2003).	
	10	ROTHER et al., "Discovery and development of the complement inhibitor eculizumab for the treatment of paroxysmal nocturnal hemoglobinuria," Nature Biotechnology, vol. 25 (11): 1256-1264 (2007)	
	11	Safety and Effectiveness of h5G1.1-mAb for dermatomyositis" clinicaltrials.gov identifier NCT00005571, April 25, 2000, pp. 1-4	

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	12	SIERRA, G. et al., "Vaccine against group B Neisseia meningitidis: Protection trial and mass vaccination results in Cuba," NIPH ANNALS 1991, vol. 14(2):195-210, ISSN: 0332-5652 (1991)	
	13	Soliris® (eculizumab) Highlights of prescribing information, 8 pages	
	14	STEBLER et al., "High-dose recombinant human erythropoietin for treatment of anemia in myelodysplastic syndromes and paroxysmal nocturnal hemoglobinuria: a pilot study," Exp. Hematol., vol. 18:1204-1208 (1990).	
	15	STRAUSS et al. "Alternative pathway of complement in sickle cell disease," Pediat. Res., vol. 11:285-289 (1977)	
	16	STUART et al., "Sickle-cell disease," Lancet, vol. 364:1343-1360 (2004)	
	17	TANG, et al., "Pikal, Design of Freeze-Drying Processes for Pharmaceuticals: Practical Advice," Pharmaceutical Research, Vol. 21 (2):191-200 (2004).	
	18	The MERCK MANUAL of Diagnosis and Therapy, Seventeenth Edition, Chapter 127 Anemias,; pp. 849-883 (1999).;	
	19	THOMAS et al., "Inhibition of complement activity by humanized anti-C5 antibody and single-chain Fv, " Mol. Imm., vol. 33(17-18):1389-1401 (1996)	
	20	US Pharmacopeia (USP29-NF24), p. 2989, retrieved from http://www.pharmacopeia.cn/v29240/usp29nf24s0 c1136.html on May 17, 2017, 4 pages.	
	21	VAKEVA, et al., "Myocardial infarction and apoptosis after myocardial ischemia and reperfusion," Circulation vol. 97:2259-2267 (1998).	
	22	WANG, W. et al., "Antibody Structure, Instability, and Formulation" Journal of Pharmaceuticals, vol. 96(1): 26 pages (2007)	

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	Attorney Docket Number	AXJ-114BUSCN5

If you wish to add additional non-patent literature document citation information please click the Add button Add

EXAMINER SIGNATURE

Examiner Signature	/JAMES L ROGERS/	Date Considered	04/30/2019

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through a citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

[1] See Kind Codes of USPTO Patent Documents at www.USPTO.GOV or MPEP 901.04. [2] Enter office that issued the document, by the two-letter code (WIPO Standard ST.3). [3] For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. [4] Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16 if possible. [5] Applicant is to place a check mark here if English language translation is attached.

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Name/Print	Jill Gorny Sloper, Esq.	Registration Number	60,760

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ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /J.L.R/

PTO/SB/08a (03-15)
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U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

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INFORMATION DISCLOSURE STATEMENT BY APPLICANT
(Not for submission under 37 CFR 1.99)

Application Number	15642096
Filing Date	2017-07-05
First Named Inventor	Leonard BELL
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Attorney Docket Number	AXJ-114BUSCN5

U.S.PATENTS Remove

Examiner Initial*	Cite No	Patent Number	Kind Code[1]	Issue Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear
	1	4686100		1987-08-11	Raffin et al.	
	2	5135916		1992-08-04	Sims et al.	
	3	5660825		1997-08-26	Sims et al.	
	4	6171586		2001-01-09	Lam et al.	
	5	6355245		2002-03-12	Evans et al.	
	6	7361339		2008-04-22	Bell	
	7	7482435		2009-01-27	Bowdish et al.	
	8	9718880		2017-08-01	Bell et al.	

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	9	9725504		2017-08-08	Bell et al.	
	10	9732149		2017-08-15	Bell et al.	

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	First Named Inventor	Leonard BELL
	Art Unit	1662
	Examiner Name	Not Yet Assigned
	Attorney Docket Number	AXJ-114BUSCN5

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Signature	/Jill Gorny Sloper, Esq./	Date (YYYY-MM-DD)	2017-08-22
Name/Print	Jill Gorny Sloper, Esq.	Registration Number	60,760

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INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
	Application Number	15642096
	Filing Date	2017-07-05
	First Named Inventor	Leonard BELL
	Art Unit	1644
	Examiner Name	J. L. Rogers
	Attorney Docket Number	AXJ-114BUSCN5

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	30	U.S. Patent No. 9,725,504 B2, File History, 836 pages.	
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See attached certification statement.

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A certification statement is not submitted herewith.

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Signature	/Jill Gorny Sloper, Esq./	Date (YYYY-MM-DD)	2019-04-29
Name/Print	Jill Gorny Sloper, Esq.	Registration Number	60,760

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Doc description: Information Disclosure Statement (IDS) Filed

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	First Named Inventor	Leonard BELL
	Art Unit	1644
	Examiner Name	J. L. Rogers
	Attorney Docket Number	AXJ-114BUSCN5

U.S.PATENTS

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	First Named Inventor	Leonard BELL
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	Examiner Name	J. L. Rogers
	Attorney Docket Number	AXJ-114BUSCN5

	1	Termination of opposition proceedings of European Patent No. 1720571, dated April 13, 2018, 16 pages.	☐

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Signature	/Jill Gorny Sloper, Esq./	Date (YYYY-MM-DD)	2018-04-27
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L252          0 FILE DGENE
L253          0 FILE DRUGB
L254          0 FILE DRUGU
L255          0 FILE ESBIOBASE
L256          0 FILE FSTA
L257          0 FILE GENBANK
L258          0 FILE IFIALL
L259          0 FILE IMSRESEARCH
L260          0 FILE KOSMET
L261          0 FILE MEDLINE
L262          0 FILE NTIS
L263          0 FILE PCTGEN
L264          0 FILE PS
L265          0 FILE RDISCLOSURE
L266          0 FILE SCISEARCH
L267          0 FILE TOXCENTER
L268          0 FILE USGENE
L269          1 FILE USPATFULL
L270          0 FILE USPATOLD
L271          0 FILE USPAT2
L272          0 FILE VETB
L273          0 FILE VETU
L274          0 FILE IPA
L275          0 FILE NAPRALERT
     TOTAL FOR ALL FILES
L276          1 S L230 AND ((SINGLE (2A) UNIT) (50A) (300 (2A) MG))
L277          0 FILE DISSABS
L278          0 FILE 1MOBILITY
L279          0 FILE AGRICOLA
L280          0 FILE BIOTECHNO
```

supplemental STN search

```
L281          0 FILE COMPENDEX
L282          0 FILE EMBASE
L283          0 FILE INSPEC
L284          0 FILE PQSCITECH
L285          0 FILE ADISCTI
L286          0 FILE ADISINSIGHT
L287          0 FILE ADISNEWS
L288          0 FILE ANABSTR
L289          0 FILE BIOSIS
L290          0 FILE BIOTECHDS
L291          0 FILE CABA
L292          0 FILE CAPLUS
L293          0 FILE CEABA-VTB
L294          0 FILE CIN
L295          0 FILE CROPB
L296          0 FILE CROPU
L297          0 FILE DDFB
L298          0 FILE DGENE
L299          0 FILE DRUGB
L300          0 FILE DRUGU
L301          0 FILE ESBIOBASE
L302          0 FILE FSTA
L303          0 FILE GENBANK
L304          4 FILE IFIALL
L305          0 FILE IMSRESEARCH
L306          0 FILE KOSMET
L307          0 FILE MEDLINE
L308          0 FILE NTIS
L309          0 FILE PCTGEN
L310          0 FILE PS
L311          0 FILE RDISCLOSURE
L312          0 FILE SCISEARCH
L313          0 FILE TOXCENTER
L314          0 FILE USGENE
L315          9 FILE USPATFULL
L316          0 FILE USPATOLD
L317          3 FILE USPAT2
L318          0 FILE VETB
L319          0 FILE VETU
L320          0 FILE IPA
L321          0 FILE NAPRALERT
     TOTAL FOR ALL FILES
L322         16 S ((SINGLE (2A) UNIT) (50A) (300 (2A) MG)) AND (ECULIZUMAB OR S
L323         12 DUP REM L322 (4 DUPLICATES REMOVED)
L324         94 FILE DISSABS
L325          0 FILE 1MOBILITY
L326        109 FILE AGRICOLA
L327       1690 FILE BIOTECHNO
L328         57 FILE COMPENDEX
L329      29082 FILE EMBASE
L330         23 FILE INSPEC
L331       2229 FILE PQSCITECH
L332        410 FILE ADISCTI
L333         88 FILE ADISINSIGHT
L334        685 FILE ADISNEWS
L335          5 FILE ANABSTR
L336      14004 FILE BIOSIS
L337        513 FILE BIOTECHDS
L338        508 FILE CABA
```

supplemental STN search

```
L339       7140 FILE CAPLUS
L340         10 FILE CEABA-VTB
L341         50 FILE CIN
L342          4 FILE CROPB
L343          4 FILE CROPU
L344       1030 FILE DDFB
L345     118208 FILE DGENE
L346       1030 FILE DRUGB
L347       2537 FILE DRUGU
L348       2749 FILE ESBIOBASE
L349         17 FILE FSTA
L350        318 FILE GENBANK
L351       1434 FILE IFIALL
L352         64 FILE IMSRESEARCH
L353          3 FILE KOSMET
L354      18461 FILE MEDLINE
L355         58 FILE NTIS
L356       2981 FILE PCTGEN
L357          0 FILE PS
L358          1 FILE RDISCLOSURE
L359      14044 FILE SCISEARCH
L360       8142 FILE TOXCENTER
L361      28347 FILE USGENE
L362      13906 FILE USPATFULL
L363         14 FILE USPATOLD
L364       5331 FILE USPAT2
L365         24 FILE VETB
L366         51 FILE VETU
L367        357 FILE IPA
L368         10 FILE NAPRALERT
     TOTAL FOR ALL FILES
L369     275822 S (NOCTURNAL (2A) HEMOGLOBINURIA) OR (APLASTIC (2A) ANEMIA) OR
L370          0 FILE DISSABS
L371          0 FILE 1MOBILITY
L372          0 FILE AGRICOLA
L373         25 FILE BIOTECHNO
L374          0 FILE COMPENDEX
L375         81 FILE EMBASE
L376          0 FILE INSPEC
L377         24 FILE PQSCITECH
L378         48 FILE ADISCTI
L379          6 FILE ADISINSIGHT
L380         71 FILE ADISNEWS
L381          0 FILE ANABSTR
L382         54 FILE BIOSIS
L383          1 FILE BIOTECHDS
L384          6 FILE CABA
L385         32 FILE CAPLUS
L386          0 FILE CEABA-VTB
L387          0 FILE CIN
L388          0 FILE CROPB
L389          0 FILE CROPU
L390          0 FILE DDFB
L391        168 FILE DGENE
L392          0 FILE DRUGB
L393         91 FILE DRUGU
L394         37 FILE ESBIOBASE
L395          0 FILE FSTA
L396          0 FILE GENBANK
```

supplemental STN search

```
L397          15 FILE IFIALL
L398           1 FILE IMSRESEARCH
L399           0 FILE KOSMET
L400          45 FILE MEDLINE
L401           0 FILE NTIS
L402           0 FILE PCTGEN
L403           0 FILE PS
L404           0 FILE RDISCLOSURE
L405          39 FILE SCISEARCH
L406          22 FILE TOXCENTER
L407           0 FILE USGENE
L408         110 FILE USPATFULL
L409           0 FILE USPATOLD
L410          52 FILE USPAT2
L411           0 FILE VETB
L412           0 FILE VETU
L413           4 FILE IPA
L414           0 FILE NAPRALERT
     TOTAL FOR ALL FILES
L415         932 S L369 (50A) (PLATELET (5A) COUNT)
L416           0 FILE DISSABS
L417           0 FILE 1MOBILITY
L418           0 FILE AGRICOLA
L419           3 FILE BIOTECHNO
L420           0 FILE COMPENDEX
L421          10 FILE EMBASE
L422           0 FILE INSPEC
L423           3 FILE PQSCITECH
L424          18 FILE ADISCTI
L425           0 FILE ADISINSIGHT
L426          27 FILE ADISNEWS
L427           0 FILE ANABSTR
L428           2 FILE BIOSIS
L429           1 FILE BIOTECHDS
L430           1 FILE CABA
L431           1 FILE CAPLUS
L432           0 FILE CEABA-VTB
L433           0 FILE CIN
L434           0 FILE CROPB
L435           0 FILE CROPU
L436           0 FILE DDFB
L437          15 FILE DGENE
L438           0 FILE DRUGB
L439          22 FILE DRUGU
L440           6 FILE ESBIOBASE
L441           0 FILE FSTA
L442           0 FILE GENBANK
L443           1 FILE IFIALL
L444           0 FILE IMSRESEARCH
L445           0 FILE KOSMET
L446           3 FILE MEDLINE
L447           0 FILE NTIS
L448           0 FILE PCTGEN
L449           0 FILE PS
L450           0 FILE RDISCLOSURE
L451           1 FILE SCISEARCH
L452           1 FILE TOXCENTER
L453           0 FILE USGENE
L454          47 FILE USPATFULL
```

supplemental STN search

```
L455          0 FILE USPATOLD
L456         20 FILE USPAT2
L457          0 FILE VETB
L458          0 FILE VETU
L459          1 FILE IPA
L460          0 FILE NAPRALERT
     TOTAL FOR ALL FILES
L461        183 S L415 (50A) TRANSFUSION
L462          0 FILE DISSABS
L463          0 FILE 1MOBILITY
L464          0 FILE AGRICOLA
L465          0 FILE BIOTECHNO
L466          0 FILE COMPENDEX
L467          0 FILE EMBASE
L468          0 FILE INSPEC
L469          0 FILE PQSCITECH
L470          7 FILE ADISCTI
L471          0 FILE ADISINSIGHT
L472          0 FILE ADISNEWS
L473          0 FILE ANABSTR
L474          0 FILE BIOSIS
L475          0 FILE BIOTECHDS
L476          0 FILE CABA
L477          0 FILE CAPLUS
L478          0 FILE CEABA-VTB
L479          0 FILE CIN
L480          0 FILE CROPB
L481          0 FILE CROPU
L482          0 FILE DDFB
L483          0 FILE DGENE
L484          0 FILE DRUGB
L485          0 FILE DRUGU
L486          0 FILE ESBIOBASE
L487          0 FILE FSTA
L488          0 FILE GENBANK
L489          0 FILE IFIALL
L490          0 FILE IMSRESEARCH
L491          0 FILE KOSMET
L492          0 FILE MEDLINE
L493          0 FILE NTIS
L494          0 FILE PCTGEN
L495          0 FILE PS
L496          0 FILE RDISCLOSURE
L497          0 FILE SCISEARCH
L498          0 FILE TOXCENTER
L499          0 FILE USGENE
L500          0 FILE USPATFULL
L501          0 FILE USPATOLD
L502          0 FILE USPAT2
L503          0 FILE VETB
L504          0 FILE VETU
L505          0 FILE IPA
L506          0 FILE NAPRALERT
     TOTAL FOR ALL FILES
L507          7 S L461 (50A) (LACTATE (3A) DEHYDROGENASE)
L508          7 DUP REM L507 (0 DUPLICATES REMOVED)
L509          0 FILE DISSABS
L510          0 FILE 1MOBILITY
L511          0 FILE AGRICOLA
```

supplemental STN search

```
L512          0 FILE BIOTECHNO
L513          0 FILE COMPENDEX
L514          4 FILE EMBASE
L515          0 FILE INSPEC
L516          1 FILE PQSCITECH
L517         18 FILE ADISCTI
L518          5 FILE ADISINSIGHT
L519          3 FILE ADISNEWS
L520          0 FILE ANABSTR
L521          4 FILE BIOSIS
L522          0 FILE BIOTECHDS
L523          0 FILE CABA
L524         54 FILE CAPLUS
L525          0 FILE CEABA-VTB
L526          0 FILE CIN
L527          0 FILE CROPB
L528          0 FILE CROPU
L529          0 FILE DDFB
L530         20 FILE DGENE
L531          0 FILE DRUGB
L532          3 FILE DRUGU
L533          5 FILE ESBIOBASE
L534          0 FILE FSTA
L535          3 FILE GENBANK
L536          2 FILE IFIALL
L537          5 FILE IMSRESEARCH
L538          0 FILE KOSMET
L539          3 FILE MEDLINE
L540          0 FILE NTIS
L541          0 FILE PCTGEN
L542          0 FILE PS
L543          0 FILE RDISCLOSURE
L544          3 FILE SCISEARCH
L545          1 FILE TOXCENTER
L546          0 FILE USGENE
L547          6 FILE USPATFULL
L548          0 FILE USPATOLD
L549          3 FILE USPAT2
L550          0 FILE VETB
L551          0 FILE VETU
L552          0 FILE IPA
L553          0 FILE NAPRALERT
     TOTAL FOR ALL FILES
L554        143 S (NOCTURNAL (2A) HEMOGLOBINURIA) (50A) (LACTATE (3A) DEHYDROGE
L555          0 FILE DISSABS
L556          0 FILE 1MOBILITY
L557          0 FILE AGRICOLA
L558          0 FILE BIOTECHNO
L559          0 FILE COMPENDEX
L560          1 FILE EMBASE
L561          0 FILE INSPEC
L562          0 FILE PQSCITECH
L563         11 FILE ADISCTI
L564          3 FILE ADISINSIGHT
L565          1 FILE ADISNEWS
L566          0 FILE ANABSTR
L567          0 FILE BIOSIS
L568          0 FILE BIOTECHDS
L569          0 FILE CABA
```

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```
L570          2 FILE CAPLUS
L571          0 FILE CEABA-VTB
L572          0 FILE CIN
L573          0 FILE CROPB
L574          0 FILE CROPU
L575          0 FILE DDFB
L576          0 FILE DGENE
L577          0 FILE DRUGB
L578          2 FILE DRUGU
L579          2 FILE ESBIOBASE
L580          0 FILE FSTA
L581          0 FILE GENBANK
L582          0 FILE IFIALL
L583          1 FILE IMSRESEARCH
L584          0 FILE KOSMET
L585          0 FILE MEDLINE
L586          0 FILE NTIS
L587          0 FILE PCTGEN
L588          0 FILE PS
L589          0 FILE RDISCLOSURE
L590          0 FILE SCISEARCH
L591          0 FILE TOXCENTER
L592          0 FILE USGENE
L593          1 FILE USPATFULL
L594          0 FILE USPATOLD
L595          0 FILE USPAT2
L596          0 FILE VETB
L597          0 FILE VETU
L598          0 FILE IPA
L599          0 FILE NAPRALERT
     TOTAL FOR ALL FILES
L600         24 S L554 (50A) TRANSFUSION
L601          0 FILE DISSABS
L602          0 FILE 1MOBILITY
L603          0 FILE AGRICOLA
L604          0 FILE BIOTECHNO
L605          0 FILE COMPENDEX
L606          0 FILE EMBASE
L607          0 FILE INSPEC
L608          0 FILE PQSCITECH
L609          7 FILE ADISCTI
L610          0 FILE ADISINSIGHT
L611          0 FILE ADISNEWS
L612          0 FILE ANABSTR
L613          0 FILE BIOSIS
L614          0 FILE BIOTECHDS
L615          0 FILE CABA
L616          0 FILE CAPLUS
L617          0 FILE CEABA-VTB
L618          0 FILE CIN
L619          0 FILE CROPB
L620          0 FILE CROPU
L621          0 FILE DDFB
L622          0 FILE DGENE
L623          0 FILE DRUGB
L624          0 FILE DRUGU
L625          0 FILE ESBIOBASE
L626          0 FILE FSTA
L627          0 FILE GENBANK
```

supplemental STN search

```
L628          0 FILE IFIALL
L629          0 FILE IMSRESEARCH
L630          0 FILE KOSMET
L631          0 FILE MEDLINE
L632          0 FILE NTIS
L633          0 FILE PCTGEN
L634          0 FILE PS
L635          0 FILE RDISCLOSURE
L636          0 FILE SCISEARCH
L637          0 FILE TOXCENTER
L638          0 FILE USGENE
L639          0 FILE USPATFULL
L640          0 FILE USPATOLD
L641          0 FILE USPAT2
L642          0 FILE VETB
L643          0 FILE VETU
L644          0 FILE IPA
L645          0 FILE NAPRALERT
     TOTAL FOR ALL FILES
L646          7 S L600 (50A) (PLATELET (5A) COUNT)
L647         18 FILE DISSABS
L648          0 FILE 1MOBILITY
L649         21 FILE AGRICOLA
L650        451 FILE BIOTECHNO
L651         11 FILE COMPENDEX
L652       6118 FILE EMBASE
L653          3 FILE INSPEC
L654        447 FILE PQSCITECH
L655        136 FILE ADISCTI
L656         42 FILE ADISINSIGHT
L657         81 FILE ADISNEWS
L658          0 FILE ANABSTR
L659       3067 FILE BIOSIS
L660        100 FILE BIOTECHDS
L661         22 FILE CABA
L662       1906 FILE CAPLUS
L663          0 FILE CEABA-VTB
L664         19 FILE CIN
L665          0 FILE CROPB
L666          0 FILE CROPU
L667        135 FILE DDFB
L668      50579 FILE DGENE
L669        135 FILE DRUGB
L670        345 FILE DRUGU
L671        724 FILE ESBIOBASE
L672          0 FILE FSTA
L673         69 FILE GENBANK
L674        342 FILE IFIALL
L675         33 FILE IMSRESEARCH
L676          1 FILE KOSMET
L677       2909 FILE MEDLINE
L678          5 FILE NTIS
L679       2941 FILE PCTGEN
L680          0 FILE PS
L681          1 FILE RDISCLOSURE
L682       3916 FILE SCISEARCH
L683        893 FILE TOXCENTER
L684      27311 FILE USGENE
L685       3532 FILE USPATFULL
```

supplemental STN search

```
L686          1 FILE USPATOLD
L687       1082 FILE USPAT2
L688          0 FILE VETB
L689          0 FILE VETU
L690         42 FILE IPA
L691          0 FILE NAPRALERT
     TOTAL FOR ALL FILES
L692     107438 S (NOCTURNAL (2A) HEMOGLOBINURIA) (5A) PAROXYSMAL
L693          0 FILE DISSABS
L694          0 FILE 1MOBILITY
L695          0 FILE AGRICOLA
L696          1 FILE BIOTECHNO
L697          0 FILE COMPENDEX
L698          3 FILE EMBASE
L699          0 FILE INSPEC
L700          2 FILE PQSCITECH
L701         15 FILE ADISCTI
L702          0 FILE ADISINSIGHT
L703          2 FILE ADISNEWS
L704          0 FILE ANABSTR
L705          1 FILE BIOSIS
L706          0 FILE BIOTECHDS
L707          1 FILE CABA
L708          3 FILE CAPLUS
L709          0 FILE CEABA-VTB
L710          0 FILE CIN
L711          0 FILE CROPB
L712          0 FILE CROPU
L713          0 FILE DDFB
L714          0 FILE DGENE
L715          0 FILE DRUGB
L716          9 FILE DRUGU
L717          1 FILE ESBIOBASE
L718          0 FILE FSTA
L719          0 FILE GENBANK
L720          0 FILE IFIALL
L721          0 FILE IMSRESEARCH
L722          0 FILE KOSMET
L723          1 FILE MEDLINE
L724          0 FILE NTIS
L725          0 FILE PCTGEN
L726          0 FILE PS
L727          0 FILE RDISCLOSURE
L728          1 FILE SCISEARCH
L729          1 FILE TOXCENTER
L730          0 FILE USGENE
L731         15 FILE USPATFULL
L732          0 FILE USPATOLD
L733         12 FILE USPAT2
L734          0 FILE VETB
L735          0 FILE VETU
L736          1 FILE IPA
L737          0 FILE NAPRALERT
     TOTAL FOR ALL FILES
L738         69 S L692 (50A) (PLATELET (5A) COUNT)
L739          0 FILE DISSABS
L740          0 FILE 1MOBILITY
L741          0 FILE AGRICOLA
L742          0 FILE BIOTECHNO
```

supplemental STN search

```
L743           0 FILE COMPENDEX
L744           0 FILE EMBASE
L745           0 FILE INSPEC
L746           0 FILE PQSCITECH
L747           9 FILE ADISCTI
L748           0 FILE ADISINSIGHT
L749           0 FILE ADISNEWS
L750           0 FILE ANABSTR
L751           0 FILE BIOSIS
L752           0 FILE BIOTECHDS
L753           0 FILE CABA
L754           0 FILE CAPLUS
L755           0 FILE CEABA-VTB
L756           0 FILE CIN
L757           0 FILE CROPB
L758           0 FILE CROPU
L759           0 FILE DDFB
L760           0 FILE DGENE
L761           0 FILE DRUGB
L762           2 FILE DRUGU
L763           1 FILE ESBIOBASE
L764           0 FILE FSTA
L765           0 FILE GENBANK
L766           0 FILE IFIALL
L767           0 FILE IMSRESEARCH
L768           0 FILE KOSMET
L769           0 FILE MEDLINE
L770           0 FILE NTIS
L771           0 FILE PCTGEN
L772           0 FILE PS
L773           0 FILE RDISCLOSURE
L774           0 FILE SCISEARCH
L775           0 FILE TOXCENTER
L776           0 FILE USGENE
L777           8 FILE USPATFULL
L778           0 FILE USPATOLD
L779           6 FILE USPAT2
L780           0 FILE VETB
L781           0 FILE VETU
L782           1 FILE IPA
L783           0 FILE NAPRALERT
     TOTAL FOR ALL FILES
L784          27 S L738 (50A) TRANSFUSION
L785          27 DUP REM L784 (0 DUPLICATES REMOVED)
L786           0 S L785
L787           0 FILE DISSABS
L788           0 S L785
L789           0 FILE 1MOBILITY
L790           0 S L785
L791           0 FILE AGRICOLA
L792           0 S L785
L793           0 FILE BIOTECHNO
L794           0 S L785
L795           0 FILE COMPENDEX
L796           0 S L785
L797           0 FILE EMBASE
L798           0 S L785
L799           0 FILE INSPEC
L800           0 S L785
```

supplemental STN search

```
L801          0 FILE PQSCITECH
L802          9 S L785
L803          0 FILE ADISCTI
L804          0 S L785
L805          0 FILE ADISINSIGHT
L806          0 S L785
L807          0 FILE ADISNEWS
L808          0 S L785
L809          0 FILE ANABSTR
L810          0 S L785
L811          0 FILE BIOSIS
L812          0 S L785
L813          0 FILE BIOTECHDS
L814          0 S L785
L815          0 FILE CABA
L816          0 S L785
L817          0 FILE CAPLUS
L818          0 S L785
L819          0 FILE CEABA-VTB
L820          0 S L785
L821          0 FILE CIN
L822          0 S L785
L823          0 FILE CROPB
L824          0 S L785
L825          0 FILE CROPU
L826          0 S L785
L827          0 FILE DDFB
L828          0 S L785
L829          0 FILE DGENE
L830          0 S L785
L831          0 FILE DRUGB
L832          2 S L785
L833          1 FILE DRUGU
L834          1 S L785
L835          1 FILE ESBIOBASE
L836          0 S L785
L837          0 FILE FSTA
L838          0 S L785
L839          0 FILE GENBANK
L840          0 S L785
L841          0 FILE IFIALL
L842          0 S L785
L843          0 FILE IMSRESEARCH
L844          0 S L785
L845          0 FILE KOSMET
L846          0 S L785
L847          0 FILE MEDLINE
L848          0 S L785
L849          0 FILE NTIS
L850          0 S L785
L851          0 FILE PCTGEN
L852          0 S L785
L853          0 FILE PS
L854          0 S L785
L855          0 FILE RDISCLOSURE
L856          0 S L785
L857          0 FILE SCISEARCH
L858          0 S L785
L859          0 FILE TOXCENTER
```

supplemental STN search

```
L860          0 S L785
L861          0 FILE USGENE
L862          8 S L785
L863          0 FILE USPATFULL
L864          0 S L785
L865          0 FILE USPATOLD
L866          6 S L785
L867          0 FILE USPAT2
L868          0 S L785
L869          0 FILE VETB
L870          0 S L785
L871          0 FILE VETU
L872          1 S L785
L873          1 FILE IPA
L874          0 S L785
L875          0 FILE NAPRALERT
     TOTAL FOR ALL FILES
L876          3 S L785 AND PY<2009

     FILE 'STNGUIDE' ENTERED AT 15:07:32 ON 30 APR 2019

     FILE 'DRUGU, ESBIOBASE, IPA' ENTERED AT 15:10:14 ON 30 APR 2019

     FILE 'STNGUIDE' ENTERED AT 15:10:14 ON 30 APR 2019

     FILE 'DRUGU, ESBIOBASE, IPA' ENTERED AT 15:12:39 ON 30 APR 2019
```

Doc code: IDS
Doc description: Information Disclosure Statement (IDS) Filed

PTO/SB/08a (02-18)
Approved for use through 11/30/2020. OMB 0651-0031
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INFORMATION DISCLOSURE STATEMENT BY APPLICANT
(Not for submission under 37 CFR 1.99)

Application Number	15642096
Filing Date	2017-07-05
First Named Inventor	Leonard BELL
Art Unit	1644
Examiner Name	J. L. Rogers
Attorney Docket Number	AXJ-114BUSCN5

U.S.PATENTS Remove

Examiner Initial*	Cite No	Patent Number	Kind Code[1]	Issue Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear
	1	6407213		2002-06-18	Carter et al.	

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Examiner Initial*	Cite No	Publication Number	Kind Code[1]	Publication Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear
	1	20030232972	A1	2003-12-18	Bowdish et al.	
	2	20040146948	A1	2004-07-29	Britton et al.	

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Examiner Initial*	Cite No	Foreign Document Number[3]	Country Code[2]	Kind Code[4]	Publication Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear	T[5]
	1	1720571	EP	B9	2012-10-24	Alexion Pharmaceuticals, Inc		
	2	1755674	EP	B1	2014-11-19	Alexion Pharmaceuticals, Inc		

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /J.L.R/

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
	Application Number	15642096
	Filing Date	2017-07-05
	First Named Inventor	Leonard BELL
	Art Unit	1644
	Examiner Name	J. L. Rogers
	Attorney Docket Number	AXJ-114BUSCN5

	3	2006122257	WO	A2	2006-11-16	Alexion Pharmaceuticals, Inc		
	4	1988882	EP	B1	2014-12-17	Alexion Pharmaceuticals, Inc		X
	5	2013235	EP	A1	2009-01-14	Alexion Pharmaceuticals, Inc		☐
	6	2061810	EP	B1	2014-11-12	Alexion Pharmaceuticals, Inc		☐
	7	2089058	EP	A2	2009-08-19	Alexion Pharmaceuticals, Inc		☐
	8	2815767	EP	A1	2014-12-24	Alexion Pharmaceuticals, Inc		☐
	9	2910253	EP	A1	2015-08-26	Alexion Pharmaceuticals, Inc		☐
	10	3056218	EP	A1	2016-08-17	Alexion Pharmaceuticals, Inc		☐
	11	2380907	EU	B1	2016-11-30	Alexion Pharmaceuticals, Inc		☐
	12	2004/050017	WO	A2	2004-06-17	Alexion Pharmaceuticals, Inc		☐
	13	2004/071439	WO	A2	2004-08-26	Elan Pharmaceuticals, Inc		☐

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ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /J.L.R/

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
	Application Number	15642096
	Filing Date	2017-07-05
	First Named Inventor	Leonard BELL
	Art Unit	1644
	Examiner Name	J. L. Rogers
	Attorney Docket Number	AXJ-114BUSCN5

	14	2004/108158	WO	A1	2004-12-16	Alexion Pharmaceuticals, Inc		☐
	15	2005/092073	WO	A2	2005-10-06	Protein Design Labs, Inc		☐
	16	2006003179	WO	A2	2006-01-12	Novo Nordisk As		☐

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NON-PATENT LITERATURE DOCUMENTS Remove

Examiner Initials*	Cite No	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc), date, pages(s), volume-issue number(s), publisher, city and/or country where published.	T5
	1	ADDERSON, E., et al., "Immunoglobulin Light Chain Variable Region Gene Sequences for Human Antibodies to Haemophilus influenza Type b Capsular Polysaccharide Are Dominated by a Limited Number of Vk and VI Segments and V J Combinations," J. Clin. Invest. vol. 89: 729-738 (1992).	
	2	ALBERTS, B. et al., "Intracellular Compartments and Protein Sorting," in Molecular Biology of the Cell, Chapter 12:55 pages (1994).	
	3	Alexion Pharmaceuticals, Inc.: "FDA Approves Alexion's Soliris(TM) for All Patients With PNH Alexion First Therapy Approved for This Rare and Life-Threatening Blood Disease," Press Release, March 16, 2007, 3 pages.	
	4	Amgen Inc., Petitioner v. Alexion Pharmaceuticals, "Petition for Inter Partes Review of U.S. Patent No, 9,718,880," Case IPR2019-00740, filed February 28, 2019, 84 pages.	
	5	Amgen Inc., Petitioner v. Alexion Pharmaceuticals, "Petition for Inter Partes Review of U.S. Patent No, 9,725,504," Case IPR2019-00739, filed February 28, 2019, 88 pages.	
	6	Amgen Inc., Petitioner v. Alexion Pharmaceuticals, "Petition for Inter Partes Review of U.S. Patent No, 9,732,149," Case IPR2019-00741, filed February 28, 2019, 62 pages.	

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /J.L.R/

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
	Application Number	15642096
	Filing Date	2017-07-05
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	Art Unit	1644
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	Attorney Docket Number	AXJ-114BUSCN5

	7	ASHP statement on unit dose drug distribution, Am. J. Hosp. Pharm., vol. 46:2346: 3 pages (1989).	
	8	Australian Government Department of Public Health, Pharmaceutical Benefits Advisory Committee, "Public Summary Document" for Eculizumab, 6 pages (2009).	
	9	Bessler, M., et al., "Paroxysmal nocturnal haemoglobinuria (PNH) is caused by somatic mutations in the PIG-A gene," The EMBO Journal, vol. 13: 110 - 117 (1994).	
	10	Biogen Idec Inc., Tysabri 2004 Package Insert, 11 pages.	
	11	Boehringer Ingelheim Int'l GmbH, Verluma 1996 Package Insert, 25 pages.	
	12	Centocor Ortho Biotech, LP, Orthoclone OKT3 Package Insert, retrieved 1/24/2019, 14 pages.	
	13	Centocor, Inc., Remicade 1998 Package Insert, 12 pages.	
	14	Corixa Corp., Bexxar 2003 Package Insert, 49 pages.	
	15	Cytogen Corp., ProstaScint 1996 Package Insert, 17 pages.	
	16	Declaration by Prof. Ronald Taylor and Curriculum Vitae, November 21, 2018, 9 pages.	
	17	Declaration of Dr. Alexander Klibanov, dated November 24, 2018, 45 pages.	

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	Filing Date	2017-07-05
	First Named Inventor	Leonard BELL
	Art Unit	1644
	Examiner Name	J. L. Rogers
	Attorney Docket Number	AXJ-114BUSCN5

	18	Declaration of Dr. Bruce Andrien with Exhibits, dated May 23, 2017, 36 pages.	
	19	Declaration of Dr. Bruce Andrien, dated August 15, 2018, 2 pages.	
	20	Declaration of Dr. Miano, dated March 22, 2018, 27 pages.	
	21	Declaration of Joseph P. Balthasar, Ph.D. and Curriculum Vitae, dated February 27, 2019, 129 pages.	
	22	Declaration of Stephen A. Saxe, with Exhibits A, B, C, dated January 12, 2018, 10 pages.	
	23	Eli Lilly & Co., ReoPro 1997 Package Insert, 17 pages.	
	24	Emery, P. et al., "The efficacy and safety of rituximab in patients with active rheumatoid arthritis despite methotrexate treatment: Results of a phase IIB randomized, double blind, placebo controlled, dose ranging trial," Arthritis & Rheumatism, vol. 54(5): 1390-1400 (2006).	
	25	European Application No. 11001632.6, Patentee's Response to Oppositions, dated March 22, 2018, 24 pages.	
	26	European Application No. 11001632.6, Summons to Attend Oral Proceedings, dated July 5, 2018, 10 pages.	
	27	European Application No. 11001632.6, Urgent Oral Proceedings of the Patentee, dated January 14, 2019, 2 pages.	
	28	European Application No. 11001632.6, Written Submission in Preparation of Oral Proceedings of the Patentee, dated November 24, 2018, 7 pages.	

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	First Named Inventor	Leonard BELL
	Art Unit	1644
	Examiner Name	J. L. Rogers
	Attorney Docket Number	AXJ-114BUSCN5

	29	European Application No. 16172335.8, Summons to Attend Oral Proceedings, dated March 27, 2019, 13 pages.	
	30	European Application No. 16172335.9, Reply To Written Opinion, dated October 30, 2017, 7 pages.	
	31	European Application No. 16195355.9, Extended European Search Report, dated March 17, 2017, 8 pages.	
	32	European Application No. 16195355.9, Reply to Third Party Communication, dated January 16, 2018, 3 pages.	
	33	European Application No. 16195355.9, Reply To Written Opinion, dated July 10, 2017, 7 pages.	
	34	European Application No. 16195355.9, Summons to Attend Oral Proceeding, dated May 7, 2018, 10 pages.	
	35	European Application No. 16195355.9, Table of Alexion European patents and patent applications, cited in Third Party Observation filed on December 12, 2017, 1 page.	
	36	European Application No. 16195355.9, Written Submission in Preparation of Oral Proceedings, dated August 15, 2018, 13 pages.	
	37	European Patent No. 1720571, Opposition File History, 515 pages.	
	38	European Patent No. 1720571, Pfizer Inc's Opposition statement, dated August 15, 2018, 13 pages.	
	39	European Patent No. 1720571, Third Party Observation filed on December 12, 2017, 1 page.	

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	Art Unit	1644
	Examiner Name	J. L. Rogers
	Attorney Docket Number	AXJ-114BUSCN5

	40	European Patent No. 2359834, Graphical representation of D20 Table 2, cited in Opposition on March 22, 2018, 1 page.	
	41	European Patent No. 2359834, Opposition File History, 2685 pages.	
	42	European Patent No. 2359834, Summary of antibodies listed in D20/D21 Tables, cited in Opposition on March 22, 2018.	
	43	European Patent No. 2359834, Summary of antibody products approved by EMA since filing date EMA Approved Antibodies C411599EP, cited in Opposition on March 22, 2018, 2 pages.	
	44	European Patent No. 3167888, File History, 348 pages.	
	45	Extracts from Kabat et al., Sequences of Proteins of Immunological Interest, US Dept, Health and Human Services, 10 pages (1991).	
	46	FDA Approval Letter dated March 16, 2007, 8 pages.	
	47	FDA Medical Review for Application Number 125166 (eculizumab), March 28, 2017, 122 pages.	
	48	FDA Pharmacometrics Review for Application Number 125166 (eculizumab), dated February 28, 2007, 21 pages.	
	49	Genentech, Inc., Avastin 2004 Package Insert, 27 pages.	
	50	Genentech, Inc., Herceptin 1998 Package Insert, 2 pages.	

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	Art Unit	1644
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	Attorney Docket Number	AXJ-114BUSCN5

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EXAMINER SIGNATURE

Examiner Signature	/JAMES L ROGERS/	Date Considered	04/30/2019

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through a citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

[1] See Kind Codes of USPTO Patent Documents at www.USPTO.GOV or MPEP 901.04. [2] Enter office that issued the document, by the two-letter code (WIPO Standard ST.3). [3] For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. [4] Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16 if possible. [5] Applicant is to place a check mark here if English language translation is attached.

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	Art Unit	1644
	Examiner Name	J. L. Rogers
	Attorney Docket Number	AXJ-114BUSCN5

CERTIFICATION STATEMENT

Please see 37 CFR 1.97 and 1.98 to make the appropriate selection(s):

That each item of information contained in the information disclosure statement was first cited in any communication from a foreign patent office in a counterpart foreign application not more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(1).

OR

☐ That no item of information contained in the information disclosure statement was cited in a communication from a foreign patent office in a counterpart foreign application, and, to the knowledge of the person signing the certification after making reasonable inquiry, no item of information contained in the information disclosure statement was known to any individual designated in 37 CFR 1.56(c) more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(2).

See attached certification statement.

The fee set forth in 37 CFR 1.17 (p) has been submitted herewith.

☒ A certification statement is not submitted herewith.

SIGNATURE

A signature of the applicant or representative is required in accordance with CFR 1.33, 10.18. Please see CFR 1.4(d) for the form of the signature.

Signature	/Jill Gorny Sloper, Esq./	Date (YYYY-MM-DD)	2019-04-29
Name/Print	Jill Gorny Sloper, Esq.	Registration Number	60,760

This collection of information is required by 37 CFR 1.97 and 1.98. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 1 hour to complete, including gathering, preparing and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

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3. A record in this system of records may be disclosed, as a routine use, to a Member of Congress submitting a request involving an individual, to whom the record pertains, when the individual has requested assistance from the Member with respect to the subject matter of the record.

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5. A record related to an International Application filed under the Patent Cooperation Treaty in this system of records may be disclosed, as a routine use, to the International Bureau of the World Intellectual Property Organization, pursuant to the Patent Cooperation Treaty.

6. A record in this system of records may be disclosed, as a routine use, to another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c)).

7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (i.e., GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.

8. A record from this system of records may be disclosed, as a routine use, to the public after either publication of the application pursuant to 35 U.S.C. 122(b) or issuance of a patent pursuant to 35 U.S.C. 151. Further, a record may be disclosed, subject to the limitations of 37 CFR 1.14, as a routine use, to the public if the record was filed in an application which became abandoned or in which the proceedings were terminated and which application is referenced by either a published application, an application open to public inspections or an issued patent.

9. A record from this system of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.

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EAST Search History (Prior Art)

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L1	921	("H5G1.1" or "5G1.1")	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	OFF	2019/04/30 14:28
L2	107	L1 and (single near3 unit)	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	OFF	2019/04/30 14:29
L3	47	L2 and ("300" near2 mg)	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	OFF	2019/04/30 14:30
L4	28	L3 and ("10" near2 ml)	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	OFF	2019/04/30 14:30
L5	21226	(nocturnal near2 hemoglobinuria) or (aplastic near2 anemia) or (myeladysplastic near2 syndrome)	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	OFF	2019/04/30 14:34
L6	200	L5 same (platelet near5 count)	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	OFF	2019/04/30 14:35
L7	48	L6 same transfusion	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	OFF	2019/04/30 14:35
L8	0	L7 same Eculizumab	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	OFF	2019/04/30 14:36
L9	0	L7 and Eculizumab	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	OFF	2019/04/30 14:36
L10	0	L7 same (lactate near3 dehydrogenase)	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	OFF	2019/04/30 14:37
L11	0	L7 and (lactate near3 dehydrogenase)	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	OFF	2019/04/30 14:37
L12	53	L5 same (lactate near3 dehydrogenase)	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	OFF	2019/04/30 14:37

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L14	142	(russell near3 rother).in.	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	OFF	2019/04/30 14:40
L15	525	(mark near3 evans).in.	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	OFF	2019/04/30 14:41
L16	3	L13 and L4	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	OFF	2019/04/30 14:41
L17	3	L14 and L4	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	OFF	2019/04/30 14:42
L18	3	L15 and L4	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	OFF	2019/04/30 14:42

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Page 11371

EAST Search History

EAST Search History (Prior Art)

Ref #	Hits	Search Query	DBs	Default Operator	Plurals	Time Stamp
L2	309	("5g1.1" or eculizumab).clm.	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	OFF	2019/05/14 14:34
L3	92	L2 and (PNH or paroxysmal)	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	OFF	2019/05/14 14:35
L4	19	L3 and (alexion near3 pharmaceuticals).as.	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	OFF	2019/05/14 14:36

EAST Search History (Interference)

Ref #	Hits	Search Query	DBs	Default Operator	Plurals	Time Stamp
L1	0	("(5g1.1oreculizumab).clm.").PN.	US-PGPUB; USPAT	OR	OFF	2019/05/14 14:34

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15642096	CTNF	05/31/2019	AXJ-114BUSCN5
	1449	05/31/2019	AXJ-114BUSCN5
	1449	05/31/2019	AXJ-114BUSCN5
	1449	05/31/2019	AXJ-114BUSCN5
	1449	05/31/2019	AXJ-114BUSCN5
	1449	05/31/2019	AXJ-114BUSCN5
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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
15/642,096	07/05/2017	Leonard BELL	AXJ-114BUSCN5	7606

133485 7590 06/11/2019

Nelson Mullins Riley & Scarborough LLP/Alexion
One Post Office Square
30th Floor
Boston, MA 02109-2127

EXAMINER	
ROGERS, JAMES L	

ART UNIT	PAPER NUMBER
1644	

NOTIFICATION DATE	DELIVERY MODE
06/11/2019	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

ipboston.docketing@nelsonmullins.com

Office Action Summary	**Application No.** 15/642,096	**Applicant(s)** BELL et al.	
	Examiner JAMES L ROGERS	**Art Unit** 1644	**AIA (FITF) Status** No

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTHS FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☑ Responsive to communication(s) filed on 8/24/2019.

☐ A declaration(s)/affidavit(s) under **37 CFR 1.130(b)** was/were filed on _____.

2a)☐ This action is **FINAL.** 2b) ☑ This action is non-final.

3)☐ An election was made by the applicant in response to a restriction requirement set forth during the interview on _____; the restriction requirement and election have been incorporated into this action.

4)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims*

5) ☑ Claim(s) 52-59 is/are pending in the application.

5a) Of the above claim(s) _____ is/are withdrawn from consideration.

6) ☐ Claim(s) _____ is/are allowed.

7) ☑ Claim(s) 52-59 is/are rejected.

8) ☐ Claim(s) _____ is/are objected to.

9) ☐ Claim(s) _____ are subject to restriction and/or election requirement

* If any claims have been determined allowable, you may be eligible to benefit from the **Patent Prosecution Highway** program at a participating intellectual property office for the corresponding application. For more information, please see http://www.uspto.gov/patents/init_events/pph/index.jsp or send an inquiry to **PPHfeedback@uspto.gov.**

Application Papers

10)☐ The specification is objected to by the Examiner.

11)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

Certified copies:

a)☐ All b)☐ Some** c)☐ None of the:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

** See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)

2) ☐ Information Disclosure Statement(s) (PTO/SB/08a and/or PTO/SB/08b) Paper No(s)/Mail Date _____.

3) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date _____.

4) ☐ Other: _____.

Notice of Pre-AIA or AIA Status

The present application is being examined under the pre-AIA first to invent provisions.

This Office Action vacates the Office Action mailed on 5/31/2019 and resets the time to respond. The Office Action is identical to the correspondence mailed on 5/31/2019 except that the Office Action includes a TC Director's signature.

DETAILED ACTION

1. Claims 52-59 pending and under consideration in the instant examination.

2. Applicant's IDSs filed on 8/22/2017, 3/28/2018, 4/27/2018, and 4/29/2019 are acknowledged and have been considered.

Priority

3. Applicant's claim for the benefit of a prior-filed application under 35 U.S.C. 119(e) or under 35 U.S.C. 120, 121, or 365(c) is acknowledged. The priority date of the instant claims of the current application is considered to be 3/15/2007, the filing date of PCT/US2007/006606.

Claim Rejections - 35 USC § 103

4. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained even though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the

various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

5. Claim 52 is rejected under 35 U.S.C. 103(a) as being unpatentable over Hillmen et al. (N Engl J Med 2004; 350: 552-9; IDS 8/22/2017), in view of Evans et al. (US 6,355,245 B1, issued 3/12/2002; IDS 8/22/2017), Wang (US 2005/0271660; IDS 8/22/2017), and Bowdish et al. (US 2003/232972; IDS 4/29/2019).

Hillmen teaches a method for treating a human patient that suffers from paroxysmal nocturnal hemoglobinuria (PNH) by administering to the patent an effective amount of eculizumab (p. 552, "methods) which specifically binds to the terminal complement protein C5, inhibiting its cleavage into C5a and C5b (p. 553, 3rd ¶).

Hillmen differs from the claimed invention in the recitation that the pharmaceutical composition comprises a 300 mg single-use formulation of 30 ml of a 10 mg/ml sterile, preservative free solution as in claim 6. Instead, Hillmen teaches that patients received infusion of 600 mg of eculizumab (treatment schedule at p. 554).

Evans teaches the antibody 5G1.1, eculizumab, is effective at doses of 2.2, 3, or 5 mg per kg body weight; this corresponds to 154, 210, or 350 mg of antibody for a 70kg adult human ('245 patent, column 16 lines 10-30). Evans (the '245 patent) also teaches that eculizumab is therapeutically effective when as little as 210 mg are present (column 16 lines 10-15). Evans teaches that the antibodies are particularly advantageous in that they are highly active even when administered in low doses (col 8 lines 25-32), providing a reasonable expectation of success in treating PNH with a dose less than what was disclosed by Hillmen. The reference teaches that it is within the skill of an artisan, particularly a physician, to determine the optimal dose (column 18 lines 15-30). Evans teaches formulations of the anti-C5 antibodies may be formulated in a pharmaceutically effective carrier such saline, which is considered to be a "preservative free solution". (col 18 lines 30-45).

Neither Hillmen nor the '245 patent (Evans) teaches a 300 mg single unit dosage as recited in the claims.

Nevertheless it would have been obvious to one of ordinary skill in the art to modify the teachings of Hillmen to administer 300 mg single unit dosages. Hillmen teaches that both 600 and 900 mg dosages can be used, and since Evans patent teaches that 210 or 350 mg of antibody would be expected to be therapeutically effective, arriving at the 300 mg dosage would be routine, convenient and obvious. One of ordinary skill in the art would have a reasonable expectation of success, as Evans teaches that the antibody exerts its effect at low doses.

It is further noted, [I]t is not inventive to discover the optimum or workable ranges by routine experimentation." In re Aller, 220 F.2d 454, 456 (CCPA 1955); see also In re Peterson, 315 F.3d 1325 (Fed. Cir. 2003). "Only if the 'results of optimizing a variable' are 'unexpectedly good' can a patent be obtained for the claimed critical range." In re Geisler, 116 F.3d 1465, 1469 (Fed. Cir. 1997) (quoting In re Antonie, 559 F.2d 618, 620 (CCPA 1977)). "[Discovery of an optimum value of a result effective variable in a known process is ordinarily within the skill of the art." In re Boesch, 617 F.2d 272, 276 (CCPA 1980).

Finally, **Wang** teaches that eculizumab is highly soluble, including at up to 30 mg per ml (paragraph 0171, Figure 10). Wang further teaches that pharmaceutically acceptable carriers include pyrogen-free water may be used in formulation of the antibody (¶71) (sterile, preservative free solution). Therefore the artisan of ordinary skill would have had a reasonable expectation of success in making a 10 mg / ml solution of the antibody sterile, preservative free solution.

The combined references still do not precisely teach that the antibody that binds C5 has a heavy chain consisting of SEQ ID NO: 2 and a light chain consisting of SEQ ID NO: 4 as currently claimed.

Bowdish teaches construction of a 5G1.1+peptide antibody (see ¶191 which references Figs. 13A and 13B) having a humanized antibody H chain with an amino acid sequence (SEQ ID NO: 67) which has 96% sequence identity to the currently claimed heavy chain SEQ ID NO: 2. (see sequence alignment below)

```
Query Match             96.0%;  Score 2300.5;  DB 1;  Length 472;\par
  Best Local Similarity   95.4%;  \par
  Matches  437;  Conservative    2;  Mismatches    4;  Indels   15;  Gaps    2;\par
\par
Qy          1 QVQLVQSGAEVKKPGASVKVSCKASGYIFSNYWIQWVRQAPGQGLEWMGEILPGSGSTEY 60\par
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||\par
Db         20 QVQLVQSGAEVKKPGASVKVSCKASGYIFSNYWIQWVRQAPGQGLEWMGEILPGSGSTEY 79\par
\par
Qy         61 TENFKDRVTMTRDTSTSTVYMELSSLRSEDTAVYYCAR----------YFFGSSPNWYFD 110\par
              |||||||||||||||||||||||||||||||||||||||          :    :|     \par
Db         80 TENFKDRVTMTRDTSTSTVYMELSSLRSEDTAVYYCARLPIEGPTLRQWLAARAP----- 134\par
\par
Qy        111 VWGQGTLVTVSSASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTS 170\par
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||\par
Db        135 VWGQGTLVTVSSASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTS 194\par
\par
Qy        171 GVHTFPAVLQSSGLYSLSSVVTVPSSNFGTQTYTCNVDHKPSNTKVDKTVERKCCVECPP 230\par
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||\par
Db        195 GVHTFPAVLQSSGLYSLSSVVTVPSSNFGTQTYTCNVDHKPSNTKVDKTVERKCCVECPP 254\par
\par
Qy        231 CPAPPVAGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQFNWYVDGVEVHNAKT 290\par
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||\par
Db        255 CPAPPVAGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQFNWYVDGVEVHNAKT 314\par
\par
Qy        291 KPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQVY 350\par
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||\par
Db        315 KPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQVY 374\par
\par
Qy        351 TLPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSR 410\par
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||\par
Db        375 TLPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSR 434\par
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Qy        411 LTVDKSRWQEGNVFSCSVMHEALHNHYTQKSLSLSLGK 448\par
              ||||||||||||||||||||||||||||||||||||||\par
Db        435 LTVDKSRWQEGNVFSCSVMHEALHNHYTQKSLSLSLGK 472\par
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Bowdish also teaches that the 5G1.1+ peptide has a humanized antibody L chain with an amino acid sequence (SEQ ID NO: 69) which has 100% sequence identity to the currently claimed light chain SEQ ID NO: 4 (see sequence alignment below).

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Query Match             100.0%;  Score 1110;  DB 4;  Length 236;
  Best Local Similarity   100.0%;
  Matches  214;  Conservative    0;  Mismatches    0;  Indels    0;  Gaps    0;

Qy          1 DIQMTQSPSSLSASVGDRVTITCGASENIYGALNWYQQKPGKAPKLLIYGATNLADGVPS 60
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db         23 DIQMTQSPSSLSASVGDRVTITCGASENIYGALNWYQQKPGKAPKLLIYGATNLADGVPS 82

Qy         61 RFSGSGSGTDFTLTISSLQPEDFATYYCQNVLNTPLTFGQGTKVEIKRTVAAPSVFIFPP 120
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db         83 RFSGSGSGTDFTLTISSLQPEDFATYYCQNVLNTPLTFGQGTKVEIKRTVAAPSVFIFPP 142

Qy        121 SDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLT 180
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        143 SDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLT 202

Qy        181 LSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC 214
              |||||||||||||||||||||||||||||||||
Db        203 LSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC 236
```

Bowdish further teaches that the sequence of the above **humanized antibody H chain** SEQ ID NO: 67, which as noted supra has 96% sequence identity to the currently claimed H chain SEQ ID NO: 2, is based on Evan's eculizumab 5G1.1 antibody framework from U.S. Application Ser. No. 06/487,263, which is the USD 6,355,245 Evans Patent supra, with the exception that the CD3 region was replaced with a TPO mimetic peptide sequence (¶191). (see Fig. 13A of Bowdish which depicts the TPO H chain sequence where the CDR3 region that has been substituted with the TPO mimetic is highlighted in bold).

(SEQ ID NO: 67)

5G1.1 – TPO Heavy Chain (Bold denotes TPO mimetic) Amino acid sequence:

*MKHVSHVVILFLLSVTAGVHS*QVQLVQSGAEVKKPGASVKVSCKASGYIFSNYWIQW
VRQAPGQGLEWMGEILPGSGSTEYTENFKDRVTMTRDTSTSTVYMELSSLRSED
TAVYYCARLPIEGPTLRQWLAARAPVWGQGTLVTVSSASTKGPSVFPLAPCSR
STSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTV
PSSNFGTQTYTCNVDHKPSNTKVDKTVERKCCVECPPCPAPPVAGPSVFLFPPKP
KDTLMISRTPEVTCVVVDVSQEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTY
RVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQVYTLPPSQ
EEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSRL
TVDKSRWQEGNVFSCSVMHEALHNHYTQKSLSLSLGK.

However, Evan's '245 Patent in Fig. 19 provides the missing CD3 sequence for the5G1.1 eculizumab antibody (see Fig. 19 from Evans, which shows framework 5G1.1

antibody with the CDR3 sequence underlined).

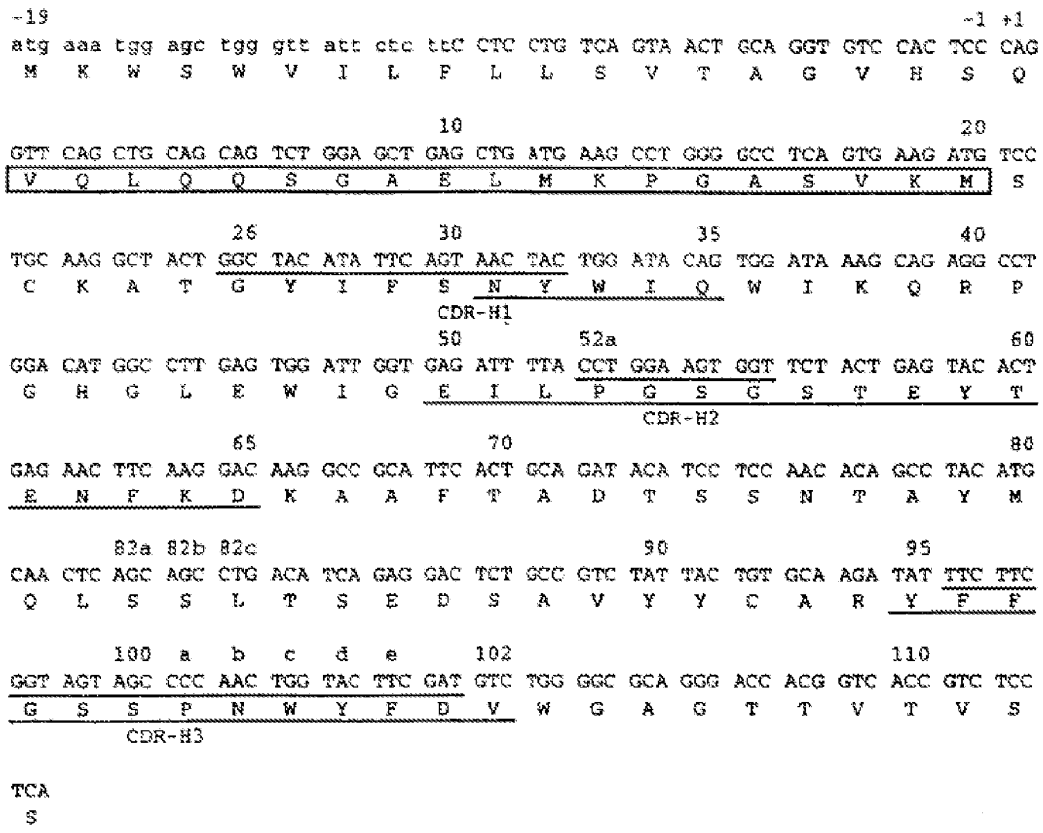


FIG.19

It would have been obvious to one of ordinary skill in the art at the time the invention was made to substitute Bowdish's TPO mimic amino acid sequence in Bowdish's H chain published SEQ ID NO: 67 which is 96% identical with currently claimed H chain SEQ ID NO: 2 with Evan's CDR3 5G1.1 eculizumab amino acid sequence, thereby arriving at a H chain sequence having 100% sequence identity to currently claimed H chain SEQ ID NO: 2 and to have combined that H chain sequence with Bowdish's L chain SEQ ID NO 69 that has 100% sequence identity to currently claimed L chain SEQ ID NO: 4.

One of ordinary skill in the art at the time the invention was made would have been motivated to do so because Bowdish teaches that the 5G1.1+peptide antibody H chain is based on the 5G1.1 antibody framework taught by Evans, with the exception that the

CDR3 was replaced with a TPO mimic sequence. But the substituted CDR3 was taught by Evans. One of skill in the art would accordingly look to the '245 Evans Patent for the native CDR3. Evans Fig. 19 shows the heavy chain variable region as residues 95-102. Substituting the CDR3 from Evans into the heavy chain 5G1.1+ taught by Bowdish would result in a sequence having 100% sequence identity to currently claimed SEQ ID No: 2. Bowdish also teaches that the light chain of 5G1.1" (published SEQ ID NO: 69), which as shown supra has 100% amino acid sequence identity to currently claimed L chain SEQ ID NO:4.

Thus upon reading Bowdish, one of ordinary skill in the art would have found it obvious to substitute CDRH3 from the 5G1.1 of Evans into the H chain SEQ ID NO: 67 which is only 96% identical in sequence identity due to the missing CDR3 region as taught by Bowdish to arrive at 100% sequence identity for the H chain of currently claimed SEQ ID NO: 2 and to pair it with the L chain SEQ ID NO: 69 from Bowdish, thereby producing an antibody identical to currently claimed SEQ ID NO: 2 and 4. The motivation to do so comes directly form the two references, as Bowdish indicates that the 5G1.1 sequence is that of Evans, albeit with an altered CDR3 in the heavy chain.

From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

6. Claims 52-59 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hillmen et al. (N Engl J Med 2004; 350: 552-9; IDS 8/22/2017), in view of Evans et al. (US 6,355,245 B1, issued 3/12/2002; IDS 8/22/2017), Wang (US 2005/0271660; IDS 8/22/2017), and Bowdish et al. (US 2003/232972; IDS 4/29/2019), as applied to claim 52 above, and further in view of Bell et al. (US 2005/0191298; IDS 8/22/2017).

The prior art teachings of Hillmen, Evans, Wang, and Bowdish are discussed supra.

The teachings differs with respect to the characteristics of the patient population. For example, the references differ in the recitation that the patient has received at least four transfusion in the twelve months prior to administration of the antibody (claims 53 and 57), has a platelet count greater than or equal to 100k per microliter prior to administration of the antibody (claims 54 and 58).

The teachings also differ in the recitation that the patient exhibits decreased lactate dehydrogenase levels (claim 56).

The teachings also differ in the recitation that the patient is treated with the antibody for at least 26 weeks as in claims 55 and 59.

However, Hillmen further teaches that the patients in its study had received at least four red-cell transfusions in the preceding 12 months (p. 553, last 2 lines).

Bell also teaches treating PNH using an anti-C5 antibody such as h5G1.1 mAb eculizumab (¶52). Bells teaches that PNH patients were transfusion dependent and hemolytic with a history of four or more transfusion within 12 months (¶81).

Bell further teaches that the patient for treatment has a platelet count preferably in excess of 150k per microliter (¶67).

Bell further teaches that that patients received weekly intravenous infusion of anti-C5 antibody for 64 weeks (¶82).

Bell also teaches that lactate dehydrogenase levels (LDH) are used as an objective indicator of hemolysis and that LDH levels were decreased as a result of the treatment (¶85).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to have continued eculizumab treatment for PNH for a period of at least 26 weeks to a patient population having received at least four transfusion in the twelve months prior to administration of eculizumab and having a platelet count in excess of 100k per microliter prior to administration of the antibody as well as to have also used a decreased LDH as a measure of clinical outcome in a method of treating PNH as taught by Hillmen. Those of skill in the art would have had reason to do so because Hillmen itself teaches that patients for treatment of PNH by administration of eculizumab had received at least 4 transfusion in the preceding 12 months, most preferably having a platelet count in excess of 150k, and Bell teaches that in the treatment of PNH with eculizumab, LDH is a known indicator of efficacy and that treatment can continue for 64 weeks, which is a period of greater than 26 weeks. The combination of familiar elements according to known methods is obvious when it does no more than yield predictable results (see KSR Int'l v. Teleflex Inc., 127 S. Ct. 1727, 1739 (2007).

From the teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

Double Patenting

7. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper time wise extension of the "right to exclude" granted by a patent

and to prevent possible harassment by multiple assignees. A nonstatutory double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on nonstatutory double patenting provided the reference application or patent either is shown to be commonly owned with the examined application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement. See MPEP § 717.02 for applications subject to examination under the first inventor to file provisions of the AIA as explained in MPEP § 2159. See MPEP §§ 706.02(l)(1) - 706.02(l)(3) for applications not subject to examination under the first inventor to file provisions of the AIA. A terminal disclaimer must be signed in compliance with 37 CFR 1.321(b).

The USPTO Internet website contains terminal disclaimer forms which may be used. Please visit www.uspto.gov/patent/patents-forms. The filing date of the application in which the form is filed determines what form (e.g., PTO/SB/25, PTO/SB/26, PTO/AIA/25, or PTO/AIA/26) should be used. A web-based eTerminal Disclaimer may be filled out completely online using web-screens. An eTerminal Disclaimer that meets all requirements is auto-processed and approved immediately upon submission. For more information about eTerminal Disclaimers, refer to www.uspto.gov/patents/process/file/efs/guidance/eTD-info-I.jsp.

8. Claims 52-59 are rejected on the ground of nonstatutory obviousness- type double patenting as being unpatentable over claim 1 of **US Patent 9,732,149,** in view of Bell et al. (US 2005/0191298; IDS 8/22/2017).

Although the conflicting claims are not identical, they are not patentably distinct from each other because both the current application and 149 Patent claim the same antibody having a H chain of SEQ ID NO: 2 and L chain of SEQ ID NO: 4.

While the ‘149 Patent is drawn to a composition whereas the current application is drawn to administering the antibody to a patient suffering from PNH, it is clear from the specification of the ‘149 that the intended use for the antibody is PNH (see abstract) and that said antibody is administered as a single unit dosage form at 300 mg in 30 ml of a 10 mg/ml sterile, preservative free solution (¶ before detailed description). See *Sun Pharmaceuticals Industries, Ltd., v. Eli Lilly and Company*, Fed. Cir. 2010 for the

appropriateness of making an ODP to a product claim where one of the intended uses of the product is for the method as now claimed).

While the '149 does not specifically recite some of the limitations contained in the dependent claims such as that the patient exhibits decreased LDH levels, these limitations would have been obvious in view of Bell as is discussed supra.

9. Claims 52-59 are rejected on the ground of nonstatutory obviousness- type double patenting as being unpatentable over claims 1-3 of **US Patent 9,718,880,** in view of Bell et al. (US 2005/0191298; IDS 8/22/2017).

Although the conflicting claims are not identical, they are not patentably distinct from each other because both the current application and 880 Patent claim the same antibody having a H chain of SEQ ID NO: 2 and L chain of SEQ ID NO: 4, in a sterile, preservative free 300 mg single-use dosage form comprising 30 ml of a 10 mg/ml solution..

While the '880 Patent is drawn to a composition whereas the current application is drawn to administering the antibody to a patient suffering from PNH, it is clear from the specification of the '149 that the intended use for the antibody is PNH (see abstract) and that said antibody is administered as a single unit dosage form at 300 mg in 30 ml of a 10 mg/ml sterile, preservative free solution (¶ before detailed description). See *Sun Pharmaceuticals Industries, Ltd., v. Eli Lilly and Company*, Fed. Cir. 2010 for the appropriateness of making an ODP to a product claim where one of the intended uses of the product is for the method as now claimed).

While the '880 does not specifically recite some of the limitations contained in the dependent claims such as that the patient exhibits decreased LDH levels, these limitations would be obvious in view of Bell as is discussed supra.

10. Claims 52-59 are rejected on the ground of nonstatutory obviousness- type double patenting as being unpatentable over claims 1-10 of **US Patent 9,725,504,** in view of Bell et al. (US 2005/0191298; IDS 8/22/2017).

Although the conflicting claims are not identical, they are not patentably distinct from each other because both the current application and 504 Patent claim the same method of treating PNH using an antibody having a H chain of SEQ ID NO: 2 and L chain of SEQ ID NO: 4, in a sterile, preservative free 300 mg single-use dosage form comprising 30 ml of a 10 mg/ml solution. See in particular claims 1, and 4-6 of the '504 patent.

The '504 also claims a decreased in mean levels of LDH after administration (claim 9).

11. Claims 52-59 are rejected on the ground of nonstatutory obviousness- type double patenting as being unpatentable over claims 1-17 of **US Patent 9,409,980,** in view of Evans et al. (US 6,355,245 B1, issued 3/12/2002; IDS 8/22/2017), Wang (US 2005/0271660; IDS 8/22/2017) and Bell et al. (US 2005/0191298; IDS 8/22/2017).

Although the conflicting claims are not identical, they are not patentably distinct from each other because both the current application and 980 Patent appear to claim the same anti-C5 antibody (see claim 1 of the '980). In addition, the '980 claim using the antibody to treat PNH (see claim 17).

While the '980 does not specifically recite that the antibody is a single-unit dosage form of 300 mg in 30 mL of sterile, preservative free solution or the various limitations contained in the dependent claims, those limitation would be obvious in view of Evans, Wang and Bell as is discussed supra.

12. Claims 52-59 are rejected on the ground of nonstatutory obviousness- type double patenting as being unpatentable over claims 1-15 of **US Patent 9,415,102,** in view of Evans et al. (US 6,355,245 B1, issued 3/12/2002; IDS 8/22/2017), Wang (US 2005/0271660; IDS 8/22/2017) and Bell et al. (US 2005/0191298; IDS 8/22/2017).

Although the conflicting claims are not identical, they are not patentably distinct from each other because both the current application and 102 Patent appear to claim the same anti-C5 antibody (see claims 1-2 of the '102). In addition, the '102 claims using the antibody to treat PNH (see claim 17).

While the '102 Patent is drawn to a composition whereas the current application is drawn to administering the antibody to a patient suffering from PNH, it is clear from the specification of the '102 that the intended use for the antibody is PNH (see methods of treatment in the specification) See *Sun Pharmaceuticals Industries, Ltd., v. Eli Lilly and Company*, Fed. Cir. 2010 for the appropriateness of making an ODP to a product claim where one of the intended uses of the product is for the method as now claimed).

While the '102 does not specifically recite that the antibody is a single-unit dosage form of 300 mg in 30 mL of sterile, preservative free solution or the various limitations contained in the dependent claims, those limitation would be obvious in view of Evans, Wang and Bell as is discussed supra.

13. Claims 52-59 are rejected on the ground of nonstatutory obviousness- type double patenting as being unpatentable over claims 1-14 of **US Patent 9,556,263,** in view of Evans et al. (US 6,355,245 B1, issued 3/12/2002; IDS 8/22/2017), Wang (US 2005/0271660; IDS 8/22/2017) and Bell et al. (US 2005/0191298; IDS 8/22/2017).

Although the conflicting claims are not identical, they are not patentably distinct from each other because both the current application and 256 Patent appear to claim the same eculizumab antibody (see claim 1 of the '263). In addition, the '263 claim using the antibody to treat PNH (see claim 3).

While the '263 does not specifically recite that the antibody is a single-unit dosage form of 300 mg in 30 mL of sterile, preservative free solution or the various limitations contained in the dependent claims, those limitation would be obvious in view of Evans, Wang and Bell as is discussed supra.

14. Claims 52-59 are rejected on the ground of nonstatutory obviousness- type double patenting as being unpatentable over claims 1-12 of **US Patent 9,352,035,** in view of Evans et al. (US 6,355,245 B1, issued 3/12/2002; IDS 8/22/2017), Wang (US 2005/0271660; IDS 8/22/2017) and Bell et al. (US 2005/0191298; IDS 8/22/2017).

Although the conflicting claims are not identical, they are not patentably distinct from each other because both the current application and 035 Patent appear to claim the same eculizumab antibody (see claim 1 of the '035).

While the '035 Patent is drawn to a composition whereas the current application is drawn to administering the antibody to a patient suffering from PNH, it is clear from the specification of the '035 that the intended use for the antibody is PNH (see ¶129 of the '35 which lists PNH as one of the complement associated disorders that can be treated by the composition) See *Sun Pharmaceuticals Industries, Ltd., v. Eli Lilly and Company*, Fed. Cir. 2010 for the appropriateness of making an ODP to a product claim where one of the intended uses of the product is for the method as now claimed).

While the '035 does not specifically recite that the antibody is a single-unit dosage form of 300 mg in 30 mL of sterile, preservative free solution or the various limitations contained in the dependent claims, those limitation would be obvious in view of Evans, Wang and Bell as is discussed supra.

15. Claims 52-59 are rejected on the ground of nonstatutory obviousness- type double patenting as being unpatentable over claims 1-13 of **US Patent 9,925,262,** in view of Evans et al. (US 6,355,245 B1, issued 3/12/2002; IDS 8/22/2017), Wang (US 2005/0271660; IDS 8/22/2017) and Bell et al. (US 2005/0191298; IDS 8/22/2017).

Although the conflicting claims are not identical, they are not patentably distinct from each other because both the current application and 262 Patent claim the same method of treating PNH using an eculizumab antibody. See in particular claims 1, and 4 of the '262 patent.

While the '262 does not specifically recite that the antibody is a single-unit dosage form of 300 mg in 30 mL of sterile, preservative free solution or the various limitations contained in the dependent claims, those limitation would be obvious in view of Evans, Wang and Bell as is discussed supra.

16. Claims 52-59 are rejected on the ground of nonstatutory obviousness- type double patenting as being unpatentable over claims 1-33 of **US Patent 10,239,937,** in view of Evans et al. (US 6,355,245 B1, issued 3/12/2002; IDS 8/22/2017), Wang (US 2005/0271660; IDS 8/22/2017) and Bell et al. (US 2005/0191298; IDS 8/22/2017).

Although the conflicting claims are not identical, they are not patentably distinct from each other because both the current application and 937 Patent claim the same method of treating PNH using an eculizumab antibody. See in particular claims 1, and 11 of the '937 patent.

While the '937 does not specifically recite that the antibody is a single-unit dosage form of 300 mg in 30 mL of sterile, preservative free solution or the various limitations contained in the dependent claims, those limitation would be obvious in view of Evans, Wang and Bell as is discussed supra.

17. No claim is allowed.

18. Any inquiry concerning this communication or earlier communications from the examiner should be directed to James Rogers whose telephone number is (571) 270-5374. The examiner can normally be reached Monday through Friday from 8:00 am to 5:30 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, **Daniel Kolker** can be reached on (571) 272-3181. The fax number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

June 6, 2019

/JAMES ROGERS/
Art Unit 1644

/DANIEL E KOLKER/
Supervisory Patent Examiner, Art Unit 1644

/W GARY JONES/
Director, Technology Center 1600

To: ipboston.docketing@nelsonmullins.com,,
From: PAIR_eOfficeAction@uspto.gov
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Jun 11, 2019 03:34:51 AM

Dear PAIR Customer:

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Application	Document	Mailroom Date	Attorney Docket No.
15642096	CTNF	06/11/2019	AXJ-114BUSCN5

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PATENT APPLICATION INFORMATION RETRIEVAL SYSTEM

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
15/642,096	07/05/2017	Leonard BELL	AXJ-114BUSCN5	7606

133485 7590 11/18/2019

Nelson Mullins Riley & Scarborough LLP/Alexion
One Post Office Square
30th Floor
Boston, MA 02109-2127

EXAMINER	
ROGERS, JAMES L	

ART UNIT	PAPER NUMBER
1644	

NOTIFICATION DATE	DELIVERY MODE
11/18/2019	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

ipboston.docketing@nelsonmullins.com

Applicant-Initiated Interview Summary	**Application No.** 15/642,096	**Applicant(s)** BELL et al.	
	Examiner JAMES L ROGERS	**Art Unit** 1644	**AIA (FITF) Status** No

All participants (applicant, applicants representative, PTO personnel):

(1) JAMES L. ROGERS.

(2) DANIEL KOLKER, SPE.

(3) JANE REMILLARD.

(4) JILL SLOPER.

Date of Interview: 12 November 2019.

Type: ☐ Telephonic ☐ Video Conference
☑ Personal [copy given to: ☐ applicant ☐ applicant's representative]

Exhibit shown or demonstration conducted: ☐ Yes ☑ No.
If Yes, brief description: _____.

Issues Discussed ☐101 ☐112 ☐102 ☑103 ☐Others
(For each of the checked box(es) above, please describe below the issue and detailed description of the discussion)

Claim(s) discussed: 52.

Identification of prior art discussed: _____.

Substance of Interview
(For each issue discussed, provide a detailed description and indicate if agreement was reached. Some topics may include: identification or clarification of a reference or a portion thereof, claim interpretation, proposed amendments, arguments of any applied references etc...)

In addition to the above named participants, Tara Rahemba was present for the applicant. The outstanding 35 USC 103 (a) rejection was discussed as well as possible strategies for overcoming the rejection, including indicia of nonobviousness..

Applicant recordation instructions: The formal written reply to the last Office action must include the substance of the interview. (See MPEP section 713.04). If a reply to the last Office action has already been filed, applicant is given a non-extendable period of the longer of one month or thirty days from this interview date, or the mailing date of this interview summary form, whichever is later, to file a statement of the substance of the interview.

Examiner recordation instructions: Examiners must summarize the substance of any interview of record. A complete and proper recordation of the substance of an interview should include the items listed in MPEP 713.04 for complete and proper recordation including the identification of the general thrust of each argument or issue discussed, a general indication of any other pertinent matters discussed regarding patentability and the general results or outcome of the interview, to include an indication as to whether or not agreement was reached on the issues raised.

☐ Attachment

/JAMES L ROGERS/ Examiner, Art Unit 1644	/DANIEL E KOLKER/ Supervisory Patent Examiner, Art Unit 1644

Summary of Record of Interview Requirements

Manual of Patent Examining Procedure (MPEP), Section 713.04, Substance of Interview Must be Made of Record
A complete written statement as to the substance of any face-to-face, video conference, or telephone interview with regard to an application must be made of record in the application whether or not an agreement with the examiner was reached at the interview.

Title 37 Code of Federal Regulations (CFR) 1.133 Interviews
Paragraph (b)

In every instance where reconsideration is requested in view of an interview with an examiner, a complete written statement of the reasons presented at the interview as warranting favorable action must be filed by the applicant. An interview does not remove the necessity for reply to Office action as specified in §§ 1.111, 1.135. (35 U.S.C. 132)

37 CFR §1.2 Business to be transacted in writing.
All business with the Patent or Trademark Office should be transacted in writing. The personal attendance of applicants or their attorneys or agents at the Patent and Trademark Office is unnecessary. The action of the Patent and Trademark Office will be based exclusively on the written record in the Office. No attention will be paid to any alleged oral promise, stipulation, or understanding in relation to which there is disagreement or doubt.

The action of the Patent and Trademark Office cannot be based exclusively on the written record in the Office if that record is itself incomplete through the failure to record the substance of interviews.

It is the responsibility of the applicant or the attorney or agent to make the substance of an interview of record in the application file, unless the examiner indicates he or she will do so. It is the examiners responsibility to see that such a record is made and to correct material inaccuracies which bear directly on the question of patentability.

Examiners must complete an Interview Summary Form for each interview held where a matter of substance has been discussed during the interview by checking the appropriate boxes and filling in the blanks. Discussions regarding only procedural matters, directed solely to restriction requirements for which interview recordation is otherwise provided for in Section 812.01 of the Manual of Patent Examining Procedure, or pointing out typographical errors or unreadable script in Office actions or the like, are excluded from the interview recordation procedures below. Where the substance of an interview is completely recorded in an Examiners Amendment, no separate Interview Summary Record is required.

The Interview Summary Form shall be given an appropriate Paper No., placed in the right hand portion of the file, and listed on the "Contents" section of the file wrapper. In a personal interview, a duplicate of the Form is given to the applicant (or attorney or agent) at the conclusion of the interview. In the case of a telephone or video-conference interview, the copy is mailed to the applicants correspondence address either with or prior to the next official communication. If additional correspondence from the examiner is not likely before an allowance or if other circumstances dictate, the Form should be mailed promptly after the interview rather than with the next official communication.

The Form provides for recordation of the following information:
- Application Number (Series Code and Serial Number)
- Name of applicant
- Name of examiner
- Date of interview
- Type of interview (telephonic, video-conference, or personal)
- Name of participant(s) (applicant, attorney or agent, examiner, other PTO personnel, etc.)
- An indication whether or not an exhibit was shown or a demonstration conducted
- An identification of the specific prior art discussed
- An indication whether an agreement was reached and if so, a description of the general nature of the agreement (may be by attachment of a copy of amendments or claims agreed as being allowable). Note: Agreement as to allowability is tentative and does not restrict further action by the examiner to the contrary.
- The signature of the examiner who conducted the interview (if Form is not an attachment to a signed Office action)

It is desirable that the examiner orally remind the applicant of his or her obligation to record the substance of the interview of each case. It should be noted, however, that the Interview Summary Form will not normally be considered a complete and proper recordation of the interview unless it includes, or is supplemented by the applicant or the examiner to include, all of the applicable items required below concerning the substance of the interview.

A complete and proper recordation of the substance of any interview should include at least the following applicable items:
1) A brief description of the nature of any exhibit shown or any demonstration conducted,-
2) an identification of the claims discussed,
3) an identification of the specific prior art discussed,
4) an identification of the principal proposed amendments of a substantive nature discussed, unless these are already described on the Interview Summary Form completed by the Examiner,
5) a brief identification of the general thrust of the principal arguments presented to the examiner,
(The identification of arguments need not be lengthy or elaborate. A verbatim or highly detailed description of the arguments is not required. The identification of the arguments is sufficient if the general nature or thrust of the principal arguments made to the examiner can be understood in the context of the application file. Of course, the applicant may desire to emphasize and fully describe those arguments which he or she feels were or might be persuasive to the examiner.)
6) a general indication of any other pertinent matters discussed, and
7) if appropriate, the general results or outcome of the interview unless already described in the Interview Summary Form completed by the examiner.

Examiners are expected to carefully review the applicants record of the substance of an interview. If the record is not complete and accurate, the examiner will give the applicant an extendable one month time period to correct the record.

Examiner to Check for Accuracy

If the claims are allowable for other reasons of record, the examiner should send a letter setting forth the examiners version of the statement attributed to him or her. If the record is complete and accurate, the examiner should place the indication, Interview Record OK on the paper recording the substance of the interview along with the date and the examiners initials.

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Nov 18, 2019 03:31:00 AM

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Application	Document	Mailroom Date	Attorney Docket No.
15642096	INTV.SUM.APP	11/18/2019	AXJ-114BUSCN5

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PATENT APPLICATION INFORMATION RETRIEVAL SYSTEM

I hereby certify that this paper (along with any paper referred to as being attached or enclosed) is being transmitted via the Office electronic filing system in accordance with 37 CFR § 1.6(a)(4).

Dated: **December 11, 2019**
Electronic Signature for Jill Gorny Sloper, Esq.: /Jill Gorny Sloper, Esq./

Docket No.: AXJ-114BUSCN5
(PATENT)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of:
Leonard Bell *et al.*

Application No.: 15/642,096

Confirmation No.: 7606

Filed: July 5, 2017

Art Unit: 1644

For: TREATMENT OF PAROXYSMAL NOCTURNAL HEMOGLOBINURIA PATIENTS BY AN INHIBITOR OF COMPLEMENT

Examiner: J. L. Rogers

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

DECLARATION PURSUANT TO 37 CFR 1.132 BY DR. DEEPAK JAIN

I, Deepak Jain, MD, MBA, declare the following:

1. I have been employed by Alexion Pharmaceuticals ("Alexion") since April 2015. In my first role at Alexion, I was the Senior Director of Global Medical Affairs and directed a team focused on Soliris® for treating paroxysmal nocturnal hemoglobinuria (PNH). From March 2017 to May 2018, I was the Head of Alexion's Canada Medical Affairs Department in Vaughan, Ontario. I am presently the Executive Director of Global Medical Affairs, Leader of the Hematology and Global Program Team Leader of the Ultomiris® PNH Program at Alexion Pharmaceuticals, which is located in Boston, Massachusetts. Alexion Pharmaceuticals is the Assignee of the above-referenced patent application. I received a Medical Degree (MD) from Maharaja Sayajirao University (Baroda, India), a Master of Science (MS) from McGill University (Montreal, Quebec), and a Master of Business Administration (MBA) in Pharmaceutical Management from Drexel University (Philadelphia, USA). My *curriculum vitae* is provided herewith.

2. I have reviewed the Office Action dated June 11, 2019 and provide the following statements.

3. Soliris® (eculizumab) satisfies a long-felt, but previously unmet need, for a safe and effective means for treating the rare, debilitating, and potentially fatal blood disease, PNH (see Appendix E). Soliris® (eculizumab) is not only the first FDA-approved anti-C5 antibody, but also the first FDA-approved treatment for PNH. In 2006, the FDA granted Soliris® (eculizumab) "Priority Review" status, demonstrating just how groundbreaking and transformative the FDA believed it could be for PNH patients (see Appendix D). Prior to FDA approval of Soliris® (eculizumab), patients with PNH had to suffer from debilitating symptoms, such as anemia, fatigue, thrombosis, hemoglobinuria, dyspnea, dysphagia, erectile dysfunction, hypertension and kidney problems for 10 to 15 years, with extremely limited treatment options (see Appendix D). In the absence of treatment, PNH resulted in a 5-year mortality rate of up to ~35% (see Appendix T). The FDA approval of the orphan drug Soliris® (eculizumab) in March 2007 marked a distinct change in how physicians were able to treat patients with PNH (see Appendices E-F). Importantly, Soliris® (eculizumab) has not only transformed the standard of care for PNH patients, but it has also significantly improved individual patient lives (see Appendices E-J). Specifically, treatment with Soliris® (eculizumab) has dramatically improved their quality of life and eliminated painful and debilitating symptoms that once plagued their lives and made day-to-day life challenging and unbearable (see Appendices G-J). Moreover, the cumulative survival rate increased from 66.8% before Soliris® (eculizumab) to 95.5% with Soliris® (eculizumab) (see Appendices U-W). It is the complete structure (*i.e.*, particular full length heavy and light chain sequences - SEQ ID NOs: 2 and 4) recited in the present claims that imparts Soliris® (eculizumab) with the therapeutically advantageous features that made it the "gold" standard of treatment and forever changed the standard of care for PNH patients.

4. There are at least four instances of commercial copying of Soliris® (eculizumab):

A. Amgen is developing a biosimilar eculizumab ("ABP 959") for use in treating paroxysmal nocturnal hemoglobinuria (PNH), atypical hemolytic uremic syndrome (aHUS), and generalized myasthenia gravis (gMG) (see Appendix K).

B. Samsung Bioepis is developing a biosimilar eculizumab ("SB12") and is currently recruiting for a clinical trial to compare "SB12 (Proposed Eculizumab Biosimilar) to Soliris in subjects with Paroxysmal Nocturnal Haemoglobinuria" (see Appendices L-M).

C. Generium is developing a biosimilar eculizumab ("Elizaria®"), which launched in April 2019 in Russia (see Appendix N).

D. Biocad is developing a biosimilar of eculizumab ("BCD-148"), which was to be tested in a clinical trial alongside eculizumab in an early healthy volunteer study (see Appendix O).

These companies are copying Soliris® (eculizumab) and developing biosimilars because the antibody as a whole (*i.e.*, the antibody's complete sequence) renders it effective and advantageous in treating PNH, as claimed.

5. In 2008, Soliris® (eculizumab) received the Prix Galien USA Award for Best Biotechnology Product. The Prix Galien Award recognizes the technical, scientific and clinical research skills necessary to develop innovative medicines and is considered the industry's equivalent of the Nobel Prize, the highest accolade for biomedical research and innovation (see Appendix P). Soliris® (eculizumab) received this prestigious award because it is a groundbreaking, first-in-line treatment that is effective in treating PNH patients. It is the complete structure (*i.e.*, the particular full length heavy and light chain sequences - SEQ ID NOs: 2 and 4) recited in the present claims that imparts Soliris® (eculizumab) with the features that has made it exceptionally therapeutically effective and worthy of the Prix Galien USA Award.

6. Soliris® (eculizumab) has been one of the twenty top selling biopharmaceutical products in recent history (see Appendix Q). Soliris® (eculizumab) has generated over one billion dollars of annual revenue during each of the last three years, and more than $3.4 billion

since its launch in 2007 has been attributed to sales for PNH treatment (see Appendices R-S). It is the complete structure (*i.e.*, the particular full length heavy and light chain sequences - SEQ ID NOs: 2 and 4) recited in the present claims that impart Soliris® (eculizumab) with efficacious and advantageous functional features (*e.g.*, binds to C5 with sufficient affinity and specificity to prevent cleavage of C5, while not activating complement and having no effector function) that have made it a groundbreaking blockbuster product.

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or of any patent issued thereon.

Deepak Jain, MD, MBA — Date: Dec 10, 2019

DEEPAK JAIN, MD, MBA
Boston, MA

==========

EDUCATIONAL QUALIFICATION

- M.D. from Maharaja Sayajirao University of Baroda, India
- Master of Science (MSc.) from McGill University, Montreal, Quebec
- MBA in Pharmaceutical Management from Drexel University, Philadelphia

PROFESSIONAL PROFILE

Excellent track record of leadership and advancement in the pharmaceutical / biotech industry spanning from global medical affairs, clinical development & strategic planning. I have extensive pre-launch, launch, life cycle management experience, and have developed and led high performing teams.

Clinical background covering wide range of therapeutic disciplines including Infectious disease (antiviral/antibacterial), Transplant (Liver, BMT), Medical Countermeasures (Anthrax/Vaccinia), Hematology (PNH, ITP), Immunology (PID), Neurology (Multiple Sclerosis, MG), and other areas in Internal Medicine.

Solid understanding of product launches & Life cycle planning for major brands Soliris, (WinRho (Plasma derived anti-D), HepaGam B (Plasma derived Hep IgG), AVONEX (recombinant IFN), Plegridy (recombinant IFN), Zerbaxa (Ceftolozane/tazobactam, Surotomycin including early asset development, health outcomes & market access challenges (Canada and EU), managed care & prescription benefit management, global regulatory, biomarker, pharmacovigilance & epidemiology, strategic planning & transactions.

Strong background in the development, roll out and implementation of early asset, pre-launch and in-market product integrated strategic summaries and functional plans.

Strong entrepreneurial drive, excelling in diversified, fast-paced, cross-functional teaming business environments, with a focus on building a high performing organization and culture.

PROFESSIONAL HISTORY

May, 2018- Present — **Executive Director, Global Medical Affairs Leader Hematology and Global Program Team Leader, Ultomiris PNH**
Alexion Pharmaceuticals, Boston, MA

- Lead team of 3 direct reports Global Medical Directors and direct global medical affairs team to support Hematology therapeutic area
- Responsible to develop and implement global medical (TA) strategy and plan for GMA activities (pre-launch and post -launch as applicable) for Hematology by providing medical leadership, insight and strategy to TA global medical affairs team across functions and countries globally.
- Responsible for providing strategic direction and leading the Ultomiris PNH Global Program Team.
- Global Program Team Leader (GPTL), leads and chairs the Global Program Team (GPT), leading the creation of an integrated development plan, maintaining a strategic focus and ensuring the GPT's commitments are met.
- Lead on the situational assessment and the global product strategy development including harmonization of activities involving KOLs.
- Develop in-year global medical strategy, Implementation and budget plan for global initiatives
- Provide medical strategic recommendation for in-line life cycle management (LCM) and late phase pipeline programs
- Develop Phase 3b/4 and ISR evidence generation strategy for late phase pipeline and in-line TA programs
- Develop and oversee clinical study design (non-registration phase IIIb/IV, registries, outcomes research etc.) for late phase pipeline and in-line TA programs in close collaboration with relevant functions
- Provide medical review and ensure alignment with TA strategy of Investigator sponsored research (ISR) proposals
- Provide clear strategic guidance to scientific communication, internal medical training, external medical education (CME, Symposia, medical education), Medical info, PEVT teams in developing functional plans supporting global medical strategy
- Develop medically appropriate commercial strategy/tactic, planning and execution
- Provide global medical guidance to country medical teams in developing country medical plans aligned with global medical strategy
- Collaborate with country medical TA lead to ensure local activities are aligned with global medical strategy and that Global Medical is sufficiently aware of country insights and needs. Alignment among Global and Country Medical Plans, adjust if needed.
- Monitor team performance in terms of goals and delivery of global medical plans

- Responsible for development and execution of major registration LCM program and geographically expansion strategy

Mar, 2017- May, 2018 **Head of Medical Affairs Canada**
Alexion Pharmaceuticals, Vaughan, ON

- Lead Canadian strategic planning, all in-country Medical Affairs activities and manage the performance and development of the local Medical team.
- Led team of 4 direct reports (3 Medical Directors) and manage Canadian medical affairs group of 12

Canada Medical Affairs Management:

- Develop local Medical Plan aligned with Global TA Plan and manage execution
- Develop field-based medical teams objectives and performance metrics
- Assess and maximize the performance of the medical affairs team
- Lead and manage direct reports to ensure achievement of objectives, personal development, and ensuring the team is trained and equipped to achieve established goals
- Define the country Medical resource and budget needs and lead the Medical budget planning, resource allocation and budget management
- Manage country pharmacovigilance activities, in conjunction with Regional and Global pharmacovigilance
- Manage the country patient support program setup and execution
- Manage the country medical information function, ensure timely response to medical information inquiries and collation of requests, utilizing global medical information resources and in line with local regulatory requirements and company policy
- Identify training needs with other functional leaders and ensure implementation of training programs for the commercial teams and other functions, providing medical leadership and education in line with local and global strategy and preparing staff to handle interactions with customers

April, 2015- Feb, 2017 **Sr. Director, Medical Affairs/Global Medical Affairs Lead PNH**
Alexion Pharmaceuticals, Lexigton, MA

Lead and direct global medical affairs team to support Paroxysmal Nocturnal Hemoglobinuria therapeutic area for Soliris and ALXN1210

Global Medical Affairs Management:

- Lead the development and execution of Global Medical Affairs Plans in support of best clinical practices and overall corporate objectives aligned with Global Medical Affairs plans and commercial Brand strategy for Soliris and ALXN1210
- Develop Phase IIIb-IV data generation strategy (observational cohort/ registries. HEOR, Biomarker, label expansion for Soliris and ALXN1210
- Provide medical leadership, insight and strategy to all Alexion activities, collaborating across functions to ensure the highest level of medical support for all Alexion products within a therapeutic area that maximize patient outcomes
- Provide medical input to the development of impactful scientific and medical education
- Lead the implementation of medical affairs practices to assess new indications, the treating community, patient pathways, identifying patients for clinical research and to develop a thorough understanding of the disease area
- Support cross-functional teams to ensure patient-focused activities at all times, including rapid responses to internal and external requests for support to all stakeholders
- Engage thought leader network to support the successful execution of Global Medical Affairs tactics
- Establish and manage scientific/clinical relations with global KOL and identify emerging global KOLs of the therapeutic area
- Leadership in planning and development of Global Scientific Advisory boards/working groups with National Associations/Societies Medical lead in providing input and medical accuracy review for Outcomes Research (OR) teams to develop materials and programs to support (OR) initiatives in the preparation of formulary documents and Global Economic Dossiers

June 2013 – March, 2015 **Medical Director, Clinical Research & Medical Affairs/Global Medical Lead Zerbaxa & Surotomycin Cubist Pharmaceuticals, Lexington, MA**

- Lead the late phase clinical development strategy and execution for anti-infectives and acute care franchise and early access strategy (compassionate use, named patient program and Canadian Special Access Program)- Zerbaxa & Surotomycin
- Led team of 3 direct reports (1 Medical Monitors and 2 Clinical Research Scientist) to manage late phase clinical development program for Zerbaxa & Surotomycin

Clinical Program Management

- Develop Phase IIIb-IV data generation strategy (observational cohort/ registries. HEOR, Biomarker, label expansion, new indication(e.g. Nosocomial Pneumonia, Cystic Fibrosis, Bacteremia) for Ceftolozane/tazobactam

- Oversee the planning, execution and reporting of clinical studies for Surotomycin (Phase III)
- Ensure that studies planned by subsidiaries and affiliates fit into the global product strategy (global ←→regional ←→ local alignment)
- Oversee Clinical Trials Review Committee review process, protocol review and revision, and facilitate the development of an approved clinical trial protocol and the associated contractual documents
- Ensure appropriate documentation, tracking and retrievability of study activities
- Monitor performance of phase IIIb- IV activities (e.g. value creation through publication of clinical study results) and take corrective actions
- Contribute to continuous improvement of phase IV study related processes

KOL Management

- Engage thought leader network to support the successful execution of Global Medical Affairs tactics
- Establish and manage scientific/clinical relations with global KOL and identify emerging global KOLs of the therapeutic area

General Management and Leadership Activities

- Develop and led team to support product lifecycle initiatives
- Manage budget assigned to Phase IIIb & IV activities for life cycle management Oversee and monitor adherence to program timelines
- Member of Clinical Development Leadership Team

December 2011 – June, 2013 **Medical Director**
Biogen Idec, Boston, MA, USA

- Lead the Global Medical Affairs Team activities associated with product life cycle management of Interferon Beta-1a (AVONEX indicated for Multiple Sclerosis) and launch of Plegridy (Pegylated Interferon).

Global Medical Affairs Management:

- Guide cross-functional Medical Affairs teams to develop the Global Medical Affairs tactics in support of global brand plan strategies
- Develop and support short- and long-term goals of Global Medical Affairs with respect to prioritization of research interests and in collaborations local and regional Medical Affairs (global ←→regional ←→ local alignment)
- Develop Phase IIIb-IV data generation strategy (HEOR, Biomarker, label expansion, new indication etc) for Interferon franchise
- Develop and manage a thought leader network to support the successful execution of Global Medical Affairs tactics

General Management and Leadership Activities

- Provide leadership and oversight of the review and approval of scientific communication plans , global medical education as well as medical, marketing and sales training materials for individual markets
- Manage budget GMA budget for Avonex and Plegridy
- Oversee and monitor adherence to timelines of all GMA related activities

March 2008- December 2011 **Manager, Medical Affairs**
Cangene Corporation, Toronto, ON, Canada

Role/Responsibilities

- Lead the MSL Team activities associated with product life cycle management of WinRho SDF – Liquid and launch of HepaGam B
- Led team of 3 direct reports (2 MSLs and 1 Medical Information Scientist) to manage WinRho SDF – Liquid and launch of HepaGam B

Build Medical Affairs strategy and field based MSLs team

- Medical Lead for Hepatology, Infectious Disease and Hematology Portfolios.
- Advisory Board Meetings, investigator meetings and CMEs.
- Successful launch of new products (WinRho SDF – Liquid and HepaGam B)
- Development of Key Opinion Leaders (KOLs) for Canada plus ex-US market : Hepatology, Infectious disease specialist, Hematologist, Immunologist, Transplant surgeons, and Pharmacy Directors
- Interaction with Medical Affairs, Clinical Development and Commercial colleagues for development and implementation of medical strategies for key portfolios.
- Member of the Therapeutic Area Team and the Brand Team.
- Medical training to field force during launch of products as well as training programs at regular intervals.
- Support Market Access Team for successful product launch
- Review of promotional material. Slide decks and all other material related to promotion of the product to HCPs in accordance with Canadian PAAB regulations

Medical Information

- Established Medical information department, facilitated development of medical info process and setting up electronic database to capture medical info
- Ensured rapid and timely generation of ethical and scientific medical responses to questions posted by doctors.
- Sound experience in development of standard response letters, FQA and researching manuscripts/publications online.

Oct 2006- Feb 2008 **Clinical Research Scientist**
Cangene Corporation, Winnipeg, MB, Canada

- Development of the clinical research programs and clinical research protocol for Hepatitis, Anthrax and Vaccinia program
- CRO and site selection and contract negotiation Manage coordination of on-site monitoring, TMF filing, and clinical trial administration
- Writing investigator's brochure, clinical study report, package insert and other marketing documents.
- Presenting clinical study protocols and results to regulatory authorities and investigators
- Training medical affairs and sales team
- Networking with key opinion leaders
- Developing product development plans
- Planning and conducting market survey
- Strategic inputs for regulatory approval

Oct 2005 – Oct 2006 **Operations Manager**
Richardson Center, Winnipeg, MB, Canada

- Managing centre resources
- Financial management
- Management of all clinical and pre-clinical studies
- Purchasing analytical and pilot plant equipment
- Writing, establishing and enforcing SOPs related to GMP, GLP and GCP
- Commissioning and validating research equipment
- Develop operating budgets and strategic plans for the centre
- Networking with opinion leader and business development.

Mar 2002 – Apr 2004 **Medical Officer**
Bhailal Amin Hospital, Baroda, Gujarat, India

EDUCATION

2008- 2010 MBA in Pharmaceutical Management
Drexel University, Philadelphia

2004 – 2005 Master of Science
McGill University, Montreal, Quebec

1996 – 2002 Doctor of Medicine, MD
Maharaja Sayajirao University of Baroda, India.
(University degree recognized by World Health Organization (WHO) included a one year of rotating clinical internship)

CERTIFICATIONS

2007 Certified Clinical Research Professional (C.C.R.P.)
Awarded by Society of Clinical Research Associates (SoCRA).

MEMBERSHIPS

- Society of Clinical Research Associates (SoCRA)
- Canadian Society of Transplant (CST)
- American Association Study of Liver Disease (AASLD)
- American Society of Hematology (ASH)
- Drug Information Association (DIA)
- American Academy of Neurology (AAN)
- Consortium of Multiple Sclerosis Centers (CMSC)
- Infectious Diseases Society of America (IDSA)

CONTINUING EDUCATION

Mar 2015	Leadership and Decision Making, Harvard Professional Programs
Sep 2013	Negotiation & Dispute Resolution Program at Harvard Law School
Feb 2012	Media Training& Executive Speech Coaching
Feb 2010	Off-label Promotion vs. Scientific Exchange
Nov 2009	DIA Conference on Signal Detection and Data Mining
Oct 2009	Risk Management and Drug Safety Summit
May 2008	Public Speaking: Conveying Your Message with Confidence
Sep 2008	Ethics and Code of Conduct – Working on U.S. Gov. Contracts
Feb 2007	Submission Ready, Winnipeg Technical College
Feb 2007	Good Clinical Practice, CFPIE
Jan 2007	Report Writing, HCPAM
Dec 2006	Risk Management Strategy
Nov 2006	FDA Prescription Drug Labeling

REVIEWER

- Canadian Institutes of Health Research (CIHR) - China-Canada Joint Health Research Initiative Grants

PUBLICATIONS

Röth A, Maciejewski J, Nishimura J, **Jain D,** Weitz J. Screening and Diagnostic Clinical Algorithm for Paroxysmal Nocturnal Hemoglobinuria: Expert Consensus. Eur J Haematol. Mar 2018

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Röth A, Maciejewski J, Nishimura J, Jain D, Weitz J. Developing a Screening and Diagnostic Consensus-based Clinical Algorithm for Paroxysmal Nocturnal Hemoglobinuria: A Modified Delphi Panel Approach, EHA, 2017

Jain D, Ebine N, Jia X, Kassis A, Marinangeli C, Hicks K, Moreau R and Jones P. Cholesterol kinetics and intestinal sterol transporter gene expression in response to corn fiber oil and its constituents in hamsters. Proceedings of Experimental Biology 2006, San Francisco, California.

Jain D, Ebine N, Kassis A, Marinangeli C, Hicks K, Moreau R and Jones P. Effect of dietary ferulate stanyl esters on plasma lipids and red blood cell fragility in hamsters. Proceedings of Second Northern Lights Summer Conference, 48th Annual Meeting of the Canadian Federation of Biological Societies, Guelph Ontario.

Jain D, Ebine N, Jia X, Kassis A, Marinangelia C, Hicks K, Moreau R and Jones P. Effects of corn fiber oil and plant stanols on plasma lipids and gene expression of intestinal sterol transporter in hamsters. Proceedings of Second Northern Lights Summer Conference, 48th Annual Meeting of the Canadian Federation of Biological Societies, Guelph Ontario.

Kassis A, Marinangeli C, **Jain D,** Ebine N and Jones P. Effect of two different mixtures of policosanol on lipid levels in hamsters. Proceedings of Second Northern Lights Summer Conference, 48th Annual Meeting of the Canadian Federation of Biological Societies, Guelph Ontario.

Jain D, Genereux MG,Li D, Hall C, Sinclair CJD. Pharmacokinetics of Intravenous HepaGam B in Hepatitis B Liver Transplant Patients, Canadian Society of Transplant-2008 Annual General Meeting

Aguilar R, Genereux MG, **Jain D,** Sinclair CJD. Comparative Pharmacokinetics of HepaGam B® and BayHep B™ in Normal Healthy Subjects, Canadian Society of Transplant- 2009 Annual General Meeting

Samsung Bioepis Exhibit No. 1002
Page 11405

APPENDIX A

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

AMGEN INC.
Petitioner,

v.

ALEXION PHARMACEUTICALS, INC.
Patent Owner.

Case IPR2019-00741
U.S. Patent No. 9,732,149

DECLARATION OF ARTURO CASADEVALL, M.D., PH.D.

Mail Stop **PATENT BOARD**
Patent Trial and Appeal Board
U.S. Patent and Trademark Office
P.O. Box 1450
Alexandria, VA 22313-1450

TABLE OF CONTENTS

I. Introduction.....Error! Bookmark not defined.

II. Experience and Qualifications.....3

III. Bases of Opinions and List of Documents Considered.....8

IV. Summary of Opinions.....9

V. Legal Standards.....10

A. Standards for Anticipation.....11

B. Standards for Obviousness.....13

VI. Background.....15

A. Overview of the '149 Patent.....15

B. SOLIRIS® and its Use for Treatment of Paroxysmal Nocturnal Hemoglobinuria ("PNH").....16

C. Mechanism of Action for SOLIRIS® in Treating PNH.....18

D. State of the Art Regarding Humanized Monoclonal Antibodies as of March 15, 2007.....20

1. General Antibody Structure.....20

2. Design and Development of Humanized Monoclonal Antibodies for Human Therapeutic Use.....23

3. Nomenclature and Naming for Humanized Monoclonal Antibodies.....37

4. Changes to Amino Acid Sequence, Including in the Constant Region, Can Significantly Impact the Binding, Safety, and Efficacy of Therapeutic Antibodies.....42

5. A POSA as of March 15, 2007 Would Have Understood "Eculizumab" To Be an IgG4-Isotype Humanized Antibody.....52

Samsung Bioepis Exhibit No. 1002
Page 11408

E. The Novel, Uniquely-Engineered Amino Acid Sequence of SOLIRIS® Was Not Known to a POSA as of March 15, 2007 65

VII. Opinions 68

A. Dr. Balthasar's Opinions Misread the Prior Art and Rely on Hindsight Analysis 68

1. A POSA Before March 15, 2007 Would Not Have Understood "Eculizumab" To Contain the Uniquely-Engineered Heavy Chain Constant Region Reflected in SEQ ID NO: 2 of the '149 Patent 68

2. The Antibody Sequence Recited in the '149 Patent Was Not Publicly Known Before March 15, 2007 76

B. Claim 1 of the '149 Patent Was Not Anticipated by Hillmen or Hill (Grounds 1 and 2) 87

C. Claim 1 of the '149 Patent Was Not Anticipated by Bowdish (Ground 3) 91

D. Claim 1 of the '149 Patent Would Not Have Been Obvious Over Bell, Bowdish, and Evans (Ground 4) 101

1. Bell Did Not Disclose the Specific Sequence of Claim 1, and Would Not Have Motivated a POSA to Make An Antibody With the Claimed Sequence 101

2. A POSA Without the Benefit of Hindsight Would Not Have Been Motivated to Combine Bell with Bowdish and Evans 105

3. A POSA Without the Benefit of Hindsight Would Not Have Reasonably Expected Success in Making An Antibody with the Specific Amino Acid Sequence Claimed in the '149 Patent 114

E. Claim 1 of the '149 Patent Would Not Have Been Obvious Over Evans and Mueller (Ground 5) 119

1. A POSA Without the Benefit of Hindsight Would Not Have Combined Evans and Mueller to Make the Specific Claimed Antibody of the '149 Patent 120

2. A POSA Without the Benefit of Hindsight Would Not Have Reasonably Expected Success in Making An Antibody with the Specific Amino Acid Sequence Claimed in the '149 Patent.....128

F. Objective Indicia Support the Nonobviousness of Claim 1 of the '149 Patent.....130

1. SOLIRIS® is the Commercial Embodiment of the '149 Patent.....131

2. SOLIRIS® Fulfilled a Long-Felt, Unmet Need for a Treatment of PNH, Which Others Failed to Satisfy.....133

3. SOLIRIS® Is A Commercial Success.....137

4. Industry Praise.....137

5. Copying.....138

VIII. CONCLUSION.....139

Samsung Bioepis Exhibit No. 1002
Page 11410

I, Arturo Casadevall, hereby declare and say as follows:

I. INTRODUCTION

1. I am over the age of eighteen (18) and otherwise competent to make this declaration.

2. I have been retained by Alexion Pharmaceuticals, Inc. ("Alexion") as an independent expert consultant in this proceeding before the United States Patent and Trademark Office. Although I am being compensated at my normal consulting rate of $ 500/hr for the time I spend on this matter, no part of my compensation is dependent on the outcome of this proceeding, and I have no other interest in this proceeding.[1]

3. I understand the Patent Trial and Appeal Board ("PTAB") issued an Institution Decision (Paper No. 15) granting Amgen Inc.'s ("Amgen") Petition to institute this *Inter Partes* Review ("IPR") regarding claim 1 of United States Patent No. 9,732,149 ("the '149 patent") on five "Grounds" alleging that claim 1 of the '149 patent is unpatentable as anticipated or obvious. I understand that the PTAB's Institution Decision regarding the '149 patent (Paper No. 15) is not a final decision, and is based on the PTAB's "preliminary review of the challenged

[1] All opinions expressed and implied in this Declaration are solely my own and do not represent or reflect the views of my employer, the Johns Hopkins University.

claims, the asserted prior art, and the opinions set forth in the as-yet-unrebutted Balthasar Declaration." (Paper No. 15 at 59-60.)

4. I have reviewed and considered Amgen's Petition regarding the '149 patent (Paper No. 2) ("Amgen's Petition"), the Declaration of Dr. Joseph P. Balthasar regarding the '149 patent (AMG1002) ("Balthasar Declaration"), the Institution Decision regarding the '149 patent (Paper No. 15) ("Institution Decision"), and the other documents cited throughout this Declaration. For the reasons I explain in this Declaration, it is my opinion that Amgen has failed to show that claim 1 of the '149 patent is anticipated or obvious in view of any of Amgen's five "Grounds."

5. As stated in the Institution Decision, the PTAB found based on its "preliminary review" that Amgen had demonstrated a "reasonable likelihood" that it would prevail under two Grounds: (1) alleged anticipation by Bowdish (AMG1008) ("Ground 3"), and (2) alleged obviousness in view of Bell (AMG1005), Bowdish (AMG1006), and Evans (AMG1007) ("Ground 4"). (Paper No. 15 at 36, 45.) For the reasons I explain in this Declaration, it is my opinion that Amgen has failed to show that claim 1 of the '149 patent is unpatentable under either of these Grounds.

6. In its Institution Decision, the PTAB also stated that Amgen had not demonstrated a reasonable likelihood that it would prevail in showing the

challenged claims were unpatentable with respect to three other Grounds: (1) alleged anticipation by Hillmen '04 (AMG1004) ("Ground 1"), (2) alleged anticipation by Hill '05 (AMG1047) ("Ground 2"), and (3) alleged obviousness in view of Evans (AMG1007) and Mueller (AMG1008) ("Ground 5"). (Paper No. 15 at 20, 27, 54.) For the reasons I explain in this Declaration, it is my opinion that Amgen has failed to show that claim 1 of the '149 patent is unpatentable under any of these Grounds.

II. EXPERIENCE AND QUALIFICATIONS

7. I am currently a Bloomberg Distinguished Professor of Molecular Microbiology & Immunology and Infectious Diseases at the Johns Hopkins Bloomberg School of Public Health, and the Alfred and Jill Sommer Professor and Chair of the W. Harry Feinstone Department of Molecular Microbiology and Immunology at the Johns Hopkins Bloomberg School of Public Health.

8. My educational background includes a B.A. in Chemistry, which I received from Queens College, City University of New York, in 1979. In 1983 and 1984, I received my M.S. and Ph.D. in Biochemistry, respectively, both from New York University. I also received my M.D. from New York University in 1985.

9. After I earned my M.D., I went on to complete an internship and residency in internal medicine at Bellevue Hospital from 1985-1988. From 1988-

Samsung Bioepis Exhibit No. 1002
Page 11413

1989, I completed a fellowship in infectious diseases at the Montefiore Medical Center. Under the guidance of Matthew D. Scharff, I completed a postdoctoral fellowship in cell biology at the Albert Einstein College of Medicine from 1989-1991.

10. I became an Assistant Professor of Medicine and Microbiology & Immunology at the Albert Einstein College of Medicine in 1992, and I was promoted to Associate Professor in 1996 and Professor in 2001. I became the Director of the Division of Infectious Diseases at Montefiore Medical Center in 2000.

11. Between 2002 and 2015, I assumed a number of additional roles at the Albert Einstein College of Medicine. I was named the Selma and Jacques Mitrani Professor in Biomedical Research in 2002. In 2006, I became the Chair of the Department of Microbiology & Immunology, and was named the Leo and Julia Forchheimer Professor of Microbiology & Immunology. In 2013, I became the Director of the Center for Immunological Sciences.

12. In 2015, I accepted my current position at the Johns Hopkins Bloomberg School of Public Health. I was also named a Bloomberg Distinguished Professor.

13. I am a member of multiple scientific societies, including the American Academy of Arts and Sciences and the American Association of

Immunologists. I currently serve as the Elected Chair of the Board of Governors of the American Academy of Microbiology.

14. I also serve on the editorial boards of multiple scientific journals, including the Journal of Infectious Diseases and the Journal of Experimental Medicine. I am the Founding Editor and Editor-in-Chief of mBio, the first open access general journal of the American Society for Microbiology. I am also Deputy Editor of the Journal of Clinical Investigation.

15. During my career, I have served and continue to serve on scientific advisory committees. These include the CDC Advisory Panel on Anthrax Immune Globulin, on which I served in 2004; the Scientific Advisory Board for the NIAID Immune Epitope Database, on which I served from 2004-2006; the Abbott Laboratories Award in Clinical and Diagnostic Immunology Selection Committee, on which I served from 2004 to 2007; and the National Science Advisory Board for Biosecurity, on which I served from 2005-2014.

16. My work has been recognized with a number of awards and distinctions, including a Merit Award from the National Institutes of Health, which I was awarded in 2007. I have been elected to the National Academy of Medicine and the American Academy of Arts and Sciences.

17. Over the course of my career, I have authored over 800 publications, books, book chapters, and monographs. I am also an inventor on multiple issued patents and pending patent applications.

18. I have over 25 years' experience in the fields of immunology and microbiology, including therapeutic antibody design. In particular, I have worked extensively for over 15 years to research the effect of antibody constant regions on antibody binding and specificity. I first started working on this issue in 1992. In 2002, my laboratory published our first significant paper on the subject, McLean *et al.*, Isotype can affect the specificity of an antibody for a polysaccharide antigen, J IMMUNOL., 169:1379-86 (2002) (ALXN2013), which I co-authored.

19. Following McLean 2002, my laboratory continued to publish research related to the impact of antibody constant regions on antibody binding and specificity. For example, I co-authored Torres *et al.*, Variable region identical antibodies differing in isotype demonstrate differences in fine specificity and isotype, J. IMMUNOL., 174:2132-2142 (2005) (ALXN2040), and Torres *et al.*, The Immunoglobulin Heavy Chain Constant Region Affects Kinetic and Thermodynamic Parameters of Antibody Variable Region Interactions with Antigen, J. OF BIOL. CHEM., 282(18):13917-27 (2007) (ALXN2009). I also co-authored a major review article, Janda *et al.*, Ig Constant Region Effects on Variable Region Structure and Function, FRONT. MICROBIOL., 7(22):1-10 (2016)

(ALXN 2010) in 2016. In total, I have published 15 publications related to the effect of antibody constant regions on antibody binding and specificity.

20. In addition to my academic research work, I have also been directly involved in the development of two monoclonal antibodies for therapeutic treatment. The first was an antibody for treatment of cryptococcal meningitis, which was developed in my lab and tested in clinical trials in 2001. The second was an antibody to treat melanoma, which was developed in my lab in partnership with Pain Therapeutics, and tested in clinical trials in 2007. I also served on Pfizer's advisory board for therapeutic antibodies from 2011 to 2014.

21. My additional research interests include fungal and bacterial pathogenesis. Research from my lab has led to development of an antibody to fungal melanin that is currently in evaluation for the treatment of melanoma. We are also currently working to develop antibody-based countermeasures to protect against anthrax.

22. I am board certified in Infectious Diseases and in Internal Medicine until 2023.

23. As reflected by my education and experience discussed above, and further reflected in my curriculum vitae, I am an expert in the design, development, evaluation, and testing (including biological and physiochemical analysis) of monoclonal antibodies for use in human clinical therapy, including humanized

monoclonal antibodies. I was also an expert in these fields prior to March 15, 2007. A copy of my curriculum vitae is attached to this Declaration as **Appendix A** (ALXN2022.)

III. BASES OF OPINIONS AND LIST OF DOCUMENTS CONSIDERED

24. The opinions contained in this declaration are based on the documents I reviewed and my knowledge and professional judgment. In forming the opinions expressed in this declaration, I reviewed the documents discussed throughout this declaration, as well as the documents listed in **Appendix B**. My opinions are further based on background, education, and my over 25 years of experience and knowledge of therapeutic antibody design, including both academic research and development work for monoclonal antibody therapeutics.

25. In forming my opinions, I have also considered the perspective of a person of ordinary skill in the art ("POSA") as of March 15, 2007, including the knowledge available to a POSA as of that date, and how a POSA would have read and understood the literature pertinent to the invention claimed in the '149 patent.

26. I understand that, in its Institution Decision, the Board accepted that a POSA in the field of the '149 patent would typically have "an M.D. and/or Ph.D. in immunology, biochemistry, cell biology, molecular biology, pharmaceutics, or a related discipline," who would have "at least two years of experience engineering monoclonal antibodies for human therapeutic use, either in the laboratory or

industry." (Paper No. 15 at 10-11.) I agree with this definition of a POSA, and provide my opinions in this Declaration from the perspective of a POSA as of March 15, 2007.

IV. SUMMARY OF OPINIONS

27. I have considered the opinions of Dr. Joseph P. Balthasar, as set forth in his February 27, 2019 declaration ("Balthasar Declaration") (AMG1002), and the documents cited therein. I submit this Declaration in order to respond to opinions offered by Dr. Balthasar.

28. It is my opinion that claim 1 of the '149 patent is not anticipated by, or obvious in view of, any of the alleged prior art or combinations of prior art at issue in Amgen's five "Grounds" in this proceeding.

29. I disagree with Dr. Balthasar's conclusions that claim 1 of the '149 patent was anticipated by any of Hillmen '04 (AMG1004) (as alleged in "Ground 1"), Hill '05 (AMG1047) (as alleged in "Ground 2"), or Bowdish (AMG1006) (as alleged in "Ground 3"). In my opinion, none of these three documents disclosed each and every element recited in claim 1 as arranged in the claim, whether expressly or inherently.

30. I further disagree with Dr. Balthasar's conclusions that claim 1 of the '149 patent was obvious in view of the combination of Bell (AMG1005), Bowdish (AMG1006), and Evans (AMG1007) (as alleged in "Ground 4"), or in view of the

combination of Evans (AMG1007) and Mueller (AMG1008) (as alleged in "Ground 5"). In my opinion, a POSA without the benefit of hindsight, and with the benefit of the full scope of prior art available as of March 15, 2007, would not have found the claimed invention obvious; and to the contrary, the art would have led a POSA in a direction divergent to the path taken by the claimed invention. It is also my opinion that a POSA, without the benefit of hindsight, would not have been motivated to combine the teachings of any of these references because there was no teaching, motivation, suggestion, or other reason to do so, and that a POSA would not have had a reasonable expectation of success with respect to the claimed invention.

31. It is also my opinion that "objective indicia" further support the non-obviousness of the invention recited in claim 1 of the '149 patent, including at least the fulfillment of a long-felt, unmet need; commercial success; failure of others; copying; and industry praise.

V. LEGAL STANDARDS

32. I have been advised by counsel of the following legal principles, which I have considered and applied in forming my opinions set forth in this Declaration.

33. I understand the burden of proving unpatentability of the '149 patent rests with Amgen in this proceeding.

Samsung Bioepis Exhibit No. 1002
Page 11420

A. Standards for Anticipation

34. I have been informed by counsel that, to establish anticipation, Amgen must show that a single prior art reference discloses each and every element of the claimed invention, within the four corners of the document, arranged as in the claim.

35. I understand that a document may "incorporate by reference" the disclosure of another document. I understand that a document may be incorporated by a reference in its entirety, or only with respect to certain information, depending on the language setting out the incorporation by reference. To the extent a document is incorporated by reference, I understand that its disclosures should be considered as part of the incorporating document.

36. I have been informed by counsel that a prior art document may anticipate either expressly or inherently. I understand a document does not anticipate just because it refers to a molecule or formulation that is later revealed to be the one claimed. Counsel has explained that, for a prior art document to inherently anticipate a patent claim, elements that are not disclosed expressly in the reference must be necessarily present in the document. I understand that a document is not anticipatory if any elements are only probably or possibly present.

37. I have been informed that, to anticipate, it is not enough that the prior art document discloses part of the claimed invention, which a POSA might

supplement to make the whole. I also understand from counsel that, to anticipate, it is not enough that the prior art includes multiple, distinct teachings that a POSA might somehow combine to achieve the claimed invention.

38. I have been informed by counsel that, to anticipate, a document must provide every element of the claimed invention arranged or combined as in the claim, or permit a POSA reading the document to "at once envisage" the claimed invention. In other words, I understand that a reference does not anticipate a claimed invention if, on reading it, a POSA would not be able to immediately understand that the claim elements disclosed in the document should be arranged or combined in the manner recited in the claim.

39. Counsel has further informed me that, to anticipate, a single document must describe the claimed invention with sufficient precision and detail to establish that the subject matter existed in the prior art, and that ambiguous references do not anticipate a claim.

40. I have also been informed by counsel that, to anticipate a claimed invention, a prior art reference must be "enabled," such that a POSA could make and use the claimed invention without undue experimentation. I understand that the PTAB will consider the following factors in assessing whether a disclosure requires undue experimentation: (1) the quantity of experimentation necessary; (2) the amount or guidance presented; (3) the presence or absence of working

Samsung Bioepis Exhibit No. 1002
Page 11422

examples; (4) the nature of the invention; (5) the state of the prior art; (6) the relative skill of those in the art; (7) the predictability or unpredictability of the art; and (8) the breadth of the claims.

B. Standards for Obviousness

41. I have been informed by counsel that, to establish obviousness, Amgen must show that the claimed invention as a whole would have been obvious to a POSA prior to the date on which the claimed invention was invented, without the benefit of hindsight knowledge. I have been informed that, for purposes of these proceedings, the relevant date of invention, or "priority date," is March 15, 2007, the earliest filing date for the '149 patent.

42. I have been informed by counsel that the Board will consider the following factors in determining whether Amgen has met its burden to establish invalidity based on obviousness: (1) the scope and content of the prior art; (2) differences between the prior art and the claims at issue; (3) the level of ordinary skill in the art; and (4) objective evidence of non-obviousness.

43. Counsel has explained that objective indicia supporting nonobviousness can include: that the invention satisfied a long-felt but unmet need that existed at the time of the invention; commercial success of products embodying the claimed invention; failure of others to solve the problem addressed by the claimed invention; copying of the invention; and industry praise.

Samsung Bioepis Exhibit No. 1002
Page 11423

44. I understand from counsel that, in assessing obviousness, it is improper to use hindsight knowledge of the invention claimed and described in the '149 patent, or other documents or information that would not have been available to a POSA prior to March 15, 2007.

45. I further understand from counsel that, in the obviousness analysis, that the full scope and content of the prior art available to a POSA must be considered, and it is improper to use hindsight in selecting documents from the prior art for use in an obviousness analysis. I also understand it would be improper to assume obviousness by following the path that led the inventors to the claimed invention, and instead prior art must be viewed from the perspective of a POSA without the benefit of knowing how the inventors successfully achieved the claimed invention.

46. I understand from counsel that, in assessing obviousness, I must consider a prior art reference as a whole, for all that it teaches, including any portions that would have discouraged or pointed away from the claimed invention.

47. I have been informed that, to establish obviousness, Amgen must also show that, for a particular combination of prior art references, a POSA without the benefit of hindsight would have had a motivation or reason to combine those prior art references. I also understand from counsel that Amgen must show that a POSA, without the benefit of hindsight, would have had a reasonable expectation

of success with respect to the claimed invention. I understand that hindsight bias must be avoided in assessing whether a particular combination of references would have been obvious prior to the date of invention.

VI. BACKGROUND

A. Overview of the '149 Patent

48. In forming my opinions, I have reviewed the '149 patent, titled "Treatment of Paroxysmal Nocturnal Hemoglobinuria Patients by an Inhibitor of Complement."

49. I understand from counsel that the '149 patent claims priority back to U.S. Application No. 12/225,040, filed as PCT/US2007/006606 on March 15, 2007. I have been informed that March 15, 2007 is the earliest priority date for the '149 patent.

50. I understand that the '149 patent reflects the work of Alexion scientists in developing SOLIRIS® as a safe and effective treatment for paroxysmal nocturnal hemoglobinuria ("PNH"). The '149 patent has one claim, as follows:

> 1. An antibody that binds C5 comprising a heavy chain consisting of SEQ ID NO: 2 and a light chain consisting of SEQ ID NO: 4.

(AMG1001 at 39:1-4.)

51. Claim 1 of the '149 patent recites the complete amino acid sequence for the active compound in SOLIRIS® (eculizumab): the heavy chain consisting of SEQ ID NO: 2, and the light chain consisting of SEQ ID NO: 4. (AMG1001 at cols. 31-33, 35.) As I discuss below, a POSA prior to March 15, 2007 would not have known that eculizumab had the specific sequence recited in claim 1, and would not have known of any other monoclonal antibody having that specific sequence.

52. The '149 patent also provides data from the Phase III "TRIUMPH" clinical study, confirming that the claimed antibody is safe and effective for treating PNH, and identifying the safe and effective dosing regimen for that use. (AMG1001 at abstract, 19:50-28:35.)

53. Claim 1 of the '149 patent reflects the purpose of the '149 patent's invention: the development of a humanized monoclonal antibody that can bind to C5 and thereby block its cleavage, and can be used as a safe and effective therapy for patients with PNH.

B. SOLIRIS® and its Use for Treatment of Paroxysmal Nocturnal Hemoglobinuria ("PNH")

54. PNH is a rare, life-threatening blood disorder characterized by chronic destruction of red blood cells ("hemolysis"), with periodic acute exacerbations of hemolysis ("paroxysms") that result in dark urine ("hemoglobinuria"). (AMG1047 at 2559.) Patients afflicted with PNH have

Samsung Bioepis Exhibit No. 1002
Page 11426

symptoms including chronic and potentially disabling fatigue, dysphagia (difficulty swallowing), and recurrent pain, resulting in an impaired quality of life. (AMG1004 at 6; AMG1047 at 2559; AMG1012 at 1234.) PNH patients also often suffer from severe anemia requiring frequent blood transfusions for survival, and can be susceptible to life-threatening blood clots ("thrombosis"). (AMG1047 at 2559.)

55. Prior to FDA approval of SOLIRIS®, there was a substantial need for a safe and effective therapy for the treatment of PNH. As stated in the pivotal Phase III clinical trial report for SOLIRIS® published in the New England Journal of Medicine, "there [was] no therapy that effectively reduce[d] intravascular hemolysis or improves the symptoms in patients with PNH" prior to SOLIRIS®. (AMG1012 at 1234; *see also* AMG1047 at 2559 ("There is ***no effective treatment*** for the ongoing hemolysis in PNH.").)[2] Before the availability of SOLIRIS®, PNH patients were often "transfusion-dependent," meaning that their survival depended on receiving frequent blood transfusions. (AMG1004 at 557; AMG1047 at 2559.)

56. In clinical trials of SOLIRIS®, PNH patients showed reduced hemolysis and substantial improvements in outcomes, including reduced or eliminated need for blood transfusions, lessened anemia and fatigue, and improved

[2] Unless otherwise indicated, all emphasis is added.

Samsung Bioepis Exhibit No. 1002
Page 11427

quality of life. (AMG1033 at 1261.) Those trials also confirmed the safety of SOLIRIS® for long-term administration. (AMG1047 at 2564.)

57. SOLIRIS® received accelerated approval (under the "Priority Review" program for groundbreaking therapies) by the U.S. Food & Drug Administration ("FDA") on March 16, 2007. (ALXN2006 at 993; ALXN2030 at 1.) SOLIRIS® was the first therapy approved by the FDA for treatment of PNH. (ALXN2030 at 1.) By improving efficacy outcomes while reducing the need for more invasive therapies, SOLIRIS® represented a significant advance in PNH treatment.

C. Mechanism of Action for SOLIRIS® in Treating PNH

58. The active ingredient in SOLIRIS® is eculizumab, a humanized monoclonal antibody. SOLIRIS® works by binding with high "affinity" (*i.e.*, tightness) and "specificity" (*i.e.*, directed to a single target or "antigen") to the human protein "C5," a key component of the body's "complement" pathway.

59. PNH is caused by a genetic mutation resulting in abnormal blood cells that are unprotected from the body's "complement" system. (AMG1004 at 553; AMG1047 at 2559; AMG1012 at 1234.) The complement system is a component of the human immune system that normally protects the body against invading infectious cells (*e.g.*, pathogenic bacteria), by forming a "membrane-attack complex" that causes invading cells to burst ("lysis"). (ALXN2019 at 1265-66.) If

Samsung Bioepis Exhibit No. 1002
Page 11428

unimpeded, the complement system also has the potential to attack the body's own cells, causing dangerous disease conditions. (ALXN2019 at 1266-68.)

60. In PNH patients, the red blood cells of PNH patients are constantly under attack by the complement system ("chronic intravascular hemolysis"). (AMG1012 at 1239-1240.) Normally, red blood cells are protected against such attack from the complement system by membrane-bound proteins such as "CD59," which blocks the formation of the cell-lysing "membrane attack complex" on the cell surface. (AMG1012 at 1234.) In PNH patients, however, a genetic mutation in the "PIG-A" gene results in the absence of CD59 on red blood cells, leaving them chronically susceptible to destruction by the complement system. (AMG1012 at 1234.)

61. Without SOLIRIS® treatment, the body naturally cleaves C5 into two components, "C5a" and "C5b," which lead to the various downstream effects of the complement pathway, including hemolysis in PNH patients. When SOLIRIS® is administered, however, it binds to a critical location ("epitope") on C5 with sufficient affinity, specificity, and "fine specificity" (*i.e.*, binding to the right spot) to prevent cleavage of C5 into C5a and C5b. (AMG1004 at 2; AMG1047 at 2559; AMG1012 at 1233.) By binding to C5 and blocking its cleavage, SOLIRIS® blocks the downstream effects of the complement pathway, and spares PNH

Samsung Bioepis Exhibit No. 1002
Page 11429

patients' red blood cells from destruction. (AMG1004 at 2; AMG1047 at 2559; AMG1012 at 1233.)

D. State of the Art Regarding Humanized Monoclonal Antibodies as of March 15, 2007

1. General Antibody Structure

62. As of March 15, 2007, antibodies were known to be complex three-dimensional proteins characterized by one or more flexible, Y-shaped structures each formed from four polypeptide chains – two identical "heavy chains" and two identical "light chains." (ALXN2007 at 104-05; AMG1018 at 4.)

63. Each heavy and light chain polypeptide can be divided into a "variable" region, where the antigen binds, and a "constant" region, which may interact with other components of the immune system. (ALXN2007 at 105-106.) As discussed below in Section VI.D.4, however, a POSA as of March 15, 2007 would have been aware that antibodies are complex three-dimensional molecules, and that the structure of the constant region could potentially impact the antibody-antigen interactions of the variable region, even if the constant region is not directly in contact with the antigen.

64. The variable region of each of the two heavy chains and two light chains includes three "complementarity-determining regions" ("CDRs"), which together directly interact with a single epitope on a specific antigen. (AMG1018 at

Samsung Bioepis Exhibit No. 1002
Page 11430

9.) Portions of the variable region flanking the CDRs are termed "framework" regions. (AMG1029 at 6.)

65. Antibodies are divided into classes, or "isotypes," based on their constant regions. (ALXN2007 at 105; AMG1018 at 4; AMG1029 at 5.) There are five different naturally-occurring isotypes – IgA, IgD, IgE, IgG, and IgM – which determine the functional activity of the antibody. (ALXN2007 at 105; AMG1018 at 4-7; AMG1029 at 5.) These isotypes differ structurally in the amino acid sequences of their heavy chain constant regions, the number and location of their disulfide bonds, and the lengths of their "hinge" regions. (*See, e.g.*, ALXN2008 at 172; *see also* ALXN2009 at 13924; AMG1029 at 5.) The IgG isotype is the most abundant in humans and, as of March 15, 2007, was the most common class used for human therapy. (ALXN2007 at 105; AMG1018 at 4; AMG1029 at 2-5.)

66. IgG antibodies contain a single Y-shaped structure. IgG constant regions can be subdivided into different parts, with the light chain including a variable region ("VL") and a constant region ("CL"), and the heavy chain including a variable region ("VH") followed by constant region domains known as "CH1," the "hinge" region, "CH2," and "CH3." (ALXN2007 at 106.)

67. Antibody domains were also sometimes referred to in the art by the fragments that would be produced from proteolytic degradation. For example, the "CH2" and "CH3" domains together form what was known as the "Fc" region

Samsung Bioepis Exhibit No. 1002
Page 11431

("fragment crystallizable"), and the light chain associated with a truncated heavy chain containing only VH and CH1 form what was known as the "Fab" region ("fragment antigen binding"). (ALXN2007 at 106; AMG1018 at 8.)

68. Figure 1 (adopted from Amgen's Petition) depicts the basic structure of a full-length, intact IgG antibody in a simplified, two-dimensional diagram. This type of diagram is useful for simple illustrations of antibody structure – but as I discuss further below in Section VI.D.4, a POSA as of March 15, 2007 would have understood that these diagrams do not reflect the complexity of the three-dimensional structures of antibodies that are integral to the nature of their antibody-antigen interactions, including binding affinity and specificity (including fine specificity).

Samsung Bioepis Exhibit No. 1002
Page 11432

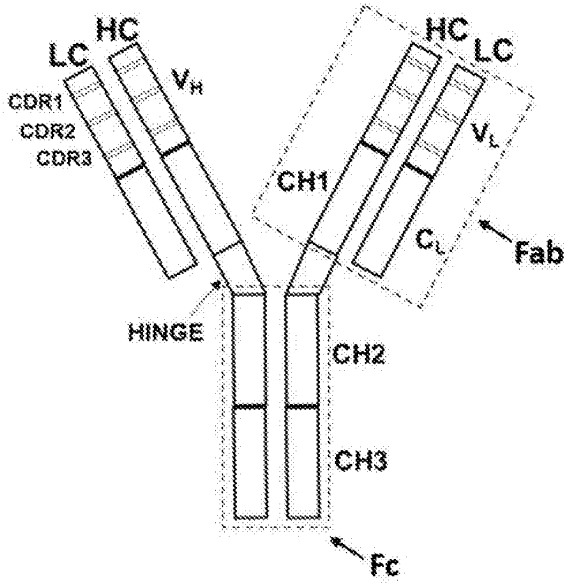


Figure 1: Basic structure of an IgG antibody
(simplified two-dimensional depiction)

2. Design and Development of Humanized Monoclonal Antibodies for Human Therapeutic Use

69. As of March 15, 2007, it was known that antibodies produced in an animal's natural immune response to an antigen are "polyclonal," meaning that they include a set of different antibodies having a mixture of different affinities and specificities. (ALXN2031 at 696; ALXN2032 at 210:18-211:12.) A set of polyclonal antibodies produced in a natural immune response will thus include multiple distinct antibodies, each with their own unique "primary amino acid sequence" for their heavy and light chain polypeptides. (*See* ALXN2031 at 696; AMG1018 at 11-17.)

Samsung Bioepis Exhibit No. 1002
Page 11433

70. By contrast, a POSA as of March 15, 2007 would have understood a "monoclonal antibody" was a single, unique antibody with one specific, defined structure. (ALXN2031 at 697; ALXN2032 at 10:9-22, 11:10-17.) In contrast to a set of polyclonal antibodies, a POSA would have understood that a monoclonal antibody has a single unique primary amino acid sequence for the entire antibody, including for both the variable region and constant region. (ALXN2031 at 697; ALXN2032 at 10:9-22, 11:10-17.) And associated with that unique sequence and structure, a POSA would have understood that each monoclonal antibody has its own specific binding properties (affinity and specificity) for the antigen against which it is directed. (ALXN2031 at 697; *see* ALXN2032 at 10:9-22, 11:10-17.)

71. As of March 15, 2007, technology existed to produce, isolate and characterize new monoclonal antibodies by laboratory means. Such new monoclonal antibodies were typically developed and discovered using hybrid antibody-forming cells called "hybridomas." (ALXN2031 at 697.) To generate monoclonal antibodies this way, first a mouse would be immunized with a target antigen. (ALXN2031 at 697.) Antibody-producing B cells from the immunized mouse would then be fused with immortalized cells from a mouse myeloma, a type of tumor. (ALXN2031 at 697.) The resulting unique hybrid cell lines cloned from individual antibody-producing cells ("hybridomas") could each make a unique, monoclonal mouse (murine) antibody directed to the target antigen. (ALXN2031

Samsung Bioepis Exhibit No. 1002
Page 11434

at 697.) Because the cells used to create hybridomas were of mouse origin, hybridomas made using this particular technology would only produce mouse antibodies. (ALXN2031 at 697.)

72. As of March 15, 2007, it was conventional to name a mouse monoclonal antibody after the hybridoma from which it was derived. For example, as I discuss further below, the anti-C5 mouse monoclonal antibody that Alexion obtained from the "5G1.1" hybridoma was referred to in the literature as "the 5G1.1 antibody" or "the 5G1.1 mAb." (AMG1007 at 38:43-67; AMG1023 at 1390, 1393, 1395; ALXN2032 at 10:9-22; 97:23-99:8; 165:11-21.)

73. Hybridomas generated in this process would then need to be screened for those producing mouse monoclonal antibodies with appropriate specificity. (ALXN2031 at 697.) Additional tests would need to be performed to further characterize promising candidates, including assays to assess binding affinity and appropriate biological activity. For example, with respect to the "5G1.1" mouse antibody, Evans states that the researchers (1) identified the "5G1.1" antibody by screening for C5 binding and activity in inhibiting complement-mediated hemolysis; (2) determined the specific binding affinity of "5G1.1" antibody for its antigen target C5; and (3) further studied the "5G1.1" antibody in various in vitro assays showing that it blocked the cleavage of C5 and protected blood cells from lysis. (AMG1007 at 38:43-39:16; 39:36-40:29; ALXN2032 at 165:11-169:23; *see*

Samsung Bioepis Exhibit No. 1002
Page 11435

also ALXN2029 at 12 (requiring characterization of antibody specificity, cross-reactivity, affinity, avidity, and immunoreactivity prior to human clinical trials).)

74. Finally, after a mouse monoclonal antibody with suitable properties was identified, its amino acid sequence could be determined using sequencing techniques, and the obtained sequence could be used as a basis to make more of the mouse monoclonal antibody, or fragments or derivatives of it. For example, in Evans, after identification and initial characterization, researchers sequenced and cloned the variable light chain and variable heavy chain regions of the "5G1.1" antibody. (AMG1007 at 40:36-42:54; ALXN2032 at 165:11-169:23.)

75. As of March 15, 2007, it was generally understood that, while mouse antibodies may be useful as laboratory research agents, they were generally not desirable for therapeutic use in humans. Specifically, a POSA understood that mouse antibodies can elicit immune reactions in human patients ("HAMA"), which could cause the mouse antibody to be ineffective or even harmful to human patients, particularly upon repeated administration. (ALXN2033 at 18; ALXN2034 at 3-4.) Such immune reactions were particularly undesirable in the context of treating chronic inflammatory or immune conditions requiring prolonged treatment. (*See* AMG1023 at 1390.)

76. For that reason, a POSA would have known of technologies for developing therapeutic antibodies that were intended to reduce immune reactions

Samsung Bioepis Exhibit No. 1002
Page 11436

to non-human sequences, by designing new antibody structures that combines the mouse-derived sequences associated with antigen binding with human-derived antibody sequences. One such approach involved creating "chimeric" antibodies, where the sequences for variable regions of a mouse-derived antibody were combined with the constant region sequences (CL, CH1, hinge, CH2 and CH3) from a human IgG antibody. (ALXN2033 at 18; ALXN2034 at 3; AMG1029 at 8.) To further reduce the non-human character of therapeutic antibodies for human use, "humanization" technology was developed, whereby mouse sequences thought to be directly involved in antigen binding (including the "CDRs") would be integrated into the sequence of an otherwise fully human antibody or fragment. (ALXN2033 at 18; ALXN2034 at 3; AMG1029 at 8.)

77. While the general concepts of making chimeric and humanized antibodies were known well before March 15, 2007, it was still true at that date that designing antibodies for human therapeutic use was an unpredictable art that required extensive experimentation and testing. (*See, e.g.*, ALXN2035 at 58-59; ALXN2036 at 141.) With humanization technology specifically, a POSA would have understood that there were many choices to make in the process of attempting design an antibody that could potentially be suitable for therapeutic use. Further, a POSA would not have been able to reasonably predict the impact that these various design choices would have upon the safety or efficacy of a newly-designed,

Samsung Bioepis Exhibit No. 1002
Page 11437

unstudied antibody without conducting at least some human clinical testing. (ALXN2036 at 141 ("Only favorable results from clinical studies can confirm the success of a humanization experiment."); ALXN2037 at 1343-44 (discontinuing clinical trial of humanized monoclonal antibody due to development of human antihuman antibodies ("HAHA") in 73% of study patients); (ALXN2038 at 624 (as of 2008, success rate of humanized monoclonal antibodies entering clinical trials was 17%).)

78. First, a POSA would have had to make choices about, and then empirically test, different designs for the variable regions of the humanized antibody. As of March 15, 2007, humanized antibodies were often constructed using a technique known as "CDR-grafting," also known as "re-shaping," which involved the transfer of mouse CDRs into human framework regions. (ALXN2035 at 58; ALXN2036 at 135-137.) It was known at the time, however, that insertion of the mouse CDRs into a human framework could have unpredictable effects. For example, a POSA would have understood that the simple transfer of mouse CDRs into corresponding positions of the human framework regions could significantly reduce antibody binding and specificity compared to the parent mouse antibody. (ALXN2035 at 58; ALXN2036 at 140; ALXN2033 at 19.)

79. To attempt to maintain the same specificity and binding of the parent mouse antibody, additional amino acids from the mouse framework regions may

Samsung Bioepis Exhibit No. 1002
Page 11438

have had to be inserted into the framework regions of the humanized antibody, but this could increase the risk of an immunogenic effect. (ALXN2036 at 140.) Furthermore, each modification step carried a risk of losing existing activity since antibody engineering then was a largely empirical exercise. (ALXN2035 at 58-60; ALXN2036 at 140-41; ALXN2033 at 19; *see* AMG1023 at 1394.) Accordingly, a POSA designing a humanized variable region would have had to make various choices, including: (1) the extent of the mouse CDRs to be transferred; (2) the human framework regions to be used; and (3) whether additional amino acids from the parent mouse antibody would need to be inserted into the framework regions (called "back mutation") to maintain the same antibody binding and specificity as the parent antibody. (ALXN2035 at 58; ALXN2036 at 137-141; ALXN2033 at 19.) Finally the POSA would have to make decisions on what cell line to express the recombinant antibody molecule, a choice that could affect immunoglobulin glycosylation, and thus affect antibody functions.

80. Even if a humanized variable region fragment (scFv or Fab, as discussed below) was developed and shown to have the desired antigen-binding and biological properties, a POSA would have understood that further development would be required – and additional choices would have to be made – to design a full-length, intact chimeric or humanized IgG-class monoclonal antibody. For example, a POSA would have had to choose which human constant regions to use.

Samsung Bioepis Exhibit No. 1002
Page 11439

In designing appropriate constant regions, as of March 15, 2007, a POSA would have understood that there were four naturally occurring subclasses or "isotypes" – IgG1, IgG2, IgG3, and IgG4, and that humanized monoclonal antibodies approved by the FDA were predominantly of the IgG1 or IgG4 isotypes. (ALXN2007 at 105; AMG1029 at 2-4 (Table 1), 5.) As of March 15, 2007, all of the full-length chimeric or humanized commercial antibodies used one of the naturally-occurring IgG constant regions. (AMG1029 at 2-4 (Table 1).)

81. As discussed in Section VI.D.4 below, a POSA would have understood that, while the antibody constant regions do not directly contact the antigen, the choice of isotype for an intact humanized monoclonal antibody could potentially impact many different properties, including antigen binding affinity and specificity; immunogenicity and immune system responses; antibody pharmacokinetics; antibody stability and ultimately, safety and efficacy when administered to people. A POSA would not have reasonably expected that every possible full-length antibody made by combining sequences from a variable region fragment with desirable binding and biological activity and sequences from an intact human constant region or a full human antibody would retain the same properties, and would have understood that empirical testing would be required to assess the efficacy of any full-length humanized antibodies that were generated. (*See* AMG1023 at 1394; Section VI.D.4 below.)

Samsung Bioepis Exhibit No. 1002
Page 11440

82. Ultimately, a POSA as of March 15, 2007 would not have been able to predict from the primary amino acid sequence alone whether a particular newly-designed humanized antibody would bind to its target with appropriate affinity and specificity, at the appropriate epitope to provide the desired biological activity. These attributes would need to be tested empirically with in vitro studies, including assays of binding affinity and in vitro biological activity assays. (*See* ALXN2036 at 150-153; ALXN2035 at 59; AMG1023 at 1391-1393.) Even such in vitro testing would not reliably predict whether an antibody would ultimately succeed as a therapeutic agent that was suitably safe to give to patients – it would only be the beginning of the analysis.

83. As my group wrote in one of our 2007 studies, "[t]here is extensive anecdotal and unpublished evidence that many attempts to generate humanized mAbs based on mouse V regions have failed to produce useful Abs because of loss of specificity or affinity." (ALXN2039 at 1.) I have personally observed loss of binding affinity and specificity as a result of replacing the mouse constant region with a human constant region while working to develop melanin-binding monoclonal antibodies for the therapy of melanoma. I have also personally observed that exchanging murine and human constant regions alters the binding characteristics of antibodies to Cryptococcus neoformans polysaccharide. (ALXN2039 at 1-2, 3-4.) Finally, we have reported that the simple act of changing

Samsung Bioepis Exhibit No. 1002
Page 11441

the constant region of antibody could potentially result in new properties such as "polyreactivity," or reactivity with multiple antigens, a phenomenon of particular concern with regards to therapeutic antibodies where it is desirable to avoid all off-target reactivity with host tissues. (ALXN2009 at 13917, 13924-25; ALXN2039 at 4; *see also* ALXN2038 at 626.)

84. As discussed in Section II above, I oversaw development of a murine monoclonal antibody for treatment of cryptococcal meningitis, which began clinical trials in 2001, and in the mid-2000s, I was closely involved with the development of a murine antibody to treat melanoma. In the case of the antibody for the treatment of cryptococcosis we observed that in creating mouse-human chimeric antibodies that these differed in fine specificity from the parent murine mAb. (ALXN2013 at 1379.) In fact, concerns about changing the fine specificity of the anti-cryptococcal antibody were a major consideration in our decision to eventually use the parental murine mAb in human trials.

85. Likewise, in the case of the IgM antibody to melanin that we developed for the therapy of melanoma, efforts to create a mouse-human chimeric antibody led to loss of binding, and the difficulty involved in antibody engineering led this effort to abandon the original murine mAb used in clinical trials in favor of isolating a new murine IgG that could be more amenable to humanization. These

Samsung Bioepis Exhibit No. 1002
Page 11442

experiences illustrate the unpredictable outcome associated with modifying murine mAbs to create more desirable mouse-human chimeric antibodies.

86. Further, whether or not a POSA had data from in vitro or animal studies, a POSA as of March 15, 2007 would have not reasonably expected success with a newly-designed humanized monoclonal antibody without further conducting clinical testing to study the safety and efficacy of the antibody in a relevant patient population. (*See* ALXN2029 at 29-39 (outlining preclinical and clinical studies for approval of monoclonal antibodies).) A POSA would have understood that at least some human clinical testing was required to demonstrate that the antibody produces the desired clinical effect in people, and that the antibody is otherwise sufficiently safe and suitable for human administration – including whether it results in any undesirable immunogenic effects that limits efficacy or creates potential safety issues. (ALXN2042 at 91; *see* ALXN2029 at 37-39.) For example, although it was generally humanization efforts were generally intended to reduce potential immunogenicity as compared to a fully mouse antibody, a POSA would have understood that humanized antibodies – and even fully human antibodies – could still produce unwanted immune reactions in patients, and that safety would need to be assessed in clinical trials. (*See* ALXN2033 at 22; ALXN2034 at 4.) Those concerns would be exacerbated if a POSA were to consider using a unique, non-naturally occurring constant region for which there

Samsung Bioepis Exhibit No. 1002
Page 11443

were no published reports of clinical testing in people, such as a hybrid IgG2/IgG4 constant region.

87. Accordingly, if a humanized antibody appeared sufficiently promising based on in vitro testing, a POSA would have understood that the antibody would need to be further studied in clinical trials with human patients. In general, such clinical studies would include "Phase I" studies that primarily assess safety; Phase II studies that further assess safety and also study the desired biological effects in the relevant clinical population; and larger Phase III trials (typically placebo-controlled) to fully establish the drug is safe and effective for human clinical use. (ALXN2042 at 82; *see also* ALXN2029 at 34-37.)

88. As of March 15, 2007, the clinical trials needed to show the safety and efficacy of a therapeutic monoclonal antibody were rigorous, and required substantial resources. Particularly for a rare disease such as PNH, even small clinical trials to test for early signs of therapeutic effect and study safety were challenging, including, among other things, finding a sufficient number of appropriate patients for the study, developing and manufacturing antibody (and pharmaceutical compositions of the antibody) in suitable quantities and of suitable quality to be used in a human clinical trial, and coordinating with investigators across multiple sites.

Samsung Bioepis Exhibit No. 1002
Page 11444

89. Even prior to the start of human clinical trials, the antibody would have to be tested in preclinical studies, including animal studies assessing cross-reactivity of the antibody with non-target tissues, toxicology, and pharmacokinetics. (ALXN2029 at 29-33.)

90. And, even for use in an experimental, clinical trials, an appropriate pharmaceutical formulation would have to be developed. This would include development of a stability testing program and multiple studies, including accelerated stability testing, to ensure the drug would retain its biological activity and not degrade in the formulation to be administered. (ALXN2029 at 23.) If a new antibody was not sufficiently stable to be developed into a suitable formulation that could be stored and used for testing, it would have been unlikely for the FDA to permit experimental human testing to go forward.

91. A POSA as of March 15, 2007 would have known that, in addition to full-length, intact humanized antibodies, as of March 15, 2007, humanized monoclonal antibody "fragments" could be created for use in laboratory exploration and potential therapeutic applications. While commonly referred to as "fragments," these compounds were typically created using recombinant DNA technology that expressed the protein segment of interest, rather than enzymatic digestion of an intact humanized monoclonal antibody. (*See* ALXN2043 at 456; ALXN2044 at 188.)

Samsung Bioepis Exhibit No. 1002
Page 11445

92. For example, genetic engineering could be used to produce an antibody portion known as a "single-chain variable fragment," or "scFv." (ALXN2007 at 107; ALXN2044 at 188-189.) An scFv consists of only the variable domain of a light chain (VL) and the variable domain of a heavy chain (VH), connected by a synthetic peptide "linker" sequence. (ALXN2007 at 107; ALXN2044 at 190.) A "Fab" fragment, containing the complete light chain, but only the VH and CH1 domains from the heavy chain (also known as "Fd"), could also be made by recombinant means. (ALXN2007 at 106; ALXN2044 at 190; ALXN2043 at 456.) Figure 2 below presents the basic structure of an scFv and an Fab, in a simplified two-dimensional diagram.

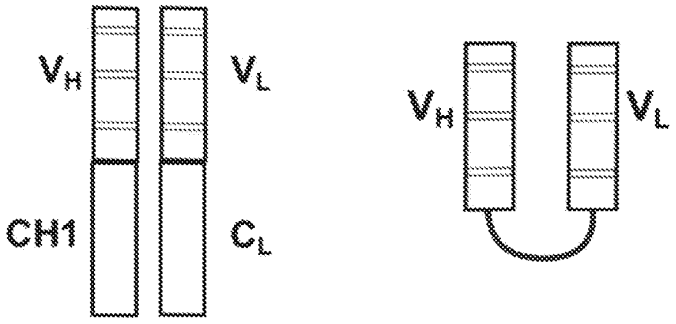


Figure 2: Left: Basic structure of an "Fab" (fragment antigen binding)

Right: Basic structure of an "scFv" (single-chain fragment, variable region)

Samsung Bioepis Exhibit No. 1002
Page 11446

93. A POSA as of March 15, 2007 would have understood that fragments such as scFv and Fab were structurally and functionally very different from a full-length, intact humanized antibody. Structurally, both the scFv and Fab fragments lack the complete, intact heavy chain constant region. For example, a POSA as of March 15, 2007 would have known that full-length, intact IgG antibodies have a prolonged plasma half-life relative to scFv and Fab fragments, due to their larger size and receptor interactions with the "Fc" region that is absent in the fragments. (AMG1023 at 1399; ALXN2044 at 188; ALXN2043 at 456.) A POSA would also have known that the smaller scFv and Fab fragments have more rapid rates of tissue penetration relative to the larger, full-length IgG antibodies. (AMG1023 at 1390; ALXN2007 at 107; ALXN2044 at 189; ALXN2043 at 456.) Further, as discussed in Section VI.D.4 above, a POSA would have understood that the constant regions of full-length antibodies could impact their binding affinity and specificity as well as immunogenicity and could also have other impacts on the immune system.

3. Nomenclature and Naming for Humanized Monoclonal Antibodies

94. A POSA as of March 15, 2007 would have known of various naming conventions for humanized antibodies used at different stages of development. Certain naming conventions used in early stages of development could be used to refer to groups or classes of related antibodies with different primary amino acid

Samsung Bioepis Exhibit No. 1002
Page 11447

sequences, and consequently, different binding affinities, specificities, and potentially different profiles in terms of biologic activity, efficacy and safety. In contrast, a POSA would have understood that, in later stages of development, the use of specific, non-proprietary names and proprietary brand names would indicate the identification and development of a single, unique humanized monoclonal antibody with a single primary amino acid sequence and activity profile.

95. In early stages of humanized antibody design and development, it was a common (but informal) convention to refer to such antibodies by reference to the original mouse hybridoma and mouse antibody from which they were developed. For example, Alexion identified the "5G1.1." hybridoma as producing the "5G1.1" mouse antibody, and often referred to the humanized antibodies and fragments derived from the "5G1.1" antibody as "humanized 5G1.1" or "h5G1.1." (*E.g.*, AMG1007 at 38:43-51; 47:28-32; AMG1023 at 1389, 1391; ALXN2032 at 97:22-99:20.)

96. I agree with Dr. Balthasar's deposition testimony that, without further context, the use of the terms such as "h5G1.1" would leave ambiguity as to exactly what particular antibody or set of antibodies are being referred to. (ALXN2032 at 98:2-99:8, 159:1-10, 202:24-203:14.) In fact, as Dr. Balthasar correctly testified, even the use of additional terminology indicating the isotype of a humanized antibody (*e.g.*, "h5G1.1 HuG4" or "h5G1.1 HuG2/G4") would leave ambiguity as

Samsung Bioepis Exhibit No. 1002
Page 11448

to the exact structure and complete primary amino acid sequence of the antibody. (ALXN2032 at 241:23-242:12.)

97. Likewise, while a POSA would have had a good understanding of the naturally occurring human isotype constant regions (IgG1, IgG4, etc.), the use of terminology such as "IgG2/IgG4" to refer to a non-natural, engineered hybrid of constant region sequences would be unclear, and that terminology would not necessarily specify any one specific constant region structure or sequence.

98. In contrast to the informal naming conventions used by researchers in early development, the international and U.S. naming systems for therapeutic monoclonal antibodies as of March 15, 2007 account for the importance of an antibody's specific amino acid sequence to its activity. A POSA would have understood that, after a specific humanized monoclonal antibody with a single, unique sequence had progressed into clinical development, it may be assigned a "non-proprietary" name by authorities including INN and USAN (*e.g.*, "eculizumab"). (ALXN2045 at 1207; ALXN2046 at 10.) These unique, non-proprietary names were typically assigned around the time of clinical trials or entry into the clinical trial research stage, so that unique names would not be wasted on compounds with no clear potential to becoming a marketed product. (ALXN2045 at 11, 1207 (request should be filed after submission of Investigational New Drug (IND) application); *see also* ALXN2046 at 10.)

Samsung Bioepis Exhibit No. 1002
Page 11449

99. As explained by the 1997 INN Guidelines, "[a]n International Nonproprietary Name (INN) identifies a pharmaceutical substance or active pharmaceutical ingredient by a unique name that is globally recognized and is public property." (ALXN2046 at 1.) The purpose of assigning non-proprietary names to monoclonal antibodies, as for other drugs, is "to provide health professionals with a unique and universally identifiable name to identify each pharmaceutical substance." (ALXN2046 at 1.)

100. Under the non-proprietary naming system that existed in 2007, monoclonal antibodies all received the suffix "-mab," and humanized monoclonal antibodies in particular were given the suffix "-zumab." (ALXN2045 at 1210; ALXN2046 at 27.) Monoclonal antibodies modifying the body's immune response were given the additional naming element "li" before the suffix. (ALXN2045 at 1210; ALXN2046 at 28.) Accordingly, an immunomodulatory humanized monoclonal antibody would end with the suffix "-lizumab," with a unique, arbitrary prefix (*e.g.*, "ecu-"). (ALXN2045 at 1210; ALXN2046 at 27-28.) A POSA would have understood that these INN/USAN names with respect to humanized monoclonal antibodies would refer to one – and only one – specific antibody as defined by its unique primary amino acid sequence. (*See* ALXN2045 at 1210; ALXN2046 at 1.)

101. Accordingly, I agree with Dr. Balthasar's deposition testimony that a POSA as of March 15, 2007 would have understood that the term "eculizumab" referred to a single, unique antibody with a single defined structure and primary amino acid sequence – not a class or genus of antibodies. (ALXN2032 at 10:9-11:17, 98:19-99:8, 100:3-10; *see also* ALXN2045 at 304 (listing "eculizumab").) I disagree, however, with Dr. Balthasar's unsupported position that a POSA prior to March 15, 2007 would have understood that unique "eculizumab" monoclonal antibody to have a hybrid IgG2/IgG4 constant region, or the specific sequence recited in SEQ ID NOS: 2 and 4 of the '149 patent. As I explain in Section VI.D.5 below, the prior art consistently instructed a POSA that the antibody named "eculizumab" was an IgG4 isotype antibody with a different structure and amino acid sequence than the antibody recited in claim 1 of the '149 patent.

102. A POSA as of March 15, 2007 would have further understood that, when a humanized monoclonal antibody is in the very advanced stages of clinical testing and nearing submission for approval by FDA and other regulatory authorities, the research sponsor can select and propose a unique branded trade name (*e.g.*, "SOLIRIS®"). This is an arbitrary name associated with the specific unique antibody, subject to review by regulatory authorities to ensure no confusion with other brand-name products.

Samsung Bioepis Exhibit No. 1002
Page 11451

103. In my opinion, a POSA as of March 15, 2007 would have no doubt that a humanized monoclonal antibody assigned a non-proprietary "-zumab" suffix name (*e.g.*, "eculizumab), tested in Phase III clinical trials, and submitted to the U.S. FDA for approval under a proposed trade name (*e.g.*, "SOLIRIS®"), was a single, unique monoclonal antibody with a single, unique amino acid sequence.

4. Changes to Amino Acid Sequence, Including in the Constant Region, Can Significantly Impact the Binding, Safety, and Efficacy of Therapeutic Antibodies

104. As discussed in Section VI.D.2 above, a POSA as of March 15, 2007 would have understood that designing monoclonal antibodies for human clinical therapy was a complex and unpredictable process. One particular complicating factor was the inability to reasonably predict the in vitro and in vivo properties and effects of an untested monoclonal antibody based only on its primary amino acid sequence. A POSA as of March 15, 2007 would have understood that antibodies are not simply flat, two-dimensional "Y" structures, but are complex, three-dimensional molecules that can be sensitive to changes in primary amino acid sequence – such that even small changes to the amino acid sequence could significantly impact antigen-binding affinity and specificity, and clinical safety and efficacy. (*See, e.g.*, ALXN2015 at 506, 508; ALXN2017 at 961-62.)

105. The classical view was that an antibody's variable regions, and its CDRs in particular, were the determinants of antigen binding, since they contained

Samsung Bioepis Exhibit No. 1002
Page 11452

the amino acid residues that most directly interact with the antigen through non-covalent bonding. (ALXN2013 at 1379; ALXN2009 at 13917.) But well before March 15, 2007, a POSA in the field of the '149 patent would have been attuned to an increasing body of scientific literature showing that antibody binding (including affinity and specificity) could be impacted by amino acid changes outside the CDR regions.

106. For example, a POSA would have known that changes to "framework" amino acids within the variable regions, but outside the CDRs, could have a significant impact on antibody binding. (*See, e.g.*, Foote 1992 at 487; ALXN2052 1995 at 253.) As discussed in Section VI.D.2 above, it was known that the transfer of murine CDRs into human framework regions would often reduce the specificity and affinity of a humanized variable antibody or fragment relative to a parent mouse antibody. (ALXN2035 at 58-60; ALXN2036 at 140-41; ALXN2033 at 19.) For that reason, in the context of designing humanized antibody variable regions, a POSA would have known that amino acid changes might be required to human sequences flanking the mouse-derived CDRs in order to achieve the desired binding properties. (*See* ALXN2035 at 58-60; ALXN2036 at 140-41.)

107. A POSA as of March 15, 2007 also would have known that changes related to the constant regions – whether combining constant region sequences, or

Samsung Bioepis Exhibit No. 1002
Page 11453

portions thereof, with variable region sequences from other antibodies or truncated antibody derivatives (*e.g.*, "fragments" such as Fab or scFv), or switching the type of constant regions used in a full-length antibody – could impact antigen binding and other properties of the original antibody/fragment. For example, a POSA would have understood that "isotype switching" – changing an antibody's constant region sequences while retaining sequences from the variable region – could impact critical properties such as an antibody's specificity and affinity, as well as other properties such as immunogenicity. (*See, e.g.*, ALXN2013 at 1379.) Prior to March 15, 2007, I personally was involved in research on this phenomenon, and published three articles prior to that date discussing my research. (ALXN2013; ALXN2040; ALXN2009.) In addition, there were several observations in the literature dating to the 1990s that the constant regions could affect the properties of the variable regions. Since that date, I have also published reviews discussing my work and the work of other groups establishing the impact of "isotype switching" on antigen binding, including research that was performed and published prior to March 15, 2007. (*See* ALXN2010.)

108. My laboratory's first major publication on this subject was McLean (ALXN2013), published in 2002. In that article, we compared the binding specificity of chimeric antibodies containing the same mouse antibody variable regions but different human constant regions – specifically, IgA, IgG 1/2/3/4, and

Samsung Bioepis Exhibit No. 1002
Page 11454

IgM constant regions. (ALXN2013 at 1379.) We performed a number of *in vitro* experiments to assess the specificity and affinity of the chimeric antibodies compared to the parent mouse antibody, including ELISAs and immunofluorescence and competition experiments. (ALXN2013 at 1380-82.) We observed that each of the chimeric antibodies had different binding characteristics from each other, and the parent murine antibody. (*See* ALXN2013 at 1380-81 (Fig. 1).) In particular, we observed that the chimeric antibodies had differences in "fine specificity" from each other and the parent mouse antibody despite having identical variable region sequences – meaning that the antibodies could still bind the target antigen, but they appeared to bind different epitopes, which can significantly impact their biological activity. (ALXN2013 at 1379, 1383-84.) As we described in our paper, "[g]iven that each [chimeric antibody] type had identical [variable] region sequence, we were surprised to find large differences in binding to [target antigens]." (ALXN2013 at 1379.) We concluded that "[o]ur observations add to the growing body of evidence that in certain circumstances, the [immunoglobulin constant] region can affect the fine specificity of an [antibody] molecule," and, further, that "it is critical that each [chimeric antibody] be carefully tested for specificity to insure the fidelity of the [antibody] engineering process." (ALXN2013 at 1385-86.)

Samsung Bioepis Exhibit No. 1002
Page 11455

109. Our findings in McClean were significant because they contributed to a growing body of work describing the impact of changes to antibody constant regions, including isotype-switching, on antibody binding. Prior to McClean, there were already a number of studies reporting that the constant regions could influence antibody binding. For example, in 1995, Greenspan and Cooper published an article describing how IgG3 monoclonal antibodies had been observed to more effectively bind target antigens than IgG1 and IgG2b monoclonal antibodies or IgG3-derived Fab fragments with the same variable sequences. (ALXN2014 at 227.) As stated in Greenspan, "[t]hus, it was established that differences in the heavy chain constant (CH) domains, and in the Fc region in particular, substantially influence the apparent functional affinities (avidities) of these IgG mAbs." (ALXN2014 at 227.)

110. In 1996, Pritsch et al. published a study comparing the binding activity of two antibodies with identical variable regions sequences and either the IgG or IgA isotype. The authors found that, "in spite of sharing identical variable domain sequences, having identical light chain constant domains and recognizing overlapping epitopes on the [antigen], both [antibodies] significantly differed" in their affinity for the target antigen. (ALXN2011 at 2239.) The authors concluded that "changes in the [constant heavy] domains can affect the functional affinity and specificity of [antibodies], through a complex mechanism involving [antibody]

Samsung Bioepis Exhibit No. 1002
Page 11456

flexibility and cooperative interactions in the case of [antibodies] bound to multivalent [antigens]." (ALXN2011 at 2242.)

111. A POSA would also have been aware of McCloskey (ALXN2008), also published in 1996. McCloskey taught that, despite having the same variable region sequences, "human antibodies of different IgG subclasses which bind the same antigen have been shown to differ in functional affinity." (ALXN2008 at 169.) The McCloskey publication used surface plasmon resonance (BIAcore) to assess the affinity and binding kinetics of chimeric antibodies made using the same mouse variable region sequences, but combined with different human IgG constant regions. (ALXN2008 at 169.) As illustrated by, *e.g.*, Figure 1, the authors found that each IgG subclass had different antibody binding characteristics. (ALXN2008 at 170-71.) The authors also found that, for IgG2 and IgG4, there was "a significant difference in the [binding] pattern obtained" with the full-length antibodies as compared to antibody fragments. (ALXN2008 at 171.) The authors concluded that, "[e]ngineered antibodies may differ in their functional affinity and hence in their function, depending upon their subclass. Such consideration may be of importance when considering the choice of antibodies for therapeutic use." (ALXN2008 at 172.)

112. Following McClean, in 2005 and 2007, my laboratory published additional studies on the impact of the constant regions on antibody binding and

Samsung Bioepis Exhibit No. 1002
Page 11457

specificity (ALXN2040; ALXN2009; ALXN2039), which I also co-authored. In all of these papers, we observed that changes to the constant region could affect antibody binding and specificity. (ALXN 2040 at 2132-33, 2135-38, 2140-41 (differences in fine specificity observed in two families of mouse isotype switch variants); ALXN2009 at 13917-18, 13924 (differences in antibody-antigen interactions observed in variable region identical mouse antibody isotype switch variants); ALXN2039 at 1310-11 (mouse antibody and mouse-human chimeric with identical variable regions had different binding affinity).) In our 2005 study, we concluded that "[f]rom a practical perspective, the findings that isotype can influence the fine specificity should be an important consideration in the development of genetically engineered [antibodies] for therapeutic use because it is conceivable that humanization techniques or the synthesis of mouse-human chimeric Abs can alter the fine specificity of the original [antibody]." We also observed that antibodies with the same variable regions – but different constant regions – could exhibit polyreactive characteristics (*i.e.*, could bind multiple antigens), and that this could have implications for self-reactivity. (ALXN2009 at 13924-25; ALXN2039 at 1310 ("[Observed polyreactivity] implies that mouse-human [chimeric antibody] construction may yield [immunoglobulins] with binding characteristics that are different from the parental murine mAb, including the possibility for unexpected self-reactivity.").)

Samsung Bioepis Exhibit No. 1002
Page 11458

113. Based on publications such as these, by March 15, 2007, a POSA would have understood that the constant regions of an antibody can have an impact on antibody binding. Mechanistically, a POSA would have been aware of publications describing how changes to the "CH1" and "hinge" portions of the heavy chain constant region could impact antibody binding, suggesting that these regions in particular modulated the antibody-antigen interaction. (ALXN2012 at 3388; ALXN2009 at 13924.) For example, in 2000, in a follow-on study to their 1996 publication, Pritsch et al. assessed the impact of heavy chain regions on the antibody-antigen interaction, and concluded that their results provided "definitive evidence" both that "isotype can influence binding affinity to antigen" and that the CH1 domain can play an important role in the antigen-antibody interaction." (ALXN2012 at 3387-88.) In one of our 2007 studies, in which we used surface plasmon resonance (BIAcore) to further assess the impact of the constant heavy chain region on antibody binding, my group similarly concluded it was likely that "structural differences in the CH1 domain are responsible for the differences in affinity constants and, consequently, for variations in [antigen] binding." (ALXN2012 at 13924.)

114. More recently, in 2016, I co-authored a review article, Janda, summarizing the work of various groups related to the impact of the constant regions on antibody binding, including work that was published prior to March 15,

Samsung Bioepis Exhibit No. 1002
Page 11459

2007. As described in Janda, by the first decade of the twenty-first century, at least eight different groups had independently described changes to antibody specificity resulting from isotype-switching despite the conservation of variable region sequences. (ALXN2010 at 3-4.) These publications, including some of the studies I discussed above, were based on experiments involving a variety of techniques, including ELISA, ITC, and surface plasmon resonance (BIAcore). (ALXN2010 at 3-4.) Based on the growing number of publications showing differences in antibody binding following isotype-switching, by March 15, 2007, a POSA would have been aware that changes to the constant region sequences of an antibody could impact antibody binding, even when leaving variable regions untouched.

115. In addition to potentially affecting binding, by March 15, 2007, a POSA would have understood that switching to a uniquely-engineered, non-naturally occurring (*i.e.*, "foreign") heavy chain constant region, such as a hybrid sequence constructed from portions of the IgG2 and IgG4 heavy chains, could also raise heightened immunogenicity concerns since it could have perceived by the immune system as antigenically "foreign." In particular, a POSA would have known that administering an antibody with a "foreign" heavy chain isotype to human patients could potentially result in harmful immunogenic reactions. (*See, e.g.*, ALXN2015 at 508 (describing how single amino acid substitution in an antibody drastically impacted how other antibodies ("anti-idiotype" antibodies)

Samsung Bioepis Exhibit No. 1002
Page 11460

would bind to it); ALXN2036 at 141 ("[I]mmunogenicity is a complex issue; intrinsic factors such as protein sequence and structure are likely to be as important as extrinsic ones"); ALXN2037 at 1343-44; ALXN2038 at 624-26.)

116. Because of the unpredictability and complexity inherent in antibody design, a POSA as March 15, 2007 would not have been able to reasonably extrapolate the in vitro or clinical properties of one monoclonal antibody with a unique amino acid sequence to a different antibody with a different sequence. A POSA would have understood that a monoclonal antibody's specific amino acid sequence was critical to its function, and that even small changes in an antibody's sequence could potentially affect its binding affinity and specificity, and thus, its safety and efficacy in humans.[3] (*See, e.g.*, ALXN2010 at 3; ALXN2011 at 2240-42; ALXN2008 at 171-72; ALXN2012 at 3391-92; ALXN2013 at 1384-86; ALXN2009 at 13924-26.)

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[3] Furthermore, a POSA could not reliably predict that a hybrid IgG2/IgG4 would be expressed efficiently in cells in sufficient quantities for therapeutic antibody production since it was known that even point mutations in the constant region affected antibody secretion and here was an antibody with a very different and unnatural constant region. (ALXN2047 McClean 2005 at 1111-12, 1117-18.)

117. In sum, as of March 15, 2007, a POSA would have known that antibody affinity and specificity could be substantially influenced even by sequence changes outside of the antigen-binding site, including changes in the heavy chain constant region. (*See, e.g.*, ALXN2013 at 1379; ALXN2014 at 226-27; ALXN2011 at 2239; ALXN2008 at 169; ALXN2012 at 3388; ALXN2009 at 13924; ALXN2010 at 3-4.) A POSA would have understood that such sequence changes could potentially result in harmful immune reactions following human administration, and that the immune consequences could not be reasonably predicted without human clinical testing. (*See, e.g.*, ALXN2015 at 508; ALXN2036 at 141 ("[I]mmunogenicity is a complex issue; intrinsic factors such as protein sequence and structure are likely to be as important as extrinsic ones"); ALXN2038 at 624-26.)

5. A POSA as of March 15, 2007 Would Have Understood "Eculizumab" To Be an IgG4-Isotype Humanized Antibody

118. In my opinion, a POSA as of March 15, 2007 would have understood that "eculizumab" was a single, unique humanized monoclonal antibody developed by Alexion, having a single, unique structure and primary amino acid sequence. I have reviewed the deposition transcript of Dr. Balthasar, and understand that he agrees with me fully on this point. (ALXN2032 at 10:9-11:17, 98:19-99:8, 100:3-10.)

Samsung Bioepis Exhibit No. 1002
Page 11462

119. I also have reviewed the Board's Institution Decision, which contained the statement that "'eculizumab' referred to and refers to a class or category of anti-C5 antibodies, also called 5G1.1 or h5G1.1 mAbs." (Paper No. 15 at 21-22.) I respectfully disagree with the Board on this point, and I understand Dr. Balthasar does as well.

120. While it is correct that, as I explain in Section VI.D.3 above, a POSA would have understood that the terms "5G1.1" or "h5G1.1" could potentially refer to multiple different antibody structures (when not further limited or clarified by additional context), a POSA as of March 15, 2007 would have understood that the term "eculizumab" was a non-proprietary name referring to one unique antibody with a unique structure and primary amino acid sequence. And, for the reasons explained below, a POSA would have understood that structure and sequence to be consistent with the intact humanized IgG4 isotype monoclonal antibody described in Thomas (AMG1023).

121. By March 15, 2007, a POSA would have understood that "eculizumab" was at a very late stage of development, with Alexion having published results of Phase II and Phase III human clinical trials showing that "eculizumab" was safe and effective for the treatment of PNH. (*See, e.g.*, AMG1012 at 1239, 1241-1242; AMG1004 at 552, 558; AMG1047 at 2559, 2564; AMG1005 at ¶¶ [0081-0096].) A POSA would have further known that, as of

Samsung Bioepis Exhibit No. 1002
Page 11463

September 2006, Alexion had applied for marketing approval of "eculizumab" from the U.S. FDA and European authorities based on the results of those human clinical trials, and had proposed the trade name "SOLIRIS®" for marketing the product following a future approval. (ALXN2054; ALXN2055; *see also* AMG1012 at 1239.) A POSA would have had no doubt that "eculizumab" and "SOLIRIS®," at that very late stage of development, was limited to a single humanized monoclonal antibody with a single structure and primary amino acid sequence.

122. If a POSA as of March 15, 2007 were to inquire further as to the specific structure of "eculizumab," they could have reached only one conclusion after considering the full scope of the literature: that "eculizumab" was an intact, humanized monoclonal antibody with the humanized variable region and IgG4 isotype constant region as described in Thomas (AMG1023). That is because, as illustrated in Table 1 below, the literature concerning "eculizumab" and its clinical properties consistently and uniformly cited to Thomas (AMG1023) for the identify of "eculizumab." The only reasonable conclusion in view of the pre-March 15,

Samsung Bioepis Exhibit No. 1002
Page 11464

2007 literature's repeated reference to Thomas for the description of "eculizumab" was that Thomas in fact described "eculizumab."[4]

Table 1: References to "Eculizumab" as Thomas's Humanized IgG4 Antibody

Exhibit	Statement Identifying "Eculizumab" as the IgG4 Humanized Antibody of Thomas
Hillmen 2004 (AMG1004) at 553, reporting on a Phase II clinical trial for PNH, and citing Thomas, Ref. No. 15	"Eculizumab is a recombinant humanized monoclonal antibody that was designed to block the activation of terminal complement components.[14, 15] It binds specifically to the terminal complement protein C5, inhibiting its cleavage into C5a and C5b. . . ."

[4] A POSA would not have understood these references as citing Thomas only for a general discussion of the "humanization" of "5G1.1," as Dr. Balthasar appeared to suggest at his deposition. (*See* ALXN2032 at 82:10-83:1, 86:6-23.) The references I discuss above cite Thomas for what "eculizumab" *is*, which a POSA would have understood as referring to a specific structure. And Dr. Balthasar does not dispute that Thomas disclosed a full-length, intact, IgG4 isotype humanized antibody derived from the "5G1.1" mouse antibody. (*See* AMG1002 at ¶ 47; ALXN2032 at 242:21-243:4.)

Samsung Bioepis Exhibit No. 1002
Page 11465

Exhibit	Statement Identifying "Eculizumab" as the IgG4 Humanized Antibody of Thomas
Hill 2005 (AMG1047) at 2559, reporting on a Phase II clinical trial for PNH, and citing Thomas, Ref. No. 9	Eculizumab is a humanized monoclonal antibody that specifically targets the complement protein C5 and prevents its cleavage.[9]"
Hillmen 2006 (AMG1012) at 1234, reporting on a pivotal Phase III clinical trial for PNH, and citing Thomas, Ref. No. 13	Eculizumab (Soliris, Alexion Pharmaceuticals) is a humanized monoclonal antibody directed against the terminal complement protein C5."[13]
Hill 2007 (ALXN2028) at 31, reporting on successful treatment of PNH in a patient with aplastic anemia and citing Thomas, Ref No. 6	"Eculizumab is a novel humanized monoclonal antibody directed against the complement protein C5.[6]"
Bell (AMG1005) at [0052], in a patent application describing results of Phase II clinical trials for PNH, citing Thomas	"Methods for the preparation of h5G1.1-mAb, h5G1.1-scFv and other functional fragments of h5G1.1 are described in U.S. Pat. No. 6,355,245 and [Thomas], the disclosures of which are incorporated herein in their entirety by this reference. The antibody h5G1.1-mAb is currently undergoing clinical trials under the tradename eculizumab."

Samsung Bioepis Exhibit No. 1002
Page 11466

Exhibit	Statement Identifying "Eculizumab" as the IgG4 Humanized Antibody of Thomas
Kaplan (AMG1021) at 1018, in a review article discussing development of "eculizumab," citing Thomas, Ref. No. [258884]	"Humanized 5G1.1, Fab and scFv molecules were produced by grafting the complementary determining regions of 5G1.1 on to human framework regions [258884]."
Brekke (AMG1019) at 56, in a review article discussing development of therapeutic antibodies, citing Kaplan (AMG1021), Ref. No. 31, which in turn cites to Thomas	"Eculizumab (5G1.1; Alexion Pharmaceuticals) is a humanized monoclonal antibody that prevents the cleavage of human complement component C5 into its pro-inflammatory components[31], ..."

Exhibit	Statement Identifying "Eculizumab" as the IgG4 Humanized Antibody of Thomas
Pierangeli (AMG1020) at 2123, in a journal article studying mechanisms for a complement-mediated disease, citing Hillmen 2004 (AMG1004), Ref. No. 18, which in turn cites to Thomas	Eculizumab (5G1.1), the humanized anti-C5 mAb, is considered a potential treatment for several chronic inflammatory diseases . . . [E]culizumab has been shown to prevent C5 activation in humans and to have beneficial effects in patients with [PNH]; specifically, it reduces intravascular hemolysis, hemoglobinuria, and the need for transfusion in these patients, providing a proof-of-concept that blockade of complement activation is feasible and tolerable in patients with chronic disease (18)."

123. Thomas, in turn, describes Alexion's design and testing of a full-length, IgG4-isotype humanized antibody ("humanized 5G1.1") with anti-C5 affinity, specificity, and complement-blocking activity comparable to the original mouse "5G1.1" antibody. (AMG1023 at 1389.) First, Thomas describes the humanization of variable region sequences from a mouse anti-C5 monoclonal antibody "5G1.1." (AMG1023 at 1393-94.) Next, the humanized variable region sequences were used to produce antibody fragments (*i.e.*, recombinant Fab and scFv), which were assessed for binding to human C5 and the ability to inhibit complement. (AMG1023 at 1394-95.) Finally, Thomas described the production

of "an intact humanized antibody (IgG4 isotype)," which was shown to bind C5 with similar affinity to the original "5G1.1" mouse antibody, and to inhibit complement activity in an in vitro hemolysis assay with equal potency to the mouse "5G1.1" antibody. (AMG1023 at 1396, 1399.) The researchers explained how they specifically selected the human IgG4 isotype because it "does not activate human complement," and expressed their view that it was "likely to be minimally immunogenic in patients." (AMG1023 at 1399.)

124. Unlike Thomas and the following literature regarding "eculizumab," a POSA would not have understood that Evans (AMG1007) disclosed "eculizumab." A POSA instead would have understood Evans to describe some of the early stage research leading to the later development of the antibody identified as "eculizumab" as described in Thomas. As Dr. Balthasar testified, and I agree, a POSA would have seen that Evans does not ever use the term "eculizumab," and does not teach any full-length humanized antibodies. (ALXN2032 at 199:15-17, 163:5-15.)

125. Initially, in Example 7, Evans describes the generation of a "hybridoma designated as 5G1.1," producing a mouse antibody referred to throughout Evans as "the 5G1.1 antibody" or "the 5G1.1 mAb." (AMG1007 at 37:34-39:30; ALXN2032 at 165:11-21.) Evans also describes experiments to characterize the properties of the "5G1.1" antibody, including assays to assess its

Samsung Bioepis Exhibit No. 1002
Page 11469

C5 binding and ability to inhibit complement by blocking C5 cleavage. (AMG1007 at 38:43-51, 39:62-40:19; ALXN2032 at 38:43-39:16; 39:62-40:29.) In Example 10, Evans describes experiments to determine the amino acid sequence of "the 5G1.1 mAb" and copy (or "clone") the DNA sequences for its heavy and light chain variable regions. (AMG1007 at 40:32-42:54; ALXN2032 at 169:19-23.)

126. As Dr. Balthasar agreed during deposition, Evans does not teach any full-length antibodies other than the mouse "5G1.1" monoclonal antibody described in Examples 7 through 10. (ALXN2032 at 169:13-18.) In Example 11, Evans only describes the development of mouse and humanized "fragments" by recombinant DNA means, including (1) "Fab" molecules comprised of light chains and "Fd" sequences (the heavy chain portion of an Fab, consisting of VH and CH1 only, *see* AMG1007 at 43:21-61, SEQ ID NOs: 10-12, 16); and (2) "scFv" molecules (variable domain of a heavy chain connected by a synthetic linker to the variable domain of a light chain). (AMG1007, Example 11; ALXN2032 at 169:13-18.) As Dr. Balthasar admitted, these "fragments" were never part of, or extracted from, any full-length antibody, but rather were cloned and produced directly by recombinant means. (ALXN2032 at 163:5-15, 228:4-16.)

Samsung Bioepis Exhibit No. 1002
Page 11470

127. Figure 3 below illustrates (1) the structures that a POSA as of March 15, 2007 would see when reading Evans – the mouse antibody "5G1.1" and humanized recombinant "fragments" with no intact heavy chain constant region, and (2) what a POSA reading Evans would ***not*** have seen – a full-length, humanized monoclonal antibody.

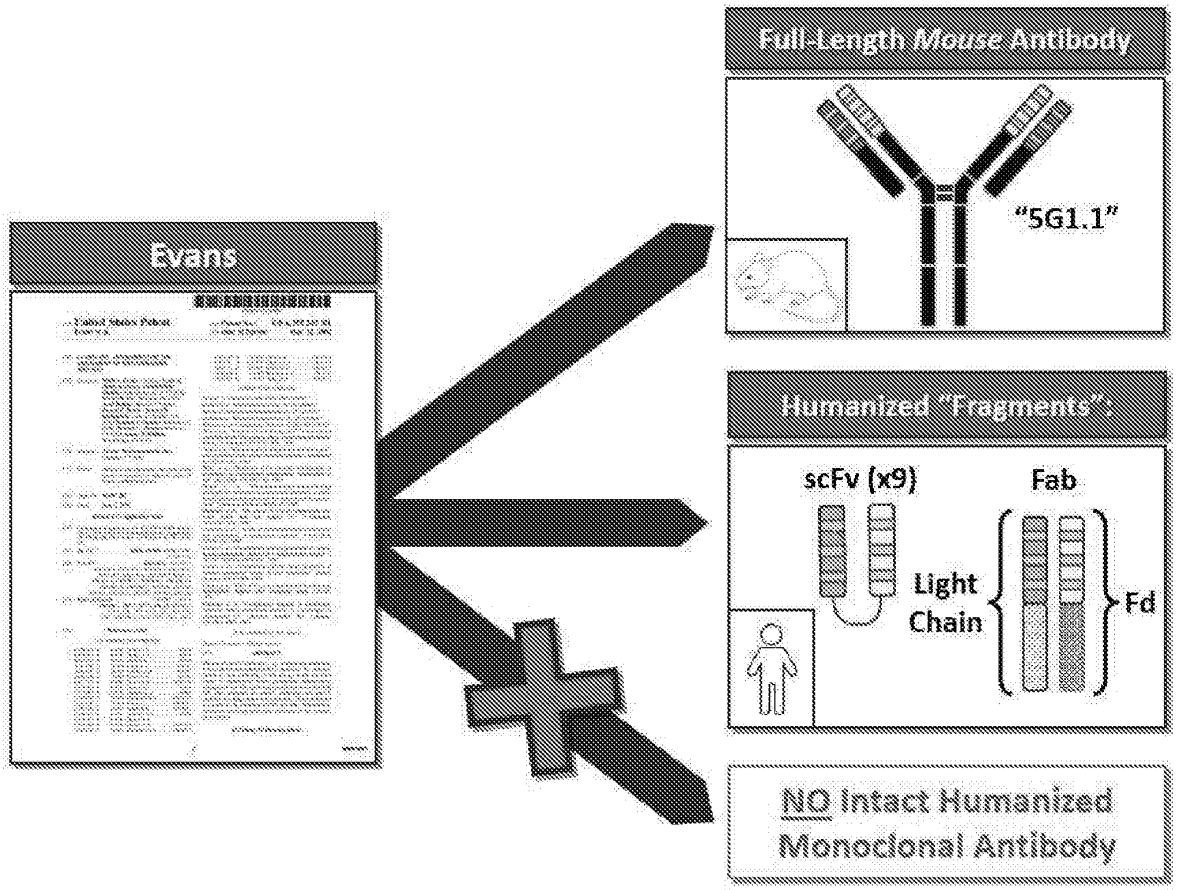


Figure 3: A POSA's understanding of structures disclosed in Evans (AMG1007)

128. Accordingly, I disagree with Dr. Balthasar's Figures 10, 11, 12, 14, 15, and 16 of his Declaration that depict the humanized scFvs of Evans as variable

regions on a full-length, intact, bivalent "Y" antibody structure. (AMG1002 at 42, 60, 62, 72, 81, and 84.) Among other things, by including an image of the full heavy chain regions in his depiction of the disclosure of Evans, Dr. Balthasar's figures suggest that Evans disclosed a full-length humanized monoclonal antibody derived from the original "5G1.1" mouse antibody, when in fact the mouse antibody was the ***only*** full-length antibody that Evans described.

129. I also note that, while Dr. Balthasar has selected one of the scFv sequences from Evans that he says aligns "perfectly" with variable region sequences from SEQ ID NOs: 2 and 4 of the '149 patent (*see* AMG1002 ¶ 55, Figs. 6 and 7), that is only because he used his hindsight knowledge of the sequences disclosed in the '149 patent to identify that alignment. A POSA without hindsight might have instead looked to the humanized Fab sequences of Evans, which are disclosed in Evans as light chain and "Fd" sequences. (SEQ ID NOs: 11 and 12, AMG1007 at 43:22-34 and Certificate of Correction at 21-24.) A POSA would have understood that an Fab was a more "complete" structure as compared to an scFv, since a humanized Fab contains both humanized variable regions and CH1 and CL human constant regions. And as the following Figures 5 and 6 demonstrate, the sequence of the Fab fragments in Evans would not have guided a POSA toward the specific amino acid sequence claimed in the '149 patent, because

in particular, there are significant differences between Evans's "Fd" sequences (the heavy chain portion of an Fab) and the claimed sequence of the '149 patent:

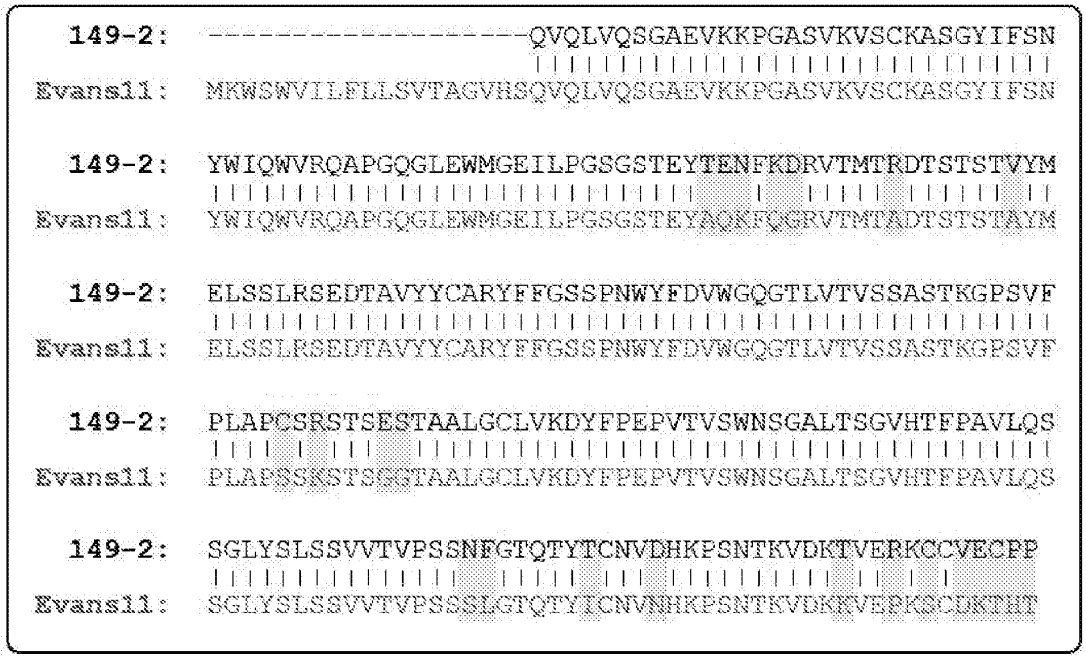


Figure 4: '149 patent SEQ ID No. 2 compared with Evans SEQ ID No. 11

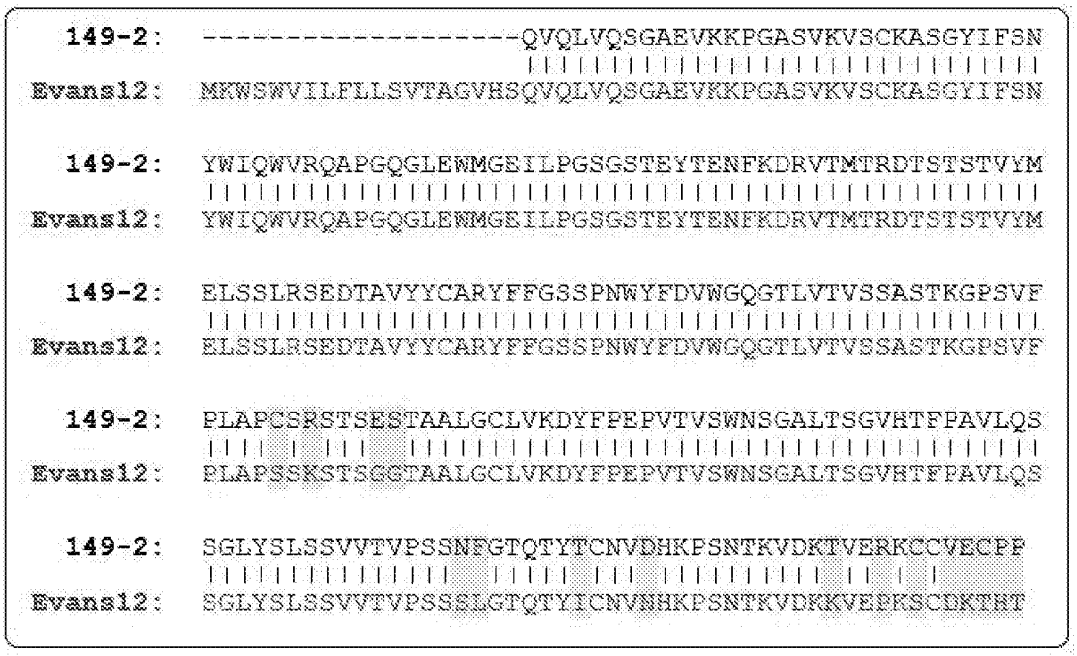


Figure 5: '149 patent SEQ ID No. 2 compared with Evans SEQ ID No. 12

130. This would have been consistent with a POSA's understanding of Evans as describing an early stage of research, prior to the selection of the final, IgG4 isotype, described in clinical study publications.

131. I disagree with Dr. Balthasar's opinions suggesting that a POSA would have had any reason to look to Bowdish (AMG1006) or Mueller (AMG1008) for the structure or sequence of "eculizumab." As Dr. Balthasar admitted at deposition, neither Bowdish nor Mueller mention "eculizumab," and none of the references prior to March 15, 2007 describing "eculizumab" and its clinical properties cite to Bowdish or Mueller for a description of "eculizumab." (ALXN2032 at 199:9-12, 102:10-19.) Further, neither Bowdish nor Mueller

disclose any in vitro or in vivo data suggesting that an antibody with a structure different from the IgG4-isotype antibody of Thomas would be effective in binding C5, blocking its cleavage, and safety and effectively treating patients with conditions such as PNH.

132. As of March 15, 2007, references relating to anti-C5 binding and clinical trial publications relating to PNH cited either Thomas, teaching an IgG4 isotype antibody, or Evans, which does not provide clear guidance as to isotype for a therapeutically effective antibody. Based on the art as a whole, as of that date, a POSA would have understood "eculizumab" to be an IgG4 antibody.

E. The Novel, Uniquely-Engineered Amino Acid Sequence of SOLIRIS® Was Not Known to a POSA as of March 15, 2007

133. Currently, but not prior to March 15, 2007, it is known that Alexion's SOLIRIS® utilizes a uniquely engineered, non-naturally occurring heavy chain constant region corresponding to SEQ ID NO: 2 of the '149 patent. I understand that SOLIRIS® was the first antibody with a heavy chain of its kind (containing a hybrid of sequences from both IgG2 and IgG4 constant regions) to be clinically tested in humans, and that Alexion was the first to show that such an antibody could be safe and effective when administered to human patients. (AMG1033 at 1257-58.) I also understand that SOLIRIS® was the first FDA-approved product containing Alexion's uniquely-engineered heavy chain constant region.

Samsung Bioepis Exhibit No. 1002
Page 11475

134. ***Prior*** to March 15, 2007, however, a POSA would not have been aware of any published clinical testing showing the safety or efficacy in humans of an antibody with the uniquely engineered heavy chain constant region known today to be used SOLIRIS®. Rather, POSA as of March 15, 2007 would have understood "eculizumab" to be an antibody with an ***IgG4*** constant region as described in Thomas (*see* Section VI.D.5 above), and would have attributed the safety and efficacy shown in Phase II and Phase III clinical trials (*e.g.* AMG1004, AMG1047, AMG1012, AMG1005) to that IgG4 antibody.

135. Accordingly, from the perspective of a POSA as of March 15, 2007, a humanized derivative of the "5G1.1" antibody with a hybrid IgG2/IgG4 constant region was an unstudied, uncharacterized entity with no known or characterized C5 binding, no known ability to block C5 cleavage, and no evidence that it was therapeutically useful to treat PNH or any other condition, or even suitable for administration to human patients.[5]

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[5] I understand Dr. Balthasar argues that a POSA nonetheless would have been motivated to construct a "humanized 5G1.1" antibody using a hybrid "IgG2/IgG4" constant region, in view of literature at the time that speculated about the potential benefits of such a constant region. (AMG1002 at ¶¶ 22, 46 (citing AMG1031, AMG1032).) As I explain below, a POSA would have

136. The structure of the active molecule in SOLIRIS® that is claimed in the '149 patent and is known today – but was not known before March 15, 2007 – is shown below in comparison to the IgG4 isotype antibody described in Thomas. Unlike the IgG4 antibody of Thomas, the claimed antibody uses the CH1 and "hinge" regions of IgG2, thereby providing a very different antibody than that identified in the literature citing to Thomas.

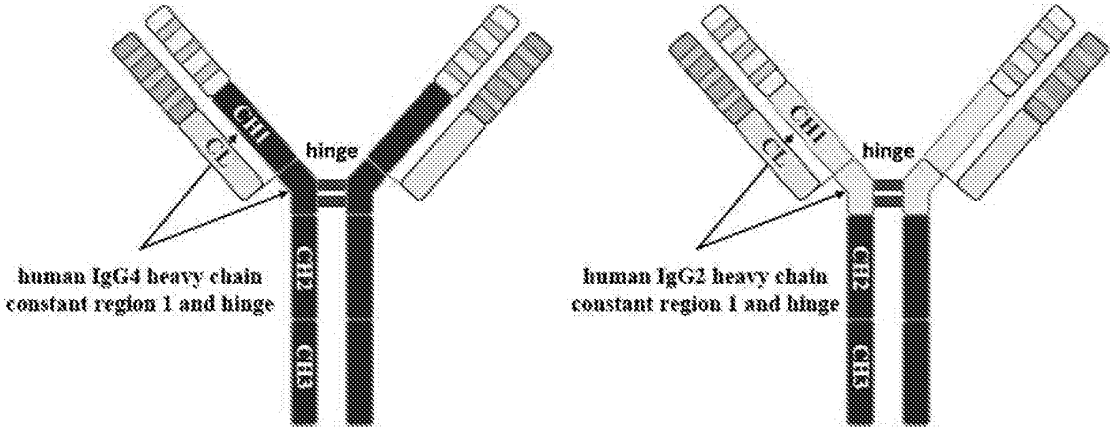


Figure 6: Left – Structure of the IgG4 isotype antibody referenced to as "eculizumab" in the literature as of March 15, 2007

Right – Structure of SOLIRIS®, having a non-naturally occurring, protein-engineered isotype

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viewed such statements as speculation based solely on *in vitro* data, and would not have reasonably expected that such a constant region that had never been clinically tested, let alone commercialized, would result in a product suitable and useful for human administration.

Samsung Bioepis Exhibit No. 1002
Page 11477

VII. OPINIONS

A. Dr. Balthasar's Opinions Misread the Prior Art and Rely on Hindsight Analysis

137. I have considered Dr. Balthasar's Declaration in this proceeding, dated February 27, 2019. I disagree with a number of Dr. Balthasar's conclusions, which I believe overstate the teachings in the prior art and reflect a narrative created with significant hindsight bias.

1. A POSA Before March 15, 2007 Would Not Have Understood "Eculizumab" To Contain the Uniquely-Engineered Heavy Chain Constant Region Reflected in SEQ ID NO: 2 of the '149 Patent

138. I disagree with Dr. Balthasar's statement that, as of March 15, 2007, "[a] POSA would have been aware that eculizumab was a humanized anti-C5 monoclonal antibody (h5G1.1) containing a hybrid IgG2/IgG4 constant region . . . ." (AMG1002 at ¶ 42.) Taken as a whole, the prior art that described what "eculizumab is" did not disclose an antibody with such a structure; and to the extent the prior art described antibodies with such a structure (*e.g.*, for use as "isotype control" antibodies), a POSA would not have understood such antibodies to be "eculizumab," or to have any of the properties attributed to "eculizumab" in the clinical literature. To the contrary, the prior art repeatedly would have told a POSA as of March 15, 2007 that "eculizumab" contained an IgG4 isotype, as indicated by Thomas and following publications. *See* Section VI.D.5 above.

Samsung Bioepis Exhibit No. 1002
Page 11478

139. I understand from Dr. Balthasar's deposition testimony that he admits key facts contrary to his position regarding the POSA's understanding of "eculizumab" as of March 15, 2007. For example, Dr. Balthasar agreed that:

- Hillmen '04 (AMG1004), Hill '05 (AMG1047), and Hillmen '06 (AMG1012) all cite to Thomas in statements identifying what "eculizumab" is. (ALXN2032 at 125:13-126:9; 128:20-129:10; 129:13-22.)
- Bell (AMG1005) cites to Thomas and Evans (AMG1007) for "[m]ethods for the preparation of h5G1.1-mAb [identified in Bell as "eculizumab"], h5G1.1-scFv, and other functional fragments" – but only Thomas describes a full-length, intact humanized antibody. (ALXN2032 at 160:18-162:12 (quoting AMG1005 ¶ 52) (quotation marks omitted.).)
- A POSA would have understood that Thomas's IgG4 antibody is different in structure and sequence from a hybrid IgG2/G4 antibody. (ALXN2032 at 97:7-21.)

140. Dr. Balthasar ignores these clear teachings towards Thomas's IgG4 antibody from the clinical literature regarding "eculizumab," and instead relies on a single sentence taken out of context from a single publication, Tacken (AMG1034), to support his conclusion that a POSA as of March 15, 2007 would

Samsung Bioepis Exhibit No. 1002
Page 11479

have understood "eculizumab" to be a hybrid IgG2/IgG4 antibody. (*See* AMG1002 at ¶¶ 44-45 (citing AMG1034 at 1279.) At his deposition, I understand that Dr. Balthasar admitted that Tacken (AMG1034) was the only document that he relies on dated prior to March 15, 2007 that he contends associates "eculizumab" with an IgG2/IgG4 constant region. (ALXN2032 at 104:6-20.)

141. Specifically, Dr. Balthasar relies on the following statement from Tacken, which ends with a citation to Thomas (footnote 19).

> An isotype control antibody, h5G1.1-mAb (5G1.1, eculizamab [sic]; Alexion Pharmaceuticals) containing the same IgG2/IgG4 constant region, is specific for the human terminal complement protein C5.[19]

(AMG1034 at 1279, 1285; ALXN2032 at 78:10-15.)

142. In view of the language of the statement itself, and all the literature available to a POSA as of March 15, 2007, including the many clinical references identifying "eculizumab" as the IgG4 antibody of Thomas, a POSA would not have read this statement in Tacken as teaching that "eculizumab" had a hybrid IgG2/IgG4 isotype. As discussed above in Section VI.D.3, a POSA would have understood that the term "eculizumab" could refer to only one single antibody with a distinct structure and primary amino acid sequence – and this one isolated statement in Tacken regarding an "isotype control antibody" was at most

Samsung Bioepis Exhibit No. 1002
Page 11480

ambiguous and far outweighed by the repeated, consistent references in the New England Journal of Medicine and other prominent publications identifying eculizumab as Thomas's IgG4 antibody.

143. First, in my opinion, a POSA would have seen that the language in the cited sentence does not unambiguously state that the IgG2/IgG4 "isotype control antibody" used in Tacken is "eculizumab." The cited sentence vaguely refers to both "h5G1.1-mAb," which could refer to a class of humanized antibodies, and "5G1.1," which could refer to multiple antibodies or antibody fragments, including the original mouse 5G1.1 antibody. *(See, e.g.*, ALXN2032 at 98:22-99:8, 100:16-24, 165:5-21; 169:6-18; 202:24-203:16.) Moreover, by citing to Thomas, which describes an IgG4 isotype antibody that the other prior art consistently identified as "eculizumab," this sentence at most would be confusing to a POSA. One possible reading could be that Thomas's antibody was "eculizumab" while Tacken's IgG2/G4 "isotype control" antibody was a different derivative; and another possible interpretation is that Tacken referred to the IgG2/IgG4 "isotype control" antibody as "eculizumab" by mistake (just as it misspelled "eculizamab" [sic]). Either way, a POSA would not have understood Tacken as teaching that "eculizumab" had an IgG2/IgG4 because Tacken does not clearly state what eculizumab is. Moreover, Dr. Balthasar has not explained why a POSA would have credited this isolated, ambiguous statement regarding an "isotype control

Samsung Bioepis Exhibit No. 1002
Page 11481

antibody" in Tacken, while disregarding the numerous clear statements in the key publications regarding "eculizumab" that identify it as the IgG4 antibody of Thomas.

144. In contrast to the multiple publications referencing Thomas, Tacken contains no assessment of the clinical safety or efficacy of eculizumab, but instead is directed to unrelated subject matter – use of a different antibody, "hD1," to increase vaccine efficacy by targeting antigens to dendritic cells. (*See* AMG1034 at 1278.) Tacken provides neither C5 binding data, nor sequence information, for its isotype control antibody, instead citing to Thomas to support the sentence cited by Dr. Balthasar. (AMG1034 at 1278.) This would have suggested to a POSA that the "eculizumab" referred to was not Tacken's isotype control antibody, but rather the IgG4 antibody described in Thomas.

145. I also disagree with Dr. Balthasar's opinion that Tacken would have indicated to a POSA that Alexion had moved on from the IgG4 isotype antibody of Thomas as its clinical candidate and replaced it with an antibody containing a hybrid IgG2/IgG4 constant region. In particular, references published after Tacken continued to cite Thomas for the structure of "eculizumab." For example, Hillmen 2006 (AMG1012), a September 2006 publication by Alexion in the New England Journal of Medicine, describes a successful Phase III trial of "eculizumab" in

Samsung Bioepis Exhibit No. 1002
Page 11482

treating PNH and unambiguously references Thomas in defining what "eculizumab" is, stating:

> Eculizumab (Soliris, Alexion Pharmaceuticals) ***is*** a humanized monoclonal antibody directed against the terminal complement protein C5.[(13)]

(AMG1012 at 1234, 1243 (citing Thomas (AMG1023), Ref. No. 13)[6]; *see also* ALXN2032 at 116:16-117:1.) Hill '05 (AMG1047), a one-year extension study of the 11-patient study reported in Hillmen '04 (AMG1004), was notably published two months after Tacken, in the same journal as Tacken (Blood), and like Hillmen '06, identified "eculizumab" as the IgG4 antibody of Thomas. (AMG1047 at 2559, Ref. No. 9; ALXN2032 at 113:14-21, 114:19-115:10.) Bell, published a month after Tacken, and Hill '07, a case report published on March 1, 2007, likewise both identify "eculizumab" as the IgG4 antibody of Thomas. (AMG1005 at ¶ [0052]; ALXN2028 at 31, Ref. No. 6.) These later references would have confirmed to a POSA prior to March 15, 2007 that Tacken did not represent any change in the identify of "eculizumab," which, from the perspective of a POSA, remained the IgG4 antibody structure described in Thomas.

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[6] Unless otherwise noted all emphasis is added.

Samsung Bioepis Exhibit No. 1002
Page 11483

146. Given Tacken's unrelated subject matter, and only limited and ambiguous reference to "eculizumab," a POSA would not have read Tacken as identifying an IgG2/IgG4 isotype for "eculizumab." Rather, as of March 15, 2007, a POSA would have understood "eculizumab" to have an IgG4 isotype, as taught by the art as a whole. In my opinion, a POSA would have either understood Tacken to be consistent with "eculizumab" being an IgG4 isotype (because of its citation to Thomas as Ref. No. 19), or otherwise, they would have thought that Tacken's referring to its IgG2/IgG4 isotype control antibody by the name of "eculizumab" was a mistake.

147. Dr. Balthasar states that Tacken "cites a publication by Mueller et al. (AMG1031; 'Mueller II') as providing information about the hybrid IgG2/IgG4 constant region portion of eculizumab." (AMG1002 at ¶ 54.) I disagree with this statement. Tacken does not refer to "eculizumab" in connection with Mueller II. Rather, Tacken states:

> The humanized variable heavy and variable light regions [of the hD1 antibody] were then genetically fused with a human hybrid IgG2/IgG4 constant domain[17] and a human kappa chain constant domain, respectively.

(AMG1034 at 1279 (citing Mueller II, Ref. No. 17).) A POSA would not have read this vague reference to Mueller II in the context of an "hD1" antibody as

Samsung Bioepis Exhibit No. 1002
Page 11484

teaching that the antibody "eculizumab" had an IgG2/IgG4 hybrid constant region. The reference in Tacken to Mueller is for description of the "human hybrid IgG2/IgG4 constant domain" described in Tacken; Mueller is not cited as describing "eculizumab."

148. Dr. Balthasar also cites prosecution history statements in an unrelated Alexion patent application (AMG1049, "the '438 application") that he characterizes as demonstrating a POSA's understanding that "eculizumab" had a hybrid IgG2/IgG4 antibody. (AMG1002 at ¶ 45 (citing AMG1049).) I have been informed that these statements, made after the priority date and in an unrelated patent application, are not prior art to the '149 patent. (*See* ALXN2032 at 61:13-24.) But, even if these statements were to be considered prior art, they would not change my opinion that a POSA would have understood "eculizumab" to have an IgG4 isotype, based on the teachings of the prior art as a whole.

149. I further note that Dr. Balthasar also relies on (1) a non-prior art article by Rother *et al*, published in November 2007, and (2) the non-prior art "Boone Declaration' dated in 2017 from the prosecution history of the '149 patent, for his understanding of "eculizumab's heavy chain." (AMG1002 at ¶ 54 (citing AMG1033); AMG1002 ¶ 13 (citing AMG1015 at 736-738 (Boone Declaration ¶ 6); ALXN2032 at 64:8-19.) I understand that such information was not available to a POSA as of March 15, 2007, and it does not change my opinion that the prior

Samsung Bioepis Exhibit No. 1002
Page 11485

art as of that date consistently and uniformly indicated to a POSA that "eculizumab" was the IgG4 antibody described in Thomas.

150. Figure 7 below illustrates (1) the consistent teaching in the literature prior to March 15, 2007 that "eculizumab" was identified as the IgG4 antibody of Thomas, and (2) how the information that Dr. Balthasar relies on for identifying "eculizumab" as an "IgG2/IgG4" hybrid isotype antibody was dated after the March 15, 2007 date:

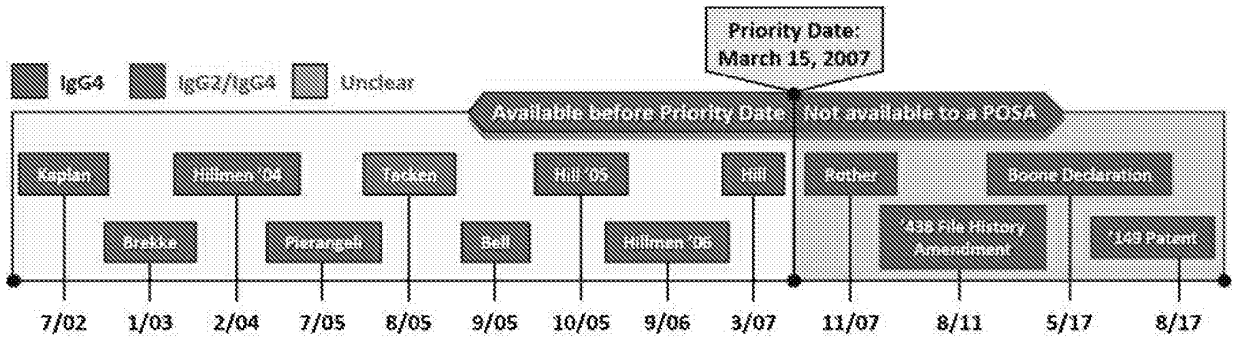


Figure 7: Documents referring to "eculizumab" before and after March 15, 2007

2. The Antibody Sequence Recited in the '149 Patent Was Not Publicly Known Before March 15, 2007

151. I also disagree with Dr. Balthasar's assertion that, prior to March 15, 2007, "[a] POSA would have been aware of the amino acid sequence of eculizumab . . . ." (AMG1002 at ¶ 49.) Before March 15, 2007, a POSA would not have known the complete, full-length amino acid sequence of SOLIRIS® (eculizumab) – now claimed in the '149 patent – which was not publicly available before that date. The references cited by Dr. Balthasar to support his conclusion

do not disclose the complete amino acid sequence claimed in the '149 patent prior to March 15, 2007, and do not change my opinion that a POSA would not have understood that "eculizumab" or any other antibody had the complete claimed sequence prior to that date.

152. Dr. Balthasar first cites a declaration by an Alexion employee, submitted during prosecution of the '149 patent, and that Dr. Balthasar characterizes as showing Alexion used eculizumab – which is now known to correspond to claimed SEQ ID Nos: 2 and 4 – in clinical trials prior to March 15, 2007. (AMG1002 at ¶ 49 (citing the Boone Declaration, AMG1015 at 734-741.) Dr. Balthasar does not argue that the full-length sequence of eculizumab was expressly disclosed over the course of any of the eculizumab clinical trials prior to March 15, 2007, and I understand that the declaration Dr. Balthasar cites was submitted on May 11, 2017, and would not have been accessible to a POSA prior to March 15, 2007. (*See* ALXN2032 at 58:23-59:3.) I understand that the use of an antibody in clinical trials by itself is insufficient to disclose the antibody's sequence, and so this does not change my opinion that the full-length sequence of eculizumab was not publicly available prior to March 15, 2007.

153. In the following paragraphs of his Declaration, Dr. Balthasar also relies on Evans, Bowdish, Mueller, and Mueller II (AMG1031). I disagree with Dr. Balthasar's depiction of these references in his Declaration, which significantly

overread the references' teachings. When read correctly, it is clear that none of these references, either alone or in combination, teach the specific, full-length antibody sequence claimed in the '149 patent, as described more fully in Sections VII.D and VII.E below.

154. First, Evans does not teach or suggest the specific, full-length antibody sequence described in claim 1 of the '149 patent, or that an antibody having that sequence would bind C5 or be safe and effective in human patients.

155. Evans does not use the term "eculizumab," and does not disclose any full-length humanized antibodies. The only full-length antibody disclosed in Evans is the parental "5G1.1" mouse monoclonal antibody. (*E.g.*, AMG1007 at 38:43-53; ALXN2032 at 169:13-18.) A POSA as of March 15, 2007 would have understood that Evans reflected an earlier stage of research involving discovery of the "5G1.1" mouse antibody and early efforts to design humanized variable region fragments, preceding Alexion's design and selection for clinical testing of a full-length, humanized antibody.

156. Evans provides nine different versions of a humanized "variable" region for anti-C5 antibodies, but does not provide any guidance as to which, if any, were being used in antibodies developed for clinical trials. (*See, e.g.*, AMG1007 at 43:6-14, 43:62-45:4.)

Samsung Bioepis Exhibit No. 1002
Page 11488

157. Evans includes only a brief, generic statement regarding "constant region domains," and does not identify any specific heavy chain constant region that could be used in a humanized antibody, or describe any specific full-length humanized antibodies that were actually made and confirmed to bind C5. (*See* AMG1007 at 45:24-33; ALXN2032 at 163:5-15, 165:5-21, 169:6-23.) Evans does not suggest or disclose the hybrid IgG2/IgG4 corresponding to SEQ ID NO:2 of the '149 patent, or teach that an antibody incorporating that sequence would be "[a]n antibody that binds C5." In fact, the only constant regions disclosed in Evans are the CH1 regions of Fd fragments, which appear to correspond to IgG1 CH1 sequences rather than IgG2/IgG4.[7] (*See* Section VI.D.5 above.)

158. Bowdish, Mueller, and Mueller II also did not disclose the specific, full-length antibody described in claim 1 of the '149 patent, or that an antibody with that sequence would bind C5 or be safe and effective in human patients.

159. The subject matter of Bowdish was unrelated to "eculizumab," C5 binding or the of PNH. (*See, e.g.*, ALXN2032 at 199:9-12, 175:22-25.) Bowdish concerned the use of an antibody for use as a "scaffold" to house a peptide (*e.g.*, the hormone TPO), thereby providing greater stability and longer half-life for the

[7] Evans refers to the chimeric version of its "Fd" series of compounds as "5G1.1M1 VH HuG1." (AMG1007 at 43:18-20.)

Samsung Bioepis Exhibit No. 1002
Page 11489

peptide in vivo. (AMG1006 at [0005]-[0006].) The antibody used for the "scaffold" in Bowdish could be any antibody, as the technique reported in Bowdish is not specific for any individual antibody sequence. (AMG1006 at [0066].)

160. Bowdish did not describe any assays related to C5 binding or blocking complement-mediated lysis. Example 4 of Bowdish, which Dr. Balthasar relies on in his Declaration, assesses the binding of TPO-mimetic peptide (presented on an antibody scaffold) with a TPO receptor (the "cMpl receptor") – a biological interaction that is not part of the complement pathway and is unrelated to cleavage of C5. (AMG1006 at [0192].)

161. I disagree with Dr. Balthasar's characterization of Bowdish as disclosing sequences of "eculizumab" or an "eculizumab-based immunoglobulin." (*See, e.g.*, AMG1002 at ¶¶ 50-51, 55.) Bowdish never uses the term "eculizumab." (*See* ALXN2032 at 199:9-12.) Further, a POSA would not understand Bowdish to be disclosing sequences of the humanized antibody "eculizumab" described in clinical trials based on Bowdish's references to "5G1.1."

162. A POSA would have understood Bowdish's incorporation by reference of Evans to be more limited than is depicted in Dr. Balthasar's Declaration. For example, in his Declaration, Dr. Balthasar states, "Bowdish references U.S. Pat. No. 6,355,245 (AMG1007; 'Evans') as describing the generation of the h5G1.1 antibody." (AMG1002 at ¶ 52.) But Bowdish does not

use the term "h5G1.1." Instead, paragraph [0191] of Bowdish states, "Construction of 5G1.1 is described in U.S. Application. Ser. No. 08/487,283, incorporated herein by reference." (AMG1006 at ¶ [0191].) A POSA would have understood that Evans,[8] in turn, used the term "5G1.1" to refer to its ***mouse*** antibody from the original hybridoma, which is the only full-length antibody disclosed in Evans. In particular, Evans consistently uses the phrase "the 5G1.1 antibody" or "the 5G1.1 mAb" to describe the original mouse antibody obtained from the 5G1.1 hybridoma. (AMG1007 at 19:47-49, Figs. 18-19, Examples 7-10 (37:34-40:29); *see also* AMG1023 at 1389, 1395 (Thomas referring to the original mouse antibody as "5G1.1" and "the 5G1.1 mAb").) Likewise, a POSA would

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[8] I understand from counsel that Bowdish does not cite Evans (AMG1007) itself, but rather cites to the "'283 application" from which Evans issued. For convenience and to address the arguments Dr. Balthasar actually made, I will use "Evans" to refer to the document referenced in Bowdish for "[c]onstruction of 5G1.1," and will discuss the contents of Evans (AMG1007) in connection with that reference. But by doing so, I am not admitting that the "'283 application" and Evans are the same document. I understand from counsel that the "'283 application" has not been introduced by Amgen in this case, and that Dr. Balthasar did not consider it. (ALXN2032 at 191:2-11, 192:7-11, 208:3-8.)

Samsung Bioepis Exhibit No. 1002
Page 11491

have recognized that Evans was not a proper reference for a full-length "h5G1.1" antibody, because Evans did not disclose any full-length humanized antibodies. (*See* ALXN2032 at 163:12-15, 169:6-18.)

163. Thus, neither Bowdish's reference to using "5G1.1" as a scaffold for a TPO-mimetic peptide (AMG1006 at [0066], [0191]), nor Bowdish's citation to Evans for "[c]onstruction of 5G1.1" (AMG1006 at [0191]), would have indicated to a POSA that Bowdish's TPO-mimetic compound relates to the structure of "eculizumab," or that the "scaffold" used to make Bowdish's compound had any C5 binding activity or utility in humans.

164. I also disagree with Dr. Balthasar that a POSA would have necessarily inferred that Bowdish disclosed a "humanized 5G1.1" based on a "goat anti-human" assay reagent in a FACS experiment with the TPO-mimetic peptide compound. (AMG1002 at ¶ 50.) As Dr. Balthasar admitted Bowdish provided no information about that "goat-anti-human" reagent, including its source, its specific target ("epitope"), whether it distinguishes between "humanized" antibodies and other antibodies such as "chimeric" mouse/human hybrids, or its cross-reactivity with antibodies from other species. (ALXN2032 at 210:13-21, 211:13-23, 212:5-9.) It was understood in the field that anti-immunoglobulin antibodies could cross-react with antibodies from non-target species. (ALXN2018 at 623.) Particularly given Bowdish's earlier reference to the mouse "5G1.1" antibody in Evans at

Samsung Bioepis Exhibit No. 1002
Page 11492

¶ [0191], a POSA could not have been certain from Bowdish's use of an unidentified, uncharacterized "anti-human" reagent alone whether Bowdish's TPO-mimetic compound was based on a humanized, chimeric, or mouse immunoglobulin structure.

165. Mueller and the associated article, Mueller II, relate generally to developing antibodies for vascular cell adhesion molecules ("VCAM") to block transplant rejection, again a subject unrelated to C5-binding. Mueller and Mueller II describe anti-VCAM antibodies with "IgG4" and hybrid "IgG2/IgG4" isotypes, as well as negative "isotype control" constructs with the same IgG4 and IgG2/IgG4 constant region, but different variable regions that would not bind VCAM. (AMG1008 at 12:19-32; AMG1031 at 442-443.) Neither Mueller nor Mueller II disclose the amino acid sequences of any anti-C5 antibody. (*See e.g.*, ALXN2032 at 232:17-21.)

166. I disagree with Dr. Balthasar's characterization of Mueller as disclosing "eculizumab's hybrid IgG2/IgG4 heavy chain constant region." (AMG1002 at 55.) Neither Mueller nor Mueller II use the term "eculizumab" or disclose the full-length antibody sequence claimed in the '149 patent. To support his assertions, Dr. Balthasar references Mueller's use of "h5G1.1 CO12 HuG2/G4 mAb" as a control antibody. (AMG1002 at 55.) A POSA, however, would not understand this antibody to correspond to "eculizumab" because, as discussed

above, the prior art consistently described "eculizumab" as an IgG4 antibody through references to Thomas. While Mueller also refers to an "h5G1.1 CO12 HuG4" control antibody, it identified ***only*** the "HuG4" control antibody as "anti-C5." (AMG1008 at 12:1-2; *see also* AMG1031 at 446.) A POSA would have understood that to be consistent with Thomas's teachings of a "h5G1.1 HuG4" antibody that binds C5 and blocks complement activity. (*See* AMG1008 at Figs. 11-13, 15, and 11:36-12:17, 12:34-13:2; AMG1023 at 1396, 1399.)

167. Mueller further did not teach: any complete "h5G1.1" or anti-C5 binding antibody sequence; the precise boundaries of the IgG2/IgG4 constant region that would be used with any "h5G1.1" or anti-C5 binding variable region; or any guidance as to what "h5G1.1" or anti-C5 binding variable region should be used with any constant regions used in Mueller,[9] and would have been too ambiguous to have led a POSA to any particular variable region sequence. (*See* Section VII.E.1 below.)

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[9] As discussed below, I disagree with Dr. Balthasar that Mueller's vague use of the alphanumeric "CO12" in naming its "h5G1.1" isotype control antibodies would have been understood by a POSA to correspond to any particular sequence or structure in Mueller or any other document.

Samsung Bioepis Exhibit No. 1002
Page 11494

168. I further disagree with Dr. Balthasar that, as of March 15, 2007, a POSA would have understood the full-length, specific sequence described in claim 1 of the '149 patent based on some combination of Evans, Bowdish, Mueller, and Mueller II. A POSA would not have looked to Bowdish, Mueller, or Mueller II for guidance on designing anti-C5 antibodies for human administration because the subject matter of those references was entirely unrelated to anti-C5 binding. A POSA also would not have read Bowdish as disclosing the '149 patent's claimed sequence through its incorporation of Evans because, as discussed above, this incorporation is ambiguous in scope and appears to refer to construction of the mouse 5G1.1 monoclonal antibody rather than humanized sequences.

169. References to the term "5G1.1" in Bowdish (AMG1006 at [0191]-[0193] and "h5G1.1" in Mueller / Mueller II (AMG1008 at 12:1-2, 12:35-37; AMG1023 at 1396, 1399) would not have led a POSA to look to those references for the structure of the anti-C5 antibody, "eculizumab," whose safety and efficacy had been reported in clinical trials. As discussed in Section VI.D.3 above, and as Dr. Balthasar agreed at his deposition, without further context, the terms "5G1.1" and "h5G1.1" could refer to multiple potential antibodies or antibody fragments. (*See* ALXN2032 at 97:23-99:8, 159:1-13, 241:23-242:12.) Accordingly, a POSA would not have understood these terms in Bowdish and Mueller / Mueller II to refer to the antibody known as "eculizumab." Further, multiple publications

discussing C5-binding and clinical trials involving "eculizumab" also used these terms – a POSA would have looked to these, more relevant publications, citing Thomas as describing the "eculizumab" antibody, rather than Bowdish or Mueller / Mueller II. (*See, e.g.*, AMG1023 at 1389; AMG1005 at ¶ [0052]; AMG1021 at 1017; AMG1019 at 56.)

170. As discussed above, as of March 15, 2007, a POSA would have understood that the design of monoclonal antibodies for human clinical therapy was a complex and unpredictable process. A POSA would have understood that small changes to antibody sequence – including in the constant region – could significantly impact antibody binding, safety, and efficacy. (*See* Sections VI.D.2 and VI.D.4 above.) Dr. Balthasar's assertions that a POSA would have read Bowdish or Mueller / Mueller II in combination with Evans to reach the full sequence claimed by the '149 patent ignore that, given the unpredictability and complexity in the art at the time, a POSA would have had no reasonable expectation that such a combination would comprise an antibody that could bind C5 or provide a therapeutic benefit to human patients.

171. With a POSA understanding that, in contrast, the IgG4 isotype antibody of Thomas was reported prior to March 15, 2007 as binding C5, blocking its cleavage, and having been used in clinical trials to safely and effectively treat PNH, a POSA would not have any reason or motivation to deviate from that

Samsung Bioepis Exhibit No. 1002
Page 11496

antibody, and instead combine Bowdish or Mueller / Mueller II with Evans to obtain an uncharacterized antibody with unknown properties that could not have reasonably been predicted.

B. Claim 1 of the '149 Patent Was Not Anticipated by Hillmen or Hill (Grounds 1 and 2)

172. Amgen's Grounds 1 and 2 contend that claim 1 of the '149 patent would have been anticipated by the clinical trial publications Hillmen (AMG1004) or Hill (AMG1047), respectively. As Grounds 1 and 2 raise overlapping issues, I disagree with both for the same reasons, and I will address them both together here.

173. In my opinion, Amgen's Grounds 1 and 2 fail because, among other things, Amgen cannot show that either Hillmen or Hill disclose each element of the claimed invention, either expressly or inherently. Neither Hillmen nor Hill disclose the full-length sequence recited in claim 1 of the '149 patent.

174. Hillmen and Hill are both journal publications reporting on the successful use of "eculizumab," a humanized monoclonal antibody targeting C5, to treat PNH in human clinical trials. (AMG1004 at 553; AMG1047 at 2564.) Neither Hillmen nor Hill disclose any amino acid sequences for "eculizumab."

175. I understand from counsel that, for a document to anticipate a patent claim, every element of the patent claim needs to be disclosed in that one document, either expressly (*i.e.*, as stated in the document), or inherently (meaning

Samsung Bioepis Exhibit No. 1002
Page 11497

that, based on what is stated in the document itself, a POSA prior to March 15, 2007 would know that the claimed invention was necessarily disclosed by that document).

176. In my opinion, neither Hillmen or Hill disclosed the claimed sequence of the '149 patent (SEQ ID NOs: 2 and 4) by their mention of "eculizumab," because a POSA prior to March 15, 2007 would not know from reading Hillmen and Hill that the term "eculizumab" ***necessarily*** disclosed an amino acid sequence corresponding to SEQ ID NOs: 2 and 4. As discussed above, the full-length sequence claimed in the '149 patent was not publicly known prior to March 15, 2007. (*See* Section VI.E above.) And in fact, a POSA reading Hillmen and Hill would have understood that "eculizumab" had a ***different*** structure and sequence than the antibody with SEQ ID NOs: 2 and 4 claimed in the '149 patent.

177. In particular, a POSA reading Hillmen, Hill, and the other literature available as of March 15, 2007 would have understood "eculizumab" to have be the IgG4 isotype antibody described in Thomas (AMG1023). *See* Section VI.D.5. As I discuss above, both Hillmen and Hill cite to Thomas for a disclosure of what "eculizumab is." (AMG1004 at 553, n. 15; AMG1047 at 2559.) This is consistent with the teachings of the prior art as a whole, and would have indicated to a POSA that the "eculizumab" antibody used in Hillmen and Hill contained an IgG4 isotype, as taught by Thomas. (*See* Section VI.D.5 above.)

Samsung Bioepis Exhibit No. 1002
Page 11498

178. A POSA would have understood that an IgG4 isotype antibody would have a different heavy chain sequence from the sequence contained SEQ ID NO: 2, which, as we know today, corresponds a non-natural, engineered IgG2/IgG4 hybrid constant region sequence. As of March 15, 2007, it was not publicly known that the unique, monoclonal antibody "eculizumab," which had been successfully tested in clinical trials, had an IgG2/IgG4 hybrid constant region, and all of the evidence in the literature as of that date pointed to it having a naturally-occurring IgG4 constant region.

179. A POSA would not have been able to independently determine the amino acid sequence of the antibody clinically tested in Hillmen and Hill because Alexion did not disclose the sequence of the clinical study drug, kept study participants under strict confidentiality, and maintained the physical antibody supplies under lock and key with strictly limited access. (AMG1015 at 734-741.) And even if the eculizumab protein was available to the public, which it was not, determining the entire sequence of a full-length antibody from protein alone would have required considerable specialized skill in protein sequence determination beyond the abilities of a POSA for the '149 patent.

180. I disagree with Dr. Balthasar's assertions that Hillmen and Hill are enabling – *i.e.*, they would have allowed a POSA to practice the claimed invention without undue experimentation – because, according to Dr. Balthasar, a

Samsung Bioepis Exhibit No. 1002
Page 11499

POSA would have looked to Bowdish and Evans, or Mueller and Evans, for the sequence of eculizumab. (*See* AMG1002 at ¶¶ 75, 85.) First, neither Hillmen nor Hill cite or incorporate by reference Bowdish, Evans, or Mueller, and I understand from counsel that it is improper to combine multiple documents for purposes of anticipation. Second, neither Hillmen nor Hill contain any indication that the "eculizumab" antibody used in those studies would have the sequences that Dr. Balthasar selects from Bowdish, Evans, and Mueller. Hillmen and Hill both cite Thomas as describing "eculizumab," from which a POSA would have understood "eculizumab" to be an IgG4 antibody with a very different sequence than the one Dr. Balthasar improperly combines from Bowdish, Evans, and Mueller. (*See* AMG1004 at 553, n. 15; AMG1047 at 2559, n. 9.) Finally, there is nothing in Bowdish, Evans, and Mueller that disclosed the specific amino acid claimed in the '149 patent in any case, for the reasons stated in Section VI.E.

181. With no sequence information available directly from Hillmen and Hill, and both these references citing Thomas, which teaches a very different antibody structure than the specific amino acid sequence claimed in the '149 patent, a POSA would not have been able to create an anti-C5 antibody, with the specific amino acid claimed in the '149 patent, based on the disclosures of Hillmen or Hill without significant experimentation.

Samsung Bioepis Exhibit No. 1002
Page 11500

C. Claim 1 of the '149 Patent Was Not Anticipated by Bowdish (Ground 3)

182. Amgen's Ground 3 contends that claim 1 of the '149 patent would have been anticipated by Bowdish.

183. In my opinion, Amgen's Ground 3 fails, because, among other things, Amgen cannot show that Bowdish disclosed each element of the claimed invention, either expressly or inherently. Bowdish did not disclose a full-length antibody with the specific amino acid sequence recited in claim 1 of the '149 patent, either alone or when read in combination with Evans. Further, nothing in Bowdish would have disclosed to a POSA that the antibody with the sequence recited in claim 1 of the '149 patent would be "an antibody that binds C5."

184. In particular, I disagree that a POSA reading Bowdish – even to the extent that it incorporates the disclosure of the '283 application or Evans (AMG1007) with respect to "[c]onstruction of 5G1.1" – would have understood that Bowdish necessarily disclosed the invention recited in claim 1 of the '149 patent, without the need for picking and choosing from Bowdish's (and Evans's) disclosures to reconstruct the claimed invention in hindsight. Dr. Balthasar overlooks the extensive ambiguity in Bowdish's disclosures, including its limited reference to "[c]onstruction of 5G1.1" in Evans, and reconstructs the antibody recited in claim 1 of the '149 patent only by using his present-day knowledge of what that antibody is.

Samsung Bioepis Exhibit No. 1002
Page 11501

185. There is no dispute that Bowdish did not disclose the entire amino acid sequence recited in claim 1 of the '149 patent. (ALXN2032 at 181:18-182:4.) Further, Dr. Balthasar admits that the amino acid sequences that he relies on from Bowdish – the sequences described in Bowdish Figs. 13A and 13B – are not the antibody recited in claim 1 of the '149 patent. (ALXN2032 at 184:10-16.) Dr. Balthasar also admits that neither Bowdish nor Evans used the term "eculizumab." (ALXN2032 at 199:9-17.)

186. Instead, I understand Dr. Balthasar goes beyond the information and sequences described in Bowdish, and combines sequences in Bowdish with other sequences that he pulls from Evans (AMG1007). (*See* AMG1002 at ¶¶ 94-96.) I further understand that Dr. Balthasar claims that, because of Bowdish's statement regarding "incorporation" of the application corresponding to Evans (AMG1007), he is entitled to combine sequences from Bowdish with any sequences taken from anywhere within Evans. (ALXN2032 at 189:23-191:1.)

187. I disagree with Dr. Balthasar's reading of Bowdish's single statement regarding Evans regarding "[c]onstruction of 5G1.1." In my opinion, Dr. Balthasar's interpretation of that statement is mistaken and contrary to how it would have been understood by a POSA. Further, I understand from counsel that Dr. Balthasar's interpretation of Bowdish's statement concerning Evans is legally mistaken as well.

188. The statement at issue appears in Example 4 of Bowdish, which stated:

> The TPO mimetic peptide graft in Fab clone X4b has been transplanted into the heavy chain CDR3 region of another antibody framework, 5G1.1. Construction of 5G1.1 is described in U.S. Application Ser. No. 08/487,283,[10] incorporated herein by reference.

(AMG1006 at [0191].)

189. First, a POSA would have understood Bowdish's reference to Evans, "Construction of 5G1.1 is described in U.S. Application Ser. No. 08/487,283, incorporated herein by reference," to be a limited statement referencing Evans's disclosure of the "5G1.1" parental mouse monoclonal antibody. As discussed above, and as Dr. Balthasar agreed at deposition, a POSA reading Evans would have understood that the "5G1.1" antibody of Evans was the original mouse

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[10] As noted above, I understand from counsel that "U.S. Application Ser. No. 08/487,283" is the patent application from which Evans issued, and that Dr. Balthasar's opinion is deficient because he failed to consider and discuss the application. For purposes of this Declaration, however, I will address Dr. Balthasar's arguments as if they were proper.

Samsung Bioepis Exhibit No. 1002
Page 11503

"5G1.1" antibody, and that Evans did not describe any other full-length antibody. (ALXN2032 at 165:11-24, 169:6-18.) I understand from counsel that a statement regarding "incorporation by reference" must be read in its context[11] – and nothing in that statement would have indicated to a POSA any intent to have incorporated the disclosures of Evans beyond what was stated: "construction of 5G1.1," a mouse antibody. Accordingly, a POSA would not have read the statement in Bowdish as incorporating, *e.g.*, the humanized scFv fragments described in Evans, which were created after construction of the 5G1.1 mouse antibody. (*See* AMG1007 at 42:56-45:48.)

190. A POSA reading Bowdish, and seeing its incorporation by reference of Evans's mouse "5G1.1" antibody, would not have understood that it necessarily disclosed the claimed antibody of the '149 patent, which is a humanized antibody. If a POSA were to have considered the sequence of Evans's mouse "5G1.1" antibody in view of Bowdish's Figs. 13A and 13B sequences, they would have seen misalignment beyond the region of Bowdish's "TPO-mimetic" peptide, and

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[11] For example, in contrast to Bowdish's incorporation by reference of Evans, ¶ [0001] of Bowdish incorporates three provisional patent applications "in their entirety." (AMG1006 at ¶ [0001].)

Samsung Bioepis Exhibit No. 1002
Page 11504

would not have further envisioned any combination of sequences that would have resulted in the claimed antibody of the '149 patent.

191. And even if Bowdish and Evans were combined in full, they did not disclose or render obvious the uniquely engineered amino acid sequence recited in claim 1 of the '149 patent. For example, if a POSA were to have looked to Evans for construction of the "scaffold" antibody used to generate Bowdish's TPO-mimetic peptide, they would have been lost. As Dr. Balthasar admitted, Evans did not describe ***any*** full-length antibody (including Bowdish's "scaffold" antibody), aside from the "5G1.1" mouse antibody, which would not have aligned with the sequences disclosed in Bowdish. (ALXN2032 at 163:12-15, 169:6-23, 221:14-16.)

192. A POSA also would not have looked to the scFv fragments of Evans to understand the sequence of the full-length "scaffold" antibody in Bowdish. As discussed in Section VI.D.2 and IV.D.4 above, scFv and full-length antibodies were understood to be very different structures with very different properties, and a POSA would not have confused an scFv for a full-length immunoglobulin from which Bowdish's TPO-mimetic compound was made.

193. I also disagree that a POSA would have understood Bowdish to have necessarily disclosed the specific claimed amino acid sequence of the '149 patent, when Dr. Balthasar's theory of anticipation requires a POSA to pick and choose through Evans's sequences, including scFv sequences not referenced anywhere in

Samsung Bioepis Exhibit No. 1002
Page 11505

Bowdish. (AMG1002 at ¶¶ 94-96.) Again, I note that Dr. Balthasar's figures are misleading in this regard, because a POSA would not have understood Evans's scFv sequences as being part of an intact antibody structure such as was used to generate Bowdish's TPO-mimetic compound, but would have understood Evans's scFvs to be a distinct, recombinant DNA compound different from the full-length structures described in Bowdish.

194. Figure 8 below illustrates (1) how a POSA prior to March 15, 2007 would have understood the information disclosed in Bowdish as it incorporates the '283 application (a mouse antibody); (2) how a POSA would have understood the other disclosures of Evans that Bowdish did not incorporate ("fragments" including scFvs and Fabs,), and (3) how Dr. Balthasar's Figure 10 is mistaken for depicting Evans as describing part of a full-length humanized antibody – which is not actually described anywhere in Evans or in Bowdish.

Samsung Bioepis Exhibit No. 1002
Page 11506

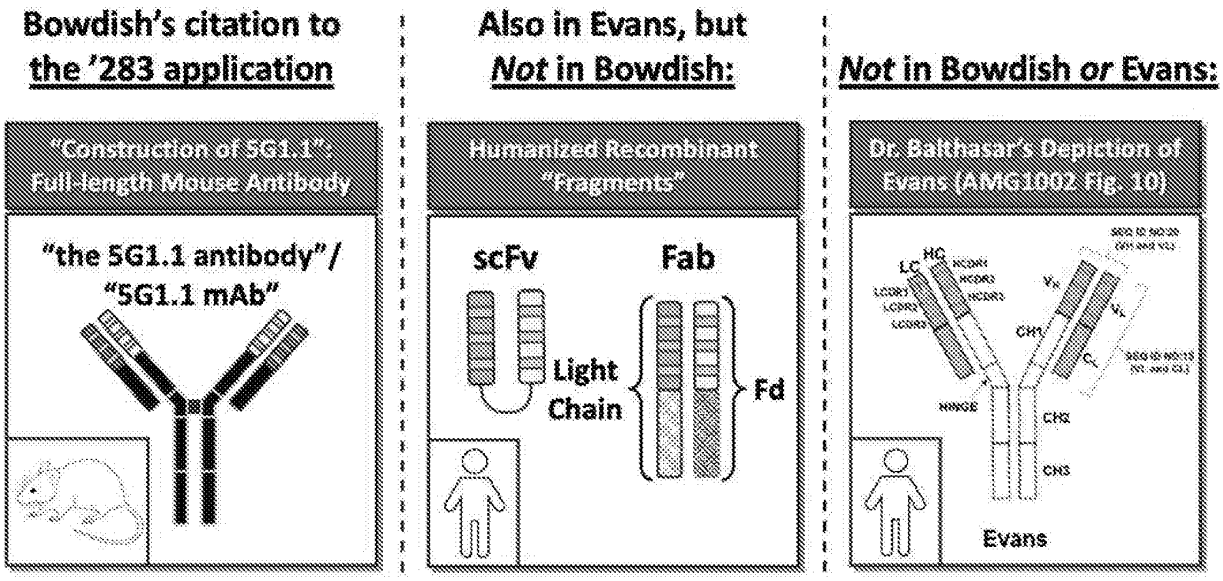


Figure 8: A POSA's understanding of Bowdish's reference to the '283 application, and what material was outside the referenced subject matter

195. A POSA further would not have understood the "5G1.1" antibody referenced in Bowdish to have necessarily disclosed SEQ ID NO: 2 because Evans referred to at least two, and possibly at least four potential definitions of the CDR region: the "sequence variability" definition (Kabat), the "structural variability" definition (Chothia), and the overlap between them. (AMG1007 at 5:15-36.) Dr. Balthasar is incorrect when he states that "all of the 5G1.1 heavy chains in Evans contain the same CDR3 sequence," as Evans actually disclosed at least two CDR3 regions – one containing 11 amino acids, and one containing 13 amino acids, and possibly two sequences of 12 amino acids in their region of overlap – based on use

of the two definitions. (*See, e.g.*, AMG1007 at 5:15-36, 42:64-43:5, Figs. 18 and 19.)

196. It is my opinion that Dr. Balthasar's Declaration demonstrates a significant use of hindsight. For example, I disagree with Dr. Balthasar's sequence alignments in Figures 5 and 13, which compare sequences from Bowdish to the claimed SEQ ID NO: 2 from the '149 patent. "SEQ ID NO: 2" was not publicly available as of the priority date. A POSA would not have had the guidance of the disclosure of SEQ ID NO:2 from the '149 patent to help select sequences to combine from Bowdish and Evans and, as a result, for the reasons stated here, a POSA would not have understood Bowdish to necessarily disclose the claimed sequence, based on the vague disclosures in Bowdish.

197. I also disagree with Dr. Balthasar's statement, "[A] POSA would have known that the only portion of the sequence disclosed in Bowdish's Figures 13A-13B that is different from the original h5G1.1 'scaffold' antibody disclosed in Bowdish is the portion of SEQ ID NO: 67 that corresponds to the TPO peptide." (*See* AMG1002 at ¶ 92.) This is not correct. Bowdish did not use the term h5G1.1, and as discussed above, a POSA would have understood based on Example 4 of Bowdish that the original "5G1.1" scaffold antibody was the mouse antibody in Evans. Comparing the mouse antibody in Evans with the sequence in

Samsung Bioepis Exhibit No. 1002
Page 11508

Figure 13, there are additional sequence differences outside of the TPO peptide region, which give the humanized and mouse antibodies different properties.

198. I also disagree with Dr. Balthasar's depiction in Figure 12. (AMG1002 at ¶ 96.) As I discussed above (*see* Section VI.D.5 above), I disagree with Dr. Balthasar's depiction of the disclosure from Evans, because Evans did not disclose a full-length, humanized antibody – only humanized antibody fragments, such as scFv. A POSA would have understood that the scFv structures of Evans were not partial sequences from a full-length antibody, but they were their own stand-alone, recombinantly-generated compounds, which were never part of any full-length humanized antibody.

199. I further disagree with Dr. Balthasar's use of the term "h5G1.1" in his depiction of the "scaffold" that was used in Bowdish. The term "h5G1.1" is not used in Bowdish, Bowdish did not describe the antibody in Example 4 of Bowdish as being humanized, and Evans did not disclose any full-length, humanized antibody sequences. I further disagree with Dr. Balthasar's depiction in Figure 14. Again, Dr. Balthasar does not accurately depict the disclosure of Evans, which did not disclose a full-length humanized antibody, but only humanized antibody fragments, such as scFv. I also disagree with the use of the term "h5G1.1," which was not used anywhere in Bowdish. Neither Figure 12 nor Figure 14 reflect the multiple steps of sequence selection and combination that a POSA would have to

have undertaken to arrive at the claimed full-length sequence from the disclosures of Bowdish.

200. A POSA also would not have understood that an antibody made from a combination of constant regions from Bowdish with a CDR from Evans would work to bind C5. Bowdish makes no disclosure regarding C5 binding activity. Bowdish Example 4 assessed binding for the cMp1 receptor, which was the target of Bowdish's TPO-mimetic construct and is unrelated to C5 or the complement pathway. (AMG1006 at ¶¶ [0192]-[0193].) Further, a POSA would have understood that if a CDR region from Evans was combined with constant regions from Bowdish, there would be a significant risk that the resulting antibody would not bind C5, due to the known complexity and unpredictability of antibody design. (*See* Sections VI.D.2 and VI.D. 4 above.)

201. I disagree with Dr. Balthasar that Bowdish would have enabled a POSA to make the claimed antibody. (*See* AMG1002 at ¶¶ 101-02.) For the reasons discussed above in Sections IV.D.2 and IV.D. 4, a POSA would have understood that changes to an antibody's sequence, including in the constant region, can significantly affect binding and specificity, as well as safety and efficacy in patients. A POSA would not have understood that the combination of a CDR from Evans with constant regions disclosed in Bowdish would effectively bind C5, or be safe for human therapy, without substantial additional study.

Samsung Bioepis Exhibit No. 1002
Page 11510

D. Claim 1 of the '149 Patent Would Not Have Been Obvious Over Bell, Bowdish, and Evans (Ground 4)

202. Amgen's Ground 4 contends that claim 1 of the '149 patent would have been obvious over the combination of Bell, Bowdish, and Evans.

203. In my opinion, Amgen's Ground 4 fails, because, among other things, Amgen cannot show that each element of the claimed invention was known or obvious in view of Bell, Bowdish, and Evans. None of Bell, Bowdish, nor Evans, when read alone or in combination, disclosed the specific amino acid sequence claimed in the '149 patent.

1. Bell Did Not Disclose the Specific Sequence of Claim 1, and Would Not Have Motivated a POSA to Make An Antibody With the Claimed Sequence

204. Dr. Balthasar relies on Bell for its disclosures regarding "eculizumab" – but he admits that Bell did ***not*** disclose the claimed amino acid sequence of the '149 patent. (AMG1002 ¶ 107; ALXN2032 at 146:17-25.) Bell, in fact, would have guided a POSA towards use of an IgG4 isotype that is different from the claimed antibody of the '149 patent, which has a different, uniquely-engineered amino acid sequence corresponding to a hybrid IgG2/IgG4 constant region. A POSA would have had no reason or motivation to deviate from the IgG4 antibody structure of Thomas that Bell associated with the therapeutically useful "eculizumab" antibody, and turn instead to (1) Bowdish, which Bell did not cite, and contained no information regarding anti-C5 antibodies; or (2) Evans, which

did not disclose any full-length humanized antibodies, and at best may have suggested an IgG1 antibody based on the Fd sequences it disclosed. (See Section VI.D.5 above.) And, a POSA provided with Bell would not have been motivated to make a new, untested antibody using a clinically-untested non-naturally occurring hybrid constant region, when Bell taught that "eculizumab," identified as an IgG4 antibody, was safe and effective for human use.

205. Bell was a U.S. Patent application relating to use of compounds to block complement for the treatment of PNH. A POSA would have read paragraph 52 of Bell as teaching that the "eculizumab" antibody described in Bell had an IgG4 isotype, based on Bell's citation and incorporation by reference of Thomas, which taught the IgG4 isotype. (*See* Section VII.D.5 above.) Specifically, Bell stated:

> Particularly useful anti-C5 antibodies are h5G1.1-mAb, h5G1.1-scFv and other functional fragments of h5G1.1. ***Methods for the preparation of h5G1.1-mAb,*** h5G1.1-scFv and other functional fragments of h5G1.1 are described in U.S. Pat. No. 6,355,245 and "Inhibition of Complement Activity by Humanized Anti-C5 Antibody and Single Chain Fv," ***Thomas et al., 1401, 1996***, the disclosures of which are incorporated herein in their entirety by this reference. ***The***

Samsung Bioepis Exhibit No. 1002
Page 11512

antibody h5G1.1-mAb is currently undergoing clinical trials under the trade-name eculizumab.

(AMG1005 at ¶ [0052].)

206. Although paragraph 52 of Bell also cited and incorporated by reference Evans, a POSA would not have understood this as teaching an alternative isotype for the "eculizumab" antibody. As discussed above, while Evans did disclose "scFv" compounds and other functional fragments like "Fab," Evans did not disclose any full-length humanized antibodies, and only described human constant regions generically. (*See* Section VI.D.5 above.) Evans in particular did not make any reference to IgG2/IgG4 antibodies. (ALXN2032 at 163:25-164:19.) In fact, the only heavy chain constant regions described in Evans are the CH1 regions of "Fd" fragments[12] (SEQ ID NOs: 11 and 12) that do not align with the constant regions of the claimed sequence. (*See* Section VI.D.5 above.)

207. Accordingly, Bell's citation to Evans was not inconsistent with the understanding that Bell, and the other available literature, identified "eculizumab" as having an IgG4 isotype. A POSA would have understood that

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[12] Evans defines an "Fd" fragment as the heavy chain portion of an "Fab," meaning a truncated heavy chain that contains VH and CH1. (AMG1007 at 43:18-19.)

Samsung Bioepis Exhibit No. 1002
Page 11513

Bell could have only referenced Evans for the humanized "fragments" it disclosed, and that Bell in turn cited Thomas for the disclosure of the full-length "eculizumab" antibody that was the subject of Bell's clinical trials in PNH. The following figure illustrates how a POSA would have understood Bell's teaching that "eculizumab" was the IgG4 antibody of Thomas, consistent with the other prior art available prior to March 15, 2007:

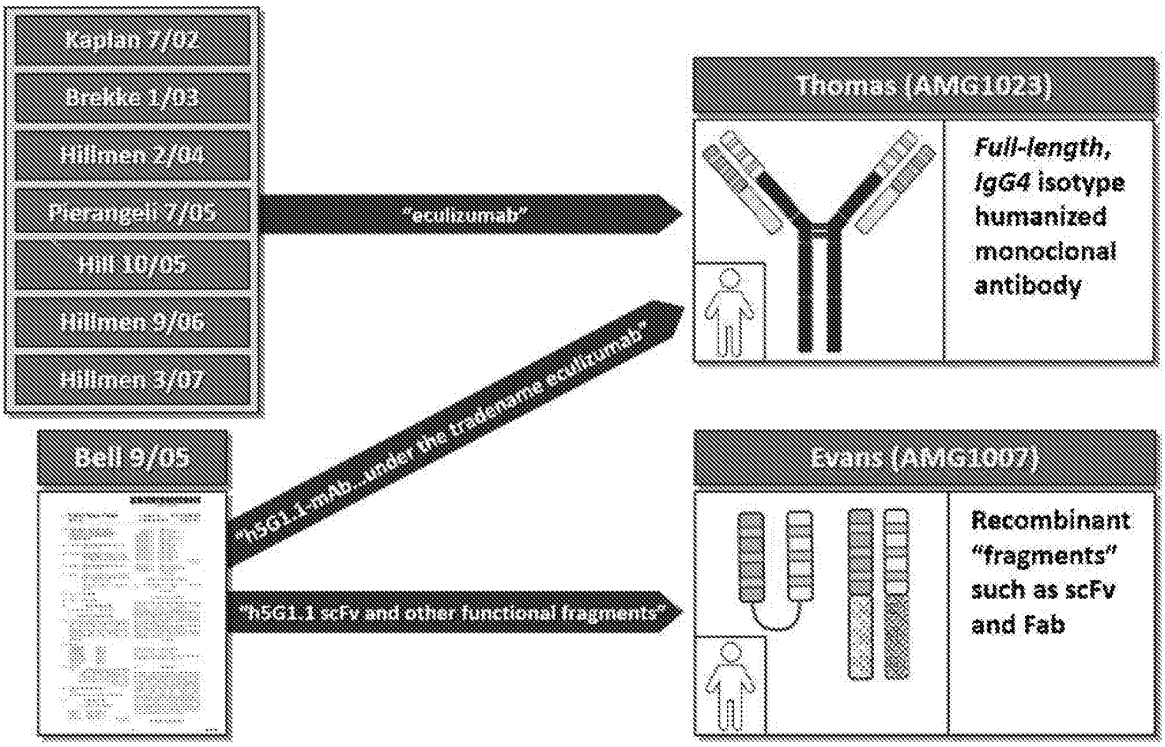


Figure 9: A POSA's understanding of Bell's teaching regarding "eculizumab," "h5G1.1 scFv," and "other function fragments

208. And if there was any doubt regarding the structure of the "eculizumab" antibody Bell referred to with respect to its evidence of clinical

safety and efficacy in treating PNH (AMG1005 at [0081]-[0096]), a POSA's review of the other related literature would have confirmed that Bell was referring to Thomas's IgG4 antibody. In particular, as Dr. Balthasar acknowledged, the clinical studies reported in Bell for "eculizumab" were the same as those reported in Hillmen (AMG1004) and Hill (AMG1047) – two references that unambiguously cited Thomas as the reference for what "eculizumab is." (AMG1004 at 553, Ref. No. 15; AMG1047 at 2559, Ref. No. 9; ALXN2032 115:16-23.)

2. A POSA Without the Benefit of Hindsight Would Not Have Been Motivated to Combine Bell with Bowdish and Evans

209. A POSA starting with Bell for its teaching of "eculizumab" as a safe and effective treatment for PNH, as Dr. Balthasar does, would have had no reason or motivation to deviate from the IgG4 antibody structure of Thomas that Bell associated with the therapeutically useful "eculizumab" antibody, and turn instead to (1) Bowdish, which Bell did not cite, and contained no information regarding anti-C5 antibodies; or (2) Evans, which did not disclose any full-length humanized antibodies, and at best may have suggested an IgG1 antibody based on the "Fd" sequences it disclosed. (*See* Section VI.D.5 above.) And, a POSA provided with Bell would not have been motivated to make a new, untested antibody using a clinically-untested non-naturally occurring hybrid constant

Samsung Bioepis Exhibit No. 1002
Page 11515

region, when Bell taught that "eculizumab," identified as an IgG4 antibody, was safe and effective for human use.

210. I disagree with Dr. Balthasar's arguments regarding why he claims a POSA would have been motivated to combine Bell, Bowdish, and Evans. Dr. Balthasar's sole explanation for why a POSA would have been motivated to combine these references is that a POSA would have looked to Bowdish and Evans to try to determine the sequence of "eculizumab" following review of Bell. I disagree that a POSA would have read Bell, and then looked to Bowdish and Evans for the "eculizumab" sequence, as Dr. Balthasar asserts. (*See* AMG1002 at ¶ 114.)

211. First, I note that that neither Bell, nor the Thomas or Evans references cited in Bell, cited to Bowdish for teaching "eculizumab," or for any other antibody. Nor would anything else in Bell have directed a POSA to Bowdish. For example, nothing in Bowdish concerns the subject matter of Bell, including, e.g., antibody binding of C5, using anti-C5 antibodies to block complement activity, or treatment of PNH.

212. Bowdish's use of the term "5G1.1" in connection with its TPO-mimetic construct would not have guided a POSA to Bowdish for teaching of "eculizumab" because, as discussed above, the term 5G1.1 was not understood to unambiguously refer to the antibody "eculizumab." (*See* Section VI.D.3 above.)

Samsung Bioepis Exhibit No. 1002
Page 11516

And as used in Bowdish, when referring to "[c]onstruction of 5G1.1," a POSA would have understood Bowdish to be referring to the mouse antibody of Evans, not "eculizumab" – a full-length intact antibody that was not disclosed anywhere in Evans.

213. Dr. Balthasar's argument to connect Bell to Bowdish requires him to assume that a POSA understood that "eculizumab" had a hybrid IgG2/IgG4 constant region. (AMG1002 ¶¶ 114-115; ALXN2032 at 196:15-23, 198:21-199:3.) His argument fails for that reason alone, because as I explained above, the teaching in Bell and the other predominant clinical literature as of March 15, 2007 was that "eculizumab" was an IgG4 isotype antibody of Thomas, not a hybrid IgG2/IgG4 isotype. (*See* Section VI.D.5 above.)

214. Bowdish's reference to Evans's mouse "5G1.1" antibody would not have taught a POSA anything about the C5 binding properties or other properties of Bowdish's TPO-mimetic compound or the "scaffold" it came from, because a POSA would that Bowdish's TPO-mimetic compound had a very different sequence and structure from Evans's original mouse antibody. The following figure illustrates the sequence alignment of Bowdish's Figs. 13A (SEQ ID NO: 67, heavy chain) and 13B (SEQ ID NO: 69, light chain) with the variable heavy chain and variable light chain of the "5G1.1" mouse antibody from Evans (Evans Fig. 19 (variable heavy chain) and Evans Fig. 18 (variable light chain)). This figure

confirms that a POSA looking from Bowdish to Evans for "[c]onstruction of 5G1.1" would not be guided towards the claimed antibody of the '149 patent:

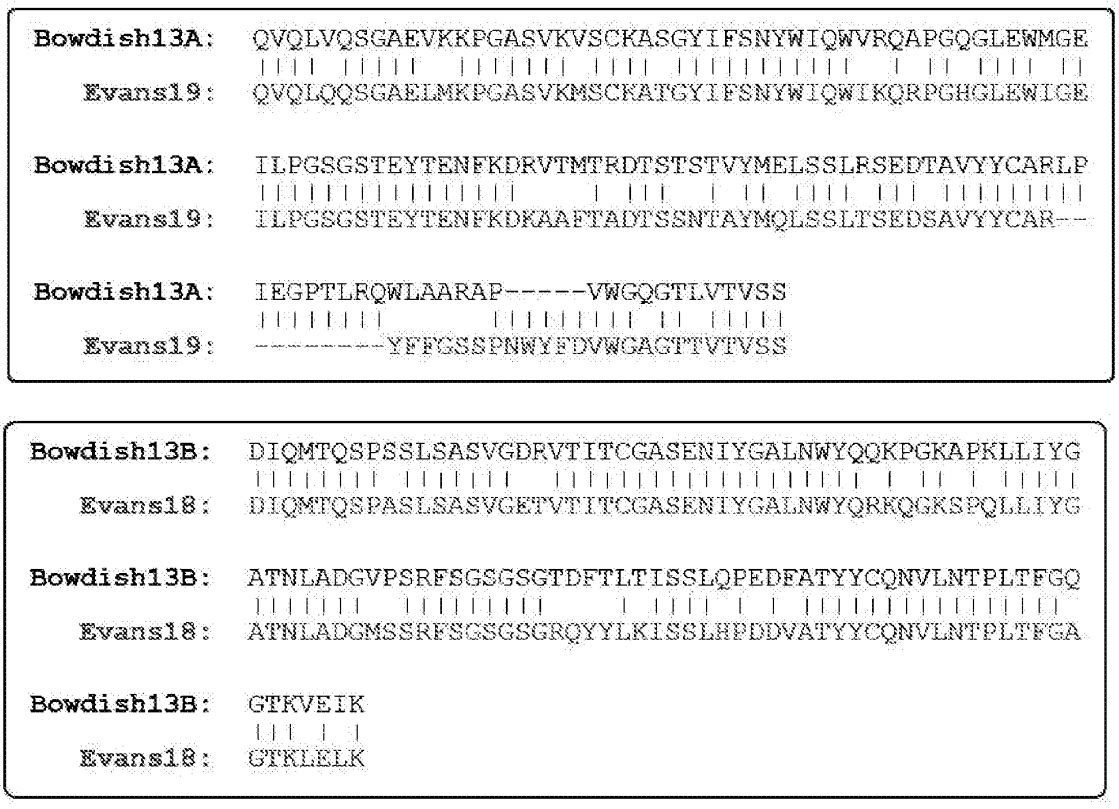


Figure 10: Bowdish Figure 13A (SEQ ID NO: 67) compared to Evans Fig. 19 **Bottom:** Bowdish Fig. 13B compared to Evans Fig. 18

Samsung Bioepis Exhibit No. 1002
Page 11518

215. Further, I understand that Alexion has obtained the full amino acid sequence of the "5G1.1" antibody of Evans from the HB-11625 hybridoma. (ALXN2075 at 2-3.) The following figure illustrates the sequence alignment of Bowdish's Fig. 13A (SEQ ID NO: 67) with the full heavy chain of the "5G1.1" mouse antibody from Evans. As with the figure above, this further confirms that a POSA looking from Bowdish to Evans for "[c]onstruction of 5G1.1" would not be guided towards the claimed antibody of the '149 patent:

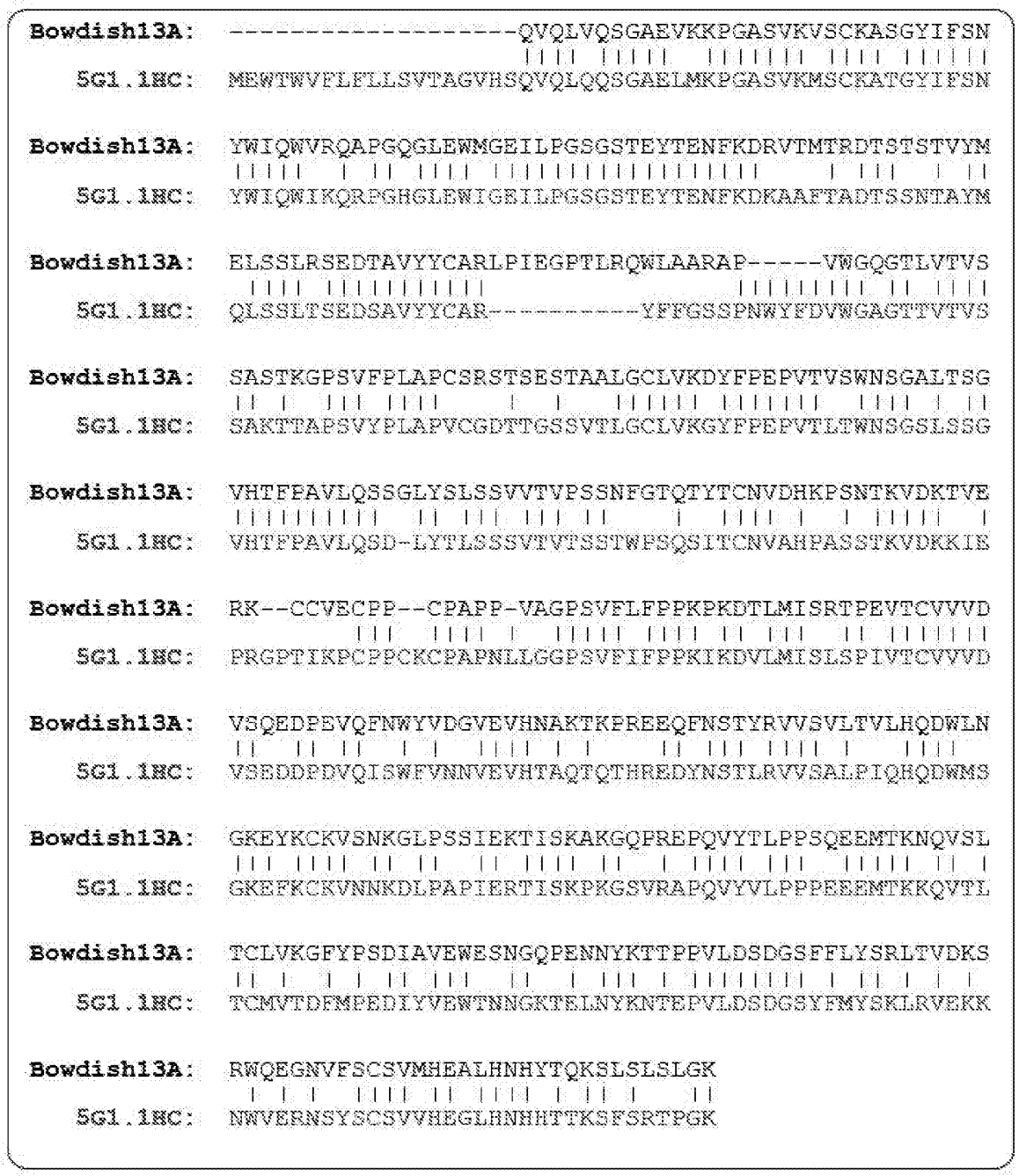


Figure 11: Bowdish Figure 13A (SEQ ID NO: 67) compared to heavy chain of 5G1.1 antibody from HB-11625

Samsung Bioepis Exhibit No. 1002
Page 11520

216. Even assuming Dr. Balthasar's incorrect position that a POSA would have understood "eculizumab" to already have an IgG2/IgG4 isotype, a POSA would not have combined Bell with Bowdish because a POSA would not have immediately recognized that the sequences in Figure 13 of Bowdish included humanized constant regions or an IgG2/IgG4 isotype. As Dr. Balthasar testified, Bowdish does not state that the sequences in Figure 13 are humanized or that they correspond to an IgG2/IgG4 constant region, and a POSA would have had to perform a sequence alignment using "BLAST" or another tool to determine these characteristics. (ALXN2032 at 199:19-23, 212:10-214:13.) A POSA attempting to design an anti-C5 antibody would have had no motivation to perform such an alignment, however, because Bowdish's TPO-mimetic was not identified as targeting C5, and, as discussed, Bowdish's reference to "5G1.1" would not have unambiguously identified the antibody "eculizumab." Nothing in Bowdish specifically guided a POSA to use BLAST or a similar search tool to analyze the sequences for its TPO-mimetic compound. (ALXN2032 at 214:19-24.) Further, Dr. Balthasar's Declaration does not provide any demonstration of what the results would have been if a POSA had performed such an alignment prior to March 15, 2007. (ALXN2032 at 214:25-215:8.)

217. I also disagree with Dr. Balthasar's conclusion that a POSA would have understood that the sequences in Bowdish Figure 13 were humanized based

Samsung Bioepis Exhibit No. 1002
Page 11521

on the FACS experiment described in Bowdish Example 4. (*See* AMG1002 at ¶ 90.) As I noted above (*see* Section VII.A.2 above), a POSA would not have been able to conclude that the sequences in Bowdish were humanized solely because Bowdish referred to use of an unspecified, uncharacterized "anti-human IgG" reagent that could have had any of a number of possible epitopes and levels of cross-reactivity.

218. Accordingly, given the unpredictability associated with humanized therapeutic antibody design as discussed in Sections VI.D.2 and VI.D.4 above, and the substantial expense and unpredictability of developing and testing a humanized monoclonal antibody for human therapeutic use as discussed in Section VI.D.2 above, a POSA would have no motivation to deviate from the thoroughly-studied "eculizumab" antibody that a POSA would have believed was an IgG4 isotype. A POSA in particular would not have been motivated to make such an untested, unstudied antibody with a non-naturally occurring hybrid IgG2/IgG4 isotype region, because there were no reports in the literature of ***any*** antibody with that isotype that had been clinically tested, and accordingly, a POSA could not have reasonably expected such an antibody to be therapeutically useful or suitable for human administration.

219. A POSA further would not have combined Bell and Bowdish based on Bell's reference to Evans. (*See* AMG1005 at ¶ [0052].) A POSA would not

Samsung Bioepis Exhibit No. 1002
Page 11522

have been motivated to combine Bowdish after review of Evans because Evans does not reference Bowdish, and Bowdish is directed to unrelated subject matter – it does not discuss antibody binding of C5 to block complement, or treatment of PNH, which is the subject of Evans. Nor would a POSA have associated Bowdish with Bell and Evans just because they all included some variant of the term "5G1.1" (*e.g.*, "5G1.1" in Evans and Bowdish; "h5G1.1-mAb" in Bell). As I discuss above in Section VI.D.3, a POSA would have understood that the term "5G1.1" and its derivates (*e.g.*, "h5G1.1") were terms that could refer to many different variants depending on their context. A POSA searching for information on "eculizumab" would have known that a search for "5G1.1" instead would have been overbroad, and would have captured information that was not instructive on the specific structure and specific properties of "eculizumab." For example, Evans used the term "5G1.1" to refer to the original mouse antibody from the "5G1.1" hybridoma, which a POSA would have understood was not "eculizumab." (AMG1007 at 19:47-49, Figs. 18-19, Examples 7-10 (37:34-40:29); *see* ¶ 164 above.) And I agree with Dr. Balthasar that, even when the term "h5G1.1" was used – which it was ***not*** in Bowdish – a POSA would have understood that term could refer to a variety of different antibody variants that are not "eculizumab," unless "eculizumab" was expressly specified. (ALXN2032 at 98:2-99:8, 159:1-10, 202:24-203:14.) Bell did specify that its "h5G1.1-mAb" was "eculizumab," but

Samsung Bioepis Exhibit No. 1002
Page 11523

then further identified it as the IgG4 antibody of Thomas (*see* Section VII.D.1 above) – which would not have motivated a POSA to look to Bowdish for its reference to "5G1.1" of Evans.

220. Even if a POSA were to have turned from Bell to Bowdish and Evans – despite there being no reason for a POSA without hindsight to have done so – nothing in the combination of those three documents would have disclosed the specific amino acid sequence recited in claim 1 of the '149 patent, or motivated a POSA to make an antibody with that sequence. Bowdish and Evans, when read alone or in combination, did not disclose the specific claimed amino acid sequence of the '149 patent, and would not have motivated a POSA to make an antibody with such a sequence, for the reasons I discussed in Section VII.C above.

3. A POSA Without the Benefit of Hindsight Would Not Have Reasonably Expected Success in Making An Antibody with the Specific Amino Acid Sequence Claimed in the '149 Patent

221. I disagree with Dr. Balthasar that a POSA would have reasonably expected success in combining Bell, Bowdish, and Evans to prepare the full-length sequence claimed in the '149 patent. (AMG1002 at ¶ 106.) In my opinion, Dr. Balthasar ignores the known complexity and unpredictability in antibody design as of March 15, 2007, including the design of humanized monoclonal antibodies; the rounds of *in vitro* and preclinical testing for such antibodies; and the challenges,

Samsung Bioepis Exhibit No. 1002
Page 11524

expenses and unpredictability of clinical research. (*See* Sections VI.D.2 and VI.D.4 above.)

222. Dr. Balthasar conclusively states that "a POSA would have had reason to combine the disclosures of Bell, Bowdish and Evans to arrive at the antibody of claim 1, and would have had a reasonable expectation of doing so because these three references provide complementary information relating to an anti-C5 antibody that would have required only routine techniques to combine." (*See* AMG1002 at ¶ 106.) He also conclusively states that such a combination would require only "basic molecular and cellular biology techniques." (AMG1002 ¶ 118.)

223. Dr. Balthasar is mistaken, because he equates the antibody he constructs from Bowdish and Evans with "eculizumab" as taught by Bell and the other clinical literature. But, as discussed above, that literature consistently identified "eculizumab" as a very different antibody (Thomas's IgG4 isotype antibody) than the claimed antibody sequence. Nothing in Bowdish and Evans, or Bell, would have taught or given a POSA a reasonable expectation of success that a different antibody with the specific amino acid sequence of claim 1 of the '149 patent would "bind[] C5," or whether it would be safe or provide a therapeutic benefit to patients.

224. Even if the IgG4 antibody of Thomas identified in the pre-March 15, 2007 literature as "eculizumab," and the different antibody with the sequence

Samsung Bioepis Exhibit No. 1002
Page 11525

claimed in the '149 patent, shared some amino acid sequences in common, a POSA would not have reasonably expected that the two antibodies shared properties in common, because the impact of their differences in amino acid sequence could not have been reasonably predicted. (*See* Section VI.D.4 above.) A POSA would have been aware that those differences impacted by amino acid sequence could include, for example, differences in affinity and specificity for C5; differences in "fine specificity" for C5 (*i.e.*, the epitope, which as discussed below, could be critical); differences in pharmacokinetic properties; differences in safety or immunogenicity in humans; differences in therapeutic effect in humans; and differences in the ability to be formulated into a pharmaceutical composition suitable for human administration. (*See* Sections VI.D.2 and VI.D.4 above.)

225. With respect to binding interactions, a POSA would have understood that, for therapy with an anti-C5 antibody, not only were binding affinity and specificity important, but "fine specificity" (the ability of the antibody to bind the antigen at a specific epitope) was understood to be critical to therapeutic activity. For example, the following figure, contained in a review article published in 1995, illustrates the complement pathway, and highlights the target of anti-C5 monoclonal antibody therapy as understood at that time (such as with Thomas's IgG4 isotype anti-C5 antibody):

Samsung Bioepis Exhibit No. 1002
Page 11526

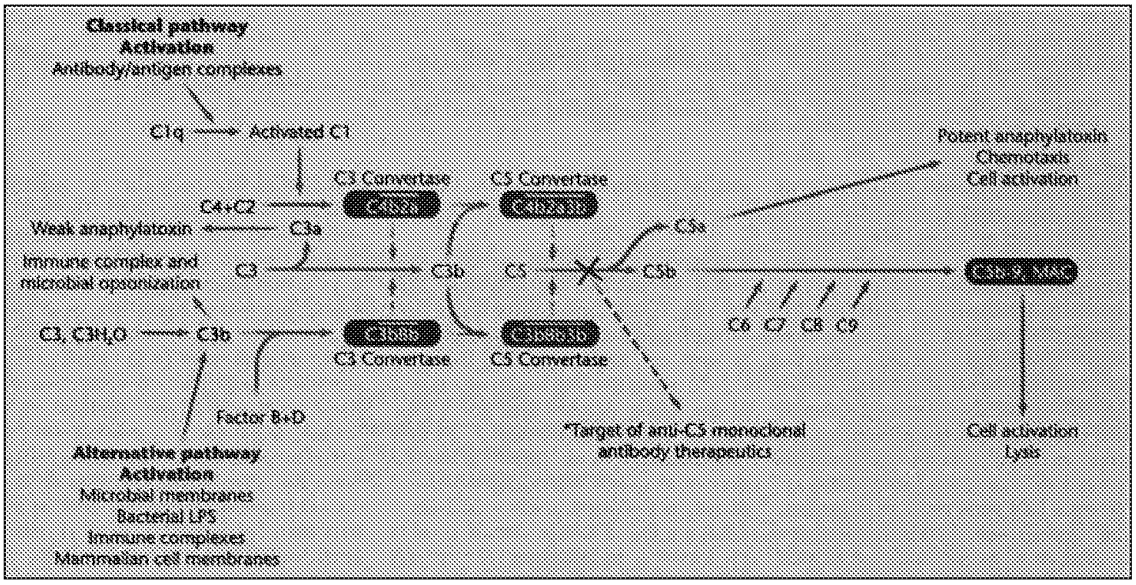


Figure 12: Mattis & Rollins (1995), Fig. 1 (AMG1039 at 840)

226. For the antibody that Dr. Balthasar constructs in hindsight from Bowdish and Evans to match the claimed sequence, a POSA would have had no information regarding any of its critical properties, including any of its binding properties, its in vitro biological assay activity (*e.g.*, in hemolytic assays), its ability to be formulated into a pharmaceutical composition, or usefulness of the antibody in treating PNH or any other condition.

227. As this figure illustrates, a POSA would have understood that it was not enough for an anti-C5 to merely bind to C5 to have its therapeutic effect, but the antibody would have to bind C5 in a way that blocks its enzymatic cleavage into C5a and C5b, and the downstream effects that result from the components C5a and C5b. For example, Thomas noted that "[a] clinically useful C5 inhibitor must

block generation of both C5a and C5b-9, as both of these molecules have potent pro-inflammatory effects," and pointed to a prior compound ("N19-8 scFv") that bound to C5 but did not effectively block C5 generation. (AMG1023 at 1398-99.)

228. The following figure illustrates how (1) a POSA prior to March 15, 2007 would have believed that there was extensive information confirming the C5 binding, *in vitro* activity, safety and efficacy for the IgG4 isotype antibody of Thomas, which the art identified as "eculizumab," and (2) how a POSA would have had no information regarding an antibody with the specific claimed sequence of the '149 patent, which was not disclosed prior to March 15, 2007 and was not reported in the literature prior to that date as having been tested *in vitro*, in animals or in humans:

Samsung Bioepis Exhibit No. 1002
Page 11528

Understanding of a POSA Prior to March 15, 2007

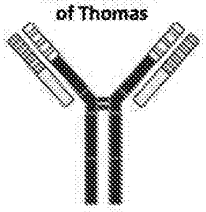
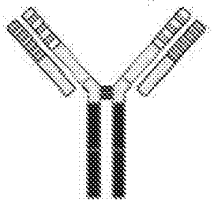
	Identified as "Ecalizumab"?	Binds to C5?	Blocks C5 activity in vitro?	Treats PNH?	Suitable for formulation and human administration?
"h5G1.1 HuG4" of Thomas 	YES	YES Similar binding to mouse 5G1.1	YES Same *in vitro* activity as mouse 5G1.1	YES Efficacy reported in Phase II/Phase III studies	YES No major safety/ immunogenicity issues in clinical trials
Claimed Antibody – Sequence *Not Known* Prior to March 15, 2007 	NO	?	?	?	?

Figure 13: A POSA's understanding prior to March 15, 2007 of (1) the IgG4 humanized antibody of Thomas, and (2) an antibody with the then-unknown amino acid sequence claimed in the '149 patent

229. Accordingly, even if a POSA provided with Bell, Bowdish and Evans could have somehow envisioned or made an antibody with the specific claimed amino acid sequence prior to March 15, 2007, they still would not have been motivated or had a reasonable expectation of success in doing so.

E. Claim 1 of the '149 Patent Would Not Have Been Obvious Over Evans and Mueller (Ground 5)

230. Amgen's Ground 5 contends that claim 1 of the '149 patent would have been obvious over the combination of Evans and Mueller.

Samsung Bioepis Exhibit No. 1002
Page 11529

231. In my opinion, Amgen's Ground 5 fails, because, among other things, Amgen cannot show that each element of the claimed invention was known or obvious in view of Evans and Mueller.

1. A POSA Without the Benefit of Hindsight Would Not Have Combined Evans and Mueller to Make the Specific Claimed Antibody of the '149 Patent

232. Neither Evans nor Mueller, alone or in combination, would have disclosed the specific, full-length antibody sequence claimed in the '149 patent. (*See* Section VII.A.2.)

233. I disagree with Dr. Balthasar that a POSA would have been motivated to combine Evans and Mueller. Evans and Mueller did not reference each other, and a POSA would not have looked to Mueller to design constant regions for the humanized variable regions described in Evans because Mueller was not related to C5-binding or treatment of PNH, the subject of Evans. Mueller disclosed no experiments or data on C5 binding or blocking complement. Mueller only referenced "h5G1.1" antibodies, with either IgG4 or IgG2/G4 heavy chain constant regions, as "isotype control[s]" in studies measuring the activity of anti-VCAM antibodies. (AMG1008 at 12:27-30; AMG1031 at 442-43, 448.)

234. Additionally, a POSA would not have looked to Mueller to design constant regions for the Evans' variable regions because the prior art taught that the clinically proven anti-C5 therapy for PNH, "eculizumab," had an IgG4 isotype.

Samsung Bioepis Exhibit No. 1002
Page 11530

Based on the teachings of Thomas and multiple other references guiding a POSA towards the IgG4 isotype, a POSA would have had no motivation to look to Mueller to alter what a POSA would have understood to be the isotype of an already tested antibody with therapeutic effect.

235. I disagree that a POSA would have been motivated to look to Mueller because of any alleged benefits regarding its hybrid "G2/G4" constant region which, from the perspective of a POSA prior to March 15, 2007, had never been used in any antibody that had been formulated as a pharmaceutical composition or tested in a clinical trial. As disclosed by Thomas and the numerous references citing Thomas, a POSA would have understood that there was already an effective, anti-C5 antibody used for treatment of PNH – eculizumab – and that this antibody had an IgG4 isotype. (AMG1004 at 553; AMG1047 at 2559; AMG1012 at 1234; ALXN2028 at 31; AMG1005 at ¶ [0052]; AMG1021 at 1018; AMG1019 at 56; AMG1020 at 2123.) As discussed in Section VI.D.2 above, as of March 15, 2007, the process of designing a functional, humanized monoclonal antibody was known to be complex and time-consuming, involving multiple rounds of design iteration and testing. Understanding the unpredictability and expense associated with this process, including due to the potential negative impacts of isotype-switching on antibody function (*see* Sections VI.D.2 and VI.D.4 above), a POSA would not have been motivated to investigate a new isotype, and risk losing the already

Samsung Bioepis Exhibit No. 1002
Page 11531

established therapeutic benefit of "eculizumab," which a POSA would have understood to be an IgG4 tested in clinical trials.

236. Even if a POSA had chosen to adopt an IgG2/IgG4 hybrid isotype – which a POSA would not have considered, given the unpredictability of antibody design, and the absence of any evidence regarding how such an isotype would perform in humans or in pharmaceutical compositions – a POSA would not have necessarily selected the IgG2/IgG4 hybrid constant regions described in Mueller. As of March 15, 2007, a POSA would have understood that a hybrid IgG2/IgG4 isotype could be constructed in multiple ways, and would have had many choices for this design other than the sequence described in Mueller.

237. I disagree with Dr. Balthasar's assertion that Evans and Mueller would have been linked because both allegedly disclosed "humanized 5G1.1" or "h5G1.1." (AMG1002 at ¶ 127.) First, this statement is inaccurate because Evans did not disclose any full-length humanized 5G1.1 antibodies, but instead only humanized antibody "fragments." Again, to be clear, a POSA would have understood that the "fragments" of Evans were not the partial sequences of a full-length antibody, in the way that Evans disclosed the variable region sequences of a full-length mouse antibody. Evan's "fragments" were standalone molecules manufactured by recombinant DNA means from the ground up, and they never

Samsung Bioepis Exhibit No. 1002
Page 11532

belonged to, and were not pieces or components of, any larger full-length humanized antibody. (*See* Section VI.D.5 above; ALXN2032 at 228:2-16.)

238. Moreover, as explained in Section VI.D.3 above, and as Dr. Balthasar confirmed at his deposition, the term "5G1.1" could encompass multiple antibodies and antibody fragments, and a POSA would not have understood "5G1.1" as necessarily identifying "eculizumab." (ALXN2032 at 97:23-99:20, 100:3-12.) For example, Dr. Balthasar admitted he could not determine that the "h5G1.1 IgG4" antibody described in Mueller was the same as the IgG4 antibody described in Thomas. (ALXN2032 at 241:23-242:12.) Multiple prior art references used the "5G1.1" terminology, including clinical publications describing C5 binding and clinical testing of eculizumab, and a POSA would not have looked to Mueller over these other, more relevant publications.

239. In addition, Dr. Balthasar cites the alphanumeric "CO12" as providing guidance for the combination of a particular variable region disclosed in Evans with constant regions disclosed in Mueller. A POSA would not have understood "CO12" to refer specifically to the clinically-tested antibody "eculizumab." A POSA would have understood "eculizumab" to be the unique name for which Alexion had sought approval for its clinical tested antibody (*see* Section VI.D.3 above), but a POSA could not have been sure what "CO12" was or referred to. For example, "CO12" is used in Evans to describe an scFv, whereas in Mueller it refers

Samsung Bioepis Exhibit No. 1002
Page 11533

to a full-length antibody. (*See* AMG1007 at 44:4-13; AMG1008 at 12:34-37.) Accordingly, a POSA could not have reasonably assumed that the term always referred to the same molecule. Particularly in view of teachings in the art that eculizumab had an IgG4 isotype, a POSA would not have been guided to Mueller, or towards any combination of sequences from Evans in combination with Mueller, based on use of the undefined designation "CO12."

240. I disagree with Dr. Balthasar that "[o]verlapping sequences" would have caused a POSA to combine sequences from Mueller and Evans. (AMG1002 at ¶ 128.) Dr. Balthasar appears to base this conclusion on overlap between the light chain constant region of Mueller's 3F4 antibody and the light chain constant region from "5G1.1 scFv CO12." Dr. Balthasar fails to explain, however, why a POSA would have been motivated to combine Evans' variable region sequences with an IgG2/IgG4 constant region, given that Mueller also disclosed a second control antibody, "h5G1.1 CO12 HuG4 mAb," that a POSA would have believed to be the clinically effective "eculizumab," and would have been more likely to follow.

241. It is my opinion that a POSA would not have been able to readily combine the correct variable region sequences from Evans with Mueller's hybrid IgG2/IgG4 constant region based on the teachings of those references. Rather, Dr.

Samsung Bioepis Exhibit No. 1002
Page 11534

Balthasar uses significant hindsight to pick and choose sequences from Evans and Mueller to reach the specific sequence claimed in the '149 patent.

242. For example, as Dr. Balthasar admitted at his deposition, Mueller did not indicate exactly where the IgG2/IgG4 heavy chain sequences in its anti-VCAM antibodies began or ended. (ALXN2032 at 233:22-234:4.) Dr. Balthasar uses hindsight to extract the correct constant regions from Mueller's disclosure of a full length "3F4" anti-VCAM antibody by inferring that the correct boundaries of the IgG2/IgG4 constant regions sequences would be what remained after subtracting the 3F4 variable region, and through comparison to the claimed sequence, which would not have been available to a POSA before March 15, 2007. (*See* AMG1002 at ¶¶ 132-135; ALXN2032 at 233:3-234:4.) As Dr. Balthasar further testified, Mueller did not disclose any complete "h5G1.1" or anti-C5 binding antibody sequences. (ALXN2032 at 232:22-233:14.) Accordingly, there is no disclosure in Mueller of how the IgG2/IgG4 constant sequences he extracts would fit with any particular, undefined "h5G1.1" variable region.

243. Even if a POSA would have understood that the term "CO12" in Mueller referred to the "CO12" scFv in Evans – which Dr. Balthasar has not shown – neither Mueller nor Evans provided guidance as to exactly which sequences, or the precise extent of the sequences, a POSA would have used from the Mueller "h5G1.1 CO12 HuG2/G4" and Evans "5G1.1-scFv-CO12" constructs

Samsung Bioepis Exhibit No. 1002
Page 11535

to create a functional, full-length, anti-C5 antibody. Without such guidance, a POSA could have easily selected sequences that failed to correspond to the claimed antibody sequence rather than those selected by Dr. Balthasar.

244. Dr. Balthasar also does not explain why, even if a POSA were to have considered using IgG2/IgG4 constant regions described in Mueller, a POSA would have selected variable regions from Evans, rather than Thomas, to combine with those constant regions. The light chain variable region sequences described in Thomas differed from the variable regions of Evans's "5G1.1-scFv-CO12" construct at light chain position 38. (*See* AMG1023 at 1396 (Fig. 4); AMG1007 at 42-44 (Certificate of Correction).) Accordingly, a POSA that chose to follow Thomas (which Bell also cited) as opposed to Evans for the variable region sequences would not have arrived at the claimed amino acid sequence of the '149 patent.

245. A POSA as of March 15, 2007 would have had no motivation to select any of the variable regions disclosed in Evans and combine them with the IgG2/IgG4 constant regions described in Mueller, thereby potentially destroying the desirable clinical properties associated with the IgG4 isotype described in Thomas and publications citing Thomas, and understood at the time to be the isotype for "eculizumab." As discussed above, the term "CO12" would have been too ambiguous to provide guidance to a POSA to select a particular set of variable

region sequences from the multiple variable region sequences disclosed in Evans, and combine it with a particular set of constant regions disclosed in Mueller.

246. Even if a POSA had sought to combine variable sequences from Evans with constant regions from Mueller, there was no guidance in either Evans or Mueller as to how to do so – for example, neither reference provided guidance as to exactly what lengths of the disclosed variable and constant regions should be combined. (*See* ALXN2032 at 233:22-234:4.) The Mueller II publication would only have created further ambiguity regarding the boundaries of the "HuG2/G4" construct, because Mueller I contained an extra amino acid after its disclosed variable regions that does not appear in the "HuG2/G4" construct described in Mueller II. (*See* AMG1008 at 59 ("3F4 Human G2/G4 Expression Plasmid Insert Sequence" at position 138); AMG1031 at 449 (Fig. 9).)

247. It is also my opinion that Dr. Balthasar's depiction of the combination of Evans and Mueller in his Declaration reflects significant use of hindsight. For example, I disagree with Dr. Balthasar's alignments in Figures 17-18 of his Declaration (*see* AMG1002 at ¶¶ 85-86), which compare sequences from Mueller and Evans against SEQ ID NO: 2 and SEQ ID NO: 4 recited in the '149 patent. A POSA as of March 15, 2007 would not have had the guidance of the disclosure of SEQ ID NO: 2 and SEQ ID NO: 4 from the '149 patent to help select sequences to

Samsung Bioepis Exhibit No. 1002
Page 11537

combine from Evans and Mueller, and accordingly would not have reached the claimed full-length sequence of the '149 patent.

2. A POSA Without the Benefit of Hindsight Would Not Have Reasonably Expected Success in Making An Antibody with the Specific Amino Acid Sequence Claimed in the '149 Patent

248. As with Ground 4, I disagree with Dr. Balthasar that a POSA would have reasonably expected success in combining Evans and Mueller to prepare the full-length sequence claimed in the '149 patent. (AMG1002 at ¶ 136.) In my opinion, Dr. Balthasar ignores the known complexity and unpredictability in antibody design as of March 15, 2007, including the design of humanized monoclonal antibodies; the rounds of *in vitro* and preclinical testing for such antibodies; and the challenges, expenses and unpredictability of clinical research. (*See* Sections VI.D.2 and VI.D.4 above.)

249. Dr. Balthasar conclusively states that a POSA would have had a reasonable expectation of success in making the specifically claimed antibody because it "would have required only basic molecular and cellular biology techniques." (AMG1002 ¶ 122.) Dr. Balthasar is mistaken, because he equates the antibody he constructs from Evans and Mueller with "eculizumab" as taught by Bell and the other clinical literature. But, as discussed above, that literature consistently identified "eculizumab" as a very different antibody (Thomas's IgG4 isotype antibody) than the claimed antibody sequence. Nothing in Mueller or

Samsung Bioepis Exhibit No. 1002
Page 11538

Evans would have taught or given a POSA a reasonable expectation of success that a different antibody with the specific amino acid sequence of claim 1 of the '149 patent would "bind[] C5," or whether it would be safe or provide a therapeutic benefit to patients.

250. Even if the IgG4 antibody of Thomas identified in the pre-March 15, 2007 literature as "eculizumab," and the different antibody with the sequence claimed in the '149 patent, shared some amino acid sequences in common, a POSA would not have reasonably expected that the two antibodies shared properties in common, because the impact of their differences in amino acid sequence could not have been reasonably predicted. (*See* Section VI.D.4 above.) A POSA would have been aware that those differences impacted by amino acid sequence could include, for example, differences in affinity and specificity for C5; differences in "fine specificity" for C5 (*i.e.*, the epitope); differences in pharmacokinetic properties; differences in safety or immunogenicity in humans; differences in therapeutic effect in humans; and differences in the ability to be formulated into a pharmaceutical composition suitable for human administration. (*See* Sections VI.D.2, VI.D.4 and VII.D.4 above.)

251. For the antibody that Dr. Balthasar constructs in hindsight from Mueller and Evans to match the claimed sequence, a POSA would have had no information regarding any of its critical properties, including any of its binding

Samsung Bioepis Exhibit No. 1002
Page 11539

properties, its *in vitro* biological assay activity (*e.g.*, in hemolytic assays), its ability to be formulated into a pharmaceutical composition, or usefulness of the antibody of the antibody in treating PNH or any other condition.

252. Accordingly, even if a POSA provided with Bell, Bowdish and Evans could have somehow envisioned or made an antibody with the specific claimed amino acid sequence prior to March 15, 2007, they still would not have been motivated or had a reasonable expectation of success in doing so.

F. Objective Indicia Support the Nonobviousness of Claim 1 of the '149 Patent

253. I understand from counsel that the nonobviousness of a patented invention may be supported by objective evidence ("objective indicia of nonobviousness").

254. In my opinion, objective evidence supports the nonobviousness of the invention claimed in the '149 patent, including: (1) a long-felt but unmet need in the industry that was satisfied by the patented invention; (2) the failure of others to develop the patented invention; (3) copying of the patented invention by others; (4) the commercial success of the patented invention; and (5) praise in the industry for the patented invention. I disagree with Dr. Balthasar's opinions to the contrary. (*See* AMG1002 ¶¶ 138-41.)

Samsung Bioepis Exhibit No. 1002
Page 11540

1. SOLIRIS® is the Commercial Embodiment of the '149 Patent

255. I understand from counsel that, to be considered, objective evidence of nonobviousness should have a "nexus" to the claimed invention. Counsel has informed me that if (1) the objective evidence is tied to a specific product, and (2) that product embodies the claimed features of the claimed invention, then there is a presumption that the objective evidence has a "nexus" to the claimed invention.

256. In my opinion, the commercial product SOLIRIS® embodies the claimed features of claim 1 of the '149 patent. Claim 1 of the '149 patent covers an antibody with the unique amino acid sequence reflected in heavy and light chain sequences SEQ ID NOs: 2 and 4. (AMG1001 at 39:2-4.) As discussed above, it is known today (but was not known prior to March 15, 2007) that the active ingredient in SOLIRIS® (eculizumab) is an antibody comprising SEQ ID NOs: 2 and 4, which works to treat PNH and other indicated complement-mediated conditions by binding to C5 and blocking its cleavage. (*See* Section VI.E above; ALXN2032 at 262:2-19.)

257. I also understand that SOLIRIS® was originally approved for, and presently has an indication for, "[t]he treatment of patients with [PNH] to reduce hemolysis." (ALXN2005 at 1, 2 (Section 1); ALXN2053 at 1, 3.) I further understand that SOLIRIS® is in supplied as a 300 mg single-dose vial that contains 30 ml of a 10 mg/ml solution of eculizumab, which is known today to have the

Samsung Bioepis Exhibit No. 1002
Page 11541

specific amino acid sequence of SEQ ID NOs: 2 and 4 recited in the '149 patent. (ALXN2005 at 1, 5 (Section 11); ALXN2053 at 1, 21.)

258. In my opinion, the objective evidence showing the success of SOLIRIS® -- therapeutically as a long-needed, life-saving therapy, as well as commercially – has a direct nexus with the patented invention of the '149 patent. The specially engineered anti-C5 antibody claimed by its unique amino acid sequence in claims 1 of the '149 patent is the agent that is directly responsible for the outstanding clinical benefits that SOLIRIS® provides as the first-approved treatment for patients suffering from PNH. (ALXN2053 at 22 (Section 12.1); ALXN2030 at 1.)

259. I further note that the claimed antibody of the '149 patent is also responsible for the clinical benefits to patients effectively treated by SOLIRIS® for several other rare conditions, including: (1) the life-threatening hemolytic condition atypical hemolytic uremic syndrome ("aHUS"); (2) the chronic autoimmune neuromuscular disease myasthenia gravis ("MG"); and (3) neuromyelitis optica spectrum disorder ("NMOSD"), a debilitating autoimmune disease of the central nervous system. (ALXN2053 at 1.)

Samsung Bioepis Exhibit No. 1002
Page 11542

2. SOLIRIS® Fulfilled a Long-Felt, Unmet Need for a Treatment of PNH, Which Others Failed to Satisfy

260. In my opinion, SOLIRIS® fulfilled a long-felt, unmet need for a treatment of PNH.

261. As I discuss in Section VI.A above, PNH was known prior to March 15, 2007, and is known today, as a chronic, debilitating and potentially life-threatening disease, where patients' red blood cells are constantly under attack by the body's own complement system. PNH has been referred to as the "most vicious acquired thrombophilic state known." (ALXN2050 1161-1170.) Symptoms of PNH, such as hemoglobinuria (dark urine caused by periods of acute hemolysis ("paroxysms"), chronic and potentially disabling fatigue, dysphagia, recurrent pain, and severe anemia, severely impacted patients' quality of life. (AMG1004 at 6; AMG1047 at 2559; AMG1012 at 1234.) Patients could also experience life-threatening blood clots, or "thrombosis." (AMG1004 at 6; AMG1047 at 2559; AMG1012 at 1234.)

262. SOLIRIS® was not only first anti-C5 antibody approved for any condition, but was the first treatment approved by the FDA for patients suffering from PNH. I understand that the FDA considered SOLIRIS® to be a significant medical breakthrough, granting it an expedited "Priority Review" that is reserved for drugs that are expected to have a substantial impact on the treatment of a serious disease. (ALXN2006 at 993; ALXN2030 at 1.) SOLIRIS® was also

Samsung Bioepis Exhibit No. 1002
Page 11543

granted "Orphan Drug" status for treatment of PNH in the FDA and the EU, recognizing that it was a much-needed therapy for a rare and untreated disease. (ALXN2019 at 1270.)

263. Prior to SOLIRIS®, there were no drugs directed to regulation of the body's complement system to treat PNH. Symptoms of PNH, such as hemoglobinuria (dark urine caused by periods of acute hemolysis ("paroxysms"), chronic and potentially disabling fatigue, dysphagia, recurrent pain, and severe anemia, severely impacted patients' quality of life. (AMG1004 at 6; AMG1047 at 2559; AMG1012 at 1234; ALXN2049 at 1-2.) Patients could also experience life-threatening blood clots, or "thrombosis." (AMG1004 at 6; AMG1047 at 2559; AMG1012 at 1234; ALXN2049 at 1-2.) Because there were no drugs directed towards regulation of complement as a treatment for PNH, patients were forced to rely on other, potentially invasive, therapies that could only address individual symptoms of the disease, such as blood transfusions. (*See* AMG1004 at 6; AMG1047 at 2559; AMG1012 at 1234.)

264. Reporting on the lack of effective treatments for PNH, Hillmen 2006, a pivotal Phase III clinical trial report for SOLIRIS® published in the New England Journal of Medicine stated, "there [was] no therapy that effectively reduce[d] intravascular hemolysis or improves the symptoms in patients with PNH" prior to SOLIRIS®. (AMG1012 at 1234; *see also* AMG1047 at 2559 ("There is no

Samsung Bioepis Exhibit No. 1002
Page 11544

effective treatment for the ongoing hemolysis in PNH.").) Prior to SOLIRIS®'s approval, PNH patients were often "transfusion-dependent," meaning that their survival depended on receiving frequent blood transfusions. (AMG1004 at 557; AMG1047 at 2559.)

265. The approval of SOLIRIS® "marked a distinct change in how physicians were able to treat patients with paroxysmal nocturnal hemoglobinuria." (ALXN2049 at 1.) I note how that physicians specializing in hematology – those responsible for managing and treating PNH patients – have praised SOLIRIS® for its marked therapeutic benefits and improvement in the lives of PNH patients. For example, as said by Dr. Peter Hillmen, a consultant hematologist at Leeds Teaching Hospital, "[e]culizumab has dramatically changed PNH…[u]ntil eculizumab arrived there was no specific treatment for PNH apart from transfusion and occasionally bone marrow transplant." (ALXN2049 at 1.)

266. Dr. Robert A. Brodsky, director of the division of hematology and Clara Lucas Lynn Chair in Medicine at The John Hopkins University, similarly praised eculizumab as a groundbreaking first-in-class treatment. According to Dr. Brodsky, prior to SOLIRIS®, "We had very little to offer patients. . . . Several years ago the only thing we would have had to offer [a PNH patient in crisis] was narcotics and maybe fluids. Now that eculizumab is approved, all I have to do is call down to the pharmacy and tell them that we need to start the patient on this

Samsung Bioepis Exhibit No. 1002
Page 11545

drug." (ALXN2049 at 2.) Others in the hematology field have offered similar testimonials and accolades for SOLIRIS®. (ALXN2050 at 1169) ("The advent of eculizumab has resulted in a dramatic improvement of the natural history of PNH patients with improvement in virtually every aspect of these patients' lives.").)

267. In sum, there is no question that the invention claim 1 of the '149 patent, as embodied by SOLIRIS®, satisfied a long-felt need, unmet need for a safe and effective means for treating the rare, debilitating, and potentially fatal blood disease, PNH, where prior existing treatment options had been limited and ineffective.

268. In my opinion, the nonobviousness of the '149 patent is also supported by the failure of others to solve the problem that was addressed by the claimed invention of the '149 patent and its commercial embodiment, SOLIRIS®. As Dr. Balthasar notes, researchers were interested in, and had published on, the concept of anti-C5 monoclonal antibody therapy, including its potential for use in the treatment of PNH, as early as the mid-1990s. (AMG1002 at ¶ 35; ALXN2032 at 262:23-264:13; AMG1039 at 2-3.) But it was not until the launch of SOLIRIS® that any solution to the severe problem of untreated PNH was introduced into the market.

269. The failure of others to develop an anti-C5 therapy, or any therapy, for the treatment of PNH over the course of more than a decade is, in my view, strong

Samsung Bioepis Exhibit No. 1002
Page 11546

objective evidence of the difficulty of developing monoclonal antibodies for human therapeutic use, and the nonobviousness of the claimed invention of the '149 patent in particular.

3. SOLIRIS® Is A Commercial Success

270. SOLIRIS® was approved by the FDA on March 16, 2007 for the treatment of patients with PNH to reduce hemolysis. (ALXN2005; ALXN2006 at 993; ALXN2030 at 1.)

271. I understand that since its approval, SOLIRIS® has been commercially successful, with over $1 billion in U.S. sales each year in each of the last three years.

272. In my opinion, the commercial success of SOLIRIS® is directly linked to the claimed invention of the '149 patent. As I explain in Section VII.F.1 above, the invention of claim 1 of the '149 patent is coextensive with the clear therapeutic benefits of SOLIRIS® that are highly valued by physicians and their patients suffering from PNH (*see* Section VII.F.2 above).

4. Industry Praise

273. Praise in the industry for SOLIRIS® further supports my opinions on the nonobviousness of the '149 patent. As shown above in Section VII.F.2, SOLIRIS®, the commercial embodiment of the claimed invention of the '149 patent, has received extensive praise from the medical industry, and in particular

Samsung Bioepis Exhibit No. 1002
Page 11547

from the physicians who are responsible for maintaining the survival and quality of life of their PNH patients, and had few options before SOLIRIS®.

274. I also understand that Alexion has received several significant awards honoring the groundbreaking nature of its development and introduction of SOLIRIS®, including the Prix Galien USA 2008 Award for Best Biotechnology Product, and the Prix Galien France 2009 Award for Most Innovative Drug for Rare Disease. (ALXN2020; ALXN2021.)

5. Copying

275. I am also aware that Amgen, who is challenging the '149 patent in this case, and other companies including Samsung Bioepis and Generium, are seeking to copy, or have already copied, eculizumab – which, as we known today, is the uniquely engineered antibody with SEQ ID NOs: 2 and 4 that is the sole active agent in SOLIRIS and the claimed pharmaceutical compositions of the '149 patent. (ALXN2088; ALXN2090; ALXN2089.)

276. The copying by others of the claimed antibody comprising SEQ ID NOs: 2 and 4 is, in my view, further objective evidence of the nonobviousness of the '149 patent's invention. If it were simple to recreate the clinical benefits of properties of SOLIRIS without using the specific amino acid sequence of eculizumab (as known today) claimed in the '149 patent, then these companies could have tried to develop their own antibodies with different amino acid

sequences not recited in the '149 patent claims. But they did not do so. Instead, it appears that these companies took the exact amino acid sequence recited and claimed in the '149 patent, and have tried to copy it in an effort to provide patients with the same clinical benefits provided by SOLIRIS®.

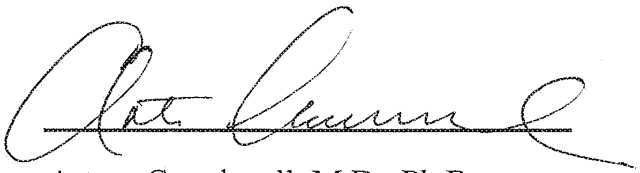
277. This supports my opinion, as explained in Sections VI.D.2 and VI.D.4 above, the process for designing a humanized, monoclonal antibody is unpredictable and requires an extensive investment of resources with no guarantee of eventual success – and these companies are more willing to copy SOLIRIS® and the claimed invention rather than develop their own unique antibodies, as Alexion did.

VIII. CONCLUSION

278. For the reasons stated above, claim 1 of the '149 patent was not anticipated or made obvious in view of any of the art or combinations of art alleged in Amgen's Grounds.

Samsung Bioepis Exhibit No. 1002
Page 11549

I declare that all statements made herein of my own knowledge are true, and that all statements made on information and belief are believed to be true, and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code.



Arturo Casadevall, M.D., Ph.D

Dated: November 22, 2019

Appendix A

Sept. 17, 2019

CURRICULUM VITAE

Arturo Casadevall

PERSONAL DATA

W. Harry Feinstone Department of Molecular Microbiology and Immunology
Johns Hopkins Bloomberg School of Public Health
615 N. Wolfe Street, E5132
Baltimore, MD 21205
Phone: 410-955-3457
FAX: 410-955-0105
E-Mail: acasad1@jhu.edu

EDUCATION AND TRAINING

Degree/Year Institution and Field Postdoctoral Training Medical or Other Licensure

Year	Degrees/Certificate	Discipline	Institution
Undergraduate			
1979	B.A. (Magna Cum Laude)	Chemistry	Queens College, CUNY
Doctoral/graduate			
1983	M.S.	Biochemistry	New York University
1984	Ph.D.	Biochemistry	New York University
1985	M.D.	Medicine	New York University
Postdoctoral			
1985-1988	Bellevue Hospital - NYU Medical Center Internship and Residency in Internal Medicine		
1988-1989	Albert Einstein/Montefiore Medical Center Fellowship in Infectious Diseases		
1989-1991	Postdoctoral Fellowship with Dr. Matthew D. Scharff of Cell Biology, Albert Einstein College of Medicine		
1991	Cold Spring Harbor Course on Yeast Genetics		

Medical Board or Other Certification

2013-2023	American Board in Internal Medicine Certified in the Subspecialty of Infectious Diseases American Board in Internal Medicine Specialist in Internal Medicine
1990	Diplomate in the Subspecialty of Infectious Diseases
1988	Diplomate in the Specialty of Internal Medicine
1986	National Board of Medical Examiners Diploma

PROFESSIONAL EXPERIENCE *(annotate as appropriate)*

Alfred & Jill Sommer Prof. & Chair Dept of Molecular, Microbiol. & Immunol	2015-Present	JH Bloomberg Sch. of Public Health
Visiting Prof of Med. & Microbiol. & Immunol.	2015-present	Albert Einstein College of Medicine
Director, Ctr for Immunological Sciences	2013-15	Albert Einstein College of Medicine
Leo and Julia Forchheimer Professorship	2006-15	Albert Einstein College of Medicine
Chair, Dept of Microbiology & Immunology	2006-15	Albert Einstein College of Medicine
Interim Chair, Dept of Microbiol. & Immunol.	2005-06	Albert Einstein College of Medicine
Selma and Jacques Mitrani Professorship	2002-06	Albert Einstein College of Medicine

Director, Division of Infectious Diseases	2000-06	Montefiore Medical Ctr-Albert Einstein
Professor, Med. & Microbiol. & Immunology	2001-15	Albert Einstein College of Medicine
Assoc. Prof, Med. & Microbiol. & Immunol.	1996-01	Albert Einstein College of Medicine
Asst. Prof. Med. & Microbiol. & Immunol.	1992-96	Albert Einstein College of Medicine

PROFESSIONAL ACTIVITIES

American Association for the Advancement of Science
American Association of Immunologists
American Society for Clinical Investigation
American Society for Microbiology
Medical Mycology Society of the Americas
Fellow, Infectious Disease Society of America
Harvey Society
Interurban Clinical Club
Practitioner's Society
National Academy of Medicine
American Academy of Arts and Sciences

Service to Scientific Societies

1998-2000	Vice-President, New York Mycology Society
2000-02	President of New York Mycology Society
1998, 2002	Nominating committee for American Society for Microbiology (ASM) Division F officers
1998-2000	Councilor, New York Society for Infectious Diseases
2005	ASM Division F Chair Elect
2005	Nominated as Candidate for President of ASM
2006-09	Chair, ASM Career Development Committee
2004-07	ASM Abbot Award Selection Committee
2007-10	ASM Committee on Awards
2008-11	ASM Membership Election committee
2008-11	ASM Communications Committee
2008-11	ASM Minority Recruitment Committee
2008-present	ASM Minority Affairs Committee
2014-16	American Association of Immunology Minority Affairs Committee
2008-09	Medical Mycology Society of America President
2011-14	Elected Member-at-Large, AAAS Section on Medical Sciences
2014-16	American Association for Immunology Minority Affairs Committee
2012-15	Research Committee of the IDSA
2016-19	Elected Chair of the Board of Governors of the American Academy of Microbiology
2017	Elected Member of the American Academy of Arts and Sciences

Conference Organizer, Session Chair

1997	13th Congress of the International Society of Human and Medical Mycology, Parma Italy. Convener of symposium titled: Cell-mediated versus antibody mediated-protection mechanisms in fungal diseases: an ongoing dilemma.
1997	Program committee: The Fourth NIAID Workshop in Medical Mycology, Lake Tahoe
1999	Scientific Committee: Fourth International Meeting on Cryptococcus and Cryptococcosis, London
2000	Organizer, Bacteriology and Mycology Horizons for the 21st century. A symposium in honor of Dr. William Branche, NIH, Shannon Building
2001	Convener, Symposium Host defense against fungi: application toward therapeutics and vaccine development. American Society of Microbiology, Orlando

2002 Scientific Committee: Fifth International Meeting on Cryptococcus and Cryptococcosis, Adelaide, Australia
2005 Scientific Committee: Six International Meeting on Cryptococcus and Cryptococcosis, Boston
2005 United States National Organizing Committee. International Union of Microbiological Societies Meeting. Representative for the American Society of Microbiology. San Francisco
2004 IDSA Program Committee
2006 IDSA Program Chair
2006 Scientific Committee. 13th Congress of the International Society of Human and Medical Mycology, Paris, France
2006 Scientific Committee. ASM Biodefense Meeting, Baltimore
2007 Co-chair, ASM colloquium on 'The fungal kingdom: diverse and essential roles in the earth's ecosystem' Developer of Division F program for ASM General meeting
2009, 2010 ASM Colloquium Advisory Committee
2010, 2012, 2015, 2017 Organizing committee for Model Host Meeting, Crete
2011 Gordon Conference on Chemical & Biological Terrorism Defense 2011 organizing committee
2010-2013 Keystone Symposia Scientific Advisory Board
2013-16 ASM General Meeting Program Chair

Consultantships
2006-11 Consultant, Pain Therapeutics
2012-14 Pfizer Resident Professors Program

Research Program Building / Leadership
2000-06 Director, Div. of Infectious Diseases Montefiore Medical Ctr-Albert Einstein
I was responsible for: 1) supervising clinical activities of the Division of Infectious Diseases in two hospitals (Montefiore and Weiler); 2) recruitment physician scientists; 3) mentoring faculty and fellows.

2006-14 Chair, Dept of Microbiology & Immunology Albert Einstein College of Medicine
I was responsible for: 1) supervising basic science department; 2) recruited siz new faculty scientists; 3) mentored faculty, fellows and graduate students.

2015-present Chair and Alfred and Jill Sommer Professor, Bloomberg Distinguished Professor, W. Harry Feinstone Department of Molecular Microbiology & Immunology Johns Hopkins Bloomberg School of Public Health

EDITORIAL ACTIVITIES
1994 Journal of Medical and Veterinary Mycology, Guest Section Editor
1995-1997 Journal of Medical and Veterinary Mycology, Associate Editor
1995-2001 International Journal of Infectious Diseases, Editor
1997-2005 Infection and Immunity - Editorial Board
2005-2009 Infection and Immunity, Editor
1997-present Revista Iberoamericana de Micologia, Editorial Board
1996-present Emerging Infections Disease Editorial Board
2000 Section Editor-Host-Pathogen Interactions. Current Opinion in Microbiology
2004-present Expert Opinion on Emerging Drugs, Editorial Board
2005-present BMC Infectious Diseases, Editorial Board
Future Microbiology – Editorial Board
Faculty of 1000 Contributor
2003-present Nature Reviews in Microbiology – Highlights Advisor
2007-present Journal of Experimental Medicine – Editorial Board
2004-2012 Journal of Clinical Investigation – Editorial Board

2012-present Journal of Infectious Diseases Editorial Board
2010-present mBio – Founding Editor and EIC
2013 Section Editor-Host-Pathogen Interactions. Current Opinion in Microbiology

Journal Reviewer (partial list)
Antimicrobial Agents and Chemotherapy
American Journal of Epidemiology
American Journal of Pathology
Canadian Journal of Microbiology
Cell
Cellular Immunology Clinical Microbiology Reviews
Clinical Infectious Diseases
Emerging Infectious Diseases
FEMS Immunology and Medical Microbiology
Fungal Genetics and Biology
Genes and Development
Journal Clinical Investigation
Journal of Experimental Medicine
Journal of Infectious Diseases
Infection and Immunity
Immunity
Journal of Clinical Microbiology
Journal of Molecular Evolution
J. Immunological Methods
Journal of Immunology
Journal of Medical and Veterinary Mycology
J. Neuroimmunology
International Journal of Infectious Diseases
Immunity
Infectious Diseases in Clinical Practice
Lancet
Microbes and Infection
Journal of Molecular Biology
Nature Medicine
Revista Iberoamericana de Micologia
Molecular and Cellular Biology
Laboratory Investigation
Life Sciences
Microbes and Infection
New England Journal of Medicine
J. Dental Res.
Pediatric Infectious Diseases
PNAS
Trends in Microbiology

Advisory Committees, Review Groups/Study Sections
1994 National Cooperative Drug Discovery Group Study Section
1995, 1996 (Member 1996-2000); Chair 1998-2000NIH Bacteriology and Mycology 2 Study Section
1995 NSF Outside Reviewer
1998 Italian AIDS Program outside Reviewer
1996, 1997, 1998, 1999, 2003 Burroughs Wellcome Trust (United Kingdom) Outside Reviewer

1998	VA Merit Review outside Reviewer
1999	AIDS Study Section AAR1 Ad hoc Reviewer
2000	USDA SBIR Ad hoc Reviewer
1999	NIAID Strategic Plan Task Force
2000-15	St. Jude Fellowship for Pediatric Infectious Diseases
2002-07	Burroughs Wellcome Fund Advisory Committee
2001-5	NIH MIDRC (Microbiology and Infectious Diseases Research Committee) Study Section
2002	NIAID Blue Panel on Bioterrorism Research
2002-05	City University of New York Jonas Salk Award reviewer
2002	Ad Hoc Consultant to Board of Scientific Counselors for NCI
2002	Ad Hoc Consultant to Board of Scientific Counselors for NIAID
2003	National Research Council Workshop on Biotechnology and Bioterrorism
2004	Chair, Expert Panel for NIAID Invasive Aspergillosis Animal Models contract
2004	External Advisory Comm. for Pathomics Strategic Initiative, Lawrence Livermoreational Lab
2004	CDC Advisory panel on Anthrax Immune Globulin
2004-06	Scientific Advisory Board for the NIAID Immune Epitope Database contract
2004-07	Abbot Laboratories Award in Clinical and Diagnostic Immunology Selection Committee
2007-10	NIAID Board of Scientific Counselors 2005-2010; Co-Chair
2005-14	National Science Advisory Board for Biosecurity (NSABB)
2005	Chair, NAS Workshop 'NEW DIRECTIONS IN THE STUDY OF ANTIMICROBIAL THERAPEUTICS – IMMUNOMODULATORS
2005	Chair, NHLBI Working group Innate Immunity HIV & HIV-related Lung Infections
2007	Army Basic Research Review
2009	External Reviewer University of Colorado Department of Microbiology 2009
2011	Keystone Symposia SAB (ad hoc) 2009; Member 2010-2013; Cbair Immunology section
2010-16	National Academy Sci Committee on Science Technology and Law
2009-11	National Academy Sci Committee to Review the FBI Investigation of the 2001 Bacillus anthracis Mailings
2010	NIAID Genomics Blue Ribbon Panel
2012	Pioneer Award Review Panel
2012-17	Co-Chair, N IAID Board of Scientific Counselors
2013	Review of Boston University Microbiology Program
2013-17	Scientific Council Institut Pasteur, Paris, France
2014	Co-Chair, Committee on the Future Direction of the NIAID Intramural Research Program
2014	NIH Advisory Council to the Director on long-term planning for the NIH intramural research program
2014	Review of Washington University Department of Microbiology
2014	Advisory Comm to the (NIH) Director Long-Term Intramural Research Program (LT-IRP)
2015	Review of Jefferson University Department of Microbiology
2015-2016	National Academy of Sciences Comm of Federal Regulations and Reporting requirement
2015-present	National Commission Forensic Science Board, Commissioner
2016	External Advisory Committee for the Mount Sinai Department of Microbiology
2016-present	National Academy of Sciences Committee on Dual Use Research of Concern: Options for Limited Communication 2016
2018	Advisory Board Center for Integrity in Forensic Science

HONORS AND AWARDS

Awards, Honors

1979	Stanley Konkol Memorial Award
1979	Chemistry Department Service Award

1979-83	Salk Scholarship
1979-85	Medical Scientist Training Program Fellowship
1989	Montefiore Fellow of the Year Award
1990	Pfizer Postdoctoral Fellowship Award
1992	James S. McDonnell Scholar Award
1996	Burroughs Wellcome Trust Fund Developmental Therapeutics Award
1997-98	Foundation for Microbiology Lectures Program
1999	Elected to the American Society for Clinical Investigation
1999	Melini Award
2001	Leo M. Davidoff Society (for outstanding teaching)
2001	Sam Rosen Award for outstanding teaching in Pre-Clinical Curriculum
2002	Alpha Omega Alpha
2002	Elected to Fellowship in American Academy of Microbiology
2002	Burroughs Wellcome Visiting Professorship to University of Wisconsin
2004	Elected to American Association of Physicians
2005	Solomon A Berson Medical Alumni Achievement Award in Basic Science -NYU Sch. of Med
2006	Elected AAAS Fellow
2006	Maxwell L. Littman Award (mycology award)
2007	Rhoda Benham Award from Medical Mycology Society of America
2007	NIH Merit Award
2008	ASM William Hinton Award (for mentoring scientists from underrepresented groups)
2008	Albert Einstein College of Medicine Faculty Mentoring Award
2010	Elected to the Interurban Club
2014	Commencementt Speech, Albert Einstein College of Medicine graduation
2014	ASM Founders Award Distinguished Service Award
2014	Elected to Institute of Medicine of the National Academy of Sciences
2015	Delta Omega Alpha Chapter

Invited Talks, Panels

NAMED LECTURES

2008 IDSA Kass Lecturer
2009 14th Farness Lecturer, U. Arizona 2009
2010 Marshall S. Horwitz Faculty Achievement Award 2010
2010 Nelson Lecture, Bozeman, Montana
2010 Theobald Smith Lecture at Albany
2010 Arthur White Lecture, U Indiana
2011 Louis Weinstein Lecture, Tufts University
2012 Jessie Boden Lloyd Visiting Professor for 2012 and gave the Jessie Boden Lloyd Lecture in Immunology, Calgary.
2012 ICAAC Lecturer
2012 Jenner Lecture, St Georges Hospital, London
2013 Michael Apicella Lecture, Iowa
2013 NIAID Kinyoun Lecture, Bethesda, MD
2013 Faculty of Science 50th Anniversary Speaker, University of British Columbia, Vancouver CA
2014 Bernard Fields Lecture Scripps, CA
2014 American Association of Immunology Minority Affairs Committee Guest Lecture
2015 McGinnis Memorial Lecture at Duke University, NC
2015 McCollum Colloquium Speaker, Dartmouth (student invited speaker)
2015 Douglas D. McGregor Research Lecture, Cornell University, Ithaca
2016 Naff Lecture, Case Western Reserve, Cleveland
2016 Robert McGhee Distinguished Lecture, University of Arkansas

2016 Medoff Lecture, Washington University Division of Infectious Disease
2016 Karling Lecture, Mycology Society of America
2017 Harry Smith Memorial Lecturer, Birmingham, United Kingdom
2017 Westmere Lecturer, Birmingham, United Kingdom
2017 Brown-Williamson Lecturer, Queens College, The City Univeristy of New York

PUBLICATIONS (813)

1. Baker AD, **Casadevall A**, Gafney HD, Gellender M (1980) Photochemical Reactions of Tris (Oxalato) Iron III. J. Chem. Ed. 57:314-315.

2. Baker AD and **Casadevall A** (1980) A Clock Reaction with Paraquat. J. Chem. Ed. 57:515-516.

3. **Casadevall A**, Day LA (1982) DNA Packing in the Filamentous Viruses fd, xf. Pf1, and Pf3. Nucleic Acids Res. 10:2467-2481.

4. **Casadevall A**, Day LA (1983) Silver and Mercury Probing of Deoxyribonucleic Acid Structures in the Filamentous Viruses fd, If1, IKe, Xf, Pf1, and Pf3. Biochem. 22:4831-4842.

5. Putterman DG, **Casadevall A**, Boyle PD, Yang H-L, Frangione B, Day LA. (1984) Major Coat Protein and Single-Stranded DNA-binding Protein of the Filamentous Virus Pf3. PNAS 81:699-703.

6. **Casadevall A**, Day LA (1985) The Precursor Complex of the Pf3 Bacteriophage. Virology 45:260-272.
7. Day LA, **Casadevall A**, Prescott B, Thomas GJ (1988) Raman Spectroscopy of Mercury (II) Binding to Two Filamentous Viruses: Ff (fd, M13, f1) and Pf1. Biochem. 27:706-711.

8. **Casadevall A**, Day LA (1988) Thermal Differences Circular Dichroism of Pf1 Filamentous Virus and Effects of Mercury (II) Siver (I), and Copper (II). Biochem. 27:3599-3602.

9. Day LA, Marzec CJ, Reisberg SA, **Casadevall A.** (1988) DNA Packing in Filamentous Bacteriophages. Ann. Rev. Biophys. Biophysical Chem. 17:509-539.

10. **Casadevall A**, Pirofski L, Catalano MT (1990) Primary Group A Streptococcal Peritonitis in Adults. Am. J. Med. 88:5-63N-64N.

11. Pirofski L, **Casadevall A**. (1990) Mixed Staphylococcal and Cryptococcal Epidural abscess in a patient with AIDS. Rev. Infect. Dis. 12:964-965.

12. Pirofski L, **Casadevall A**, Rodriquez L, Zuckier L, Scharff MD (1991) Current State of the Hybridoma Technology. J. Clin. Immunol., 10, No. 6 (November Supplement), 5S-14S.

13. **Casadevall A**, Scharff MD (1991) The Mouse Antibody Response to Infection with *Cryptococcus neoformans*: V_H and V_L Usage in Polysaccharide Binding Antibodies. J. Exp. Med. 174:151-160.

14. Pettoello-Mantovani M, **Casadevall A**, Kollmann TR, Rubinstein A, Goldstein H. (1992) Enhancement of HIV-1 Infection by the Capsular Polysaccharide of *Cryptococcus neoformans*. Lancet 339:21-23.

15. **Casadevall A**, Mukherjee J, Devi S, Schneerson R, Robbins J, Scharff, M.D. (1992) Antibodies elicited by a *Cryptococcus neoformans* -tetanus toxoid conjugate vaccine have the same specificity as those elicited in infection. J. Infect. Dis. 165:1086-93.
16. **Casadevall A**, Dobroszycki J, Small C, Pirofski, L. (1992) *Haemophilus Influenzae* Type b Bacteremia in Adults with AIDS and at Risk for AIDS. Am. J. Med. 92:587-590.

17. **Casadevall A**, Freundlich LF, Pirofski L. (1992) Septic shock from *Pseudomonas paucimobilis*. Clin. Infect. Dis. 14:784.

18. **Casadevall A**, Freundlich L, Marsh L, Scharff MD. (1992) Extensive Allelic Variation in *Cryptococcus neoformans*. J. Clin. Microbiol. 30:1080-1084.

19. **Casadevall A**, Mukherjee J, Scharff MD. (1992). Monoclonal antibody based ELISAs for Cryptococcal polysaccharide. J. Immunol. Methods. 154:27-35.

20. Mukherjee J, Scharff MD, **Casadevall A** (1992). Protective murine monoclonal antibodies to *Cryptococcus neoformans*. Infection and Immunity 60:4534-4541.

21. Mukherjee J, **Casadevall A**, Scharff, MD (1993) Molecular characterization of the humoral responses to *Cryptococcus neoformans* infection and glucuronoxylomannan-tetanus toxoid conjugate immunization. J. Exp. Med. 177:1105-1116.

22. **Casadevall A**, Fan M. (1992) The *URA5* gene of *Cryptococcus neoformans* var. *gattii*: Evidence for a close phylogenetic relationship between *C. neoformans* var. *gattii* and *C. neoformans* var. *neoformans*. J. Gen. Appl. Microbiol. 38:491-495.

23. Spitzer, ED, Spitzer S, Freundlich L, **Casadevall A.** (1993) Persistence of initial infection in recurrent *Cryptococcus neoformans* meningitis. Lancet 341:595-596.

24. **Casadevall A**, Dobroszycki J Small C, Pirofski, L. (1993) Bacteremic *H. influenzae* type b infection and HIV. Am. J. Med. 95:119.

25. Mukherjee J, Pirofski L, Scharff MD, **Casadevall A**. (1993) Antibody mediated protection in mice with lethal intracerebral *Cryptococcus neoformans* infection. PNAS 90:3636-3640.

26. **Casadevall A**, Spitzer ED, Webb D, Rinaldi MG (1993) Susceptibilities of serial *Cryptococcus neoformans* isolates from patients with recurrent cryptococcal meningitis to Amphotericin B and fluconazole. Antimicrobial.Agents.Chemotherapy 37:1383-1386.

27. Mukherjee J, **Casadevall A**, Scharff MD (1993) Mu switch region deletion is associated with both T cell independent and T cell dependent responses. Molecular Immunology 30:1049-1055.

28. Currie BP, Freundlich LF, Soto MA, **Casadevall A** (1993) False negative cerebrospinal fluid cryptococcal latex agglutination tests for patients with culture positive cryptococcal meningitis. J. Clin. Microbiol. 31:2519-2522.

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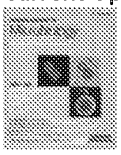
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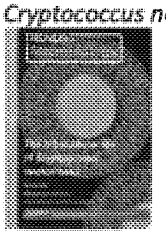
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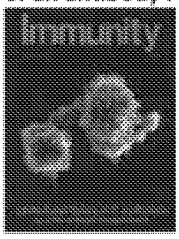
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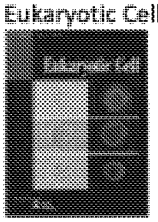
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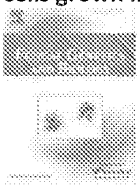
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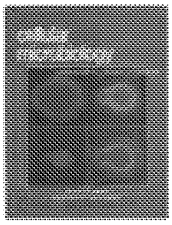
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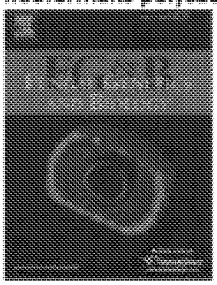
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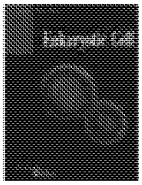
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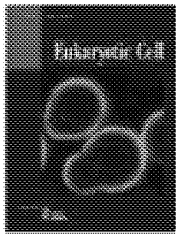
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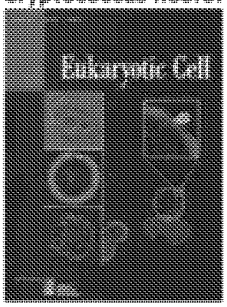
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