

Reply Declaration of Jeffrey V. Ravetch
IPR2023-01069 (U.S. Patent No. 10,590,189 B2)

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

SAMSUNG BIOEPIS CO., LTD.,
Petitioner

v.

ALEXION PHARMACEUTICALS, INC.,
Patent Owner

Case IPR2023-01069
U.S. Patent No.
10,590,189 B2

REPLY DECLARATION OF JEFFREY V. RAVETCH, M.D., PH.D.

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I, Jeffrey V. Ravetch, declare as follows:

I. INTRODUCTION

A. Background

1. I am the same Jeffrey V. Ravetch, M.D., Ph.D. who provided a declaration in support of the IPR Petition of Samsung Bioepis (“Samsung”) in this matter relating to Alexion’s U.S. Patent No. 10,590,189. Apart from updating my CV as discussed next, I incorporate by reference my previous statement of qualifications and experience. (EX1003, ¶¶1-14.)

2. My updated Curriculum Vitae, which contains information pertaining to my education, experience, and qualifications in the field of immunology, microbiology, cellular biology, and molecular genetics, as well as a list of my publications within at least the preceding 10 years, and publications on relevant subject matter is attached as **Exhibit A**.

3. I submit this declaration in response to the arguments and opinions submitted by Alexion and its experts Drs. Casadevall and Trout.

4. I am being compensated at my usual consulting rate of \$1,250 per hour for my work on this matter. I also am being reimbursed for reasonable and customary expenses associated with my work and testimony in this proceeding. My compensation is not dependent upon my opinions or testimony or the outcome of

this proceeding.

B. Materials Considered

5. The analysis that I provide in this Declaration is based on my education, research, and experience, as well as the documents I have considered. In addition to the documents discussed in my previous declarations, I have also read and considered the documents added to the table below (which comprehensively includes the documents that were listed in my previous declaration):

Exhibit No.	Description of Document
1001	U.S. Patent No. 10,590,189 B2 issued to Leonard Bell et al. (filed July 5, 2017, issued Mar. 17, 2020) (“189 patent”)
1002	Prosecution History for U.S. Patent No. 10,590,189 B2
1004	U.S. Patent Application Publication No. 2003/0232972 A1 issued to Katherine S. Bowdish et al. (filed Dec. 2, 2002, published Dec. 18, 2003) (“Bowdish”)
1005	U.S. Patent No. 6,355,245 B1 issued to Mark J. Evans et al. (filed June 7, 1995, issued Mar. 12, 2002) (“Evans”)
1006	John P. Mueller et al., <i>Humanized Porcine VCAM-Specific Monoclonal Antibodies with Chimeric IgG2/G4 Constant Regions Block Human Leukocyte Binding to Porcine Endothelial Cells</i> , 34 Molecular Immunology 441 (1997) (“Mueller 1997”)
1007	U.S. Patent Application Publication No. 2005/0191298 A1 issued to Leonard Bell et al. (filed Feb. 3, 2005, published Sept. 1, 2005) (“Bell”)

Exhibit No.	Description of Document
1008	Paul J. Tacke et al., <i>Effective induction of naive and recall T-Cell responses by targeting antigen to human dendritic cells via a humanized anti-DC-SIGN antibody</i> , 106 Blood 1278 (2005) (“Tacke”)
1009	World Intellectual Property Organization International Publication No. WO 97/11971 issued to John P. Mueller et al. (filed Sept. 27, 1996, published Apr. 3, 1997) (“Mueller PCT”)
1010	Thomas C. Thomas et al., <i>Inhibition of Complement Activity By Humanized Anti-C5 Antibody and Single-Chain Fv</i> , 33 Molecular Immunology 1389 (1996) (“Thomas”)
1011	Peter Hillmen et al., <i>Effect of Eculizumab on Hemolysis and Transfusion Requirements in Patients with Paroxysmal Nocturnal Hemoglobinuria</i> , 350 N. Engl. J. Med. 552 (2004) (“Hillmen 2004”)
1012	Anita Hill et al., <i>Abstract# 2823: Sustained Control of Hemolysis and Symptoms and Reduced Transfusion Requirements over a Period of 2 Years in Paroxysmal Nocturnal Hemoglobinuria (PNH) with Eculizumab Therapy</i> , 104 Blood 772a (2004) (“Hill 2004”)
1013	Anita Hill et al., <i>Sustained response and long-term safety of eculizumab in paroxysmal nocturnal hemoglobinuria</i> , 106 Blood 2559 (“Hill 2005”)
1014	Peter Hillmen et al., <i>The Complement Inhibitor Eculizumab in Paroxysmal Nocturnal Hemoglobinuria</i> , 355 N. Engl. J. Med. 1233 (2006) (“Hillmen 2006”)
1015	Neal S. Young et al., <i>Abstract# 971: Safety and Efficacy of the Terminal Complement Inhibitor Eculizumab in Patients with Paroxysmal Nocturnal Hemoglobinuria: Interim Shepherd Phase III Clinical Study</i> , 108 Blood 290a (2006) (“Young”)
1016	Peter Hillmen et al., <i>Abstract# 154: Eculizumab, a C5 Complement-Blocking Antibody, Abolishes Hemolysis and Renders Hemolytic</i>

Exhibit No.	Description of Document
	<i>Patients with Paroxysmal Nocturnal Hemoglobinuria (PNH) Transfusion Independent</i> , 100 Blood 44a (2002) (“Hillmen 2002”)
1017	Peter Hillmen et al., <i>Abstract# 1858: Eculizumab, a C5 Complement-Blocking Antibody, Controls Hemolysis in Paroxysmal Nocturnal Hemoglobinuria (PNH) with Responses Maintained Over a Prolonged Period of Therapy</i> , 102 Blood 509a (2003) (“Hillmen 2003”)
1018	Excerpts from <i>Recommended INN List 49, International Nonproprietary Names for Pharmaceutical Substances</i> , 17 WHO Drug Information 115, World Health Organization (2003)
1019	<i>Guidelines on the Use of International Nonproprietary Names (INNs) for Pharmaceutical Substances</i> , Programme on International Nonproprietary Names (INN), Division of Drug Management & Policies, World Health Organization, Geneva (1997)
1020	Alexion Press Release, <i>Alexion Issued Key C5 Complement Inhibitor Patent for Inflammatory Diseases</i> (Mar. 15, 2002), https://web.archive.org/web/20030621141230/http://www.alxn.com/products/index.cfm
1021	World Intellectual Property Organization International Patent Publication No. WO 2005/007809 A2 issued to Russell P. Rother et al. (filed May 28, 2004, published Jan. 27, 2005)
1022	World Intellectual Property Organization International Patent Publication No. WO 2005/110481 A2 issued to Russell P. Rother et al. (filed May 16, 2005, published Nov. 24, 2005)
1023	Mariana Kaplan, <i>Eculizumab Alexion</i> , 3 Curr. Opin. Investig. Drugs 1017 (2002)
1024	<i>Amgen Inc. v. Alexion Pharmaceuticals, Inc.</i> , IPR2019-00739, Paper 15, Decision – Institution of <i>Inter Partes</i> Review (PTAB Aug. 30, 2019)

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Exhibit No.	Description of Document
1025	<i>Amgen Inc. v. Alexion Pharmaceuticals, Inc.</i> , IPR2019-00739, Paper 22, Patent Owner Response Pursuant to 37 C.F.R. § 42.120 (PTAB Nov. 22, 2019)
1027	Opposition File History for European Patent No. 1 720 571 B1
1028	File History for European Patent No. 3 167 888
1029	Excerpt from the File History for U.S. Patent Application No. 11/127,438, Amendment in Response to Non-Final Office Action (Aug. 2, 2011)
1030	Application for Extension of Patent Term under 35 U.S.C. § 156 and 37 CFR § 1.740, U.S. Patent No. 6,355,245, Alexion Pharmaceuticals (May 11, 2007)
1031	Certificate Extending Patent Term, U.S. Patent No. 6,355,245 (June 11, 2010)
1033	Esther M. Yoo et al., <i>Human IgG2 Can Form Covalent Dimers</i> , 170 J. Immunol. 3134 (2003) (“Yoo 2003”)
1037	Jette Wypych et al., <i>Human IgG2 Antibodies Display Disulfide-mediated Structural Isoforms</i> , 283 J. Biol. Chem. 16194 (2008) (“Wypych”)
1038	Stylianos Bournazos et al., <i>Fc-optimized antibodies elicit CD8 immunity to viral respiratory infection</i> , 588 Nature 485 (2020) (“Bournazos 2020”)
1039	Stylianos Bournazos et al., <i>Human IgG Fc domain engineering enhances antitoxin neutralizing antibody activity</i> , 124 J. Clinical Investigation 725 (2014) (“Bournazos 2014”)

Exhibit No.	Description of Document
1040	Lucie Baudino et al., <i>Impact of a Three Amino Acid Deletion in the CH2 Domain of Murine IgG1 on Fc-Associated Effector Functions</i> , 181 J. Immunology 4107 (2008)
1041	Toshiyuki Takai et al., <i>FcR γ Chain Deletion Results in Pleiotropic Effector Cell Defects</i> , 76 Cell 519 (1994)
1042	Falk Nimmerjahn & Jeffrey V. Ravetch, <i>Fcγ receptors as regulators of immune responses</i> , 8 Nat. Rev. Immunol. 34 (2008)
1043	Jeffrey V. Ravetch & Jean-Pierre Kinet, <i>Fc Receptors</i> , 9 Annu. Rev. Immunol. 457 (1991)
1044	U.S. Patent Application Publication No. 2005/0271660 A1 issued to Yi Wang (filed May 11, 2005, published Dec. 8, 2005) (“Wang”)
1045	Charles A. Janeway, Jr. et al., <i>Chapter 1: Basis Concepts in Immunology</i> , and <i>Chapter 3: Antigen Recognition by B-cell and T-cell Receptors</i> , Immunobiology: the immune system in health and disease, pp. 1-34, 93-122 (5th ed. 2001)
1046	Excerpts from Pei-Show Juo, Ph.D., Concise Dictionary of Biomedicine and Molecular Biology (2nd ed. 2001)
1047	Tina Völkel et al., <i>Optimized linker sequences for the expression of monomeric and dimeric bispecific single-chain diabodies</i> , 14 Protein Engineering 815 (2001) (“Völkel”)
1048	Evelyn D. Lobo et al., <i>Antibody Pharmacokinetics and Pharmacodynamics</i> , 93 Journal of Pharmaceutical Sciences 2645 (2004) (“Lobo 2004”)
1049	Neil S. Lipman et al., <i>Monoclonal Versus Polyclonal Antibodies: Distinguishing Characteristics, Applications, and Information Resources</i> , 46 ILAR Journal 258 (2005) (“Lipman 2005”)

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1050	Benny K.C. Lo, <i>Chapter 7: Antibody Humanization by CDR Grafting</i> , Methods in Molecular Biology, Vol. 248: Antibody Engineering: Methods and Protocols, pp. 135-159 (2004) (“Lo 2004”)
1051	Lutz Riechmann et al., <i>Reshaping human antibodies for therapy</i> , 332 Nature 323 (1988) (“Riechmann”)
1052	Janice M. Reichert, <i>Marketed therapeutic antibodies compendium</i> , 4 mAbs 413 (2012) (“Reichert”)
1053	Bruce Alberts et al., <i>Chapter 12: Intracellular Compartments and Protein Sorting</i> , Molecular Biology of the Cell, pp. 551-98 (1994)
1054	Elisabeth E. Adderson et al., <i>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</i> , 89 J Clin. Invest. 729 (1992)
1055	Genentech, Inc., Avastin 2004 Package Insert, available at https://www.accessdata.fda.gov/drugsatfda_docs/label/2004/125085lbl.pdf
1056	Millennium, Campath 2001 Package Insert, available at https://www.accessdata.fda.gov/drugsatfda_docs/label/2001/alemml050701LB.htm
1057	ImClone Systems, Inc., Erbitux 2004 Package Insert, https://www.accessdata.fda.gov/drugsatfda_docs/label/2004/125084lbl.pdf
1058	Genentech, Inc., Herceptin 1998 Package Insert, available at https://www.accessdata.fda.gov/drugsatfda_docs/label/1998/trasgen092598lb.pdf

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1059	Centocor, Inc., Remicade 1998 Package Insert, available at https://www.accessdata.fda.gov/drugsatfda_docs/label/1998/inflcen082498lb.pdf
1060	Genentech, Inc., Rituxan 1997 Package Insert, available at https://www.accessdata.fda.gov/drugsatfda_docs/label/1997/ritugen112697-lab.pdf
1061	Ann L. Daugherty & Randall J. Mersny, <i>Formulation and delivery issues for monoclonal antibody therapeutics</i> , 58 Advanced Drug Delivery Reviews 686 (2006)
1062	Declaration of Cindy Ippoliti, Pharm.D.
1066	Excerpt from the File History of U.S. Patent No. 9,718,880, Response to Non-Final Office Action Under 37 C.F.R. § 1.111, dated May 12, 2017
1101	Deposition of Arturo Casadevall, dated Jan. 24, 2020
2005	SOLIRIS [®] Label
2006	Dmytrijuk et al., FDA Report: Eculizumab (SOLIRIS [®]) for the Treatment of Patients with Paroxysmal Nocturnal Hemoglobinuria, THE ONCOLOGIST, 13:993-1000 (2008)
2007	Janeway and Travers, <i>Immunobiology: The Immune System in Health and Disease</i> (Garland Science, 6th ed. (2005))
2008	McCloskey et al., Human Constant Regions Influence the Antibody Binding Characteristics of Mouse-Human Chimeric IgG Subclasses, IMMUNOLOGY, 88: 169-173 (1996)
2009	Torres et al., The Immunoglobulin Heavy Chain Constant Region Affects Kinetic and Thermodynamic Parameters of Antibody Variable

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	Region Interactions with Antigen, J. OF BIOL. CHEM., 282(18): 13917–27 (2007)
2010	Janda <i>et al.</i> , Ig Constant Region Effects on Variable Region Structure and Function, FRONT. MICROBIOL., 7(22): 1-10 (2016)
2011	Pritsch <i>et al.</i> , Can Immunoglobulin CH1 Constant Region Domain Modulate Antigen Binding Affinity of Antibodies?, J. CLIN. INVEST., 98(10): 2235-43 (1996)
2012	Pritsch <i>et al.</i> , Can Isotype Switch Modulate Antigen-Binding Affinity and Influence Clonal Selection?, EUR. J. IMMUNOL., 30: 3387-95 (2000)
2013	McLean <i>et al.</i> , Isotype Can Affect the Fine Specificity of an Antibody for a Polysaccharide Antigen, J. OF IMMUNOLOGY, 169: 1379–86 (2002)
2014	Greenspan <i>et al.</i> , Complementarity, Specificity and the Nature of Epitopes and Paratopes in Multivalent Interactions, IMMUNOL. TODAY, 16(5): 226-30 (1995)
2015	Radbruch, <i>et al.</i> , Drastic Change in Idiotypic but Not Antigen-Binding Specificity of an Antibody by a Single Amino-Acid Substitution, NATURE, 315(6): 506-508 (1985)
2017	Hawkins <i>et al.</i> , The Contribution of Contact and Non-contact Residues of Antibody in the Affinity of Biding to Antigen: The Interaction of Mutant D1.3 Antibodies with Lysozyme, J. MOL. BIO., 234: 958-964 (1993)
2018	Excerpts from Alexion Pharmaceuticals, Inc. Form 10-K for fiscal year ended December 31, 2018
2019	Ricklin & Lambris, Complement-Targeted Therapeutics, NATURE BIOTECHNOLOGY, 25(11); 1265-1275 (2007)

Exhibit No.	Description of Document
2020	Alexion Press Release, Alexion's Soliris® Receives 2008 Prix Galien USA Award for Best Biotechnology Product, September 25, 2008, available at https://news.alexion.com/press-release/company-news/alexions-soliris-receives-2008-prix-galien-usa-award-best-biotechnology-p (last visited May 15, 2019)
2021	BusinessWire, Alexion's Soliris® Receives 2009 Prix Galien France for Most Innovative Drug for Rare Disease, June 10, 2009, available at https://www.businesswire.com/news/home/20090610005826/en/Alexions-Soliris-Receive-2009-Prix-Galien-France (last visited May 15, 2019)
2022	Declaration of Arturo Casadevall, M.D., Ph.D. submitted in IPR2019-00741, dated Nov. 22, 2019
2023	Curriculum Vitae of Arturo Casadevall, M.D., Ph.D.
2024	Declaration of Bernhardt L. Trout, Ph.D. submitted in IPR2019-00739, dated Nov. 22, 2019
2025	Curriculum Vitae of Bernhardt L. Trout, Ph.D.
2028	Hill, et al., Erythropoietin treatment during complement inhibition with eculizumab in a patient with paroxysmal nocturnal hemoglobinuria, THE HEMATOLOGY JOURNAL, 31-33, 2007
2029	Points to Consider in the Manufacture and Testing of Monoclonal Antibody Products for Human Use, U.S. Dept. of Health and Human Services, Food and Drug Admin., 1997
2030	3/16/2007 FDA Approves Alexion's Soliris™ for all Patients with PNH
2031	Janeway, et al., Immunobiology, The Immune System in Health and Disease, Appendix I: Immunologists' Toolbox, 6th ed., 696-97 (2005)

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2033	Kim, et al., Antibody Engineering for the Development of Therapeutic Antibodies, MOLECULES AND CELLS, Vol. 20, No. 1, pp. 17-29, 2005
2034	Hwang, et al., Immunogenicity of engineered antibodies, SCIENCE DIRECT, 17 Jan. 2005
2035	Shepherd, et al., Monoclonal Antibodies, Oxford University Press, pp. 58-5 (Appendix) 2000
2036	Lo, Benny K., Antibody Engineering Methods and Protocols, METHODS IN MOLECULAR BIOLOGY, Vol. 248 2004
2037	Welt, et al., Phase I Study of Anticlon Cancer Humanized Antibody A33, CLINICAL CANCER RESEARCH, 2003
2038	Haller, et al., Safety Issues Specific to Clinical Development of Protein Therapeutics, NATURE PUBLISHING GROUP, 2008
2039	Torres, et al., Exchanging Murine and Human Immunoglobulin Constant Chains Affects the Kinetics and Thermodynamics of Antigen Binding and Chimeric Antibody Autoreactivity, PLOS ONE, 2007
2040	Torres, et al., Variable-Region-Identical Antibodies Different in Isotype Demonstrate Differences in Fine Specificity and Idiotype, JOURNAL OF IMMUNOLOGY, 2005
2042	Mathieu, Barbara G., Clinical Testing of Biologically Derived Therapeutics, Biologics Development: A Regulatory Overview, 3d ed., 2004
2043	Andersen, et al., Production technologies for monoclonal antibodies and their fragments, SCIENCE DIRECT, 2004
2044	Chadd, et al., Therapeutic antibody expression technology, 2001
2045	2007 USP Dictionary of USAN and International Drug Names

Exhibit No.	Description of Document
2046	Guidelines on the Use of International Nonproprietary Names (INNs) for Pharmaceutical Substances, 1997
2047	McClean, et al., A point mutation in the CH3 domain of human IgG3 inhibits antibody secretion without affecting antigen specificity, MOLECULAR IMMUNOLOGY, 2005
2049	HemOnc Today, Eculizumab’s triumph over PNH, https://www.healio.com/hematology-oncology/news/print/hemonc-today/%7B01f97d7b-36b4-4462-aab4-02918370caa1%7D/eculizumabs-triumph-over-pnh (Aug. 25, 2008)
2050	Fatimah Al-Ani et al., “Eculizumab in the management of paroxysmal nocturnal hemoglobinuria: patient selection and special considerations, Ther. Clin. Risk Manag., 12:1161-1170 (2016)
2051	Foote, Jefferson and Winter, Greg, “Antibody Framework Residues Affecting the Conformation of the Hypervariable Loops,” J. Mol. Biol., 224:487-449 (1992)
2052	Xiang, Jim et al., Framework Residues 71 and 93 of the Chimeric B72.3 Antibody are Major Determinants of the Conformation of Heavy-chain Hypervariable Loops,” J. Mol. Biol. 253:385-390 (1995)
2053	June 2019 Soliris® Label
2054	Alexion Press Release, “Alexion Pharmaceuticals Submits Biologics License Application for Soliris™ (eculizumab),” (Sept. 20, 2006)
2055	Alexion Press Release, “Alexion Submits Market Authorization Application for Soliris™ (eculizumab) in the Treatment of Paroxysmal Nocturnal Hemoglobinuria to the European Medicines Agency,” (Sept. 26, 2006)

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2075	GenScript, “Final Report- Antibody Full Length Sequencing of Hybridoma 5G1.1 T175,” Order Number: U856UEK140-1 (Nov. 15, 2019)
2079	Chang, Byeong S. and Hershenson, Susan, “Practical Approaches to Protein Formulation Development,” Pharmaceutical Biotechnology Vol. 13, 1-25 (2002)
2080	Wang, Wei, “Instability, stabilization, and formulation of liquid protein pharmaceuticals,” International Journal of Pharmaceutics, 185:129-188 (April 28, 1999)
2081	Hermeling, S. et al., “Structure-Immunogenicity Relationships of Therapeutic Proteins,” Pharmaceutical Research, 12:6, 897-903 (June 2004)
2082	Frokjaer, Sven and Otzen, Daniel E., “Protein Drug Stability: A Formulation Challenge,” Nature Reviews, Drug Discovery, 4:298-306 (April 2005)
2083	Rosenberg, Amy S., “Effects of Protein Aggregates: An Immunologic Perspective,” AAPS Journal 8, Article 59, pp. E501-E507 (Aug. 4, 2006)
2084	ICH Topic Q5C, “Quality of Biotechnological Products: Stability Testing of Biotechnological/Biological Products,” European Medicines Agency (July 1996)
2085	U.S. Depart of Health and Human Services, FDA, “Guidance for Industry Q1A(R2) Stability Testing of New Drug Substances and Products,” ICH Rev. 2 (Nov. 2003)
2086	Stebbing, R., et al., “After TGN1412: Recent developments in cytokine release assays,” J. of Immunotoxicology, 10(1): 75-82 (2013)
2088	Amgen Biosimilar Pipeline Approved Products (2019)

Exhibit No.	Description of Document
2089	Generium Pharmaceutical, “Elizaria” Product (2019)
2090	Samsung Bioepis – Biosimilar candidates and Novel biologic (2019)
2091	Harlow and Lane, Chapter 15: Antibody Molecules, in Antibodies, A Laboratory Manual, 622-25 (1988)
2104	Deposition Transcript of Jeffrey V. Ravetch, M.D., Ph.D. (Feb. 23, 2024)
2105	Declaration of Arturo Casadevall, M.D., Ph.D., 2024
2106	Deposition Transcript of Cindy Ippoliti, Pharm.D. (Feb. 20, 2024)
2107	Declaration of Bernhardt L. Trout, Ph.D., 2024
Paper 9	Decision – Institution of <i>Inter Partes</i> Review, dated Dec. 20, 2023 (“ID”)
Paper 13	Patent Owner’s Response Under 37 C.F.R § 42.120, dated Mar. 13, 2024 (“POR”)

II. Opinions Responding to Alexion’s Response

6. As set forth below, I disagree with arguments made by Patent Owner in their Patent Owner Response, and with the opinions expressed by Drs. Casadevall and Trout which were submitted in a different IPR proceeding involving Amgen that Alexion is relying on here.

A. Alexion Relied on Expert Testimony Recycled from a Different Legal Proceeding

7. Alexion's experts Dr. Casadevall and Dr. Trout submitted short declarations created for this matter, and also submitted the declarations they created for prior Amgen IPRs that pertain to different Alexion patents from the same family as the '189 patent challenged here. Specifically, in this matter, I understand that Alexion submitted a short declaration from Dr. Casadevall as Exhibit 2105 (ALXN2105). Similarly, Alexion submitted a short declaration from Dr. Trout as Exhibit 2107 (ALXN2107).

8. These declarations contain only a few pages each, and each refers back to an earlier declaration from a different legal proceeding involving Amgen. For example, Dr. Casadevall's ALXN2105 contains eleven paragraphs in total, and relies on his declaration submitted in an Amgen IPR involving a different Alexion patent, U.S. Patent No. 9,732,149, which was filed in this proceeding as ALXN2022. Similarly, Dr. Trout's ALXN2107 contains nine paragraphs in total, and relies on his declaration submitted in an Amgen IPR involving a different Alexion patent, U.S. Patent No. 9,725,504, which was filed in this proceeding as ALXN2024.

9. In both cases, each expert claims to have reviewed my declaration and that of Samsung's other expert, Dr. Ippoliti. (ALXN2105, ¶6; ALXN2107, ¶6.) Each expert then makes a blanket statement "it is my opinion that the claims of the

'189 patent are valid over all of the art ... and arguments presented by Samsung in its IPR regarding the pharmaceutical compositions recited in the claims of the '189 patent.” (ALXN2107, ¶8; *see also* ALXN2105, ¶8.) Each of these experts then states that they disagree with the opinions I expressed in my initial declaration, although neither expert says what the basis for this disagreement is, or otherwise provides any substantive response to the opinions I expressed. I respond to the arguments presented by Alexion in its Response, and opinions presented by Drs. Casadevall and Trout in their declarations from the Amgen IPRs below. I note that although Alexion's Response only cites to specific parts of Dr. Casadevall's and Dr. Trout's 2019 Amgen declarations, and sometimes seems to do so using erroneous citations, I reviewed the entirety of Dr. Casadevall's and Dr. Trout's declarations and my rebuttals to their opinions are encapsulated in the statements below.

B. Alexion Mischaracterizes the Clear Teachings of Its Own Prior Art and the Import of Its Admissions

10. Alexion's Response wrongly states that “the literature as of March 15, 2007 consistently identified ‘eculizumab’ as the antibody described in the ‘Thomas’ publication[.]” (Alexion Patent Owner's Response (Paper 13) (“POR”), 2.) As I explained in detail in my declaration, and reiterate below, this statement is incorrect, both as a simple factual matter in terms of the written content of the prior art, and

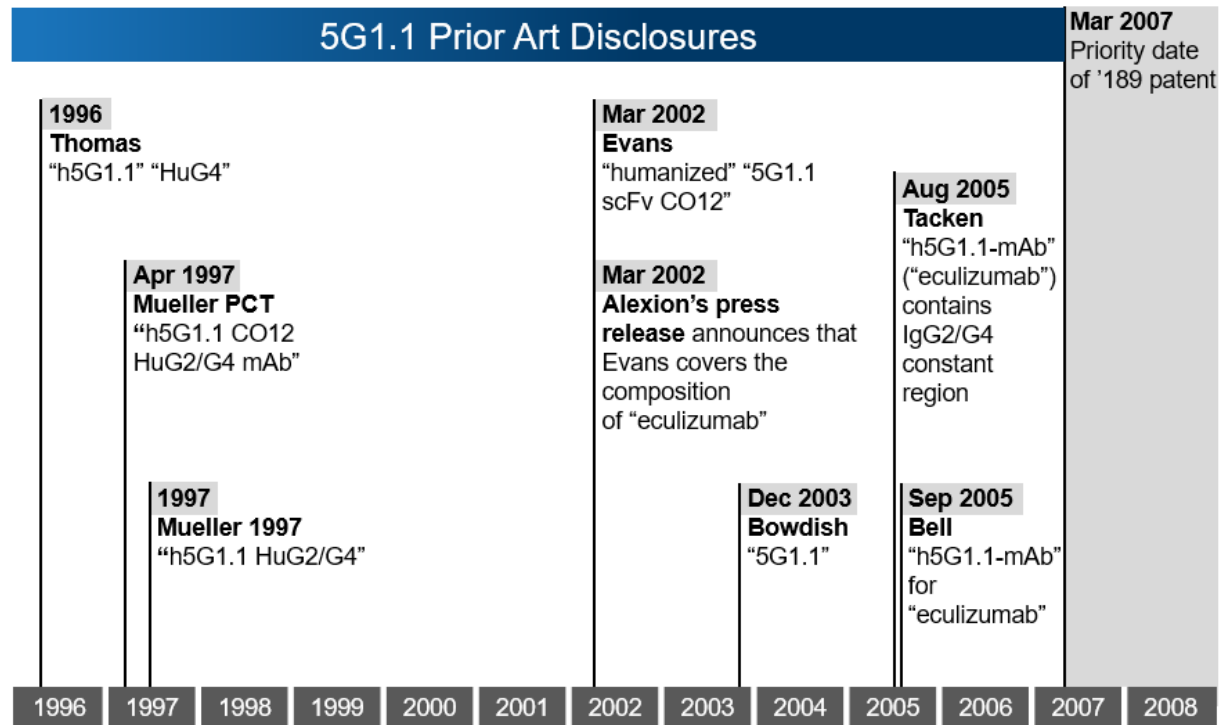
especially in terms of how the prior art would be viewed by a POSA.

11. As an initial matter, I note that Thomas does not contain the word “eculizumab” anywhere, and that even Dr. Casadevall agrees with this irrefutable reality. (EX1003, ¶160; EX1010; EX1101, 186:19-22.) On the contrary, the prior art does clearly identify eculizumab’s constant domain in the Tacke reference, which is directly associated with Alexion, and which directly states that it is an IgG2/G4 antibody. I explained the teachings of Tacke, and their major significance to a POSA, in my initial declaration. (EX1008, 011; EX1003, ¶¶64, 98, 123, 127.)

12. I disagree with any suggestion that the clear disclosure of the Tacke reference would have been ignored by a POSA, or that a POSA would have somehow downplayed that disclosure in favor of other, older references. In fact, the prior art showed a linear and direct path beginning with Thomas’ early 5G1.1 anti-C5 antibody, which originated as a mouse antibody and was humanized according to standard techniques widely in use by the 1990s. This humanized antibody was then further developed by Alexion into the hybrid IgG2/G4 form expressly disclosed by Tacke and used in Bell.

13. I specifically disagree that a POSA would have been at all confused by the use of the term 5G1.1, or by citations to the Thomas reference, in the literature. As I previously explained in my Declaration, the meaning of 5G1.1, including

whether it refers to a mouse or a human antibody, is clear to a POSA from the context in which it appears. (Paper 2, (“Pet.”), 9-13; EX1003, ¶¶61-70.) Thus, and as I further explained during my deposition, a POSA understood whether a reference discussed early discovery and humanization of a mouse anti-C5 antibody, or the further development and modification of that antibody into an IgG2/G4 form that was in clinical trials. (*Id.*; ALXN2104, 188:12-192:1.) In my previous declaration I provided a chart of the various disclosures describing the development of the antibody originally called 5G1.1 into eculizumab from 1996 through the March 2007 priority date of the patent.



(EX1003, ¶69.)

14. In my review of Alexion's Response, it appears to me that Alexion is seeking to portray the prior art, even though it comprises Alexion's own publications charting the development of its own eculizumab antibody, as somehow being confusing or misleading to a POSA. (POR, 18, 24-37.) As I have stated, and reiterate further below, there is no such ambiguity in the literature. A POSA would be able to interpret, with confidence, the art's use of terms like "5G1.1," "h5G1.1.," and "eculizumab," in combination with the specific sequence teachings of the prior art, in order to arrive at the sequence of eculizumab.

15. As one example, I note that Alexion seems to place great emphasis on the fact that Bell cites to Thomas, while also downplaying that Bell also cites Evans, and then argues that a POSA would have simply stopped with Thomas and disregarded the Tacke reference, even though it was published at approximately the same time as Tacke. (POR, 42-43, 54.) In my opinion, this portrayal of how a POSA would interpret the art greatly underestimates the level of skill and intelligence of a POSA in this field.

16. It is entirely appropriate and understandable that later references, including Tacke, cite to Thomas when discussing that eculizumab (or h5G1.1, or 5G1.1) is an anti-C5 antibody. Thomas was the original publication detailing the specific CDR sequences essential for C5 binding as well as the construction of those

sequences into various forms of humanized antibodies and antibody fragments. A POSA would not, however, conclude from citation to Thomas that eculizumab is an IgG4 antibody, merely because Thomas includes a disclosure of a full length IgG4 antibody, for one simple reason: There is not one single location in the literature that states that eculizumab is the IgG4 antibody disclosed in Thomas, while there is a clear statement in the literature that eculizumab is an IgG2/G4 antibody. (EX1008, 010-011.) A POSA would not be even slightly confused by the collective teachings of the prior art in context.

17. My views on this are supported by the fact that Alexion has agreed with me that the level of skill in this art was high, even going so far as to clarify in its briefing that under this agreed definition a POSA would have experience specifically in “engineering monoclonal antibodies for human therapeutic use[.]” (POR, 40-41.) So there is no dispute that a POSA in this field was highly skilled and well-informed, indeed specifically experienced with the exact topic of antibody engineering that covers the conversion of an antibody from an IgG4 to an IgG2/G4 form. A POSA (even without Alexion’s added level of experience with antibody engineering) would not have focused exclusively on the eleven-year-old Thomas reference, and could easily understand the meaning of the various 5G1.1 terms over the course of eculizumab’s development from the context in which they appear – as I explained

previously and during my deposition in this matter. (EX1003, ¶¶61-70, 110, 128, 146, 160, 172; ALXN2104, 34:6-35:7, 66:5-67:6.) Indeed, I note that Alexion's Response and Dr. Casadevall admit "the precise meaning of the various '5G1.1' terms depends on the context in which it appears[.]" (POR, 9; *see also* ALXN2022, ¶120 ("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)[.]").) I agree that a POSA would easily have been able to interpret the teaching of the prior art based on that context.

18. I have examined Dr. Casadevall's declaration from the previous Amgen IPR of the '149 patent on these points, and I disagree with his opinions. (*See, e.g.*, ALXN2022, ¶¶122-124, 130, 132, 138-150.) In ¶¶122-124 of his declaration, Dr. Casadevall summarizes the teachings of the Thomas reference, and uses quotation marks in a questionable manner when he refers to "Thomas and the following literature regarding 'eculizumab[.]'" (ALXN2022, ¶124; *see also id.*, ¶122.) I find Dr. Casadevall's usage of quotation marks to be misleading and inappropriate, to the extent that Dr. Casadevall wishes to create the impression by using quotation marks that Thomas expressly refers to eculizumab. For example, I note that Dr. Casadevall emphasizes in this paragraph that Evans does not contain the word "eculizumab," while curiously omitting that Thomas does not either – even though he was forced

to admit this fact in deposition. (EX1101, 186:19-22.)

19. In ¶130 of his declaration, Dr. Casadevall refers to “the final, IgG4 isotype, described in clinical study publications.” I do not understand what Dr. Casadevall is referring to and I note he provides no citation to support his statement. I find the way Dr. Casadevall presents his statements to be questionable and misleading. There is no dispute and Alexion has repeatedly admitted that the eculizumab used in the clinical study publications (e.g., Bell, Hillmen, and Hill) was an IgG2/G4 antibody and not an “IgG4 isotype” as Dr. Casadevall falsely suggests. (EX1007; EX1011; EX1012; EX1003, ¶70.)

20. In ¶132 of his declaration, Dr. Casadevall says “[b]ased on the art as a whole, as of [March 15, 2007], a POSA would have understood ‘eculizumab’ to be an IgG4 antibody.” He is wrong, and in fact the exact opposite is true. As of that date Tacke made clear that eculizumab was not an IgG4 antibody but was instead an IgG2/G4 antibody.

21. In ¶¶138-150 of his declaration, Dr. Casadevall attempts to downplay or otherwise explain away the Tacke reference’s clear disclosure. A POSA would not have understood the prior art in the cramped, myopic manner in which Dr. Casadevall does. For example, he refers to Tacke as “ambiguous,” but it is not ambiguous at all. Tacke states, in plain English, that the authors tested “h5G1.1-

mAb (5G1.1, eculizumab [sic]; Alexion Pharmaceuticals) containing the same IgG2/IgG4 constant region[.]” (EX1008, 011; EX1003, ¶98.) As I previously explained, “the same” in Tacke refers back to Alexion’s own Mueller reference (EX1006) – which is just more confirmation that eculizumab is an IgG2/G4 antibody. (EX1003, ¶98.) Dr. Casadevall’s misreading of Tacke’s citation to Mueller 1997 (ALXN2022, ¶147) is thus wrong. Dr. Casadevall also argues that Tacke’s citation to Thomas would have been read by a POSA describing “an IgG4 isotype antibody that the other prior art consistently identified as ‘eculizumab[.]’” (ALXN2022, ¶143.) Dr. Casadevall’s argument is thus circular, because it is based on his false premise that other prior art “identified” eculizumab as an IgG4 antibody, when in fact there is not one piece of prior art which states that eculizumab is an IgG4 antibody. Dr. Casadevall’s other opinions seeking to downplay Tacke are also wrong. (ALXN2022, ¶¶144-150.) For example, Dr. Casadevall criticizes Tacke for not itself containing safety or efficacy data, which is irrelevant to this issue, and even conjectures implausibly that a POSA would have thought Tacke’s disclosure that eculizumab is an IgG2/G4 antibody was “a mistake” (ALXN2022, ¶146) – even though one of Tacke’s authors was a named inventor on the challenged patent. Simply put, a POSA would not read the prior art in the way that Dr. Casadevall has chosen to read it. Instead, a POSA would accept the prior art for

all it teaches, in context, which includes the unsurprising disclosure that Alexion further developed the original IgG4 antibody of Thomas into the IgG2/G4 type disclosed by Tacken with direct reference to eculizumab – particularly unsurprising given Alexion’s well-published interest in and development of antibodies with an IgG2/G4 constant domain. (EX1003, ¶62; EX1006; EX1009.)

C. Ground 1: Claims 1-8 Are Obvious over Bell, Bowdish, Evans, and Wang in View of Tacken and Mueller PCT

1. No Dispute that the Prior Art Taught Eculizumab Was an Effective PNH Treatment; No Dispute that the Prior Art Sequences Read on the Challenged Claims

22. Alexion’s Response does not dispute that Bell teaches eculizumab as an effective treatment for PNH and does not dispute that the sequence disclosed in the Bowdish/Evans integrated document expressly discloses the claimed sequences, with a perfect match as shown in alignments.

23. Alexion also raises no disputes relating to any of the specific limitations found in challenged claims 2-8.

24. The only dispute remaining is motivation and reasonable expectation of success, and as discussed below Samsung has met its burden to show obviousness in view of those factors.

2. A POSA Would Have Followed Samsung's Obviousness Rationale

25. I note at the outset that Alexion does not seem to offer any dispute that Bell teaches eculizumab as a treatment for PNH, or that a POSA would have been motivated to prepare eculizumab based on the teachings of Bell (and other clinical trial literature like it). (EX1003, ¶¶109.) I note that Alexion also does not seem to offer any dispute that the combined teachings of the integrated Bowdish/Evans disclosure do, in fact, provide a 100% match to the sequence of eculizumab that is recited in the challenged claims as SEQ ID NOS:2 and 4. (EX1003, ¶¶111-114.) Finally, I note that there is nothing in Alexion's Response that disputes my obviousness opinions specifically with respect to challenged claims 2-8. (EX1003, ¶¶140-145.) Indeed, as I have noted, Alexion offered no substantive expert testimony at all in rebuttal to my opinions regarding the '189 patent, since that patent did not exist when Drs. Casadevall and Trout submitted their declarations in the Amgen IPRs, and in this matter they have merely referred back to their prior declarations from those IPRs, which pertain specifically to different patents and do not (indeed could not) rebut my opinions submitted in this case in support of Samsung's Petition. (*See* ALXN2022, ¶¶202-229.)

26. The obviousness route I proposed in my previous declaration was one that a POSA would have followed. As I explained above, I do not agree with the

view of the prior art in which a POSA would note repeated citation to the Thomas reference and simply end their inquiry there. To restate my original opinion: Starting with Bell's teaching that eculizumab (which it calls "the antibody h5G1.1" and "h5G1.1-mAb") is an effective treatment for PNH. From there, a POSA would have been led first to Evans and Thomas, both of which are cited and incorporated by Bell for "methods of preparation" of h5G1.1. (EX1007, [0012], [0052], [0082]; EX1003, ¶¶109-110, 130.)

27. As I have previously explained, a POSA would also have recognized with no difficulty that Evans provides variable region sequences for eculizumab. A POSA would also easily have seen that Thomas' full-length IgG4 antibody could not be correct for eculizumab, because a POSA knew from the clear teaching of Tacke that eculizumab has an IgG2/G4 domain. (Pet., 29, EX1003, ¶110.)

28. A POSA would not simply stop there as Alexion and Dr. Casadevall contend. A POSA was motivated, and highly skilled, and thus would have kept searching for relevant literature of the 5G1.1 antibody discussed by Bell and Evans. In so doing, a POSA would have found Bowdish particularly relevant. Bowdish provides express disclosures about the structure of an antibody it calls "5G1.1," Bowdish also identifies "Alexion Pharmaceuticals" as the inventors' addressee, and Bowdish also cites to and incorporates the same Evans patent as does Bell for the

structure of 5G1.1. (EX1004, Cover, [0191]; EX1003, ¶120.) I thus disagree with Alexion's argument that Bowdish is not analogous art. (POR, 44.) On the contrary, Bowdish and its incorporated reference Evans are analogous art for a POSA motivated by Bell to make eculizumab. I explained in my original declaration the standard for analogous art, which Bowdish meets for the reasons I noted in my previous declaration and reiterate in this paragraph. (EX1003, ¶¶28, 120.)

29. I similarly disagree with Alexion's argument that Thomas' IgG4 disclosure is a teaching away from the IgG2/G4 teachings of Tacke and the expectations of a POSA. (POR, 47.) I understand that a reference teaches away if it criticizes, discredits, or otherwise discourages investigation into what is claimed as an invention. The prior art does not meet this standard, at least because Tacke expressly disclosed that eculizumab was an IgG2/G4, and no reference anywhere actually offers any negative statement that would criticize or discourage research into an IgG2/G4 format for an anti-C5 antibody. At most, Thomas discloses the existence of an IgG4 format of an anti-C5 antibody (although it never uses the term eculizumab), but this does nothing to teach away from the use of other subclasses of IgG antibody structures – especially given the teachings of Tacke, Mueller PCT and Mueller 1997. (See EX1003, ¶¶62, 64.)

30. A POSA would have been further motivated to rely on Bowdish and

Evans because they would have easily been able to tell that the heavy chain sequences disclosed in Bowdish's SEQ ID NO: 67 were of a human hybrid subclass. This is the subclass Tacke taught would be expected for eculizumab, and as I previously explained, a POSA could have easily confirmed this by aligning the constant domain sequences taught in the combined Bowdish/Evans disclosure with the sequences of Mueller PCT. Such routine alignment would instantly confirm that the antibody under consideration was indeed the IgG2/G4 type as desired. (EX1003, ¶¶123-126; ALXN2104, 150:13-152:24.)

31. Alexion suggests a POSA would have been confused in reading Bowdish as to whether it dealt with human or mouse sequences, because it uses the term "5G1.1" instead of "h5G1.1." I disagree, because a POSA would know that eculizumab was a humanized antibody and would have easily recognized that Bowdish discloses humanized rather than mouse sequences. Reasons for this include the fact that Evans expressly discloses that its framework regions (which align perfectly with Bowdish's) are human, as well as Bowdish's use of an anti-human IgG for its binding assay to detect the antibody it refers to as 5G1.1. (EX1003, ¶81, 121-122; ALXN2104, 142:17-145:6.)

32. I note that Alexion accuses me of violating the rule against using "hindsight," and says I worked backwards from the claimed sequences. Alexion

seems to criticize the fact that my previous declaration included alignments that showed how the combined antibody sequences of the prior art align perfectly with the claimed sequences. (POR, 48.) I did not use hindsight in my analysis, nor did I work “backwards” from the claimed sequences. As I explained in my original declaration, I understand the need to guard against hindsight, and I did so by beginning with the motivation from Bell to make the anti-C5 antibody eculizumab and the clear knowledge from Tacke that eculizumab had an IgG2/G4 constant domain. With that foundation, I sought to identify in the prior art sequences that would be considered by a POSA to be eculizumab, in light of the art’s clear guidance. (EX1003, ¶¶24, 109-130; ALXN2104, 55:19-56:12, 93:7-21, 155:9-156:3.) I included sequence comparisons against SEQ ID NOS:2 and 4, because I understand that part of obviousness requires me to show differences (if any) between the teachings of the prior art and what is recited in the claims. (EX1003, ¶¶111-114.)

33. I have examined Dr. Casadevall’s declaration from the previous Amgen IPR of the ’149 patent on the points discussed in this section, and I disagree with his opinions as explained further below. (*See, e.g.*, ALXN2022, ¶¶188-191, 209-230.)

34. I disagree with Dr. Casadevall’s opinions of how a POSA would have interpreted the teachings of Bowdish and Evans. As an initial matter, as I noted in my original declaration, U.S. Application Ser. No. 08/487,283, which issued as the

Evans patent, was incorporated by reference into Bowdish for “Construction of 5G1.1.” (EX1003, ¶¶80, 87, 111, 119.) I have not seen any argument that there is any significance to the fact that Bowdish references the Evans disclosure in the format of an application serial number as opposed to using the format of Evans as an issued U.S. patent, and Dr. Casadevall does not identify any differences in the disclosure or any reason this distinction would matter. (ALXN2022, ¶188 n.10.)

35. First, I disagree that a POSA would have thought Bowdish was incorporating Evans for disclosures of only mouse antibody sequences. (ALXN2022, ¶¶189-190, 212-219.) Dr. Casadevall’s opinions here all seem to hinge on the fact that Bowdish uses the term “5G1.1” without preceding it with an “h,” but as I explained in my original declaration and at length above, a POSA would know from context (and the disclosures of the references) that Bowdish, like Evans, contained disclosures of human antibody sequences for 5G1.1. Dr. Casadevall also generally discusses the development of antibodies beginning with mouse polyclonal antibodies to humanized monoclonal antibodies, and the fact that mouse antibodies are generally disfavored as candidates for use as pharmaceutical compositions for use in human patients. (ALXN2022, ¶¶69-75.) While this general discussion may be correct, it does not apply to my opinions regarding the obviousness of the challenged claims, given that the prior art in this case contained extensive teachings

about eculizumab, including that it was a humanized anti-C5 antibody with a hybrid IgG2/G4 constant domain.

36. Second, I disagree that a POSA would have been “lost” or unable to combine the teachings of Evans with Bowdish. (ALXN2022, ¶¶190-194, 209-211.) Actually, and as I explained in detail, there was an easy, obvious path to obtain the full sequence of humanized 5G1.1 (which the prior art taught was eculizumab) by removing the inserted TPO peptide and swapping back in the original HCDR3 taught in Evans. (EX1003, ¶¶80-84, 111-115, 126.)

37. Third, I disagree that there would have been any confusion from the multiple scFv sequences disclosed in Evans. (ALXN2022, ¶¶195.) On the contrary, and as I explained in my previous declaration, there is apparently no dispute that Evans consistently teaches only one single HCDR3 sequence in the context of the scFv sequences which it expressly states could be used to make full length antibodies. (EX1003, ¶¶87-89, 115-118, 126, 131, Appendix A.) Dr. Casadevall’s remaining opinions in this area appear to be rebuttals of a different expert (Dr. Balthasar) in the different Amgen IPRs, and thus it is not apparent that these are pertinent or responsive to the opinions expressed in my previous declaration; to the extent they contain relevant arguments I address them herein. (ALXN2022, ¶¶196-201, 216-217.) I address reasonable expectation of success next.

3. A POSA Would Have Had a Reasonable Expectation of Success

38. As I explained in my previous declaration, a POSA would have had a reasonable expectation of success that the sequences provided by the prior art would possess the known anti-C5 properties of eculizumab. (EX1003, ¶¶130-131.) I thus disagree with the concerns of unpredictability raised in Alexion's Response. (POR, 47.) As an initial matter, a POSA already knew that eculizumab had an IgG2/G4 constant region, thus a POSA would not have any concern that they were testing a different antibody from what had already been successfully tested as a PNH therapy as shown in Bell and other clinical trial references. (EX1003, ¶¶110, 123, 125-126, 130-131.)

39. As I previously explained, antibodies with an IgG2/G4 constant region were known in the art by 2007. (EX1003, ¶¶48, 62; EX1006, 011, 013, 015-016; EX1009, 014, 097; EX1021, 011, 019, 028.)

40. Second, as also previously explained, Mueller and other references taught that a hybrid constant region made of G2 and G4 subclass components was desirable for reduced activation of the complement system. (EX1003, ¶48; EX1006, 011, 013, 015-016; EX1009, 014, 097.)

41. Third, as also previously explained, Evans expressly encouraged a POSA to construct complete 5G1.1 antibodies with different constant regions,

including constant regions made of hybrids of different antibody classes. (EX1005, 45:29-33; EX1003, ¶152.) I therefore disagree with any suggestion that Evans discloses only parts or fragments of antibodies, because Evans expressly encourages (and a POSA would know how) to construct full length antibodies following the teachings of Evans.

42. I have also examined Dr. Casadevall's declaration from the Amgen IPR relating to the '149 as it relates to these issues. I disagree with Dr. Casadevall's concerns regarding potential loss of C5 binding activity caused by what he considers to be changes to the constant region as between IgG4 and IgG2/G4. (ALXN2022, ¶¶104-117, 221-229.) I note at the outset that Dr. Casadevall acknowledged in deposition that none of the examples he relies on to support this supposed concern involved an IgG2/G4 antibody. (EX1101, 191:7-12, 192:6-12, 193:23-194:11, 196:16-197:7, 198:22-199:8, 200:13-202:11, 203:20-205:7, 208:10-209:18.) Dr. Casadevall also makes a passing reference to potential issues with efficient cellular expression of an IgG2/G4 antibody (ALXN2022, ¶116), but cites a single example involving a different antibody, and nothing in the prior art including Bell or Tacke ever suggested that there were any expression issues with eculizumab. And there was no reason to expect them, as such issues only occur rarely. Indeed, Alexion's choice to develop eculizumab as a "potential product," which Tacke again taught

was an IgG2/G4, would dispel any such concerns with the efficiency of protein production. (EX1008, 010; EX1003, ¶98.)

43. I address each of Dr. Casadevall’s specific examples from the literature, which he incorrectly attempts to generalize, in the following paragraphs. As I explain below, a POSA would have been aware of each of the specific examples Dr. Casadevall refers to, and would not have less of a reasonable expectation of success from any of these examples (none of which involve an anti-C5 or an IgG2/G4 antibody).

44. Dr. Casadevall points to “changes to ‘framework’ amino acids within the variable regions, but outside the CDRs,” citing ALXN2051 (Foote 1992) and ALXN2052 (Xiang 1995). (ALXN2022, ¶106.) These references would not have undermined a POSA’s reasonable expectation of success because changes to the framework region affecting CDR binding to an antigen are unique to the variable domain and do not implicate changes to the constant region. As I explained in my original declaration, the framework residues provide a scaffold on which the CDRs are able to access the antigenic epitope. (EX1003, ¶38.) The changes to the framework region described in this reference are in an entirely different region of the antibody than the constant region, and thus a POSA’s reasonable expectation of success would not be diminished by them.

45. Dr. Casadevall cites to ALXN2035 (Shepherd 2000). (ALXN2022, ¶106.) This reference would not have undermined a POSA's reasonable expectation of success because Shepard provides a standard protocol for variable region humanization by CDR grafting. As discussed above, changes to the framework region that may impact on CDR binding to an antigenic epitope are unique to the variable domain, and a POSA would not have been concerned by this reference in the context of the IgG2/G4 hybrid constant domain of eculizumab.

46. Dr. Casadevall cites to ALXN2036 (Lo 2004). (ALXN2022, ¶106.) This reference would not have undermined a POSA's reasonable expectation of success because, similar to the Shepard reference, Lo deals with CDR grafting and the impact of framework substitutions on CDR binding affinity. It does not suggest that changes to the constant domain would have any impact on variable region binding.

47. Dr. Casadevall opines that "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," citing to ALXN2013 (McLean 2002). (ALXN2022, ¶¶107-108.) However, this reference would not have undermined a POSA's reasonable

expectation of success because McLean is concerned with antibodies binding to polysaccharide antigens and not protein antigens, and describes results based on immunofluorescence patterns. Indeed, the authors of the reference (which includes Dr. Casadevall) recognized that the observed differences for different isotypes with the same variable region was attributed to the repetitive nature of the polysaccharide antigen. (*See* ALXN2013, 1379 (“This phenomenon may be most apparent for Abs that bind to Ag with repeating epitopes, such as polysaccharides, where the quarternary structure of the Ag-Ab complex may be influenced by such constraints as Fab-Fab angles, Fc-Fc interactions, Ab size, and solvent accessibility to exposed surfaces.”).) Because of these differences, ALXN2013 would not be of concern to a POSA dealing with anti-C5 antibodies. As I discuss below, the same is true for the rest of the references Dr. Casadevall cites as supposedly supporting his point that changes to the constant domain can impact antigen binding. Instead, the phenomenon for repeating/polysaccharide-type antigens under study in Dr. Casadevall’s laboratory would have been understood by a POSA as of 2007 as a somewhat unique phenomenon for a specific class of antigens – not a generalizable fact about antibodies overall.

48. Dr. Casadevall points to other work from his own laboratory, citing ALXN2013 (McLean 2002), ALXN2040 (Torres 2005), and ALXN2009 (Torres

2007). (ALXN2022, ¶107.) These references would not have undermined a POSA's reasonable expectation of success because Torres, similarly to McLean, deals with murine anti-polysaccharide switch variants. In addition to the reasoning set forth above, these three exhibits are also different because they point mainly to differences between mouse and human isotypes. Thus, they would not diminish the expectation of success by a POSA in developing an IgG2/G4 constant region for an anti-C5 antibody. Indeed as noted throughout my declarations, Tacke explicitly points to the IgG2/G4 hybrid constant region for the anti-C5 antibody h5G1.1 called eculizumab, and Bell provides data showing eculizumab is an effective PNH treatment, confirming that the IgG2/G4 constant region did not disturb the ability of the antibody to recognize its C5 antigen.

49. Dr. Casadevall also points to a review article he co-wrote, ALXN2010 (Janda 2016). (ALXN2022, ¶¶107, 114.) First, I note that the Janda reference is a review article that covers at a high level the same kinds of original research reports that are discussed by Dr. Casadevall, and thus I deal with those studies in other paragraphs in this section of my declaration. As a result, this reference would not have undermined a POSA's reasonable expectation of success because it again deals with the observations cited above regarding antibodies with specificity for repetitive epitopes and would not diminish the expectation of success for an POSA developing

an anti-C5 antibody with a hybrid IgG2/G4 constant domain.

50. Dr. Casadevall also points to ALXN2014 (Greenspan 1995). (ALXN2022, ¶109.) This reference would not have undermined a POSA's reasonable expectation of success because, like the literature cited above, is primarily concerned with murine switch variants and variable domains with specificity for multivalent targets, such as polysaccharides.

51. Dr. Casadevall also points to ALXN2011 (Pritsch 1996). (ALXN2022, ¶110.) This reference would not have undermined a POSA's reasonable expectation of success because Pritsch reports the results of anti-tubulin antibodies with the same variable domains but which differ in their isotypes (IgA and IgG) display differences in binding affinity. This study thus does not concern a subclass change, such as from IgG4 to IgG2/G4, but rather a switch to an entirely different isotype. A POSA would not consider this study to impact the expectation of success in generating an anti-C5 antibody with a hybrid G2/G4 constant domain because the isotype (IgG) is the same and especially given the teachings of Tacken and Bell as noted above.

52. Dr. Casadevall also points to ALXN2008 (McCloskey 1996). (ALXN2022, ¶111.) This reference would not have undermined a POSA's reasonable expectation of success because McCloskey reports results for chimeric mouse-human IgGs to a mucin-like glycoprotein, which again is a repetitive protein

that is heavily decorated with polysaccharides. The C5 target of eculizumab is not a mucin-like glycoprotein, and thus these results would not influence the expectation of success of a POSA developing humanized anti-C5 antibodies with hybrid G2/G4 constant region domains for the reasons cited above.

53. Dr. Casadevall points to three further articles from his laboratory, ALXN2040 (Torres 2005), ALXN2009 (Torres 2007), and ALXN2039 (Torres 2007 PLOS One). (ALXN2022, ¶112 (the first two of these were already referenced in ¶107 of Dr. Casadevall's declaration).) ALXN2039 would not have undermined a POSA's reasonable expectation of success because, once again, the target polysaccharide multivalent antigen is distinct from the C5 target and none of the studies address the relationship between G4 constant region and G2/G4 hybrid constant region with relation to binding specificity. In contrast, as noted throughout my declarations, Tacke explicitly points to the IgG2/G4 hybrid constant region for the anti-C5 antibody h5G1.1 called eculizumab, and Bell provides data showing eculizumab is an effective PNH treatment, confirming that the IgG2/G4 constant region did not disturb the ability of the antibody to recognize its C5 antigen.

54. Dr. Casadevall states that "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,” citing ALXN2012 (Pritsch 2000) and ALXN2009 (Torres 2007). (ALXN2022, ¶113.) I disagree. These references would not have undermined a POSA’s reasonable expectation of success because, as discussed above, each of these examples dealt with either entirely different isotypes (IgA and IgG) or multi-valent antigens such as polysaccharides, and would not influence a POSA developing an anti-C5 antibody with a hybrid G2/G4 constant region.

55. As I noted above, Dr. Casadevall’s examples are drawn from a limited class of antibodies that interact with repetitive carbohydrate epitopes. However, and as I explained in my deposition in this matter, the relevant literature actually indicated that “switching the constant region domain of the heavy chain or light chain has not impacted on the binding specificity or affinity of the original Fab domains.” (ALXN2104, 60:13-61:22.)

56. I also discuss further below why both Thomas and Mueller’s teachings further show that a POSA would not expect a subclass switch from IgG4 to IgG2/G4 in the context of the 5G1.1 antibody to impact C5 binding ability of the antibody. I noted as much during my deposition in this matter. (ALXN2104, 57:21-58:8 (“we knew quite a bit more about eculizumab than this generic discussion that Dr. Casadevall is presenting.”).) (See Part II.D.2 below.)

57. Dr. Casadevall also argues that a hybrid IgG2/G4 domain would present heightened immunogenicity concerns, citing ALXN2015 (Radbruch 1985), ALXN2036 (Lo 2004), and ALXN2038 (Haller 2008). (ALXN2022, ¶¶115, 117.) These references would not have undermined a POSA's reasonable expectation of success because these studies deal with modifications to variable domains that may influence antigenic specificity and not to constant region modifications of highly homologous subclasses. Further, a POSA would not have had immunogenicity concerns in creating eculizumab as an IgG2/G4 antibody working from the prior art as I outlined above, because the art had already confirmed that eculizumab (disclosed by Tacke as a humanized IgG2/G4 antibody) did not trigger an immunogenic response in human patients. (EX1003, ¶¶48, 58; EX1013, 013.)

4. Dose and Formulation Limitations

58. I have reviewed Alexion's Response document as relates to the dosing and formulation limitations of the challenged claims. (POR, 49-53.) I disagree that these limitations were not obvious or add anything of patentable consequence to the antibody sequence and PNH treatment limitations of the claims. I explained these opinions in detail in my initial declaration. (EX1003, ¶¶132-139.)

59. I disagree that a POSA would have had any concern about the stability of eculizumab formulations for injection. For example, and as I previously

explained, Bell expressly discloses “[f]ormulations” of eculizumab “suitable for injection” (referencing the Remington’s standard) and reports on their successful use in the clinic. (EX1007, [0062]; EX1003, ¶¶92-96, 132-137; EX1062, ¶32.) Remington’s Pharmaceutical Sciences is a standard reference for the preparation of pharmaceutical compositions widely known by a POSA in this field. Indeed, the challenged patent itself expressly references the very same Remington’s Pharmaceutical Sciences text in its own disclosure of “[f]ormulations suitable for injection.” (EX1001, 16:54-56; EX1062, ¶32.) A POSA reading Bell in view of Tacke would understand that Bell was discussing eculizumab as an IgG2/G4 antibody and teaching that it could be stably formulated for injection.

60. As I noted in my original declaration, Wang also taught stable eculizumab formulations at concentrations as high as 30 mg/ml, and 10 mg/mL was known to be a commonly used concentration for antibody formulations. (EX1044, Fig. 10, [0025], [0067], [0170]-[0173]; EX1061, 014; EX1056-EX1060; EX1003, ¶¶135, 139.)

61. I further note that no single instance of any concerns relating to the stability of eculizumab has been identified in any of the many prior art publications reporting on the PNH clinical trials, some of which ran for two years. (EX1003, ¶58.) Thus, again a POSA would not have had any reason to be concerned that the

eculizumab antibody reported in Bell and other clinical trials, which Tacke taught was an IgG2/G4 antibody, would be difficult to stably formulate. (EX1003, ¶¶138-139.) Finally, I note that none of the challenged claims require any particular level of stability, or recite any claim language relating to stability, which I understand is pertinent to the obviousness analysis because the claim should be judged according to its objective reach.

62. It appears that Alexion argues that the 30 mL (10 mg/mL) and 300 mg limitation of the claims were merely specific choices from among many options that the prior art made available to a POSA. (POR, 51-52.) My understanding is that merely selecting one option from several taught by the prior art, especially in the absence of any unexpected results or reasons why the chosen option would be special, is not inventive. And as I explained in detail in my original declaration, 10 mg/mL and 300 mg *were* particularly attractive to a POSA from within these known ranges, because 10 mg/mL was a commonly used antibody concentration and because 300 mg was the best single use dose format that would be most appropriate for use in a mixed dosing schedule that had 600 and 900 mg components. (EX1003, ¶¶134-135.)

63. And while I further agree that in a general sense stability of an antibody formulation is a relevant consideration and an important one, in this case there is

simply no evidence from the prior art that a POSA would have had any need to balance stability against other factors such as convenience, ease of use, lack of waste, sterility, etc., because a POSA knew that eculizumab had already been successfully formulated and used in clinical trials. (EX1003, ¶134; EX1062, ¶50.)

64. I note in closing that Alexion did not submit any expert testimony specifically rebutting my opinions or those of Dr. Ippoliti regarding why the dosing and formulation limitations were obvious. Alexion does rely on the Trout declaration re-used from the Amgen IPR proceeding relating to the '504 patent, which I address next.

65. I have reviewed the Trout Declaration as relied upon in Alexion's response brief. (ALXN2024, ¶¶64-91.) I note that this declaration relates to a different patent with different claim limitations than the ones challenged here, but I have done my best to apply Dr. Trout's opinions to the claims at issue in this case. As discussed below, I do not agree with Dr. Trout that a POSA would not have had a motivation to combine the prior art of Ground 1 with a reasonable expectation as it pertains to the dosing and formulation limitations.

66. In ¶¶66-67, 69 of his declaration, Dr. Trout argues that neither Bell nor Wang disclose the complete amino acid sequence of eculizumab, and generally contends that POSA would not have known that an antibody with a sequence

matching that of what is recited in the challenged claims had already been tested in clinical trials. But of course those sequences were disclosed as I previously explained by the Bowdish and Evans references, especially when viewed in combination with Mueller PCT and Tacken. (EX1003, ¶¶109-131.)

67. In ¶¶68 and 72 of his declaration, Dr. Trout contends that a POSA would not have believed that eculizumab had ever been successfully formulated for therapeutic use. But this is incorrect, because a POSA would know from Bell in view of Tacken that eculizumab, which is an IgG2/G4 antibody, had in fact been successfully used in human patients in clinical trials. (EX1003, ¶¶58, 92-96, 138-139.) Dr. Trout also places emphasis on the fact that an IgG2/G4 antibody had not previously been approved by the FDA, but this standard for motivation and reasonable expectation of success goes far beyond the appropriate standard as I understand it. As I have previously explained, there was more than sufficient detail and evidence in the prior art for a POSA to have motivation and a reasonable expectation of success. I address Dr. Trout's other opinions concerning the Bell and Wang references below.

68. In ¶¶70-71 of his declaration, Dr. Trout generally argues about alleged uncertainty in connection with the formulation of antibodies and in particular asserts that a POSA would not have had any confidence in the ability to formulate

eculizumab. First, as already noted, in the case of eculizumab as of March 2007, any such concerns would not have applied because the prior art already taught that the IgG2/G4 antibody eculizumab had been successfully formulated for injection and used in clinical trials, some of which ran for two years. (EX1003, ¶¶58, 92-96, 138-139.) Secondly, I disagree with Dr. Trout that antibody formulation was such an uncertain field that a POSA would not have had a reasonable expectation of success. Once again, it appears that Dr. Trout is applying the incorrect legal standard and arguing that a POSA would have required a virtual guarantee of success in order to proceed (“a POSA would not have known”), but as I understand what is required is a reasonable expectation of success. (ALXN2024, ¶71 (emphasis added).) And furthermore, by 2007 much was known about successful formulation of antibodies, and there was no reason to think, again given the large number of clinical trial publications relating to eculizumab, that there would be any difficulty in formulating the antibody as a pharmaceutical composition. (EX1003, ¶¶55, 58; EX1052; EX1062, ¶¶24-25, 56.)

69. In ¶¶73-74 of his declaration, Dr. Trout argues that a POSA would have been concerned with whether a POSA relying on the sequences of Bowdish and Evans for the sequence of eculizumab could have been formulated as a solution. But as I previously explained, Bell expressly disclosed that eculizumab was delivered by

intravenous infusion, which requires a solution be prepared. (EX1003, ¶134; EX1007, [0082].) I also previously explained that by 2007 it was commonplace for antibodies to be supplied in solution formulations that could be conveniently added to an IV bag for infusion. (EX1003, ¶135.) Dr. Trout also contends that pharmaceutical compositions are not necessarily supplied by the manufacturer as solutions but sometimes are supplied as lyophilized powders that are made into solutions prior to injection. I do not see why this distinction is meaningful for the challenged claims, which merely recite the common term “pharmaceutical composition” and say nothing about whether that composition might be supplied in a lyophilized powder form by the manufacturer – indeed if anything the claims are clear in their focus on the point of administration to a patient, since they recite the language “administering to a patient a pharmaceutical composition.” In other words, it appears that Dr. Trout is pointing to considerations that have nothing to do with the actual limitations of the challenged claims. And in any case, for the reasons already explained above, the prior art taught that antibodies were commonly supplied as solutions and the Bell reference specifically discloses the use of a solution formulation for IV infusion.

70. In ¶¶76-80 and 90, Dr. Trout argues that a POSA would not have been motivated to prepare eculizumab specifically in a 10 mg/mL concentration. As I

previously explained in my declaration, I disagree. (EX1003, ¶135; EX1062, ¶¶50-52.) As previously explained, a POSA would have known that 10 mg/ml was within the well-known range of concentrations of several FDA-approved antibody pharmaceutical compositions. (EX1061, 014 (Table 1); EX1056 (Campath), 013 (10 mg/ml); EX1057 (Erbitux) (2 mg/ml), 001; EX1058 (Herceptin), 001-02 (21mg/ml); EX1059 (Remicade), 001 (10 mg/ml); EX1060 (Rituxan), 001 (10 mg/ml).)

71. In ¶¶81-89 of his declaration, Dr. Trout presents his arguments concerning the Wang reference, and contends that it did not provide sufficient disclosure of dosing and formulation information, as well as stability data, to provide a POSA with motivation to combine and a reasonable expectation of success. I disagree. As previously explained, a POSA would have found the Wang reference pertinent and would have obtained further motivation to combine and reasonable expectation of success from its teachings. (EX1003, ¶¶106-107, 135, 138-139; EX1062, ¶¶51-52, 55-56.) First, Dr. Trout focuses on Wang's teachings concerning nebulization, but this subject in Wang would not have lessened the relevance to a POSA of the fact that, in order to study formulation of eculizumab for nebulization, Wang first had to prepare an aqueous solution of eculizumab and study its stability and integrity.

72. A POSA would have understood 1) the teachings of Wang that specifically referenced the range of 1-30 mg/mL, 2) the express teaching that antibodies can be stably formulated from 1-200 mg/mL, and 3) the stability data showing that eculizumab in liquid formulations maintained its stability. (EX1003, ¶¶106-107, 135, 139; EX1044, Fig. 10, [0025], [0067], [0170]-[0173].) Specifically, the experimental examples disclosed in Wang that concern eculizumab formulations begin by referring to Fig. 10, which expressly discloses “Formulation 1” a range of 1 to 30 mg/mL. (EX1044, [0170], Fig. 10.) While Wang’s [0170] references a mouse 5G1.1 antibody, the remaining related experiments in [0171]-[0173] all refer to eculizumab, expressly. Wang’s experiments then go on to prepare such formulations of eculizumab – as aqueous solutions – at concentrations as high as 30 mg/mL, and confirm their stability and integrity through an aerosolization process. (EX1044, [0171]-[0173], Figs. 12-15.) A POSA would have understood from these experiments that if eculizumab could maintain stability and integrity in an aqueous solution despite the stresses of an aerosolization procedure, it would also be stable in the initial aqueous solution. I further note that Dr. Ippoliti confirmed in her deposition that Wang specifically taught that eculizumab in aqueous solution was stable when examined by experiments using HPLC to monitor integrity of the drug. (EX2106, 59:20-60:3.) To the extent Dr. Trout seeks to add further limitations to

the claim requiring a specific shelf life or stability level over some unspecified period of time (e.g., ALXN2024, ¶¶84, 87), again I note that Dr. Trout is applying the wrong standard and not examining the actual limitations of the challenged claims as written, which do not recite any particular requirements for shelf life or stability over some period of time. Finally, I note that Dr. Trout does not point to any evidence in the prior art concerning eculizumab, including the many references detailing its use in clinical trials involving IV infusion, in which any particular stability concerns were noted for eculizumab. Thus, in my opinion, Dr. Trout is improperly generalizing from his opinion that there can be no absolute guarantee of success for the formulation of every antibody, and arguing from this that a POSA would not have had a reasonable expectation of success.

73. Last, in ¶91 of his declaration, Dr. Trout argues that there was no reason to formulate eculizumab in a 300 mg dose amount. As I previously explained, I disagree. (EX1003, ¶134; EX1062, ¶50.) In fact, 300 mg is clearly the most appropriate single dose for Bell's disclosed regimen of 600 mg and 900 mg, because a POSA would have been motivated to prepare a single dose formulation that could be easily scaled by arithmetic to reach those two common dose applications. (*Id.*) That a POSA might also think of *other*, less convenient, less scalable doses to prepare does not detract from the 300 mg dose option that would immediately

recommend itself to a POSA. I also do not agree with Dr. Trout that the existence of multiple dosage forms for other FDA approved antibodies is pertinent here, and I note his examples involve very different dose ranges and situations in which the antibody may be dosed differently for different indications. Here, we have the clear 600/900 mg disclosures of Bell for the treatment of PNH, and a POSA would have been motivated to make a 300 mg dose for use in that treatment regimen. I have also reviewed the few paragraphs of the Casadevall Declaration cited by Alexion in connection with these issues (POR, 50, *citing* ALXN2022, ¶¶189-191). This citation does not make sense because those paragraphs do not deal with these limitations or the Wang reference. In any event, his brief opinions on these issues as expressed in the '880 and '504 Amgen IPRs are entirely cumulative to Dr. Trout's opinions, which I have discussed and rebutted above (and in connection with the '880 and '504 patents in these Samsung IPRs).

D. Ground 2: Claims 1-8 Are Obvious over Bell, Evans, Mueller PCT, and Wang in View of Tacken

74. To begin, I note that as with Ground 1, there seems to be no dispute that Bell taught a POSA that eculizumab was a useful treatment for PNH, or that the amino acid sequences in the combined disclosures of Evans and Mueller PCT read exactly on SEQ ID NOS:2 and 4 of the challenged claims. (EX1003, ¶151.) I also

note, as with Ground 1, Alexion raises no disputes relating to any of the specific limitations found in challenged claims 2-8. I address Dr. Casadevall's arguments relating to the Evans and Mueller PCT combination below. (*See* ALXN2022, ¶¶230-252.)

1. A POSA Would Have Followed Samsung's Obviousness Rationale

75. As I explained in my previous declaration, a POSA working from Bell would have looked to Evans and Mueller PCT, and would have combined them to obtain the desired sequence of the eculizumab antibody. At the first step, Bell points directly to Evans and Thomas for the amino acid sequence of the anti-C5 antibody eculizumab and incorporates both by reference. (EX1003, ¶¶146-148.) A POSA would not, however, have concluded that eculizumab was an IgG4 antibody from this reference to Thomas, because of the teachings of Tacke and Mueller PCT (which were published after Thomas). (*Id*; *see also* Part II.B above.) Further, a POSA would have known how to combine Evans and Mueller, because a POSA would have been able to differentiate the disclosures of those references as they pertain to variable and constant regions. Thus, a POSA would have used Evans for the C5-binding variable regions of eculizumab, as directed by Bell, and would have used Mueller PCT for the IgG2/G4 constant domains, as directed by Tacke and

taught by Mueller PCT. (Pet., 49-52; EX1003, ¶¶148-151.)

76. Further, even if a POSA was somehow unaware of Tacken's IgG2/G4 disclosure, the prior art still contained ample motivation and reasonable expectation of success to modify the constant region of the original IgG4 antibody of Thomas. For example, Evans provides instructions for how to combine 5G1.1 variable regions with constant region domains to form a full-length antibody, and this same part of Evans expressly states that it is "[p]articularly preferred" to use "a mixture of constant domains from IgGs of various subtypes." A POSA would read this to include the IgG2/IgG4 disclosure of Tacken and Mueller PCT. (EX1005, 45:29-33; EX1003, ¶152.)

77. I understand that Alexion argues that I never identified any reason a POSA would have been motivated to move from an IgG4 to an IgG2/G4 antibody so as to avoid binding Fc receptors. (POR, 43.) This is not true. In fact, as I described in my previous declaration, the Mueller 1997 reference associated with Mueller PCT provides general motivation to convert IgG4 isotype antibodies to the "HuG2/G4 antibody design" in any human antibody intended for therapeutic use "where elimination of FcR binding and C activation may be desirable." (EX1006, 016; EX1003, ¶¶47-48, 153.) Again, as I have previously explained, and explained further in my deposition, a POSA would have recognized these teachings as

beneficial in the context of a therapeutic antibody intended for use to block part of the complement system. (EX1003, ¶153; ALXN2104, 169:5-18, 171:12-173:7.)

78. Further, my previous declaration did provide a detailed explanation of why a POSA would have combined Evans and Mueller PCT. (EX1003, ¶¶146-151.) I do not agree that a POSA would have had to apply any guesswork about which amino acids from Evans and Mueller PCT would be used, as Alexion argues. (POR, 17.) Instead, the combination was actually a very simple one involving whole, distinct large regions of the antibodies: Mueller PCT (which a POSA could have confirmed against the teachings of the related Mueller 1997 reference) clearly showed exactly how to construct an IgG2/G4 hybrid, by combining the C1 region and hinge of IgG2 with the C2 and C3 regions of IgG4. (EX1009, 8:23-26, 12:23-27; EX1006, 011, 013; EX1003, ¶¶48, 101.)

79. As I previously explained, and show with an excerpt below, the Tacke reference gives very clear direction. It explains that eculizumab contains an IgG2/IgG4 constant region, and says it is “the same” as that disclosed in Tacke’s reference 17, which is the Mueller 1997 article. Thus, contrary to the implications raised in Alexion’s arguments, Tacke does not leave any doubt about what is being disclosed concerning the constant domains used in eculizumab. Tacke provides more than ample disclosure to lead a POSA to Mueller PCT for the needed constant

domain sequences. (EX1003, ¶¶98, 152-153.)

Recombinant antibodies

The humanized antihuman DC-SIGN antibody hD1V1G2/G4 (hD1) was generated by complementarity determining region (CDR) grafting of AZN-D1 hypervariable domains into human framework regions. The humanized variable heavy and variable light regions were then genetically fused with a human hybrid IgG2/IgG4 constant domain¹⁷ and a human kappa chain constant domain, respectively. This construct was cloned into a mammalian expression vector and the final construct transfected into NSO cells. Stable transfectants were obtained using glutamate synthetase (GS) selection (Lonza Biologics, Portsmouth, NH). Supernatants containing hD1 were purified over a protein A column. An isotype control antibody, h5G1.1-mAb (5G1.1, eculizumab; Alexion Pharmaceuticals) containing the same IgG2/IgG4 constant region, is specific for the human terminal complement protein C5.¹⁹

(EX1008, 011 (citing EX1006) (highlighting added).)

80. I note that Alexion also argues that a POSA would not have been able to differentiate between Evans' multiple variable structures relating to 5G1.1 and instead would have focused on the separately disclosed mouse antibody, even though a POSA would know from Bell that eculizumab is a humanized antibody. (POR, 53-54.) I disagree and note again that Alexion is not crediting the abilities of a POSA in this field, which is admittedly-highly skilled. Nevertheless, the Evans prior art gave a direct path to a POSA as to how to interpret and use its disclosures. Specifically, Evans' Example 11, entitled "Construction and Expression of Recombinant mAbs," provides a finite set of clearly identified CDRs that bind C5. (EX1005, Cover (Title), 7:60-64, 9:44-45, 42:56-45:33, 143:22-144:14, Fig. 8, Claim 19 (emphasis added); *see also* EX1022, 16:10-12.) This would have been

clear guidance to a POSA – especially since the Mueller PCT disclosure specifically highlights the “CO12” sequence as the only one investigated in that reference. (EX1003, ¶¶147-150.)

81. I note that Alexion again complains that I used hindsight in my Ground 2 analysis. (POR, 56.) Again, I disagree. I began with motivation from Bell and knowledge from Tacken, combined the teachings of Evans and Mueller PCT, and only then did I perform a confirmatory alignment. (EX1003, ¶151 (“[t]he resulting antibody, as shown in the comparisons below, shows a perfect match [with] ... the claimed SEQ ID NOS:2 and 4” (emphasis added)).

82. I have examined Dr. Casadevall’s declaration from the previous Amgen IPR of the ’149 patent on the Evans/Mueller PCT combination as discussed in this section, and I disagree with his opinions as explained further below. (*See, e.g.*, ALXN2022, ¶¶232-247.)

83. In ¶¶232-234 of his declaration, Dr. Casadevall expresses his view that a POSA would not have been motivated to combine Evans with Mueller PCT. I disagree for the reasons articulated above in this section, and in my previous declaration. (EX1003, ¶¶146-148.)

84. In ¶235 of his declaration, Dr. Casadevall argues that a POSA would not have been motivated to construct an IgG2/G4 antibody because that process

would supposedly have been complex, time-consuming, and unpredictable. I disagree, for the reasons already noted above (§75) and in my previous declaration. A POSA would have known from reading Bell and Tacke that eculizumab was an IgG2/G4 antibody that had been successfully used in humans as a PNH treatment. There was thus nothing “new” about making an IgG2/G4 antibody, since Alexion had already published that they had done so. These facts would have removed any complexity or uncertainty from the proposition and made it simple for a POSA to follow the teachings of the prior art (Evans and Mueller PCT) to construct the eculizumab antibody. (EX1003, §§146-151.)

85. In §236 of his declaration, Dr. Casadevall makes the curious argument that a POSA, even if motivated to make an IgG2/G4 antibody, would not have known which parts of IgG2 and which parts of IgG4 to use, and might have selected various ways to hybridize those two subclasses. This argument is nonsensical – the prior art Mueller PCT and Mueller 1997 references, both of which are directly associated with Alexion, gave very clear guidance about how to construct the IgG2/G4 hybrid that Tacke expressly says is “the same” as between Mueller 1997 and eculizumab. (See §79 above and EX1003, §§152-153.) A POSA would not have had any doubt about how to build the constant region, and would not have had any need to creatively try other approaches before simply following the teachings of the

Mueller references.

86. In ¶237 of his declaration, Dr. Casadevall again argues that Evans does not teach full length antibodies, but as I have already explained, he is incorrect since Evans does expressly teach how to make full length antibodies using its disclosures, and in any event a POSA could easily have used Evans' scFv sequences relating to variable domains in the assembly of a full-length antibody according to known and conventional techniques. (*See above* ¶37; EX1005, 45:29-33; EX1003, ¶152.) For the same reason, I disagree with the suggestion in Dr. Casadevall's report that the Evans' scFv disclosures were not disclosures of variable domain sequences because they were recombinant. As I show in my previous declaration, this is wrong because the 5G1.1 C5-binding scFv fragments disclosed in Evans did provide entire variable regions, and a POSA would know how to use those sequence teachings to assemble a full-length antibody. (EX1003, ¶¶87-89, 150-151.)

87. In ¶238 of his declaration, Dr. Casadevall argues that a POSA would not have known how to interpret the term 5G1.1 as it appears in the different prior art references, but he is incorrect for the reasons I discussed in detail above in Part II.B.

88. In ¶¶239-241 and 245 of his declaration, Dr. Casadevall contends that the CO12 disclosure in Mueller PCT would have been disregarded by a POSA and

contends that a POSA would not have known how to combine the Evans and Mueller PCT teachings, but he is incorrect as I explained in my original declaration. (EX1003, ¶¶150-151.) As I explained in my previous declaration, even though it would have been simple and routine for a POSA to try Evans' nine sequences, Mueller PCT provides some additional guidance to a POSA specifically to prioritize the construct disclosed in Example 11 (12) that is identified as "humanized" "5G1.1 scFv CO12." Mueller PCT also uses the same identifier, and the only 5G1.1 with the hybrid IgG2/G4 discussed in Mueller PCT is referred to as "h5G1.1 CO12 HuG2/G4." (EX1009, 014.) Mueller PCT does not refer by name to any of the other constructs provided in Evans' Example 11. Therefore, a POSA would have been motivated to assemble a full-length antibody with Mueller PCT's IgG2/G4 region and constant light chain region, along with Evans' variable regions that use the same identifier, CO12. (EX1003, ¶¶150-151.)

89. In ¶¶242-243 of his declaration, Dr. Casadevall makes references to specific statements by Amgen's expert Dr. Balthasar which are not relevant to my declaration or my testimony. In my previous declaration, I explained how a POSA would have been able to use Mueller PCT (including by confirmation with Mueller 1997) references to easily determine the pertinent regions and subclasses of the disclosed heavy chains. (EX1003, ¶124.) I also explained how a POSA would easily

have known how to recognize the distinct regions of an IgG heavy chain of different subclasses. (EX1003, ¶126.)

90. In ¶244 of his declaration, Dr. Casadevall questions why a POSA would not have taken variable regions of 5G1.1 from the Thomas reference as opposed to Evans, and then notes that Thomas' disclosure difference at one amino acid position would not match with the sequence recited in the challenged claims. I do not understand why this argument is pertinent to my obviousness analysis, because as I understand, the prior art can render more than one combination obvious. (*See, e.g.*, EX1003, ¶149.) Evans clearly discloses C5 binding antibody variable domains, so it doesn't matter if Thomas does as well, especially since Bell cites to both Evans and Thomas.

91. In ¶246 of his declaration, Dr. Casadevall again argues that a POSA would not have known how to combine Evans and Mueller PCT and would not have known how to combine the variable and constant domains disclosed by those references. I addressed this argument above (¶¶75, 78) and in my original declaration. (EX1003, ¶¶146-151.) To summarize, the combination is an exceedingly simple one since Evans discloses full length variable regions and a POSA would know how to combine those with the full-length constant regions taught by Mueller PCT. (*Id.*)

92. In ¶247 of his declaration, Dr. Casadevall argues that Amgen's expert Dr. Balthasar used hindsight. This is not pertinent to my declaration because Dr. Casadevall makes no comments specific to my declaration, and in any event as I explained above any allegation of hindsight in my analysis is wrong. (*See above* ¶81.)

2. A POSA Would Have Had a Reasonable Expectation of Success

93. As I explained in my original declaration, a POSA would have had a reasonable expectation of success that the Mueller/Evans antibody would retain C5 binding. (EX1003, ¶154; *see also id.* ¶131.) As explained further below in this section, I disagree with Dr. Casadevall's arguments regarding possible loss of C5 binding when subclass-switching from IgG4 to IgG2/G4.

94. As a first example, Thomas itself reports that changes to the constant domain in the 5G1.1 antibodies discussed in that reference, for example when going from Fab fragments to full length, did not affect C5 binding. (EX1010, 013.) I also provided testimony on this subject in my deposition. (ALXN2104, 70:15-71:4, 176:11-25.)

95. As a second example, Mueller's IgG4 to IgG2/G4 subclass switch had no effect on target binding. (EX1006, 015-016 (noting that changing the anti-

VCAM antibody from an IgG4 to an IgG2/G4 did not impact its ability to bind to target or its avidity); EX1009, 014 (referring to discussion of the data presented at Fig. 14).) I also provided testimony on this subject in my deposition. (ALXN2104, 62:13-63:8, 175:8-25.) I further note that the Mueller 1997 reference confirms that the change from IgG4 to IgG2/G4 as disclosed in the Mueller publications actually does not involve a significant number of amino acid changes – providing still further reason why a POSA would have had a reasonable expectation of success that the IgG2/G4 antibody sequences provided by the prior art would bind to C5. (See EX1006, 016 (noting “the similarities between these two isotypes at the amino acid level[.]”).)

96. A POSA would thus have had a reasonable expectation of success that the Evans/Mueller antibody would retain C5 binding, as I explained at my deposition. (ALXN2104, 175:8-177:4; *see also* EX1003, ¶¶147-150, 154.) I have also examined Dr. Casadevall’s deposition transcript from the prior Amgen IPR, and note that Dr. Casadevall admitted that none of the examples that he argues show that constant domain changes can affect target binding pertaining to an IgG2/G4 antibody, or to a transition from an IgG4 antibody to an IgG2/G4 hybrid. (EX1101, 191:7-12, 192:6-12, 193:23-194:11, 196:16-197:7, 198:22-199:8, 200:13-202:11, 203:20-205:7, 208:10-209:18.)

97. I note that Alexion also argues that there would have been immunogenicity concerns associated with an IgG2/G4 hybrid antibody. (POR, 39.) As noted above, any such concerns are directly contradicted by the prior art, which had already confirmed that eculizumab (disclosed by Tacke as a humanized IgG2/G4 antibody) did not trigger an immunogenic response in human patients. (EX1003, ¶¶48, 58; EX1013, 013.)

98. I have examined Dr. Casadevall's declaration from the previous Amgen IPR of the '149 patent on the Evans/Mueller PCT combination and reasonable expectation of success as discussed in this section, and I disagree with his opinions as explained further below. (*See, e.g.*, ALXN2022, ¶¶248-252.)

99. In ¶¶248-249 of his declaration, Dr. Casadevall simply rehashes his general arguments against the obviousness rationale of combining Evans and Mueller PCT (in view of Bell and Tacke) and wrongly contends that the literature taught that eculizumab was an IgG4 antibody. I have already addressed these arguments and my reasons for disagreeing with them above.

100. In ¶¶250-252 of his declaration, Dr. Casadevall again restates his concern that moving from an IgG4 subclass antibody to an IgG2/G4 subclass would not reasonably be expected to retain C5 binding. As already discussed above (¶¶93-96) I disagree. In addition to the prior art disclosing that the variable domain of

5G1.1 could tolerate changes to the constant domain without affecting C5 binding, and the teaching that Mueller's antibody was not affected in terms of target binding when going from IgG4 to IgG2/G4, a POSA would have known from Tacke that eculizumab was an IgG2/G4 and would have known from Bell that eculizumab was an anti-C5 antibody that had been successfully used to treat PNH. So a POSA would absolutely have had a reasonable expectation of success that, by constructing eculizumab from combining the teachings of Evans and Mueller PCT, the resulting antibody would retain C5 binding.

101. With respect to the dosing and formulation limitations of the claims, I note that Alexion does not raise any different arguments from those it raised in connection with Ground 1, (*see* POR, 56), accordingly I refer here to my discussion above in Part II.C.4.

E. Ground 3: Claims 1-8 Are Obvious over Bell and Wang

102. Ground 3 relates to my argument that Bell inherently anticipates the amino acid sequence limitations of the challenged claims, and that this inherent disclosure, in combination with the teachings of Wang for the dose and formulation limitations, renders the challenged claims obvious. (EX1003, ¶¶157-163.) In its Response, Alexion primarily makes legal arguments and only cites to the declarations of Dr. Casadevall and Dr. Trout in two locations. (*See* POR, 57-67.)

The section of Dr. Trout's declaration cited is the same one cited for Ground 1 and pertains to his arguments on the dose and formulation limitations, to which I responded above. (*See* above Part II.C.4.) I have also generally reviewed Dr. Casadevall's declaration as it pertains to his argument that Claim 1 of the '149 patent was not anticipated under a theory of inherency by the Hillmen or Hill references, even though these references are different from the Bell reference I rely on, and respond below. (*See* ALXN2022, ¶¶172-181.)

103. Alexion's brief for the '189 patent cites ¶¶174-184 of Dr. Casadevall's declaration (POR, 66), which I have also evaluated. I note initially that this citation does not make sense and seems to be in error because most of those paragraphs relate to Amgen's anticipation arguments based on the Hillmen and Hill references, which is not directly relevant or responsive to the Bell-based arguments I made for Ground 3 as noted above. (*See* ALXN2022, ¶¶174-181.) The remaining paragraphs relate to Amgen's argument of anticipation based on Bowdish, which is again not directly relevant or responsive to my arguments for Ground 3. (*See* ALXN2022, ¶¶182-184.) This is perhaps not surprising, because Dr. Casadevall has never submitted any opinions that actually respond in any substantive way to my opinions regarding the '189 patent, given that the '189 patent did not exist when Dr. Casadevall provided declarations for the Amgen IPRs.

104. Nevertheless, Dr. Casadevall in ¶¶174-181 argues that the Hillmen and Hill references do not anticipate because the use of the term “eculizumab” (which Bell also uses) is not necessarily a disclosure of the amino acid sequences corresponding to SEQ ID NOS:2 and 4 as recited in the challenged claims. As I explained in my previous declaration, I disagree. (EX1003, ¶¶157-163.) To begin with, Alexion has admitted more than once that the eculizumab used in the clinical trial reported in Bell (and elsewhere) was *in fact* the antibody with the amino acid sequence in SEQ ID NOS:2 and 4. (EX1003, ¶158.) Beyond this the amino acid sequence of eculizumab was readily available to a POSA through either Bowdish and Evans or Evans and Mueller PCT, and a POSA would not have mistakenly thought that eculizumab was an IgG4 antibody. (EX1003, ¶¶159-160.)

105. Alexion also cites ¶¶195-199 of Dr. Casadevall’s declaration. (POR, 60.) I already addressed those paragraphs of Dr. Casadevall’s declaration above in connection with Ground 1, and reiterate those points here. (*See above* ¶¶25-37.)

F. Alexion Failed to Show Any Secondary Considerations of Non-Obviousness

106. I note that Dr. Casadevall makes a single blanket statement that he believes that secondary considerations of nonobviousness support the validity of the ’189 patent, although he does not explain in any detail why. (ALXN2105, ¶10.) He also cites to his prior declaration from an Amgen IPR (ALXN2022), even though it

relates to a different patent than the '189 patent.

107. However, I also note that Alexion did not cite to any testimony from any expert in its discussion of secondary considerations in its Response. (*See* POR, 67-70.) Accordingly, it appears that Alexion does not intend to rely on any expert testimony for its secondary considerations arguments.

108. I also note that, based on the record available to it at that time (which has not substantively changed since then), the Board in this matter agreed with my opinion that Alexion had not shown the nonobviousness of the claims through any secondary considerations. (ID, 25-29.)

109. Accordingly, I maintain and reiterate my opinions regarding secondary considerations, as follows.

110. Alexion cannot argue secondary considerations of nonobviousness based on commercial success of its drug Soliris (i.e., eculizumab) because the use of eculizumab as a treatment for PNH was already in the prior art, and thus cannot be novel to the claims. As described above, prior art publications such as Bell, Hillmen 2004 and Hill 2005 disclosed successful treatment of PNH with eculizumab well before the priority date of 2007. (EX1003, ¶¶56-58.) Indeed, the use of eculizumab as a PNH therapy cannot be disputed as prior art to the '189 patent. Moreover, Alexion also stated in 2002 that the prior art Evans patent is associated with the

claimed invention of eculizumab. (EX1020; EX1023.) Given that the prior art disclosed the eculizumab sequence and its use in PNH therapy before 2007, evidence of commercial success cannot be derived from the fact that Soliris was commercially approved in 2007.

111. Alexion similarly cannot argue that the sequence of eculizumab solved a long-felt and art-recognized need, because prior art publications, such as Bell, Hillmen 2004, and Hill 2005—which were all published at least 2-3 years before 2007—already disclosed use of eculizumab as a successful treatment for PNH. Therefore, as of March 2007, no long-felt need existed for a treatment for PNH such as Soliris (i.e., eculizumab). I understand that Soliris was not FDA-approved as a treatment for PNH until March 2007, but this does not mean that a long-felt need existed as of that time for secondary considerations purposes. This is because secondary considerations evidence must be novel with respect to the patent claim at issue, and the use of eculizumab as a treatment for PNH was indisputably not novel by March 2007.

112. Alexion also cannot argue nonobviousness based on industry praise because any evidence of industry recognition following the launch of Soliris as a successful treatment for PNH has no nexus with anything novel in the challenged claims. As described above, by 2007 there was nothing novel about the use of

eculizumab for treating PNH. Further, there is no nexus between any prizes awarded for use of Soliris and the claimed invention because nothing suggests that any prize was awarded due to the sequences claimed in claim 1, as opposed to what was already known about eculizumab in the prior art.

113. Lastly, the fact that other companies are developing biosimilars of Soliris should not be used as evidence of “copying.” I have been informed that according to statutes and regulations, biosimilars are required to be “highly similar to the reference product,” i.e., Soliris in this case. Since this similarity is required by law, I understand that development of biosimilars should not be entitled to weight in an obviousness analysis.

III. CONCLUSION

114. In signing this Declaration, I recognize that the Declaration will be filed as evidence in a contested case before the Patent Trial and Appeal Board of the United States Patent and Trademark Office. I also recognize that I may be subject to cross-examination in this proceeding. If required, I will appear for cross-examination at the appropriate time.

115. I hereby declare that all statements made herein of my own knowledge are true and that all statements are made on information and belief are believed to be true, and further that these statements were made with the knowledge that willful

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false statements and the like so made are punishable by fine or imprisonment, or both, under 18 U.S.C. § 1001.

Respectfully submitted,

A handwritten signature in black ink, appearing to read "J. Ravetch", is positioned above a horizontal line.

Jeffrey V. Ravetch, M.D., Ph.D.

EXHIBIT A

CURRICULUM VITAE

Name: Jeffrey V. Ravetch

Date and Place of Birth: May 3, 1951; New York, New York

Citizenship: United States

Residence: 500 Park Ave, New York, NY 10022

Education:

June 1973 - **B.S.**, Yale University, New Haven, CT
June 1978 - **Ph.D.**, Laboratory of Genetics (N. Zinder and P. Model), The Rockefeller University, New York, NY
June 1979 - **M.D.**, Cornell University Medical College, New York, NY

Postdoctoral Training:

1979 - 1982 Laboratory of Molecular Genetics (P. Leder), NICHD, NIH, Bethesda, MD

Positions and Appointments:

1997- **Theresa and Eugene M. Lang Chair**, The Rockefeller University
1996- **Professor**, The Rockefeller University
1993 - 1996 **Adjunct Professor**, Department of Microbiology and Immunology, Jefferson Medical College and Jefferson Cancer Institute
1990 - 1996 **Attending**, Division of Hematologic Oncology, Department of Medicine, Memorial Hospital for Cancer and Allied Diseases
1990 - 1996 **Member**, Division of Molecular Biology, Memorial Sloan-Kettering Cancer Center
Professor, Cornell University Medical College
1986 - 1990 **Associate Attending**, Division of Medical Oncology, Hematology-Lymphoma Service, Department of Medicine, Memorial Sloan-Kettering Cancer Center
1986 - 1990 **Associate Member**, Division of Molecular Biology, Memorial Sloan-Kettering Cancer Center
Associate Professor, Cornell University Medical College
1984 - 1987 **Guest Investigator**, Laboratory of Cellular Physiology and Immunology, The Rockefeller University
1982 - 1986 **Assistant Member**, Division of Molecular Biology, Memorial Sloan-Kettering Cancer Center
Assistant Professor, Cornell University Medical College
1979 - 1982 **Research Associate**, Laboratory of Molecular Genetics, NICHD, National Institutes of Health
1973 - 1979 **Biomedical Fellow**, The Rockefeller University
1972 - 1973 **Teaching Assistant**, Dept. of Chemistry, Yale University

Honors and Awards:

NSF Summer Research Fellowships, 1971, 1972
Cum laude, Yale College, 1973
Charles E. Culpeper Fellow, 1983-1985
Pew Scholar, 1985-1989
Burroughs-Wellcome Award in Molecular Parasitology, 1986
Irma T. Hirschl/Monique Weill-Caulier Trust Career Scientist Award, 1986
Boyer Research Award, Memorial Sloan-Kettering Cancer Center, 1988
Kunkel Lecturer, Rockefeller University, 1996
NIH MERIT Award, 1997
Ecker Lecturer, Case Western Reserve University, 2000
Lee J. Howley, Jr. Award, 2004
AAI-Huang Foundation Meritorious Career Award, 2005
Member, National Academy of Sciences, 2006
William B. Coley Award, Cancer Research Institute, 2007
Member, Institute of Medicine, 2007
Fellow, American Academy of Arts and Sciences, 2008
Fellow, American Association for the Advancement of Science, 2008
R.E. Dyer Lecture, NIH, 2010
Grabar Lecture, French Society of Immunology, 2010
Gairdner International Award, 2012
Sanofi-Institut Pasteur Award, 2012
Heidelberger-Kabat Lecture, Columbia University, 2013
Fahey/Rose Founders Lecture, Clinical Immunology Society, 2013
Honorary doctorate Friedrich-Alexander-University Erlangen-Nuremberg, 2013
Josephson Lecture, Downstate Medical College, 2014
Wolf Prize in Medicine, 2015
Distinguished Lecturer, Academia Sinica, 2015
Benacerraf Lecture, Harvard Medical School, 2016
Ross Prize in Molecular Medicine, 2017
Robert Koch Award, 2018
William Paul Memorial Award, 2021

Patents:

5,116,965-Methods of obtaining histidine-rich protein genes of plasmodia
5,723,593-Diagnostic assay for Charcot Marie Tooth disease type 1B
5,728,377-Methods and compositions Incorporating IP-10
5,824,487-Method for screening for targets for anti-inflammatory or anti-allergic agents.
5,876,927-Nucleic acid diagnostic assay for Charcot-Marie-Tooth Disease type IB
5,877,396-Mice mutant for Fc Receptors and method of treating autoimmune disease.
6,676,927-Animal model and methods for its use in the selection of cytotoxic antibodies
7,038,031-DNA encoding FcγR receptor protein on NK cells.
7,416,726-Enhancement of antibody-mediated immune responses
7,846,744-Methods of identifying anti-inflammatory compounds
8,470,318-Polypeptides with enhanced anti-inflammatory properties
8,470,321-Antibodies specific for the protofibril form of beta-amyloid protein

8,618,251-Fc mutants
8,815,237-Aglycosylated immunoglobulin mutant
9,134,310 Methods of identifying anti-inflammatory compounds
9,340,607-Antibodies specific for the protofibril form of beta-amyloid protein
9,481,724-hDC-SIGN binding peptides
9,587,025 Non-sialylated anti-inflammatory polypeptides
9,657,101 Fc mutants
9,845,358 Anti-inflammatory polypeptides
10,167,332 Polypeptides with enhanced anti-inflammatory and decreased cytotoxic properties
10,300,127 Immune complex
10,479,838 Antibodies to CD40 with enhanced agonist activity

Other Activities:

National

Ad hoc member, Immunobiology Study Section, 1986-1990
Ad hoc member, Tropical Medicine and Parasitology Study Section, 1988-1990
Member, Allergy and Immunology Study Section, 1990-1994
Member, Blood Diseases Advisory Panel of The New York Community Trust, 1990-1996
Founder and Organizer (with D. Wirth and L. van der Ploeg), Annual Woods Hole Molecular Parasitology Meeting, 1990-1992
NIH Task Force on Immunology and Aging, 1994
Institute of Medicine, Nat'l Academy of Sciences, Committee on Malaria Vaccines, 1995
AAI, American Association of Immunologists, Public Affairs Committee, 2003-2005

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