8359292

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UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office

March 28, 2023

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APPLICATION NUMBER: *15/148,839*
FILING DATE: *May 6, 2016*
PATENT NUMBER: *9,718,880*
ISSUE DATE: *August 1, 2017*

By Authority of the
Under Secretary of Commerce for Intellectual Property
and Director of the United States Patent and Trademark Office

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Certifying Officer

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PTO/AIA/82A (07-13)
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NOTE: This form is to be submitted with the Power of Attorney by Applicant form (PTO/AIA/82B) to identify the application to which the Power of Attorney is directed, in accordance with 37 CFR 1.5, unless the application number and filing date are identified in the Power of Attorney by Applicant form. If neither form PTO/AIA/82A nor form PTO/AIA82B identifies the application to which the Power of Attorney is directed, the Power of Attorney will not be recognized in the application.

Application Number	Not Yet Assigned
Filing Date	Concurrently Herewith
First Named Inventor	Leonard BELL
Title	TREATMENT OF PAROXYSMAL NOCTURNAL HEMOGLOBINURIA PATIENTS BY AN INHIBITOR OF COMPLEMENT
Art Unit	N/A
Examiner Name	Not Yet Assigned
Attorney Docket Number	AXJ-114BUSCN2

SIGNATURE of Applicant or Patent Practitioner

Signature	/Jill Gorny Sloper, Esq./	Date (Optional)	May 6, 2016
Name	Jill Gorny Sloper, Esq.	Registration Number	60,760
Title (if Applicant is a juristic entity)			
Applicant Name (if Applicant is a juristic entity)			

NOTE: This form must be signed in accordance with 37 CFR 1.33. See 37 CFR 1.4(d) for signature requirements and certifications. If more than one applicant, use multiple forms.

☐ *Total of 1 forms are submitted.

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Dated: May 6, 2016 Electronic Signature for Jill Gorny Sloper, Esq.: /Jill Gorny Sloper, Esq./

Doc Code: PA..
Document Description: Power of Attorney

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POWER OF ATTORNEY BY APPLICANT

I hereby revoke all previous powers of attorney given in the application identified in either the attached transmittal letter or the boxes below.

Application Number	Filing Date

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[ ] I hereby appoint Practitioner(s) named in the attached list (form PTO/AIA/82C) as my/our attorney(s) or agent(s), and to transact all business in the United States Patent and Trademark Office connected therewith for the patent application referenced in the attached transmittal letter (form PTO/AIA/82A) or identified above. (Note: Complete form PTO/AIA/82C.)

Please recognize or change the correspondence address for the application identified in the attached transmittal letter or the boxes above to:

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I am the Applicant (if the Applicant is a juristic entity, list the Applicant name in the box):

Alexion Pharmaceuticals, Inc.

[ ] Inventor or Joint Inventor (title not required below)

[ ] Legal Representative of a Deceased or Legally Incapacitated Inventor (title not required below)

[X] Assignee or Person to Whom the Inventor is Under an Obligation to Assign (provide signer's title if applicant is a juristic entity)

[ ] Person Who Otherwise Shows Sufficient Proprietary Interest (e.g., a petition under 37 CFR 1.46(b)(2) was granted in the application or is concurrently being filed with this document) (provide signer's title if applicant is a juristic entity)

SIGNATURE of Applicant for Patent

The undersigned (whose title is supplied below) is authorized to act on behalf of the applicant (e.g., where the applicant is a juristic entity).

Signature		Date (Optional)	07/20/15
Name	Todd Spalding		
Title	Vice President, Head of Intellectual Property		

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[ ] Total of 1 forms are submitted.

Doc Code: PPH.PET.652
Document Description: Petition to make special under Patent Pros Hwy

PTO/SB/20GLBL (04-15)
Approved for use through 04/30/2018. OMB 0651-0058
U.S. Patent and Trademark Office; U.S DEPARTMENT OF COMMERCE
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REQUEST FOR PARTICIPATION IN THE GLOBAL/IP5 PATENT PROSECUTION HIGHWAY (PPH) PILOT PROGRAM IN THE USPTO

Application No.:	Not Yet Assigned	First Named Inventor:	Leonard BELL
Filing Date:	Concurrently Herewith	Attorney Docket No.:	AXJ-114BUSCN2
Title of the Invention:	TREATMENT OF PAROXYSMAL NOCTURNAL HEMOGLOBINURIA PATIENTS BY AN INHIBITOR OF COMPLEMENT		

THIS REQUEST FOR PARTICIPATION IN THE PPH PILOT PROGRAM ALONG WITH THE REQUIRED DOCUMENTS MUST BE SUBMITTED VIA EFS-WEB. INFORMATION REGARDING EFS-WEB IS AVAILABLE AT HTTP://WWW.USPTO.GOV/PATENTS-APPLICATION-PROCESS/FILING-ONLINE/ABOUT-EFS-WEB.

APPLICANT HEREBY REQUESTS PARTICIPATION IN THE PATENT PROSECUTION HIGHWAY (PPH) PILOT PROGRAM AND PETITIONS TO MAKE THE ABOVE-IDENTIFIED APPLICATION SPECIAL UNDER THE PPH PILOT PROGRAM.

Office of earlier examination (OEE): Europe (European Patent Office)

OEE application number: 11001632.6

Both the OEE application and the above-identified U.S. application have the following earliest date (filing or priority date): March 15, 2006

Type of OEE work product relied upon: EPO Form 2906

Mailing date of OEE work product: July 22, 2015

Supporting Documents

One or more of the required documents below may be available electronically from the Dossier Access System or PATENTSCOPE (see https://www.jpo.go.jp/ppph-portal/filewrapper.htm). If the applicant requests the USPTO to attempt to obtain a document electronically and such attempt is unsuccessful, the applicant will be required to supply the document. Accordingly, to avoid dismissal of the initial PPH request and potential denial of participation in the PPH program, the applicant should verify that the document is actually available via the Dossier Access System or PATENTSCOPE before requesting retrieval. If the applicant is unable to verify availability, then the applicant should submit the document with the PPH request.

1. OEE Work Product and Translation

A copy of the OEE work product and translation if not already in English:

☐ Attached ☐ Previously submitted ☐ Not required because the decision to grant a patent was the first office action

☒ Applicant requests the USPTO to attempt to obtain the document(s) from the Dossier Access System or PATENTSCOPE

2. References Cited in OEE Work Product

A listing of references cited in the OEE work product and document copies (except U.S. patents and U.S. published patent applications):

☒ Attached ☐ Previously Submitted ☐ Not required because no references were cited in the OEE work product

☒ Applicant requests the USPTO to attempt to obtain the document(s) from the Dossier Access System or PATENTSCOPE

PTO/SB/20GLBL (04-15)
Approved for use through 04/30/2018. OMB 0651-0058
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REQUEST FOR PARTICIPATION IN THE GLOBAL/IP5 PPH PILOT PROGRAM IN THE USPTO
(continued)

Application No.:	Not Yet Assigned	First Named Inventor:	Leonard BELL

3. Claims Correspondence Certification Statement

All of the claims in this application sufficiently correspond to the patentable/allowable claims in the OEE application.

4. Claims Correspondence Table

Claims in US Application	Patentable Claims in OEE Application	Explanation regarding the correspondence
1	1	Both claims are identical.

Signature	/Jill Gorny Sloper, Esq./	Date	May 6, 2016
Name (Print/Typed)	Jill Gorny Sloper, Esq.	Registration Number	60,760

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

Dated: May 6, 2016 Electronic Signature for Jill Gorny Sloper, Esq.: /Jill Gorny Sloper, Esq./

PubMed

Abstract

Oncology (Williston Park). 1997 Nov;11(11A):232-5.

Linking outcomes management to quality-of-life measurement.

Cella D[1], Webster K.

Author information

Abstract

Health-care workers now accept quality of life (QOL) as an important outcome to evaluate in clinical research and as a useful measure of quality care. Indeed, current demand for QOL **assessment** in clinical practice has outpaced the availability of valid, streamlined, cost-effective methods for carrying out such **assessment**, although new tools are in the offing. This paper will highlight some of the major challenges facing outcomes management and outcomes research, with particular focus on the development of a QOL instrument to evaluate and manage **anemia** and **fatigue** in cancer patients--the **Functional Assessment** of Cancer **Therapy-Anemia** (FACT-An). The newest version of broader QOL **assessment** system, the **Functional Assessment** of **Chronic Illness Therapy** (FACIT), will also be described.

PMID:9430193[PubMed - indexed for MEDLINE]

MeSH Terms

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Samsung Bioepis Exhibit No. 1002
Page 007

AN - NLM15328683
DT - Case Reports, Journal Article, Review
TI - Complement C7 deficiency presenting as recurrent aseptic meningitis.
AU - Corvini Michael; Randolph Christopher; Aronin Steven I
PUB - Annals of allergy, asthma & immunology : official publication of the American College of Allergy, Asthma, & Immunology
- United States
- Aug 2004
ORD - 2004-08-00
LNKD - **pubmed:15328683**
IRN - ISSN 1081-1206 *(Print)*
VOL - 93
NR - 2
PG - 200 - 205
LA - eng
IW - Adult; Arthritis: diagnosis(#), etiology(#); Cerebrospinal Fluid: metabolism; Complement C7: deficiency(#); Complement Membrane Attack Complex: deficiency; Diagnosis, Differential; Humans; Immunologic Deficiency Syndromes: complications(#), diagnosis(#); Male; Meningitis, Aseptic: diagnosis(#), etiology(#); Recurrence
AW - Complement C7; Complement Membrane Attack Complex
AB - *BACKGROUND*
Complement deficiency states are rare inherited disorders that may predispose affected individuals to angioedema, collagen vascular disease, or infection due to encapsulated organisms, especially **Neisseria meningitidis**

- *OBJECTIVES*
To report the case of a 36-year-old man of Irish descent with recurrent culture-negative neutrophilic meningitis, to offer potential reasons for the inability to recover a causative pathogen, and to review the genetics and prevalence of **complement deficiency** states, the methods of screening for such deficiencies, the features of meningococcal infection as they relate to such deficiencies, and management strategies for clinicians caring for patients with such deficiencies.

- *METHODS*
The patient presented in 1988 and again in 2002 with culture-negative neutrophilic meningitis. His second episode was characterized by a rash suggestive of meningococcal infection, prompting immunologic evaluation.

- *RESULTS*
Immunologic evaluation revealed an undetectable CH50 level. Levels of C1, C2, and C5 through C9 were normal except for C7, which was undetectable. Further testing revealed that the patient's sister was also C7 deficient.

- *CONCLUSIONS*
Complement component deficiencies are relatively rare; individuals with collagen vascular disease and systemic neisserial infection should be screened using either the CH50 or the APH-50 assay. Key to the management of a late-complement component-deficient host is counseling, education about meningococcal infection, and discussions about the potential benefits of chemoprophylaxis and immunoprophylaxis. The ability to detect the bacterial cause of meningitis in such patients is organism dependent and may be influenced by factors such as cerebrospinal fluid bacterial concentration and previous antibiotic drug exposure.

AN - NLM1411724

DT - Case Reports, Journal Article

TI - Recurrence of **neisserial meningococcemia** due to deficiency of terminal complement component.

AU - Morris J T; Kelly W J

PUB - Southern medical journal
- UNITED STATES
- Oct 1992

ORD - 1992-10-00

LNKD - **pubmed:1411724**

IRN - ISSN 0038-4348 *(Print)*

VOL - 85

NR - 10

PG - 1030 - 1031

LA - eng

IW - Adult; Bacteremia: diagnosis, drug therapy, etiology(#); Complement C6: deficiency(#); Humans; Immunologic Deficiency Syndromes: complications(#); Male; Meningococcal Infections: diagnosis, drug therapy, etiology (#); **Neisseria meningitidis**(#); Penicillin G: therapeutic use; Recurrence

AW - Complement C6; Penicillin G

AB - Recurrent infections with **Neisseria meningitidis** are attributed to deficiencies of terminal complement components. The serotype most commonly responsible for recurrent N meningitidis infections is serotype Y. We have reported a case of recurrent meningitis due to N meningitidis in a patient who was found to be deficient in the sixth component of complement. **Complement deficiencies** should be considered in any patient with recurrent infections caused by N meningitidis.

NIPH ANNALS
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ISSN 0332-5652

VACCINE AGAINST GROUP B NEISSERIA MENINGITIDIS: PROTECTION TRIAL AND MASS VACCINATION RESULTS IN CUBA

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SUMMARY

The Cuban vaccine, first in the world with proven efficacy against group B-caused disease, is based on outer membrane proteins from B meningococci capable of inducing long-lasting and high-titered bactericidal antibodies in humans. This bactericidal activity has a wide spectrum against all pathogenic group B *Neisseria meningitidis* tested.

A randomized, double-blind controlled trial of the vaccine efficacy was performed during 1987-1989 with 106 000 10-14 years old students from 197 boarding schools in seven provinces.

The efficacy obtained was 83% (χ^2, $p<0.002$; Fischer exact, $p<0.001$). In a second field trial including 133 600 persons from 5 months to 24 years of age in Ciego de Avila province (30 cases/10^5 inhabitants, the highest incidence rate in Cuba) by comparing vaccinated and non-vaccinated population after 2.5 years of observation and careful follow-up, the efficacy and safety was confirmed.

Because of these results and because of the very low reactogenicity of the vaccine, the Ministry of Public Health took the advice of the Scientific Council to vaccinate all children between 3 months and 6 years of age in the most affected provinces. No severe or long lasting reactions to the vaccine were observed after the millions of doses administered. The efficacy of vaccination varied in the provinces between 83% and 94%, among age groups ranging from 3 months and 20 years.

After 3 years of massive application no severe reactions occurred and one of the most severe epidemics has been practically eradicated.

Key words: Evaluation studies; Neisseria meningitidis; Randomized controlled trials; Vaccines

INTRODUCTION

Since 1976, meningococcal disease constitutes a serious health problem in Cuba due to the significant rise in incidence of this disease and its high lethality.

The causal agents at beginning of the outbreak were predominantly group C meningococci and in second place group B meningococci; after the mass vaccination campaign conducted in 1979 using the polysaccharide Merieux A + C, group C caused meningococcal disease was practically eradicated.

In the late 70s and early 80s, a significant incidence increase took place, virtually caused by B meningococci of 4:P1.15 (95%), 15:P1.15 (3%) and 15:P1.16 (1%) serotypes and subtypes.

The peak epidemic year was 1983, although the situation differed from province to province. Higher incidence rates were observed in 1985 in children younger than 6 years (50 cases per 10^5 inhabitants) and among teenagers (20 cases per 10^5). The most affected teenagers were those attending secondary boarding schools in the central provinces of Cuba (57,7 cases per 10^3 students).

B-meningococcal disease has been the most serious infection health hazard of the last two decades in Cuba.

Repeated testing with different vaccine candicates in the United States, Europe, the Soviet Union, and South Africa, revealed many deficiencies among these; a weak, very variable and short-lasting (5-7 months) bactericidal activity; beyond 5-7 months after immunization the concentration of specific antibodies of IgG class, directed against important exposed proteins and other antigens of the bacterial envelope, was very low. In addition, weak or absent anamnestic response to a booster dose after 8 to 12 months of primary immunization was observed as one of the most critical failures.

Thus, taking into consideration the world research state in the B meningococcus vaccine development and our situation with the disease, decision was taken to obtain in short time a good candidate vaccine.

Among different vaccine formulations one was selected for which carefully conducted preclinical and phase I and phase II clinical studies revealed innocuousness, safety and very low reactogenicity, long-lasting bactericidal and specific antibody titers of a broad spectrum against different pathogenic serotypes and subtypes. On the basis of these promising serological efficacy results, this vaccine has been used in a double-blind placebo-vaccine field trials for epidemiological efficacy evaluation.

MATERIALS AND METHODS

Base-line studies

Base-line data on epidemiology of the disease and diagnostic laboratory capability were collected and evaluated during a three-year period in the provinces, before the trial-started (1984-87). Laboratory procedures, case management protocols, and the system of coordinating information from schools, hospitals, provincial, municipal and national epidemiologists, and laboratories have been carefully reviewed, evaluated and when needed established.

Case ascertainment and case definitions were established as well as the isolates and samples transport-conservation-study system.

Vaccine trial design

The trial was a randomized, placebo-controlled, double blind trial of vaccine efficacy. The protection trial was performed among teen-agers attending secondary boarding schools. The target group ranged, from 11 to 16 years of age and was distributed in 197 schools and 7 provinces with the highest incidence rates in this age group (40 cases per 10^5 students at the starting point of the trial).

Sample size was calculated according to the level of efficacy to be detected at 75% or greater, with less than a 0.05 type I error ($\alpha = 0.05$) and a power of 80% ($\beta = 0.2$, taking into account an attack rate of the disease of 40 cases per 10^5 students and a follow-up period of 1-3 year. With this incidence rate at the start of the trial and considering the other statistical factors, 106 251 students for placebo and vaccine groups were calculated to be needed in using schools as randomization units. Each school with approx. 540 students constitutes a homogeneous unit, either completely vaccinated or completely placebo inoculated.

A list of schools was assembled and stratified by province according to incidence of the disease during the last three years, to assure homogeneous distribution of exposure to risk of disease in receiving placebo or vaccine. Afterwards, placebo or vaccine were randomly allocated in each school within every stratus.

To assure blinding, lot identification was performed with randomly generated numbers having a secret master code list. Ten different numbers for placebo and ten for vaccine were used.

The vaccine

The vaccine components are purified proteins from the outer-membrane of group B meningococci enriched with proteins from the high molecular weight proteins complex (65-95 KD) having the greatest capacity of inducing long-lasting bactericidal antibodies. Some of the purified proteins, together with a good controlled proportion of phospholipide and lipopolysaccharide (LPS) form a proteoliposom, and the added amounts of High Molecular + Protein-Complex is non covalently conjugated or attached to the proteoliposome surface. In addition, the whole protein complex is conjugated non covalently, 1:1 proportion with C polysaccharide and finally the whole complex is adsorbed to aluminium hydroxide gel with a controlled particle size.

Vaccine formulation

Each dose contains:

Outer membrane proteins from B meningococci	50 mcg
Purified polysaccharide form C meningococci	50 mcg
Aluminium hydroxide gel	2 mg
Sodium thiomersalate	0.01 mg
PBS csp	0.5 ml
LPS	1%

The commercial name of this preparation is VA-MENGOC-BC®, a trade mark of Institute Finlay, Habana, Cuba.

Samsung Bioepis Exhibit No. 1002
Page 012

Control vaccine (Placebo)

The control vaccine was identical in appearance to the tested vaccine and consisted of a saline placebo containing the adjuvant aluminium hydroxide.

Vaccination, sampling and evaluation

A two 0.5 ml deltoid intramuscular dose with 6 to 8 weeks interval was the vaccination schedule established.

In each province, 300 students randomly chosen were used for immunogenicity and carrier state studies. The samples for these studies were taken immediately before applying the first dose and 4 weeks after the second one. Additional blood and exudate samples were taken every six months after vaccination. ELISA and bactericidal studies were performed as described elsewhere (1).

Only cases with the following criteria were used for efficacy evaluation: confirmed cases are only those with clinical illness from which a B meningococcus was isolated by culture or those with clinical illness with Gram-negative diplococci directly observed and where a latex or ELISA confirmed B antigen was found.

The standard forms for data collection, previously field-tested, were submitted to the Ministry of Public Health and stored in the Efficacy Trial Data Base Computer System.

SAS-PC version 6.03 and EPI-INFO were used for data analysis and study monitoring, relative risk calculation for vaccine and placebo groups with schools as randomization units, individual or cluster approaches. The comparisons between placebo and vaccinees regarding ELISA and bactericidal titer distributions were performed with the help of a computing program having common non-parametric tests, Wilcoxon Rank-Sum Test, t-Test, percentile distribution and binomial distribution analysis of probabilities and the statistical analysis significance tests-Chi-square and Fischer Exact.

RESULTS AND DISCUSSION

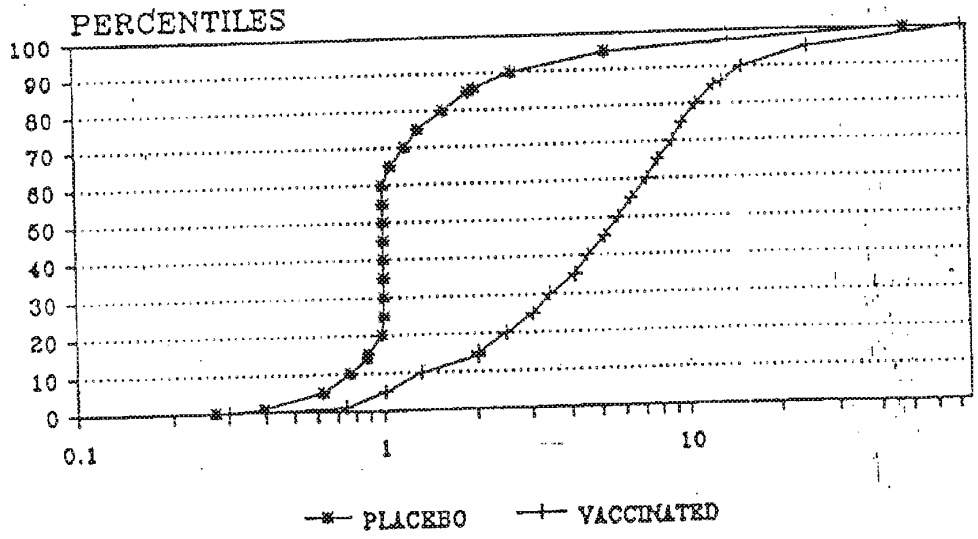


Figure 1
Cumulative distribution of the ratio ELISA2/ELISA1 four weeks after vaccination

The study of the meningococcus carrier state shows no significant difference between placebo-injected controls and vaccinees when the sample was taken four weeks after vaccination. Six months after vaccination, a significant lowering in carrier state in vaccinees was observed, but more careful assessment of variations and mechanisms must be performed in the future for conclusive statements.

In the vaccine group, an 88% of seroconversion (E2/E1) was detected using the ELISA method; in percentile 50 (median of the group), a six-fold increase was observed. On the other hand, in the placebo group, percentile 80 shows just one as E2/E1 ratio and only 14% of this group shows two-fold increase (correlating quite well with carrier state). Comparing the cumulative distribution of the E2/E1 ratio in placebo and vaccine four weeks after vaccination, a significant difference with $p < 0.001$ is seen..(Fig. 1).

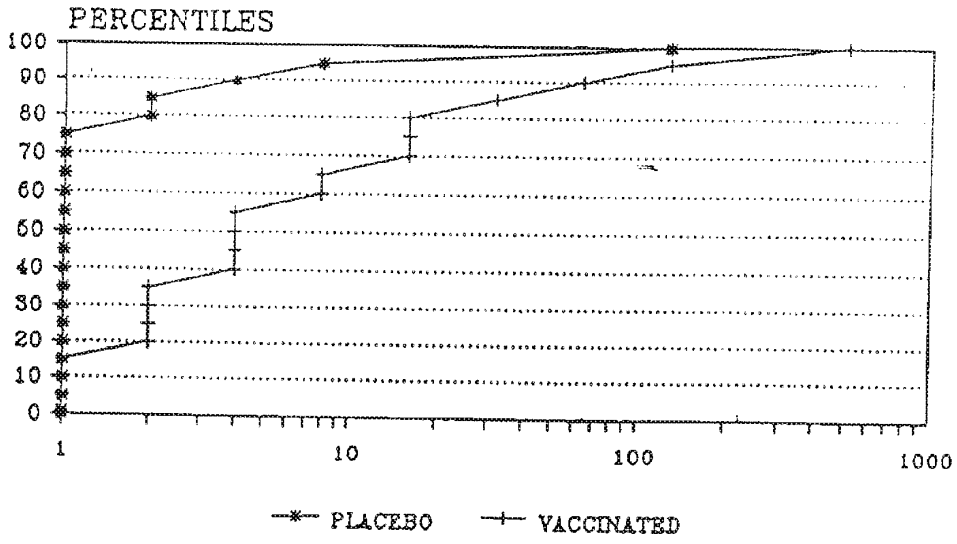


Figure 2
Cumulative distribution of the ratio BACTE2.Titer/BACTE1.Titer four weeks after vaccination

Seroconversion regarding bactericidal activity was detected in 85% of the vaccine group in which percentil 50 (median) shows a four-fold titer increase (Fig. 2). The difference with respect to the placebo group was highly significant, $p < 0.001$. Only percentil 85 shows two-fold increase in this group caused by normal contacts with meningococci in the population. The cumulative distribution of the ratio B2/B1 comparing placebo and vaccine group shows statistical significance.

This study lasted 16 months, during which 25 culture and latex positive confirmed cases occurred in the study population, four in the vaccine group and 21 in the placebo group. The timing of cumulative case occurrence among placebo and vaccine group, as seen further on, constitutes a good graphic demonstration of the vaccine effect (Fig.3). Case occurrence was distributed per school as indenpendent cases and fulfilling the criteria of «case definition» needed in order to be included in the efficacy calculation.

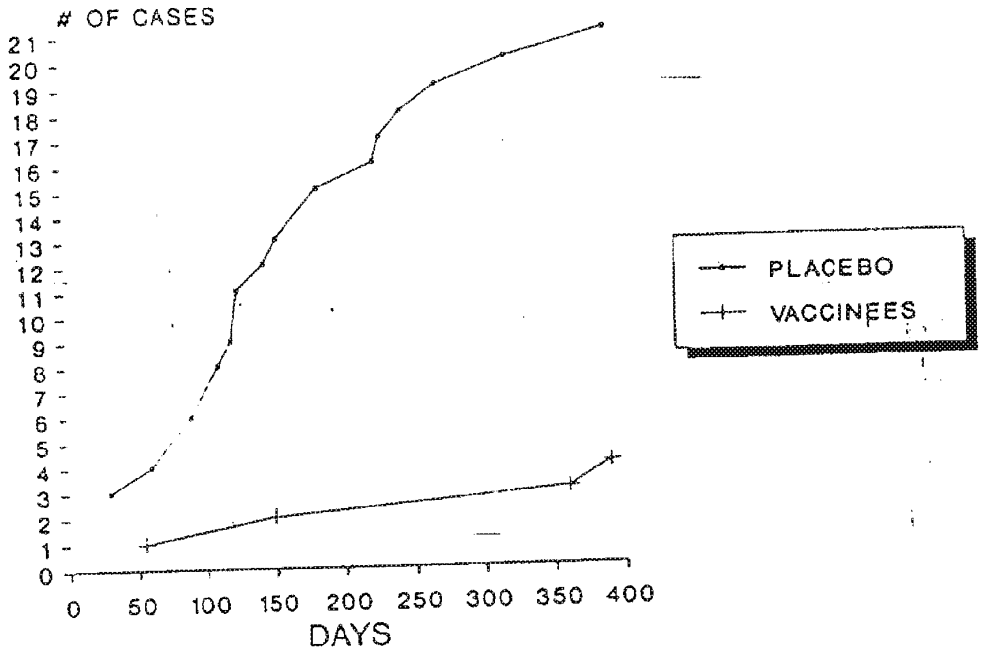


Figure 3
Timing of cumulative case occurrence

Further observation up to 24 months revealed the occurrence of five more bacteriologically confirmed cases, all in the placebo group and none among the vaccinees though not included in the following efficacy calculation:

Efficacy according to conglomerate approach

	Vaccine	Placebo	Total
Total of schools involved	99	98	197
Schools with cases	3	17	20
Total of cases	4	21	25

Analysis of Single Table
Relative risk-0.17 (0.05<RR<0.58)
Taylor series 95% confidence limits for RR

	Chi-squares	p-values
Uncorrected	11.07	0.0008791
Mantel-Haenszel	11.01	0.0009061
Yates corrected	9.55	0.0019968

Resultant efficacy: 83%
Confidence interval: 95-42%

Efficacy according to individual approach

Group	Cases	Not ill	Total
Vaccinee	4	52962	52966
Placebo	21	53264	53285
Total	25	106226	106251

Analysis of Single Table
Relative risk-0.19 (0.07< RR<0.58)
Taylor series 95% confidence limits for RR

	Chi-squares	p-values
Uncorrected	11.46	0.0007107
Mantel-Haenszel	11.46	0.0007108
Yates corrected	10.15	0.0014457

Resultant efficacy: 81%
Confidence interval: 93-44%

Vaccine impact is also shown by demonstrating the significant reduction in case-occurrence probability in vaccine schools in comparison with placebo treated schools. Immediately before the starting point of the field trial the probability of one or more cases per school in the study was calculated (Po = 0,192). After 1.3 year of follow-up period 17 cases had occurred in 98 placebo schools. The probability of case occurrence was 0.173469 (Pp). The simultaneous case occurrence in vaccine schools was 3 in 99 schools.

Binomial distribution

	N = 99	P.1734693
X	P(X)	Cumulative probability
3	.00001	.00001
4	.00005	.00006
5	.00019	.00025
6	.00062	.00086
E(X) = 17.173346	std dev = 3.76754	variance = 14.19439

A way to evaluate the impact of the vaccine is by calculating under the hypothesis that Po = 0.192 (previous value) the probability of the happening in placebo and vaccine groups. The probability associated with the occurrence of three or less schools with at least one case in a set of 99 (vaccine groups) and 17 or less of a set of 98 (placebo groups) are 0.00001 and 0.38 respectively. These results suggest that p in the vaccine group is

significantly less than Po, but not so in the placebo groups. Another approach is using the placebo value of p in determining the probability of that happening in the vaccine group. Having p the value of 0.173 (17/98), then, P (X3)0.00001. This value of p is significantly less than 0.173.

The difference in case occurrence among placebo and vaccine groups was statistically significant, considering the cases individually or effecting a conglomerate (school distribution of cases). The vaccine proved to be effective in the study population in 81% (individual treatment of cases) or 83% (conglomerate treatment), and the confidence interval from 44 to 93% or 42 to 95% respectively.

Further follow-up studies

Furthermore, a good correlation between serological evolution and protection as well as the low reactogenicity and safety of the vaccine was confirmed.

The comparison of ELISA and bactericidal ratios E4/E1 and B4/B1 respectively constitutes an objective proof of duration of the vaccine protective capacity. E4 and B4 represent ELISA and bactericidal values one year after vaccination (Figs. 4 & 5).

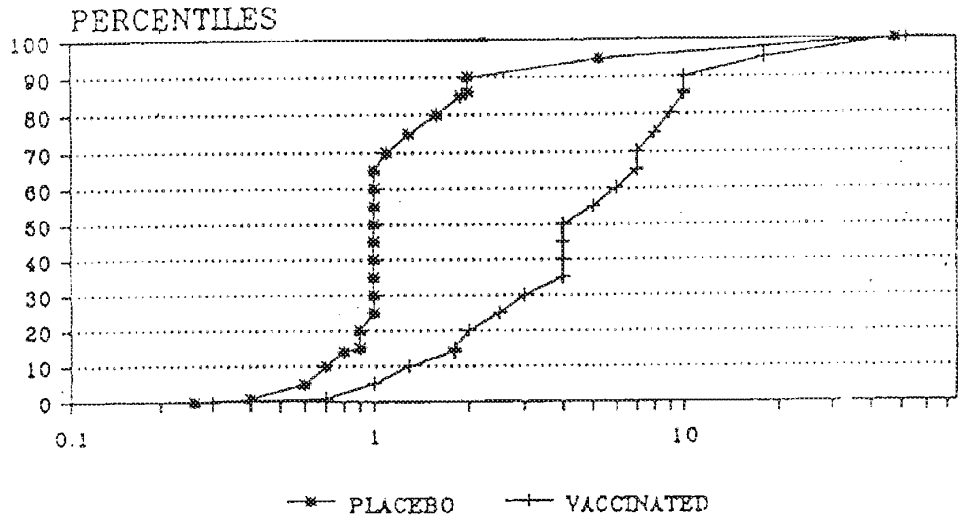


Figure 4
Cumulative distribution of the ratio ELISA4/ELISA1 one year after vaccination

The anamnestic antibody response was studied in army recruits, in parallel. A booster dose was tested in one group after one year and another group after 18 months. Before boostering (12 to 18 months) blood plasma from the vaccine group of the parallel study was collected, and the IgG fraction was purified and tested by ELISA and bactericidal activity (Figs. 6 and 7).

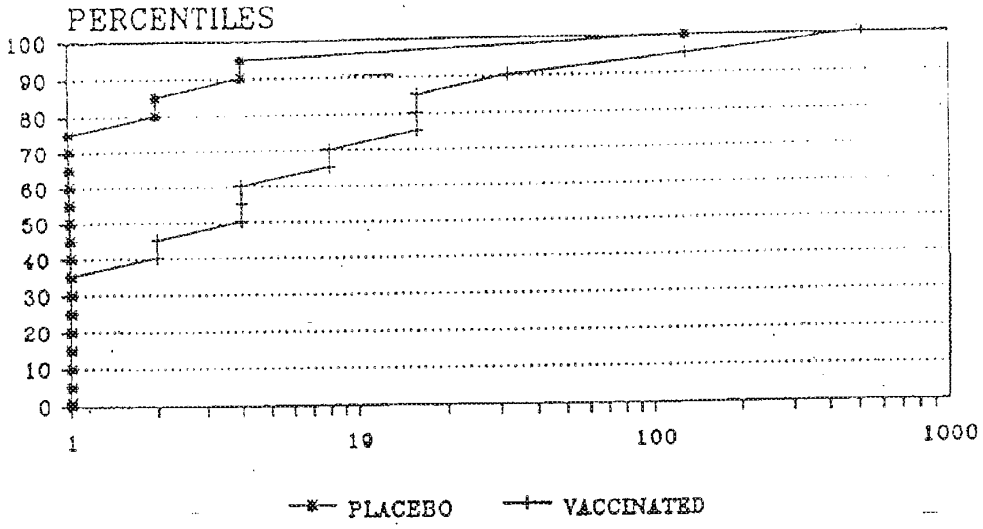


Figure 5
Cumulative distribution of the ratio BACTE4.Titer/BACTE1.Titer one year after vaccination

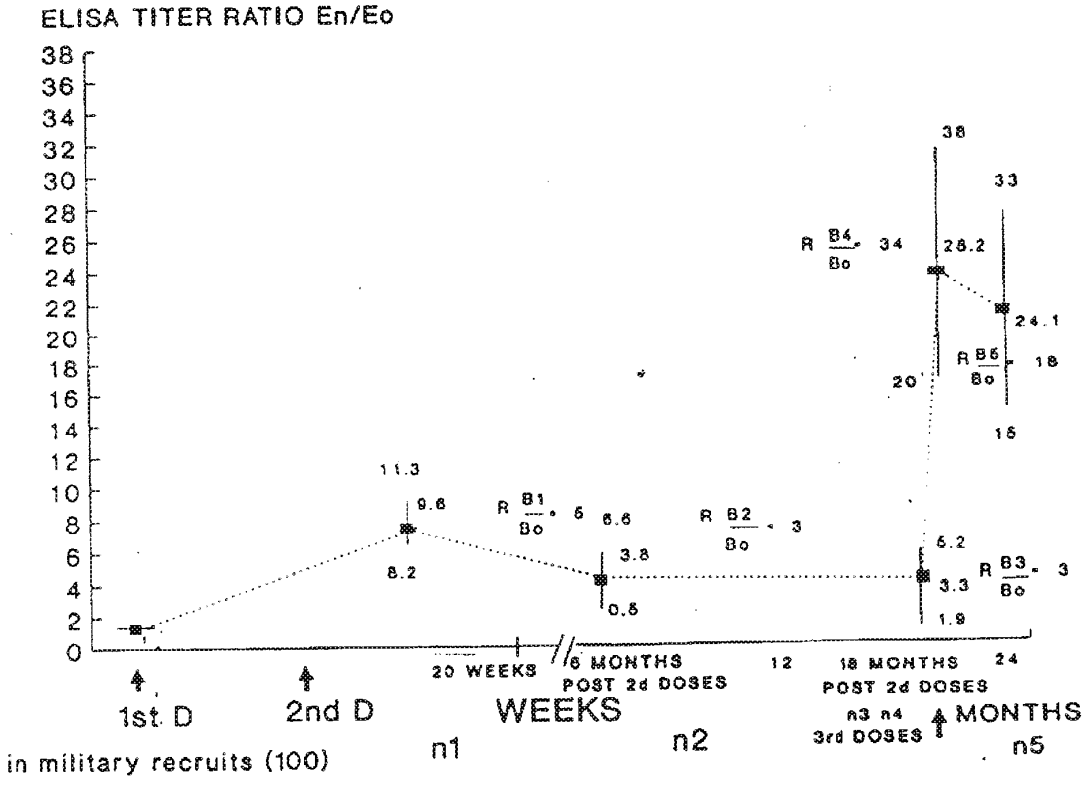


Figure 6
Increasing bactericidal and specific antibodies with a booster

The results of these tests indicated long-lasting bactericidal and specific antibodies against some of the most frequent pathogenic B serotypes. After boostering the specific antibody increased by more than 5 times and the bactericidal titer increased more than 10 times, showing an excellent anamnestic specific response.

Summary of mass vaccination results

Taking into consideration the high incidence of meningococcal disease among children up to six years of age occurring in Cuba and the satisfactory reactogenicity and efficacy studies with the Antimeningococcal BC Vaccine «VA-MENGOC-BC®» evaluated during the last years, a mass vaccination campaign was organized, starting with this age-group (1989-90). Table 1 shows the percentage of vaccination per province in the age-group below six years.

An independent group of the Tropical Medicine Institute «Pedro Kouri» of Ministry of Public Health evaluated in a carefully conducted study, the effectivity of the mass vaccination campaign. Table 2 shows the summary of efficacy, in general reaching 92.5%.

One very clear example of the vaccine impact was observed in the province Havana City, Fig. 8, where the incidence rate among children below six years rose constantly (1986 - 27.5/10^5, 1987 - 30/10^5, 1988 - 42.5/10^5) and after the vaccination the strong epidemic wave was stopped (1989 - 15/10^5, 1990 - 3.8/10^5, 1991 - 1/10^5) and among vaccinees less than 0.08/10^5).

Actually in Cuba the population between 3 months and 20 years is vaccinated; the VA-MENGOC-BC® vaccine is incorporated to the infancy vaccine scheme (for 3 months children).

Also the vaccination of other risk-groups is practically concluded; elderly homes, military camps, big schools, industries, *etc.*

In a very short time the meningococcal disease will be completely controlled.

Reference

(1) Sierra GVG, Campa HC. Preclinical and clinical studies with the antimeningococcal vaccine BC: VA-MENGOC-BC®. Rev Interferon y Bio-tecnologia, Special. 1990.

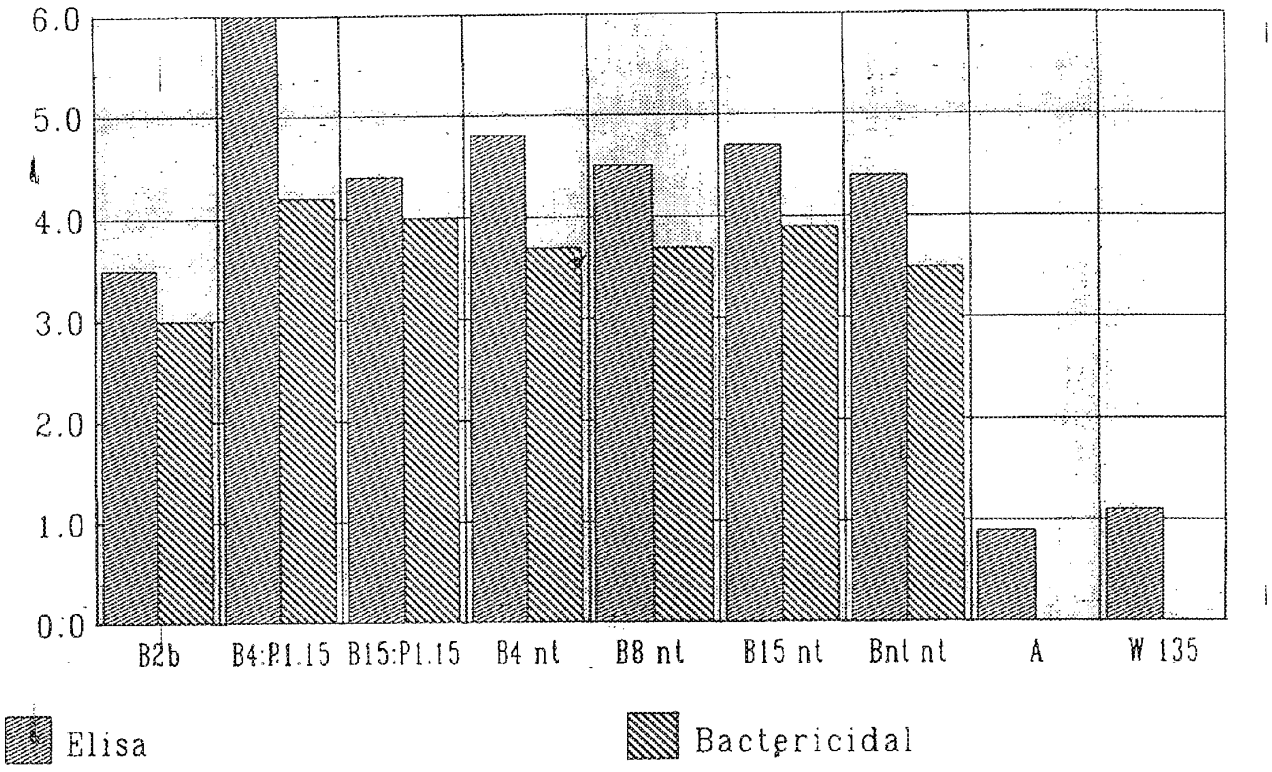


Figure 7
Specific and bactericidal antibody titer increases maintained up to 18 months after vaccination in military recruits against different pathogenic serotypes

Table 1
Percentage of vaccination per province in age group < 6 years

Province	Population	Vaccinees	%
PR	67 500	56 623	83.8
CH	182 400	161 670	88.6
MT	53 000	48 815	92.1
VC	70 000	61 047	87.2
CF	33 800	32 094	95.0
SS	37 700	31 935	84.7
CM	73 500	61 917	84.2
LT	53 100	43 808	82.5
HO	102 900	91 191	88.6
GM	94 800	72 898	76.9
SC	116 600	100 820	86.5
GT	61 100	53 679	87.9
TOTAL	1 013 900	866 148	85.4

Source: Division of Epidemiology, Ministry of Public Health

Table 2
Relative risk and efficacy per province in age group < 6 years

Province	Relative Risk	Efficacy %
PR	9.37	89.3
CH	39.06	97.44
MT	23.33	88.57
VC	24.55	95.90
CF	23.00	95.68
SS	11.08	90.97
CM	7.48	86.60
LT	23.60	89.28
HO	97.49	98.97
GM	29.99	96.66
SC	6.84	85.47
GT	18.11	94.47
TOTAL	13.44	92.56

Source: Tropical Medicine Institute «PEDRO KOURI», Ministry of Public Health

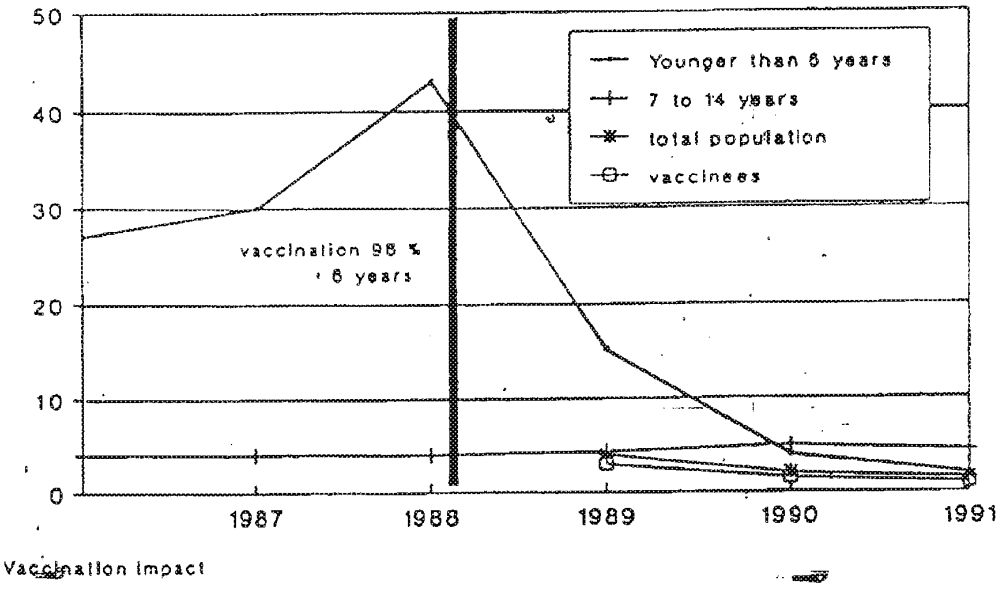


Figure 8
Meningococcal Disease in Havana city, indicence rate per 100 000

DISCUSSION

Gotschlich:
To what do you attribute the broad specificity of the vaccine? What strains were tested for bactericidal effect, and what is the relative bactericidal effect against other strains?

Sierra:
All the results are related to the vaccine strain B:4:P1.15. We have also evaluated the spectrum of specific antibodies in ELISA and in bactericidal assay using different strains.

Gotschlich:
Could you just give us a list of the strains against which the bactericidal test was performed?

Sierra:
We have used B:4:P1.15, B:15:P1.15, B:4:NT, B:2a, B:2b, B:2c, B:8.

Gotschlich:
Could you try to speculate on the reason for the wide cross reactivity; which antigens do you think this is due to?

Sierra:
We think that this long lasting cross reactivity is due to the presence of high molecular weight proteins. There are six important proteins in this rank between 65 to 95 000 daltons. Two or three of these are iron-regulated proteins.

Gotschlich:
Which ones are iron-regulated?

Sierra:
One is a protein of 80 000 daltons, the other is very near to 90 000 daltons. We have now cloned, expressed, and purified some of these high molecular weight proteins, and we have characterized them. It is very difficult to obtain these in sufficient amount for characterization. We have demonstrated the importance of these proteins, especially for the immunological memory and for the cross reactivity.

Gotschlich:
There was yesterday a remarkably careful follow-up of patients that had been vaccinated, in terms of long term sequelae. Have you had the opportunity to investigate this in the same details as what was presented yesterday?

Sierra:
Yes, we studied it in Cuba very carefully. The first group of people was vaccinated in Cuba in 1985, and we have until now followed all the groups of the phase 1, phase 2, and phase 3 trials. We have no long-lasting sequelae at all. We have no disease caused and established through the vaccine. The most important reactions we have observed are the purpuric reactions. Very few cases have occurred, all over the country, especially in very small children. They were very short-lasting reactions. There were no sequelae and no neurologic diseases at all.

Peltola:
What do you mean by purpuric reactions? Do you mean petecchiae? If so, they usually are not very short-lived.

Sierra:
There are two types of reactions. One type of rash seems to be some type of allergy to some of the components and the other type of reaction consists of very small petecchiae. Both are short lasting. I think it is very important also to take into consideration the experience that we have in collaboration with Brazil in São Paulo. They have vaccinated nearly two and a half million children below six-seven years of age within in one week. They have experience in evaluating these side reactions.
They also observed a small number of these purpuric reactions or petecchiae. As far as I know, in Cuba or in Brazil we don't have long-lasting sequelae disease or severe reactions caused through the vaccine.

Griffiths:
You think that these iron-regulated proteins are important in your vaccine. Do you take any special measures to insure that they are expressed?

Sierra:
I have not said that the iron regulated proteins are the only ones responsible for the efficacy. I have said that among the four most important high molecular weight proteins responsible for the long lasting bactericidal response, at least two proteins were related to iron metabolism.

Gotschlich:
The question was: Do you purposely limit iron for growth?

Sierra:
We have performed some changes in media regarding the concentration of some nutrients, but not especially iron limitation.

Wetzler:
Were there any non-volunteers in your study, and if there were, what was the incidence of disease in that group?

Sierra:
The incidence among people not volunteering in the study, in the same region or in the neighbourhood of these schools, has remained on the same level. In that age group we have studied this question intensively. We are going to publish all these results very soon.

Robbins:
I have two questions. The dose of the vaccine you mentioned was 50 micrograms. Was that based upon protein? And if it was based upon the protein, what was the total weight of all the material in the vaccine per dose? And the second question: what percentage of cases of bacterial meningitis were you unable to diagnose either by culture or by serological methods?

Sierra:
The vaccine composition is 50 micrograms of proteins per dose. Between 12 and 18% of these are proteins of the high molecular weight complex. We purify the outer membrane proteins, purify the proteoliposomes and we enrich these preparations with high molecular weight proteins. This is not simply a purification route. The composition is approx. 85% of the normal serotype proteins and approx. 15% of high molecular weight proteins. And we try to avoid the presence of class 4 and class 5 proteins in the vaccine because we have found a great variability in the presence and expression of these proteins in the strains circulating in our country, even before the PI.15 epidemic. We have a limit for tolerance of these proteins in the vaccine. We also avoid the B polysaccharide in the vaccine. We test the preparation chemically and also for the capacity to induce antibodies. We have found that the preparation is not able to induce significant anti-B antibodies.
To the second question, related to the incidence: we were not able to find the causal agent in three cases among vaccinees and in two cases of placebo. But after these we have applied different serological analytical methods. We have tested very carefully for the presence of antigens.
A case of meningococcemia in a vaccinee in the Olgin province was excluded because through culture, latex and ELISA methods we were not able to find B antigen.

Broome:
I would like to look a little further into these excluded cases. There were clinically diagnosed two cases of meningococcemia, one fatal in vaccinees and one also fatal in the placebo recipients. They certainly did not have culture confimation, so they did not meet your primary case definition. But in adolescents vaccinated against group C experiencing a group B epidemic, I think those cases are of some consideration as potential group B cases. My expericence with group B antigen testing is that is is not particularly sensitive, certainly not as sensitive as group A or group B antigen detection. I wonder if you could tell us what is the LPS content of the vaccine.

Sierra:
The LPS content of the vaccine is 1% of the total protein amount. If we include the cases without culture the efficacy is around 75%. In one of the three cases mentioned we had not demonstrated B antigens but we have demonstrated other bacterial antigens.

Gotschlich:
You attribute a high importance to the high molecular weight proteins that you add to you vaccine. Could you outline for us the principles of how you obtain these?

Sierra:
We have found one strain with very important growth characteristics in our culture media. We limit in our culture media some of the nutrients, but not iron especially. We are thinking also of doing that in the future. We found that this strain is able to produce higher concentrations of high molecular weight proteins than the other strains. We perform very difficult steps in purification. We purify these high molecular weight proteins, with successive chromatographic steps, and precipitation, and concentration steps. Then, we use them to enrich the preparation of vesicles.

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/771,552	02/03/2004	Leonard Bell	ALXN-PO1-114	6183

28120 7590 12/22/2008

ROPES & GRAY LLP
PATENT DOCKETING 39/41
ONE INTERNATIONAL PLACE
BOSTON, MA 02110-2624

EXAMINER	
VANDERVEGT, FRANCOIS P	
ART UNIT	PAPER NUMBER
1644	

MAIL DATE	DELIVERY MODE
12/22/2008	PAPER

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

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

Office Action Summary	Application No.	Applicant(s)	
	10/771,552	BELL ET AL.	
	Examiner	Art Unit	
	F. Pierre VanderVegt	1644	

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

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

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

Status

1)☒ Responsive to communication(s) filed on *23 June 2008*.

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

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

Disposition of Claims

4)☒ Claim(s) *109-120* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *109-120* is/are rejected.

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

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

Application Papers

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

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

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

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

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

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

a)☐ All b)☐ Some * c)☐ None of:

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

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

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

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

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *20080623*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

The instant application, filed on February 3, 2004, does not claim priority to any earlier application.

Claims 1-108 and 121-171 have been canceled.

Claims 109-120 are currently pending and are the subject of examination in the present Office Action.

In view of Applicant's remarks filed June 23, 2008 the following ground of rejection is maintained.

Claim Rejections - 35 USC § 103

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

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

1. Claims 109-120 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Alexion press release dated January 6, 2003 (CG on form PTO-1449 filed 5/10/2007, of record) in view of Collard et al (Arterioscler Thromb Vasc Biol. [1999]19(11):2623-2629; U on form PTO-892, newly cited).

It was previously stated: "The Alexion press release teaches the use of the anti-C5 antibody compound eculizumab (h5G1.1-scFv) for the treatment of subjects with the hemolytic disease paroxysmal nocturnal hemoglobinuria (see entire document). It is noted that h5G1.1-scFv is the same compound recited in claim 111. The Alexion press release is silent about the treatment of NO deficiency in paroxysmal nocturnal hemoglobinuria. However, because the compound used to treat paroxysmal nocturnal hemoglobinuria in the Alexion press release and the instantly claimed compound to treat NO deficiency in paroxysmal nocturnal hemoglobinuria are the same, the treatment of NO deficiency in paroxysmal nocturnal hemoglobinuria would be an inherent property of the anti-C5 antibody compound eculizumab (h5G1.1-scFv). The prior art teaching anticipates the claimed invention.

The Alexion press release does not specifically link the hemolytic disease with NO deficiency or the effect of h5G1.1-scFv on NO levels.

Collard teaches the treatment of hypoxic HUVECs with h5G1.1-scFv (see entire document). Collard teaches that terminal complement component C5b-9 deposition results in a functional loss of NO-dependent relaxation (page 2625 in particular), increases VCAM-1 expression and decreases cGMP levels (page 2623 and page 2625 in particular). Collard teaches that decreased cGMP levels may compromise vascular blood flow because of decreased endothelium-dependent relaxation and increased adhesion of

neutrophils to the endothelium (page 2623 in particular). Collard teaches that h5G1.1-scFv treatment of the HUVECS attenuates C5b-9 deposition and preserves acetylcholine induced increases in cGMP after hypoxia/reoxygenation (page 2625 in particular).

It would have been prima facie obvious to a person having ordinary skill in the art at the time the invention was made to use the h5G1.1-scFv antibody taught by the Alexion press release for the treatment of NO deficiency in a subject. One would have been motivated to treat NO deficiency with h5G1.1-scFv with a reasonable expectation of success by the showing of Alexion that h5G1.1-scFv treatment of PNH relieved hemolysis and the teachings of Collard that C5b-9 deposition during reoxygenation after a hypoxic event inhibited NO-mediated cGMP expression, which adversely affects vascular blood flow and attracts damaging neutrophils to the endothelial surface. Collard teaches that treatment with h5G1.1-scFv inhibits this C5b-9 deposition and attenuates cGMP loss.

Claims 112-114 are included because, while the references are silent about the proportion of type III red blood cells, silence about a particular property does not necessarily constitute absence of that property. Also, claims 115-117 are included because, while the references are silent about the platelet counts in a subject, silence about a particular property does not necessarily constitute absence of that property. Furthermore claims 118-120 are included because, while the references are silent about the reticulocyte counts in a subject, silence about a particular property does not necessarily constitute absence of that property. The office does not have the facilities and resources to provide the factual evidence needed in order to establish that there is a difference between the materials, i.e., that the claims are directed to new materials and that such a difference would have been considered unexpected by one of ordinary skill in the art, that is, the claimed subject matter, if new, is unobvious. In the absence of evidence to the contrary, the burden is on the Applicant to prove that the claimed materials are different from those taught by the prior art and to establish patentable differences. See In re Best 562F.2d 1252, 195 USPQ 430 (CCPA 1977) and Ex parte Gray 10 USPQ 2d 1922 (PTO Bd. Pat. App. & Int. 1989)."

Applicant's arguments filed June 23, 2008 have been fully considered but they are not persuasive. Applicant argues that the instantly claimed invention cannot be considered obvious over the teachings of the Alexion press release in view of Collard et al because the "Alexion press release was specific to treating PNH patients" and "does not disclose that all patient populations could be treated for NO deficiency with compounds which bind to one or more complement components." Applicant further argues that the artisan would not expect that anti-C5 antibodies would relieve a functional loss of NO-dependent relaxation under all circumstances based on the teaching of Collard et al." Applicant argues therefore that because the scope of the prior art teaching is not as broad as the scope of what is recited in the instant claims, the instantly claimed invention cannot be obvious over the cited references. Applicant's arguments are without merit. In the instant case, the claims are drawn to the genus of conditions involving NO deficiency, while the teachings of the combined references are drawn to a species of NO deficiency in PNH. The prior art does not need to teach the entire genus of the claimed invention. A teaching of a species encompassed by that genus is sufficient to render the genus obvious.

Conclusion

2. No claim is allowed.

3. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

4. Any inquiry concerning this communication or earlier communications from the examiner should be directed to F. Pierre VanderVegt whose telephone number is (571)272-0852. The examiner can normally be reached on M-Th 6:30-4:00 and Alternate Fridays 6:30-3:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Eileen O'Hara can be reached on (571) 272-0878. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

F. Pierre VanderVegt, Ph.D. /PV/
Patent Examiner
March 17, 2008

/Eileen B. O'Hara/
Supervisory Patent Examiner
Art Unit 1644

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/771,552	02/03/2004	Leonard Bell	ALXN-PO1-114	6183

28120 7590 03/21/2008

ROPES & GRAY LLP
PATENT DOCKETING 39/41
ONE INTERNATIONAL PLACE
BOSTON, MA 02110-2624

EXAMINER	
VANDERVEGT, FRANCOIS P	
ART UNIT	PAPER NUMBER
1644	

MAIL DATE	DELIVERY MODE
03/21/2008	PAPER

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	F. Pierre VanderVegt	1644	

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Status

1)☒ Responsive to communication(s) filed on *10 January 2008*.

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

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

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Application Papers

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Priority under 35 U.S.C. § 119

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

a)☐ All b)☐ Some * c)☐ None of:

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

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

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2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *20080110*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

The instant application, filed on February 3, 2004, does not claim priority to any earlier application.

Claims 1-108 and 121-171 have been canceled.

Claims 109-120 are currently pending and are the subject of examination in the present Office Action.

Continued Examination Under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on January 10, 2008 has been entered.

In view of Applicant's amendment filed January 10, 2008 no outstanding ground of rejection is maintained.

Claim Rejections - 35 USC § 103

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

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

2. Claims 109-120 are rejected under 35 U.S.C. 103(a) as being unpatentable over Alexion press release dated January 6, 2003 (CG on form PTO-1449 filed 5/10/2007, of record) in view of Collard et al (Arterioscler Thromb Vasc Biol. [1999]19(11):2623-2629; U on form PTO-892, newly cited).

The Alexion press release teaches the use of the anti-C5 antibody compound eculizumab (h5G1.1-scFv) for the treatment of subjects with the hemolytic disease paroxysmal nocturnal hemoglobinuria (see entire document). It is noted that h5G1.1-scFv is the same compound recited in claim 111. The Alexion press release is silent about the treatment of NO deficiency in paroxysmal

nocturnal hemoglobinuria. However, because the compound used to treat paroxysmal nocturnal hemoglobinuria in the Alexion press release and the instantly claimed compound to treat NO deficiency in paroxysmal nocturnal hemoglobinuria are the same, the treatment of NO deficiency in paroxysmal nocturnal hemoglobinuria would be an inherent property of the anti-C5 antibody compound eculizumab (h5G1.1-scFv). The prior art teaching anticipates the claimed invention.

The Alexion press release does not specifically link the hemolytic disease with NO deficiency or the effect of h5G1.1-scFv on NO levels.

Collard teaches the treatment of hypoxic HUVECs with h5G1.1-scFv (see entire document). Collard teaches that terminal complement component C5b-9 deposition results in a functional loss of NO-dependent relaxation (page 2625 in particular), increases VCAM-1 expression and decreases cGMP levels (page 2623 and page 2625 in particular). Collard teaches that decreased cGMP levels may compromise vascular blood flow because of decreased endothelium-dependent relaxation and increased adhesion of neutrophils to the endothelium (page 2623 in particular). Collard teaches that h5G1.1-scFv treatment of the HUVECS attenuates C5b-9 deposition and preserves acetylcholine induced increases in cGMP after hypoxia/reoxygenation (page 2625 in particular).

It would have been prima facie obvious to a person having ordinary skill in the art at the time the invention was made to use the h5G1.1-scFv antibody taught by the Alexion press release for the treatment of NO deficiency in a subject. One would have been motivated to treat NO deficiency with h5G1.1-scFv with a reasonable expectation of success by the showing of Alexion that h5G1.1-scFv treatment of PNH relieved hemolysis and the teachings of Collard that C5b-9 deposition during reoxygenation after a hypoxic event inhibited NO-mediated cGMP expression, which adversely affects vascular blood flow and attracts damaging neutrophils to the endothelial surface. Collard teaches that treatment with h5G1.1-scFv inhibits this C5b-9 deposition and attenuates cGMP loss.

Claims 112-114 are included because, while the references are silent about the proportion of type III red blood cells, silence about a particular property does not necessarily constitute absence of that property. Also, claims 115-117 are included because, while the references are silent about the platelet counts in a subject, silence about a particular property does not necessarily constitute absence of that property. Furthermore claims 118-120 are included because, while the references are silent about the reticulocyte counts in a subject, silence about a particular property does not necessarily constitute absence of that property. The office does not have the facilities and resources to provide the factual evidence needed in order to establish that there is a difference between the materials, i.e., that the claims are directed to new materials and that such a difference would have been considered unexpected by one of

ordinary skill in the art, that is, the claimed subject matter, if new, is unobvious. In the absence of evidence to the contrary, the burden is on the Applicant to prove that the claimed materials are different from those taught by the prior art and to establish patentable differences. See In re Best 562F.2d 1252, 195 USPQ 430 (CCPA 1977) and Ex parte Gray 10 USPQ 2d 1922 (PTO Bd. Pat. App. & Int. 1989).

Conclusion

3. No claim is allowed.

4. Any inquiry concerning this communication or earlier communications from the examiner should be directed to F. Pierre VanderVegt whose telephone number is (571)272-0852. The examiner can normally be reached on M-Th 6:30-4:00 and Alternate Fridays 6:30-3:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Eileen O'Hara can be reached on (571) 272-0878. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

F. Pierre VanderVegt, Ph.D. /PV/
Patent Examiner
March 17, 2008

/David A Saunders/
Primary Examiner, Art Unit 1644

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/771,552	02/03/2004	Leonard Bell	ALXN-PO1-114	6183

28120 7590 08/10/2007

FISH & NEAVE IP GROUP
ROPES & GRAY LLP
ONE INTERNATIONAL PLACE
BOSTON, MA 02110-2624

EXAMINER	
VANDERVEGT, FRANCOIS P	

ART UNIT	PAPER NUMBER
1644	

MAIL DATE	DELIVERY MODE
08/10/2007	PAPER

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

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

Office Action Summary	Application No.	Applicant(s)	
	10/771,552	BELL ET AL.	
	Examiner	Art Unit	
	F. Pierre VanderVegt	1644	

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

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

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

Status

1)☒ Responsive to communication(s) filed on *10 May 2007*.

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

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

Disposition of Claims

4)☒ Claim(s) *1-171* is/are pending in the application.

4a) Of the above claim(s) *1-108 and 121-171* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *109-120* is/are rejected.

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

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

Application Papers

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

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

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

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

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

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

a)☐ All b)☐ Some * c)☐ None of:

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

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

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

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

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *20070510*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

The instant application, filed on February 3, 2004, does not claim priority to any earlier application.

Claims 1-171 are currently pending.

Election/Restrictions

1. Applicant's election without traverse of Group VI, claims 109-120, in the reply filed on November 24, 2006 is acknowledged.

Claims 1-108 and 121-171 stand withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on November 245, 2006.

Accordingly, claims 109-120 are the subject of examination in the present Office Action.

2. This application contains claims drawn to an invention nonelected without traverse in the reply filed on November 24, 2006. A complete reply to the final rejection must include cancellation of nonelected claims or other appropriate action (37 CFR 1.144) See MPEP § 821.01.

In view of Applicant's amendment filed May 10, 2007 no outstanding grounds of rejection are maintained.

The following new ground of rejection has been necessitated by Applicant's amendment.

Claim Rejections - 35 USC § 102

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

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

3. Claims 109-120 are rejected under 35 U.S.C. 102(b) as being anticipated by Alexion press release dated January 6, 2003 (CG on form PTO-1449 filed 5/10/2007).

The Alexion press release teaches the use of the anti-C5 antibody compound eculizumab (h5G1.1-scFv) for the treatment of subjects with paroxysmal nocturnal hemoglobinuria (see entire

document). It is noted that h5G1.1-scFv is the same compound recited in claim 111. The Alexion press release is silent about the treatment of NO deficiency in paroxysmal nocturnal hemoglobinuria. However, because the compound used to treat paroxysmal nocturnal hemoglobinuria in the Alexion press release and the instantly claimed compound to treat NO deficiency in paroxysmal nocturnal hemoglobinuria are the same, the treatment of NO deficiency in paroxysmal nocturnal hemoglobinuria would be an inherent property of the anti-C5 antibody compound eculizumab (h5G1.1-scFv). The prior art teaching anticipates the claimed invention.

Claims 112-114 are included because, while the references are silent about the proportion of type III red blood cells, silence about a particular property does not necessarily constitute absence of that property. Also, claims 115-117 are included because, while the references are silent about the platelet counts in a subject, silence about a particular property does not necessarily constitute absence of that property. Furthermore claims 118-120 are included because, while the references are silent about the reticulocyte counts in a subject, silence about a particular property does not necessarily constitute absence of that property. The office does not have the facilities and resources to provide the factual evidence needed in order to establish that there is a difference between the materials, i.e., that the claims are directed to new materials and that such a difference would have been considered unexpected by one of ordinary skill in the art, that is, the claimed subject matter, if new, is unobvious. In the absence of evidence to the contrary, the burden is on the Applicant to prove that the claimed materials are different from those taught by the prior art and to establish patentable differences. See In re Best 562F.2d 1252, 195 USPQ 430 (CCPA 1977) and Ex parte Gray 10 USPQ 2d 1922 (PTO Bd. Pat. App. & Int. 1989).

Conclusion

4. No claim is allowed.

5. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action

is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

6. Any inquiry concerning this communication or earlier communications from the examiner should be directed to F. Pierre VanderVegt whose telephone number is (571) 272-0852. The examiner can normally be reached on M-Th 6:30-4:00 and Alternate Fridays 6:30-3:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (571) 272-0841. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

F. Pierre VanderVegt, Ph.D. /PV/
Patent Examiner
August 6, 2007



DAVID A. SAUNDERS
PRIMARY EXAMINER

UNITED STATES PATENT AND TRADEMARK OFFICE

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/771,552	02/03/2004	Leonard Bell	ALXN-PO1-114	6183

28120 7590 02/26/2007

FISH & NEAVE IP GROUP
ROPES & GRAY LLP
ONE INTERNATIONAL PLACE
BOSTON, MA 02110-2624

EXAMINER	
VANDERVEGT, FRANCOIS P	
ART UNIT	PAPER NUMBER
1644	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	02/26/2007	PAPER

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

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	10/771,552	BELL ET AL.	
	Examiner	Art Unit	
	F. Pierre VanderVegt	1644	

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

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

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

Status

1)☒ Responsive to communication(s) filed on *24 November 2006*.

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

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

Disposition of Claims

4)☒ Claim(s) *1-171* is/are pending in the application.

4a) Of the above claim(s) *1-108 and 121-171* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *109-120* is/are rejected.

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

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

Application Papers

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

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

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

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

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

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

a)☐ All b)☐ Some * c)☐ None of:

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

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

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

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

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *20050523, 20060824, 20061124*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

The instant application, filed on February 3, 2004, does not claim priority to any earlier application.

Claims 1-171 are currently pending.

Election/Restrictions

1. Applicant's election without traverse of Group VI, claims 109-120, in the reply filed on November 24, 2006 is acknowledged.

2. Claims 1-108 and 121-171 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on November 245, 2006.

Accordingly, claims 109-120 are the subject of examination in the present Office Action..

Claim Rejections - 35 USC § 103

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

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

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

3. Claims 109-120 are rejected under 35 U.S.C. 103(a) as being unpatentable over Vakeva et al (Circulation [1998] 97:2259-2267; U on form PTO-892) in view of Reiter et al (Nature Medicine [2002] 8(12):1383-1389; V on form PTO-892) and Fitch et al (Circulation [1999] 100:2499-2506; CA cited on form PTO-1449 filed 08/24/2006), as evidenced by Claque et al (Biomed. Instrum. Technol. [1995] 29(5):419-424, Abstract only; W on form PTO-892).

The claims are drawn to the treatment of nitric oxide deficiency in a subject having a hemolytic disease. Vakeva teaches that subjects who undergo prolonged periods of myocardial ischemia experience tissue injury and cell death (Abstract and page 2259, column 1 in particular). Vakeva relates the damage to activated terminal complement components (Abstract in particular). Vakeva teaches that treatment with an anti-C5 antibody inhibits apoptosis and necrosis and blocks greater than 80% of serum hemolytic activity (Abstract, Figure 8, section bridging pages 2265-2266 and paragraph bridging 2264-2265 in particular).

Reiter teaches that cell-free hemoglobin in sickle cell disease limits the availability of nitric oxide (NO)(Abstract in particular). Reiter teaches that free hemoglobin in the serum binds to NO 1,000 more rapidly than hemoglobin sequestered in erythrocytes. Reiter teaches that NO can only reach levels needed for activating guanylyl cyclase in smooth muscle to cause vasodilation only when hemoglobin is sequestered in erythrocytes (page 1383, column 1 in particular). Reiter further teaches that this condition in sickle cell is similar to that seen in clinical diseases such as hemolysis during cardiopulmonary bypass procedures (page 1387, column 2 in particular).

Fitch teaches that coronary bypass surgery (CBP) elicits a systemic inflammatory response (page 2499, column 1 in particular). Fitch teaches a method of administering of a humanized single chain monoclonal antibody directed to human complement component C5 (h5G1.1-scFv) to subjects undergoing CBP. The h5G1.1-scFv antibody is a complement inhibitor that binds to complement component C5 and prevents the cleavage of C5 into C5a and C5b (Fitch page 2500, column 1 in particular). Fitch teaches that h5G1.1-scFv treatment inhibited pathological complement activation, had a pronounced anti-inflammatory effect, and was associated with a significant reduction in myocardial injury and blood loss (page 2504, column 2 in particular). Blood loss in bypass procedures is known to be associated with hemolysis, as evidenced by Claque (Abstract in particular). Based upon the teachings of Fitch in light of the teachings of Reiter, the artisan would recognize that this may be due to the reduced capacity for vasodilation due to the lack of NO caused by free hemoglobin resulting from hemolysis.

It would have been prima facie obvious to a person having ordinary skill in the art at the time the invention was made to treat subjects experience hemolytic disease as a result of coronary bypass surgery for nitric oxide deficiency using the anti-C5 antibody h5G1.1-scFv. One would have been motivated to combine the teachings with a reasonable expectation of success by the teachings of Vakeva that treatment of ischemia with anti-C5 antibody greatly reduced hemolysis, the teachings of Reiter that free hemoglobin resulting from hemolysis during cardiopulmonary bypass procedures greatly reduces NO levels in serum

and the teachings of Fitch that treatment of bypass patients with h5G1.1-scFv antibody reduced cell injury and blood loss.

Claims 112-114 are included because, while the references are silent about the proportion of type III red blood cells, silence about a particular property does not necessarily constitute absence of that property. Also, claims 115-117 are included because, while the references are silent about the platelet counts in a subject, silence about a particular property does not necessarily constitute absence of that property. Furthermore claims 118-120 are included because, while the references are silent about the reticulocyte counts in a subject, silence about a particular property does not necessarily constitute absence of that property. The office does not have the facilities and resources to provide the factual evidence needed in order to establish that there is a difference between the materials, i.e., that the claims are directed to new materials and that such a difference would have been considered unexpected by one of ordinary skill in the art, that is, the claimed subject matter, if new, is unobvious. In the absence of evidence to the contrary, the burden is on the Applicant to prove that the claimed materials are different from those taught by the prior art and to establish patentable differences. See In re Best 562F.2d 1252, 195 USPQ 430 (CCPA 1977) and Ex parte Gray 10 USPQ 2d 1922 (PTO Bd. Pat. App. & Int. 1989).

Conclusion

4. No claim is allowed.

5. Any inquiry concerning this communication or earlier communications from the examiner should be directed to F. Pierre VanderVegt whose telephone number is (571) 272-0852. The examiner can normally be reached on M-Th 6:30-4:00 and Alternate Fridays 6:30-3:00.

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F. Pierre VanderVegt, Ph.D.
Patent Examiner
February 20, 2007

DAVID A. SAUNDERS
PRIMARY EXAMINER

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/771,552	02/03/2004	Leonard Bell	ALXN-PO1-114	6183

28120 7590 09/26/2006

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ROPES & GRAY LLP
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BOSTON, MA 02110-2624

EXAMINER	
VANDERVEGT, FRANCOIS P	

ART UNIT	PAPER NUMBER
1644	

DATE MAILED: 09/26/2006

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

PTO-90C (Rev. 10/03)

Office Action Summary	Application No.	Applicant(s)	
	10/771,552	BELL ET AL.	
	Examiner	Art Unit	
	F. Pierre VanderVegt	1644	

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

Period for Reply

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

Status

1)☐ Responsive to communication(s) filed on _____.

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

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

Disposition of Claims

4)☒ Claim(s) *1-171* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☐ Claim(s) _____ is/are rejected.

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

8)☒ Claim(s) *1-171* are subject to restriction and/or election requirement.

Application Papers

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

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

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

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

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

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

a)☐ All b)☐ Some * c)☐ None of:

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

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

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

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

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claims 1-171 are currently pending.

Election/Restrictions

1. Restriction to one of the following inventions is required under 35 U.S.C. 121:

I. Claims 1-47, 97-108, and 121-171, drawn to a method of treating a subject with hemolytic disease or hemoglobinuria with an anti-C5 antibody, classified in class 424, subclass 145.1.

II. Claims 48-59, drawn to a method of treating a subject with dysphagia with an anti-C5 antibody, classified in class 424, subclass 145.1.

III. Claims 60-71, drawn to a method of treating a subject with erectile dysfunction with an anti-C5 antibody, classified in class 424, subclass 145.1.

IV. Claims 72-84, drawn to a method of reducing thrombosis in a subject with an anti-C5 antibody, classified in class 424, subclass 145.1.

V. Claims 85-96, drawn to a method of increasing the proportion of type III blood cells in a subject with an anti-C5 antibody, classified in class 424, subclass 145.1.

VI. Claims 109-120, drawn to a method of treating a nitric oxide deficiency in a subject with an anti-C5 antibody, classified in class 424, subclass 145.1.

The inventions are distinct, each from the other because of the following reasons:

2. Inventions I-VI are unrelated. Inventions are unrelated if it can be shown that they are not disclosed as capable of use together and they have different designs, modes of operation, and effects (MPEP § 802.01 and § 806.06). In the instant case, the different inventions use the same reagent for the treatment, but each of the conditions in Groups I-VIhas a different etiology and affects a different part of the body. The anti-C5 antibody is administered therefore to achieve different therapeutic goals in each invention.

3. Because these inventions are independent or distinct for the reasons given above and there would be a serious burden on the examiner if restriction is not required because the inventions have acquired a separate status in the art in view of their different classification. Further, a prior art search requires a literature search. It is an undue burden for the Examiner to search more than one invention and restriction for examination purposes as indicated is proper.

4. Applicant is advised that the reply to this requirement to be complete must include (i) an election of a species or invention to be examined even though the requirement be traversed (37 CFR 1.143) and (ii) identification of the claims encompassing the elected invention.

The election of an invention or species may be made with or without traverse. To reserve a right to petition, the election must be made with traverse. If the reply does not distinctly and specifically point out supposed errors in the restriction requirement, the election shall be treated as an election without traverse.

Should applicant traverse on the ground that the inventions or species are not patentably distinct, applicant should submit evidence or identify such evidence now of record showing the inventions or species to be obvious variants or clearly admit on the record that this is the case. In either instance, if the examiner finds one of the inventions unpatentable over the prior art, the evidence or admission may be used in a rejection under 35 U.S.C.103(a) of the other invention.

5. Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 CFR 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a request under 37 CFR 1.48(b) and by the fee required under 37 CFR 1.17(i).

6. Any inquiry concerning this communication or earlier communications from the examiner should be directed to F. Pierre VanderVegt whose telephone number is (571) 272-0852. The examiner can normally be reached on M-Th 6:30-4:00 and Alternate Fridays 6:30-3:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (571) 272-0841. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

F. Pierre VanderVegt, Ph.D.
Patent Examiner
September 19, 2006

CHRISTINA CHAN
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600

UNITED STATES PATENT AND TRADEMARK OFFICE

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
11/050,543	02/03/2005	Leonard Bell	ALXN-P02-114	2128

28120 7590 07/09/2010

ROPES & GRAY LLP
PATENT DOCKETING 39/41
ONE INTERNATIONAL PLACE
BOSTON, MA 02110-2624

EXAMINER	
GAMBEL, PHILLIP	
ART UNIT	**PAPER NUMBER**
1644	

MAIL DATE	DELIVERY MODE
07/09/2010	PAPER

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

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

Office Action Summary	Application No.	Applicant(s)	
	11/050,543	BELL ET AL.	
	Examiner	Art Unit	
	Phillip Gambel	1644	

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

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

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

Status

1)☒ Responsive to communication(s) filed on *06/26/2008, 10/02/2008*.

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

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

Disposition of Claims

4)☒ Claim(s) *1-135* is/are pending in the application.

4a) Of the above claim(s) *1-45,48,51-75,78,81-98,101,106 and 109-130* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *46,47,49,50,76,77,79,80,99, 100,102-105,107,108 and 131-135* is/are rejected.

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

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

Application Papers

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

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4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. The examiner of your application in the PTO has changed. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Technology Center 1600, Art Unit 1644.

2. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office Action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 10/02/2008 has been entered.

Applicant's amendment, filed 06/26/2008, has been entered
Claims 47, 79, 102 and 107 have been amended.

Claims 1-135 are pending.

Claims 46, 47, 49, 50, 76, 77, 79, 80, 99, 100, 102-105, 107, 108 and 131-135 are under consideration in the instant application as they read on the elected invention.

Claims 1-45, 48, 51-75, 78, 81-98, 101, 106 and 109-130 have been withdrawn from consideration as they read on non-elected inventions/species.

3. The title of the invention is not descriptive. A new title is required that is clearly indicative of the invention to which the claims are directed. Applicant should restrict the title to the claimed invention.

4. The application is required to be reviewed and all spelling, TRADEMARKS, and like errors corrected. Appropriate corrections are required.

Trademarks should be capitalized or accompanied by the ® or ™ symbol wherever they appear and be accompanied by the generic terminology. Although the use of trademarks is permissible in patent applications, the proprietary nature of the trademarks should be respected and every effort made to prevent their use in any manner, which might adversely affect their validity as trademarks.

The disclosure is objected to because it contains an embedded hyperlink and/or other form of browser-executable code. Applicant is required to delete the embedded hyperlink and/or other form of browser-executable code. See MPEP 608.01.
For example, see page 40 of the specification.

Appropriate corrections are required

5. The following is a quotation of the first paragraph of 35 U.S.C. § 112:
The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

6. Claims 49 and 99 are rejected under 35 U.S.C. § 112, first paragraph, as the specification does not contain a written description of the claimed invention, in that the disclosure does not reasonably convey to one skilled in the relevant art that the inventor(s) had possession of the claimed invention at the time the application was filed.
The specification as originally filed does not provide support for the invention as now claimed:

The specification as originally filed does not provide support for the invention as now claimed:
(A) "within 38% of the upper limit of normal" as recited in claim 99 and
(B) "PNH type III granulocytes" recited in claim 49.

As noted previously, claim 99 has been amended to recite "38%" in place of the original "20%" limitation. The specification as originally filed discloses only reduction of LDH levels to within 20% of the upper limit of normal at page 23, lines 6-9. Applicant has asserted that the recitation of 38% in the claim is supported by the specification as originally filed in the data of Figure 1A. The Figure in question depicts data from treated patients showing ranges of LDH levels pre- and post-treatment. The Figure "38%" is a post-treatment value obtained from within one of these ranges. The data in the Figure does not specifically lead to a teaching of 38% and there is no teaching in the specification to indicate that this is a preferred value from within the range. Picking a specific value from within a disclosed range creates a new, previously undisclosed, sub-genus and this constitutes new matter.
With respect to the recitation of "38%", applicant's arguments, filed 06/26/2008, submits the following.

> Although the embodiment referred to by the Examiner on page 23, lines 6-9 does not state "38%" this number is specifically taught by the data in Figure 1A. Specifically, Figure 1A shows the upper limit of normal (uln) is 480 U/L, and the treated patients showed an average LDH level of 622.4 + 41.1 at 64 weeks. Thus, the maximum LDH level of treated patients was 38.2% above the uln. Therefore, the upper range of the LDH levels of treated patients is reduced to within 38% of the uln. One of ordinary skill in the art could have derived this number unambiguously from Figure 1A and 38% defines the range rather than being within the range as the Examiner suggests. Accordingly, no new matter has been introduced.

In contrast to applicant's assertions, applicant is relying upon a specific example determined to be 38.2%, while the claims are now drawn to range as well as a specific point that differs from the specific example relied upon by applicant (e.g., "38%" versus "38.2%").

Further, it cannot be said that a subgenus is necessarily described by a genus encompassing it and a species upon which it reads. See In re Smith 173 USPQ 679, 683 (CCPA 1972) and MPEP 2163.05.

Upon a review of the prosecution, it is noted that claim 49 had been amended to change PNH type III granulocyte clones" to PNH type III granulocytes" (see applicant's amendment, filed 01/10/2008).

Applicant relied upon the following paragraph from page 24 of the specification.

Methods of reducing one or more symptoms associated with PNH or other hemolytic diseases are also within the scope of the present disclosure. Such symptoms include, for example, abdominal pain, fatigue, dyspnea and insomnia. Symptoms can be the direct result of lysis of red blood cells (e.g., hemoglobinuria, anemia, fatigue, low red blood cell count, etc.) or the symptoms can result from low nitric oxide (NO) levels in the patient's bloodstream (e.g., abdominal pain, erectile dysfunction, dysphagia, thrombosis, etc.). It has recently been reported that almost all patients with greater than 40% PNH type III granulocyte clone have thrombosis, abdominal pain, erectile dysfunction and dysphagia, indicating a high hemolytic rate (see Moyo et al., British J. Haematol. 126:133-138 (2004)).

Rather than claiming "PNH type III granulocytes" generically, the original claims and the instant specification as-filed limits the cells to "PHN type III granulocyte clones".
By deleting "clones", it appears that applicant has altered the cell populations recited in the claims and described in the specification.

The specification does not provide sufficient blazemarks nor direction for the instant methods encompassing the above-mentioned "limitations" as currently recited. The instant claims now recite limitations which were not clearly disclosed in the specification as-filed, and now change the scope of the instant disclosure as-filed. Such limitations recited in the present claims, which did not appear in the specification, as filed, introduce new concepts and violate the description requirement of the first paragraph of 35 U.S.C. 112.

Applicant is required to cancel the new matter in the response to this Office Action.

Alternatively, applicant is invited to provide sufficient written support for the "limitations" indicated above.
See MPEP 714.02 and 2163.06

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

A person shall be entitled to a patent unless --

(a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

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

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

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

9. Claims 46, 47, 49, 50, 76, 77, 79, 80, 99, 100, 102-105, 107, 108 and 131-135 are rejected under 35 U.S.C. § 102(a)(b) as being anticipated by Hillmen et al. (Blood 102: 1858, 2003) (1449; #CD) (see entire document).

Since the public availability of this document is not clear and given that certain claims are subject to a rejection under 35 USC 112, first paragraph, written description / new matter; this rejection is being applied under 35 U.S.C. § 102(a)(b).

Hillmen et al. teach methods of treating paroxysmal nocturnal hemoglobulinuria (PNH), intravascular hemolysis and venous thrombosis, with an anti-C5 antibody and in certain instances with erythropoietin as well, including improvement in biochemical / biological parameters associated with LDH and PNH type III cells (see entire document).

It does not appear that the claim language or limitations result in a manipulative difference in the method steps when compared to the prior art disclosure

Although the reference is silent about certain specific claimed limitations per se of a patient having paroxysmal nocturnal hemoglobulnuria (PNH) (e.g., see claims 49-50, 79-80, 99, 10—104, 107-108, 135),
it does not appear that the claim language or limitations result in a manipulative difference in the method steps when compared to the prior art disclosure. See Bristol-Myers Squibb Company v. Ben Venue Laboratories 58 USPQ2d 1508 (CAFC 2001). "{i}t is a general rule that merely discovering and claiming a new benefit of an old process cannot render the process again

patentable". In re Woodruff, 16 USPQ2d 1934, 1936 (Fed. Cir. 1990). The mechanism of action does not have a bearing on the patentability of the invention if the invention was already known or obvious. Mere recognition of latent properties in the prior art does not render nonobvious an otherwise known invention. In re Wiseman, 201 USPQ 658 (CCPA 1979). Granting a patent on the discovery of an unknown but inherent function would remove from the public that which is in the public domain by virtue of its inclusion in, or obviousness from, the prior art. In re Baxter Travenol Labs, 21 USPQ2d 1281 (Fed. Cir. 1991). See M.P.E.P. 2145.

On this record, it is reasonable to conclude that the same PNH patients are being administered the active agent anti-C5 antibodies by the same mode of administration in the same amount to achieve the same or nearly the same improvement in biochemical and biological parameters (e.g., LDH and PNH type III cells) in both the instant claims and the prior art reference. The fact that applicant may have discovered yet another beneficial effect from the method set forth in the prior art does not mean that they are entitled to receive a patent on that method.

Applicant is reminded that no more of the reference is required than that it sets forth the substance of the invention. The claimed functional limitations would be inherent properties of the referenced methods to administer anti-C5 antibodies to treat PNH patients.

10. Claims 46, 47, 49, 50, 76, 77, 79, 80, 99, 100, 102-105, 107, 108 and 131-135 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Hillmen et al. (Blood 102: 1858, 2003) (1449; #CD) AND/OR Hillmen (44th ASH Annual Meeting Abstract, Blood, Vol. 100, 2002) (1449; #CE)in view of Meyers et al. (Int. J. Hematol. 77: 125-132, 2003) and as evidenced by Garba et al. (Singapore Med. J. 46(11):632-634, 2005) (892; of record) with respect to normal LDH levels.

Hillmen et al. (2003) teach methods of treating paroxysmal nocturnal hemoglobulinuria (PNH), which is characterized by intravascular hemolysis and venous thrombosis with an anti-C5 antibody and in certain instances with erythropoietin as well, including improvement in biochemical / biological parameters associated with LDH and PNH type III cells (see entire document).

Hillmen (2002) teaches that paroxysmal nocturnal hemoglubinuria (PNH) is characterized by intravascular hemolysis and venous thrombosis. Hillmen teaches that the hemolysis is complement-mediated and due to the deficiency of complement regulatory proteins on red cells, particularly the terminal complement inhibitor CD59 (see entire document). Hillmen teaches treating transfusion-dependent PNH patients with ECULIZUMAB, a humanized anti-C5 antibody (see entire publication). Hillmen teaches that the biological parameters of hemolysis dramatically improved or normalized for all patients within a week of starting therapy. Hillmen further teaches that mean LDH decreased greater than 50%, from 4494 +/- 3380 units/liter to 636 +/- 166 units/liter.

Hillmen (2002) does not teach treating a subject with EPO.

The mean level of LDH in the PNH patients was more than 1.5 times the upper limit of a normal LDH level in a person, as evidenced by Garba, who discloses that normal LDH in a person is 247.10 +/- 19.0 units/liter (Abstract in particular). The prior art teaching clearly anticipates the claimed invention.

Meyers et al. teach management issues in the treatment of paroxysmal nocturnal hemoglobinuria (see entire document), including the hallmarks of hemolysis and anemia (e.g., see pages 125-128) as well as the treatment of this syndrome with complement inhibitors such as anti-C5 antibodies particularly for the hemolysis of PNH (see Section 2.5, Complement Inhibitors) and erythropoietin (see Section 2.6, Management of Nonhemolytic Anemia).

Given the nature of the clinical manifestations of PNH such as hemolysis and anemia, one of ordinary skill in the art at the time the invention was made would have been motivated to select and combine both anti-C5 antibodies and erythropoietin to address and manage the clinical manifestations of PNH over time. One would have been motivated to combine these therapies with a reasonable expectation of success because each treats a different aspect of the hemolytic disease in the patient and could be reasonably expected to improve the prognosis of the patient more rapidly than either therapy alone. From the teachings of the references, it was apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

"The test of obviousness is not express suggestion of the claimed invention in any or all of the references but rather what the references taken collectively would suggest to those of ordinary skill in the art presumed to be familiar with them." See In re Rosselet, 146 USPQ 183, 186 (CCPA 1965).

"There is no requirement (under 35 USC 103(a)) that the prior art contain an express suggestion to combine known elements to achieve the claimed invention. Rather, the suggestion to combine may come from the prior art, as filtered through the knowledge of one skilled in the art." Motorola, Inc. v. Interdigital Tech. Corp., 43 USPQ2d 1481, 1489 (Fed. Cir. 1997).

An obviousness determination is not the result of a rigid formula disassociated from the consideration of the facts of a case. Indeed, the common sense of those skilled in the art demonstrates why some combinations would have been obvious where others would not. See KSR Int'l Co. v. Teleflex Inc., 82 USPQ2d 1385 (U.S. 2007) ("The combination of familiar elements according to known methods is likely to be obvious when it does no more than yield predictable results.").

11. Given copending applications encompassing similar subject matter and the restriction set forth herein, applicant is invited to clarify which applications should be subject to rejections under the judicially created doctrine of obviousness-type double patenting.

12. No claim is allowed.

13. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Phillip Gambel whose telephone number is (571) 272-0844. The examiner can normally be reached Monday through Thursday from 7:30 am to 6:00 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla can be reached on (571) 272-0735.

The fax number for the organization where this application or proceeding is assigned is 571-273-8300.

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/Phillip Gambel/

Primary Examiner
Technology Center 1600
Art Unit 1644
July 6, 2010

UNITED STATES PATENT AND TRADEMARK OFFICE

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United States Patent and Trademark Office
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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
11/050,543	02/03/2005	Leonard Bell	ALXN-P02-114	2128

28120 7590 04/02/2008

ROPES & GRAY LLP
PATENT DOCKETING 39/41
ONE INTERNATIONAL PLACE
BOSTON, MA 02110-2624

EXAMINER	
VANDERVEGT, FRANCOIS P	
ART UNIT	PAPER NUMBER
1644	

MAIL DATE	DELIVERY MODE
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1)☒ Responsive to communication(s) filed on *10 January 2008*.

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Disposition of Claims

4)☒ Claim(s) *1-135* is/are pending in the application.

4a) Of the above claim(s) *1-45,48,51-75,78,81-98,101,106 and 109-130* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *46,47,49,50,76,77,79,80,99,100,102-105,107,108 and 131-135* is/are rejected.

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

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

Application Papers

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

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

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

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

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

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

a)☐ All b)☐ Some * c)☐ None of:

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

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

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

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

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *20071009, 20080110*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

This application is a continuation-in-part of U.S. Application Serial Number 10/771,552.

New claims 131-135 have been added.

Claims 1-135 are currently pending.

Election/Restrictions

1. **Claims 1-45, 51-75, 81-98 and 109-130 stand withdrawn** from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on July 16, 2007.

2. **Claims 48, 78, 101 and 106 stand withdrawn** from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected species, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on July 16, 2007.

3. Accordingly, **claims 46, 47, 49, 50, 76, 77, 79, 80, 99, 100, 102-105, 107, 108 and 131-135 are the subject of examination** in the present Office Action.

4. In view of Applicant's amendment filed January 10, 2008, only the following grounds of rejection are maintained.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5. Claim 99 stands rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a NEW MATTER rejection.

Claim 99 has been amended to recite 38% in place of the original 20% limitation. The specification as originally filed discloses only reduction of LDH levels to within 20% of the upper limit of normal at page 23, lines 6-9. Accordingly, the recitation of 38% constitutes new matter and must be removed.

Applicant's arguments filed January 10, 2008 have been fully considered but they are not persuasive. Applicant asserts that the recitation of 38% in the claim is supported by the specification as originally filed in the data of Figure 1A. The figure in question depicts data from treated patients showing ranges of LDH levels pre- and post-treatment. The figure "38%" is a post-treatment value obtained from within one of these ranges. The data in the figure does not specifically lead to a teaching of 38% and there is no teaching in the specification to indicate that this is a preferred value from within the range. Picking a specific value from within a disclosed range creates a new, previously undisclosed, sub-genus and this constitutes new matter. Accordingly, the ground of rejection is maintained.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

6. Claims 49, 79, 102 and 107 stand rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 49, 79, 102 and 107 remain ambiguous and unclear in the recitation of "greater than 40% of said subject's granulocytes are paroxysmal nocturnal hemoglubinuria (PNH) type III granulocytes. It is unclear whether this percentage of granulocytes being type III granulocytes is before or after treatment with the complement inhibitor. Clarification is required.

7. The following represents a new ground of rejection that has been necessitated by Applicant's amendment.

Claim Rejections - 35 USC § 103

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

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are

such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

8. Claims 46, 47, 50, 76, 77, 80, 100, 103-105 and 108 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hillmen (44th ASH Annual Meeting Abstract, Blood, vol. 100 [2002]; CE on form PTO-1449 filed November 24, 2006, of record), as evidenced by Garba et al. (Singapore Med. J. [2005] 46(11):632-634; U on form PTO-892, of record) in view of Stebler et al. (Exp. Hematol. [1990] 18:1204-1208; V on form PTO-892, newly cited).

Hillmen teaches that paroxysmal nocturnal hemoglubinuria (PNH) is characterized by intravascular hemolysis and venous thrombosis. Hillmen teaches that the hemolysis is complement-mediated and due to the deficiency of complement regulatory proteins on red cells, particularly the terminal complement inhibitor CD59. Hillmen teaches treating transfusion-dependent PNH patients with ECULIZUMAB, a humanized anti-C5 antibody (see entire publication). Hillmen teaches that the biological parameters of hemolysis dramatically improved or normalized for all patients within a week of starting therapy. Hillmen further teaches that mean LDH decreased greater than 50%, from 4494 +/- 3380 units/liter to 636 +/- 166 units/liter. The mean level of LDH in the PNH patients was more than 1.5 times the upper limit of a normal LDH level in a person, as evidenced by Garba, who discloses that normal LDH in a person is 247.10 +/- 19.0 units/liter (Abstract in particular). The prior art teaching clearly anticipates the claimed invention.

Hillmen does not teach treating a subject with EPO.

It is noted that the specification teaches the treatment with EPO as a combination therapy with the complement inhibitor. The specification discloses that the purpose of the EPO is to stimulate hematopoiesis and does not disclose that EPO modifies the activity of the complement inhibitor in any way. Accordingly, there is no disclosure that there any unobvious effects of the EPO on the inhibitor or vice versa.

Stebler teaches the use of high doses of recombinant human EPO to treat the anemia in patients with PNH (see entire document).

It would have been prima facie obvious to a person having ordinary skill in the art at the time the invention was made to treat a patient with PNH with ECULIZUMAB to inhibit hemolysis as taught by Hillmen and to simultaneously treat that patient with EPO to stimulate hematopoiesis and alleviate anemia as taught by Stebler. One would have been motivated to combine these therapies with a reasonable expectation of success because each treats a different aspect of the hemolytic disease in the

patient and could be reasonably expected to improve the prognosis of the patient more rapidly than either therapy alone.

Conclusion

9. No claim is allowed.

10. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

11. Any inquiry concerning this communication or earlier communications from the examiner should be directed to F. Pierre VanderVegt whose telephone number is (571)272-0852. The examiner can normally be reached on M-Th 6:30-4:00 and Alternate Fridays 6:30-3:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Eileen O'Hara can be reached on (571) 272-0878. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

F. Pierre VanderVegt, Ph.D. /PV/
Patent Examiner
March 27, 2008

/David A Saunders/
Primary Examiner, Art Unit 1644

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
11/050,543	02/03/2005	Leonard Bell	ALXN-P02-114	2128

28120 7590 10/10/2007
ROPES & GRAY LLP
PATENT DOCKETING 39/41
ONE INTERNATIONAL PLACE
BOSTON, MA 02110-2624

EXAMINER	
VANDERVEGT, FRANCOIS P	

ART UNIT	PAPER NUMBER
1644	

MAIL DATE	DELIVERY MODE
10/10/2007	PAPER

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

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

Office Action Summary	Application No.	Applicant(s)	
	11/050,543	BELL ET AL.	
	Examiner	Art Unit	
	F. Pierre VanderVegt	1644	

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

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

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

Status

1)☒ Responsive to communication(s) filed on *16 July 2007*.

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

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

Disposition of Claims

4)☒ Claim(s) *1-130* is/are pending in the application.

4a) Of the above claim(s) *1-45,48,51-75,78,81-98,101,106 and 109-130* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *46,47,49,50,76,77,79,80,99,100,102-105,107 and 108* is/are rejected.

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

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

Application Papers

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

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

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

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

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

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

a)☐ All b)☐ Some * c)☐ None of:

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

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

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

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

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *20050511, 20060824, 20061124*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

This application is a continuation-in-part of U.S. Application Serial Number 10/771,552.

Claims 1-130 are currently pending.

Election/Restrictions

1. Applicant's election with traverse of Group V, claims 46-50, in the reply filed on July 16, 2007 is acknowledged. The traversal is on the ground(s) that claims 76-80 and 99-108 should have also been included in this group because they are drawn to the same method. Upon further review of the claims in light of Applicant's remarks, the Examiner concurs and will rejoin the aforementioned claims with the invention of Group V.

Claims 1-45, 51-75, 81-98 and 109-130 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on July 16, 2007.

2. Applicant's election of the species "antibody" in the reply filed on July 16, 2007 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

Claims 48, 78, 101 and 106 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected species, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on July 16, 2007.

3. Accordingly, **claims 46, 47, 49, 50, 76, 77, 79, 80, 99, 100, 102-105, 107 and 108 are the subject of examination** in the present Office Action.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. Claim 99 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the

specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a NEW MATTER rejection.

Claim 99 has been amended to recite 38% in place of the original 20% limitation. The specification as originally filed discloses only reduction of LDH levels to within 20% of the upper limit of normal at page 23, lines 6-9. accordingly, the recitation of 38% constitutes new matter and must be removed.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

5. Claims 49, 79, 102 and 107 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 49, 79, 102 and 107 are ambiguous and unclear in the recitation of the abbreviation "PNH." The first recitation of an abbreviation in a line of claims should be in addition to a recitation of the full term, as the same abbreviation can be used to identify other cells or conditions. This ground of rejection can be overcome by amending the claim to recite --paroxysmal nocturnal hemoglubinuria (PNH)-- in place of the recitation of "PNH."

Claims 49, 79, 102 and 107 are ambiguous and unclear in the recitation of "subject has a greater than 40% PNH type III granulocytes clone. It is not clear what is exactly is supposed to be greater than 40% in the subject. Type III cells? Granulocytes? The ratio of granulocytes to type III cells? What is a "40% PNH type III granulocyte clone?" Clarification is required.

Claim Rejections - 35 USC § 102

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

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

6. Claims 46, 47, 50, 76, 77, 80, 100, 103-105 and 108 are rejected under 35 U.S.C. 102(b) as being clearly anticipated by Hillmen (44th ASH Annual Meeting Abstract, Blood, vol. 100 [2002]; CE on form PTO-1449 filed November 24, 2006), as evidenced by Garba et al. (Singapore Med. J. [2005] 46(11):632-634; U on form PTO-892).

Hillmen teaches that paroxysmal nocturnal hemoglubinuria (PNH) is characterized by intravascular hemolysis and venous thrombosis. Hillmen teaches that the hemolysis is complement-mediated and due to the deficiency of complement regulatory proteins on red cells, particularly the terminal complement inhibitor CD59. Hillmen teaches treating transfusion-dependent PNH patients with ECULIZUMAB, a humanized anti-C5 antibody 9see entire publication). Hillmen teaches that the biological parameters of hemolysis dramatically improved or normalized for all patients within a week of starting therapy. Hillmen further teaches that mean LDH decreased greater than 50%, from 4494 +/- 3380 units/liter to 636 +/- 166 units/liter. The mean level of LDH in the PNH patients was more than 1.5 times the upper limit of a normal LDH level in a person, as evidenced by Garba, who discloses that normal LDH in a person is 247.10 +/- 19.0 units/liter (Abstract in particular). The prior art teaching clearly anticipates the claimed invention.

Conclusion

7. No claim is allowed.

8. Any inquiry concerning this communication or earlier communications from the examiner should be directed to F. Pierre VanderVegt whose telephone number is (571) 272-0852. The examiner can normally be reached on M-Th 6:30-4:00 and Alternate Fridays 6:30-3:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (571) 272-0841. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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F. Pierre VanderVegt, Ph.D. /PV/
Patent Examiner
September 26, 2007

David A. Saunders
DAVID A. SAUNDERS
PRIMARY EXAMINER

UNITED STATES PATENT AND TRADEMARK OFFICE

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
11/050,543	02/03/2005	Leonard Bell	ALXN-P02-114	2128

28120 7590 06/11/2007

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BOSTON, MA 02110-2624

EXAMINER	
VANDERVEGT, FRANCOIS P	

ART UNIT	PAPER NUMBER
1644	

MAIL DATE	DELIVERY MODE
06/11/2007	PAPER

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

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	Examiner	Art Unit	
	F. Pierre VanderVegt	1644	

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

Period for Reply

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- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

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

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

Disposition of Claims

4)☒ Claim(s) *1-130* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☐ Claim(s) _____ is/are rejected.

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

8)☒ Claim(s) *1-130* are subject to restriction and/or election requirement.

Application Papers

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

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

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

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

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

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

a)☐ All b)☐ Some * c)☐ None of:

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

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

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

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

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2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

This application is a continuation-in-part of U.S. Application Serial Number 10/771,552.

Claims 1-130 are currently pending.

Election/Restrictions

1. Restriction to one of the following inventions is required under 35 U.S.C. 121:

I. Claims 1-19, 86-92 and 109-130, drawn to a method for treating a hemolytic disease in a subject comprising administering a complement-affecting compound to the subject, wherein the subject's need for transfusion is reduced or eliminated, classified in class 424, subclass 278.1.

II. Claims 20-35, drawn to a method for reducing abdominal pain in a subject comprising administering a complement-affecting compound to the subject, classified in class 424, subclass 278.1.

III. Claims 36-40, 51-55, 76-80, and 99-108, drawn to a method for treating a hemolytic disease comprising administering a complement-affecting compound to the subject wherein there is a reduction in hemoglobinuria, classified in class 424, subclass 278.1.

IV. Claims 41-45 and 81-85, drawn to a method for restoring nitric oxide homeostasis or reducing nitrous oxide deficiency in a subject comprising administering a complement-affecting compound to the subject, classified in class 424, subclass 278.1.

V. Claim46-50, drawn to a method for reducing hemolysis disease by reducing LDH levels in the bloodstream comprising administering a complement affecting compound to the subject, classified in class 424, subclass 278.1.

VI. Claims 56-60, drawn to a method for reducing dysphagia in a subject comprising administering a complement-affecting compound to the subject, classified in class 424, subclass 278.1.

VII. Claims 61-65, drawn to a method for reducing erectile dysfunction in a subject comprising administering a complement-affecting compound to the subject, classified in class 424, subclass 278.1.

VIII. Claims 66-70, drawn to a method for reducing thrombosis in a subject comprising administering a complement-affecting compound to the subject, classified in class 424, subclass 278.1.

IX. Claims 71-75, drawn to a method for increasing the proportion of Type III red blood cells in a subject's blood comprising administering a complement affecting compound to the subject, classified in class 424, subclass 278.1.

X. Claims 93-98, drawn to a method for treating a hemolytic disease in a subject comprising administering a complement affecting compound and a compound that increases hematopoiesis to the subject, classified in class 424, subclass 278.1.

2. The inventions are distinct, each from the other because of the following reasons:

Inventions I-X are unrelated. Inventions are unrelated if it can be shown that they are not disclosed as capable of use together and they have different designs, modes of operation, and effects (MPEP § 802.01 and § 806.06). In the instant case, the different inventions use the same reagent for the treatment, but each of the conditions in Groups I-X has a different etiology and/or affects a different part of the body. The anti-C5 antibody is administered therefore to achieve different therapeutic goals in each invention.

3. These inventions are independent or distinct for the reasons given above and there would be a serious burden on the examiner if restriction is not required because the inventions have acquired a separate status in the art due to their recognized divergent subject matter. Further, a prior art search requires a literature search. It is an undue burden for the Examiner to search more than one invention and restriction for examination purposes as indicated is proper.

4. This application contains claims directed to the following patentably distinct species:

a. antibodies,
b. soluble complement inhibitory compounds,
c. proteins, protein fragments, peptides,
d. small molecules,
e. RNA aptamers, L-RNA aptamers,
f. spiegelmers,
g. antisense compounds,
h. serine protease inhibitors,
i. double stranded RNA,
j. small interfering RNA,
k. locked nucleic acid inhibitors,
l. and peptide nucleic acid inhibitors.

The species are independent or distinct because each of the species has a different structure and different mode of action.

Irrespective of which group is chosen, Applicant is further required under 35 U.S.C. 121 to elect a single disclosed species for prosecution on the merits to which the claims shall be restricted if no

generic claim is finally held to be allowable. Currently, claims 1, 2, 4, 6, 7, 9-20, 25-37, 39-42, 44-47, 49-52, 54-57, 59-62, 64-67, 69-72, 74-77, 79-82, 84-87, 89-94, 96-100, 102-105, 107-112, 115, and 117-130 are generic.

Applicant is advised that a reply to this requirement must include an identification of the species that is elected consonant with this requirement, and a listing of all claims readable thereon, including any claims subsequently added. An argument that a claim is allowable or that all claims are generic is considered nonresponsive unless accompanied by an election.

Upon the allowance of a generic claim, applicant will be entitled to consideration of claims to additional species which depend from or otherwise require all the limitations of an allowable generic claim as provided by 37 CFR 1.141. If claims are added after the election, applicant must indicate which are readable upon the elected species. MPEP § 809.02(a).

5. Applicant is advised that the reply to this requirement to be complete must include (i) an election of a species or invention to be examined even though the requirement be traversed (37 CFR 1.143) and (ii) identification of the claims encompassing the elected invention.

The election of an invention or species may be made with or without traverse. To reserve a right to petition, the election must be made with traverse. If the reply does not distinctly and specifically point out supposed errors in the restriction requirement, the election shall be treated as an election without traverse.

Should applicant traverse on the ground that the inventions or species are not patentably distinct, applicant should submit evidence or identify such evidence now of record showing the inventions or species to be obvious variants or clearly admit on the record that this is the case. In either instance, if the examiner finds one of the inventions unpatentable over the prior art, the evidence or admission may be used in a rejection under 35 U.S.C.103(a) of the other invention.

6. Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 CFR 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a request under 37 CFR 1.48(b) and by the fee required under 37 CFR 1.17(i).

7. Any inquiry concerning this communication or earlier communications from the examiner should be directed to F. Pierre VanderVegt whose telephone number is (571) 272-0852. The examiner can normally be reached on M-Th 6:30-4:00 and Alternate Fridays 6:30-3:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (571) 272-0841. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

F. Pierre VanderVegt, Ph.D.
Patent Examiner
June 4, 2007

David A Saunders

DAVID A. SAUNDERS
PRIMARY EXAMINER

UNITED STATES PATENT AND TRADEMARK OFFICE

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
11/595,118	11/08/2006	Leonard Bell	ALXN-P03-114	6763

28120 7590 01/21/2011

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EXAMINER	
GAMBEL, PHILLIP	

ART UNIT	PAPER NUMBER
1644	

NOTIFICATION DATE	DELIVERY MODE
01/21/2011	ELECTRONIC

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

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

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

USPatentMail@ropesgray.com
USPatentMail2@ropesgray.com

Office Action Summary	Application No.	Applicant(s)	
	11/595,118	BELL ET AL.	
	Examiner	Art Unit	
	Phillip Gambel	1644	

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

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

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

Status

1)☒ Responsive to communication(s) filed on *03 November 2010*.

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

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

Disposition of Claims

4)☒ Claim(s) *1-191* is/are pending in the application.

4a) Of the above claim(s) *1-163 and 168-191* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *164-167* is/are rejected.

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

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

Application Papers

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

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

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

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

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

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

a)☐ All b)☐ Some * c)☐ None of:

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

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

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

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

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *10/09/2007, 01/25/2008, 01/05/2009, 01/20/2010, 11/03/2010*
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. Applicant's election of Group II (claims 164-167) for continued examination in the Response to Restriction Requirement, filed 11/03/2010 is acknowledged.

Applicant's indication that an election of species as it reads on Group II is not necessary (at this time) is acknowledged.

Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (see MPEP 818.03(a)).

Therefore, claims 164-167 being acted upon as the elected invention.

Claims 1-163 and 168-191 have been withdrawn as being drawn to the non-elected Group and its corresponding species

2. The effective filing date of the instant claims is deemed to be the filing date of the instant application USSN 11/595,118, filed 11/08/2206, as the previous priority applications do not provide sufficient written support for claims 164-167 as follows.

A method of determining whether a subject having a hemolytic disorder is susceptible to thrombosis comprising measuring the PNH granulocyte clone size of said subject, wherein if the clone size is greater than O. 1% then said subject is susceptible to thrombosis.

If applicant disagrees, applicant should present a detailed analysis as to why the claimed subject matter has clear support in the earlier priority applications.

Applicant is reminded that such priority for the instant limitations requires written description and enablement under 35 U.S.C. § 112, first paragraph.

3. If applicant desires priority under 35 U.S.C. 119(e) / 120 based upon a previously filed application, specific reference to the earlier filed application must be made in the instant application. For benefit claims under 35 U.S.C. 120, 121 or 365(c), the reference must include the relationship (i.e., continuation, divisional, or continuation-in-part) of the applications. This should appear as the first sentence of the specification following the title, preferably as a separate paragraph unless it appears in an application data sheet. The status of nonprovisional parent application(s) (whether patented or abandoned) should also be included. If a parent application has become a patent, the expression "now Patent No. _____" should follow the filing date of the parent application. If a parent application has become abandoned, the expression "now abandoned" should follow the filing date of the parent application.

Applicant should update the status of the priority documents on page 1 of the instant specification.

4. The title of the invention is not descriptive. A new title is required that is clearly indicative of the invention to which the claims are directed.

5. The application is required to be reviewed and all spelling, TRADEMARKS, and like errors corrected. Appropriate corrections are required.

Trademarks should be capitalized or accompanied by the ® or ™ symbol wherever they appear and be accompanied by the generic terminology. Although the use of trademarks is permissible in patent applications, the proprietary nature of the trademarks should be respected and every effort made to prevent their use in any manner, which might adversely affect their validity as trademarks.

Appropriate corrections are required

6. For examination purposes, it is noted the measuring the PNH granulocyte clone size refers to measuring the number or PNH granulocytes and not measuring the physical size of PNH granulocytes.

7. Claims 164-167 are objected to as "PNH" should be recited as "paroxysmal nocturnal hemoglobinuria" upon first time usage for clarity.

8. Claim 164-167 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 164-167 are indefinite in the recitation of "wherein the clone is greater than 0.1% / 1% / 10% / 50%" because a referenced control is not indicated.

Applicant is invited to consider amending the claims to include "of the total granulocyte count" as described on page 12, paragraph 4 of the instant specification to obviate this rejection.

Applicant is reminded that the amendment must point to a basis in the specification so as not to add any new matter. See MPEP 714.02 and 2163.06

9. The following is a quotation of the first paragraph of 35 U.S.C. § 112:
The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

10. Claims 164-167 are rejected under 35 U.S.C. § 112, first paragraph, because the specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention.

The instant encompass "determining whether a subject is susceptible to thrombosis" based upon measuring the related clone size of PNH granulocytes" as follows.

164. A method of determining whether a subject having a hemolytic disorder is susceptible to thrombosis comprising measuring the PNH granulocyte clone size of said subject, wherein if the clone size is greater than 0.1% then said subject is susceptible to thrombosis.

165. The method of claim 164, wherein said clone size is greater than 1%.

166. The method of claim 164, wherein said clone size is greater than 10%.

167. The method of claim 164, wherein said clone size is greater than 50%.

Moyo et al. (British Journal of Haematology 126: 133-138, 2004) (1449; #CY) teach studied and evaluated patients with paroxysmal nocturnal hemoglobinuria (PNH) using sensitive and specific diagnostic assays and concluded that their data not only confirmed that the size of PNH clones, including PNH clones as measured in granulocytes, correlates with the risk of thrombosis, but also suggests a correlation of PNH clones to more symptomatic PNH (see entire document, including Abstract, Materials and Methods, Results, including Figures 1-4, and Discussion).

Moyo et al. found a strong association between PNH clones as measured in granulocytes and thrombosis, where the cutoff between the percentage of PNH granulocytes and thrombosis was 61% and the odds ratio for thrombosis was 1:64 for a 10% change in the size of the PNH granulocyte clones (e.g., see Results, particularly, page 135, column 2, paragraphs 1-2).

Such observations would indicate that there is a lack of correlation of measuring the clone size of PNH granulocytes and thrombosis, when the clone size is less than 61% relative to total granulocyte size.

Therefore, there is a lack of predictability of correlating PNH granulocyte size and susceptibility of thrombosis when the clone is 0.1% , 1% , 10% or 50%" as recited in the instant claims.

In turn,, the specification does not enable one of skill in the art, at the time the invention was made, to practice the claimed methods of a lack of correlation of measuring the clone size of PNH granulocytes and thrombosis, when the clone size is less than 61% relative to total granulocyte size.

Also, a medical diagnosis is a process of identifying a medical condition or disease by its signs, symptoms, and from the results of various diagnostic procedures.

Several variables are used in evaluating the predictability of detection or diagnostic assays.

These include diagnostic specificity and sensitivity and positive and negative predictive values.

The sensitivity of an assay reflects the fraction of those subjects with a specific disease that the assay correctly identifies as positive; while the specificity of an assay reflects the fraction of those subjects without the disease that the assay correctly identifies as negative.

The positive predictive value refers to the probability that an individual with a positive test result has the diseases; while the negative predictive value refers to the probability that an individual with a negative test result does not have the disease.

There is an inverse relationship between the sensitivity and specificity, which is related to the assigned cutoff value that is used for a particular test to segregate diseased populations from those with no disease.

In the absence of objective evidence to the contrary and keeping with the lack of predictability of a lack of correlating measuring the clone size of PNH granulocytes and thrombosis, when the clone size is less than 61% relative to total granulocyte size as well as the differences and multiple variables associated with different hemolytic disorders wherein there is a susceptibility to thrombosis encompassed by the claimed methods,

there is insufficient disclosure on how to make and use the claimed methods to a lack of correlate measuring the clone size of PNH granulocytes and thrombosis, when the clone size is less than 61% relative to total granulocyte size.

Given the unpredictability of the art in a lack of correlation of measuring the clone size of PNH granulocytes and thrombosis, when the clone size is less than 61% relative to total granulocyte size,

the experimentation left to those skilled in the art, would be unnecessarily, and improperly, extensive and undue.

In view of the lack of predictability of the art to which the invention pertains the lack of established protocols for correlating susceptibility to thrombosis based upon the presence alone of PNH granulocytes, undue experimentation would be required to practice the claimed methods of diagnosing / determining whether a subject is susceptible to thrombosis by determining PNH granulocytes of 0.1%-50% relative to controls with a reasonable expectation of success, absent a specific and detailed description in applicant's specification of how to effectively practice the claimed methods and absent working examples providing evidence which is reasonably predictive that the claimed methods are effective for determining susceptibility to thrombosis based upon a broad range of PNH granulocyte sizes relative to control encompassed by the claimed methods.

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

A person shall be entitled to a patent unless --

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

12. Claims 164-167 are rejected under 35 U.S.C. § 102(b) as anticipated by Moyo et al. (British Journal of Haematology 126: 133-138, 2004) (1449; #CY) (see entire document).

Moyo et al. teach studied and evaluated patients with paroxysmal nocturnal haemoglobinuria (PNH) using sensitive and specific diagnostic assays and concluded that their data not only confirmed that the size of PNH clones, including PNH clones as measured in granulocytes, correlates with the risk of thrombosis, but also suggests a correlation of PNH clones to more symptomatic PNH (see entire document, including Abstract, Materials and Methods, Results, including Figures 1-4, and Discussion).

Note, too, that Moyo et al. discuss validating the work of others, who showed that large PNH clones are predictive of thrombosis (see Discussion).

While Moyo et al. does not describe "wherein the clone is greater than 0.1% / 1% / 10% / 50%" explicitly,

Moyo et al. found a strong association between PNH clones as measured in granulocytes and thrombosis, where the cutoff between the percentage of PNH granulocytes and thrombosis was 61% and the odds ratio for thrombosis was 1:64 for a 10% change in the size of the PNH granulocyte clones (e.g., see Results, particularly, page 135, column 2, paragraphs 1-2).

These values anticipate the broad ranges encompasss the claimed limitation(s) "wherein the clone is greater than 0.1% / 1% / 10% / 50%".

Regarding the recitation of "identifying a subject having or being at risk of having a condition related to an excessive T cell mediated immune response",

it is noted that this "observing" step or clause does not recite any additional active method steps, but simply states a characterization or conclusion of the results of those steps or may be performed entirely in the human mind is obviously not tied to any machine and does not transform any article into a different state or thing.

Therefore, the "identifying a subject" step or clause simply recites or choosing the intended patient population for the claimed methods taught by the prior art, given the broadest reasonable interpretation of the claims.

13. No claim allowed.

14. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Phillip Gambel whose telephone number is (571) 272-0844. The examiner can normally be reached Monday through Thursday from 7:30 am to 6:00 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla can be reached on (571) 272-0735.

The fax number for the organization where this application or proceeding is assigned is 571-272-8300.

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

/Phillip Gambel/
Primary Examiner
Technology Center 1600
Art Unit 1644
January 18, 2010

UNITED STATES PATENT AND TRADEMARK OFFICE

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
11/595,118	11/08/2006	Leonard Bell	ALXN-P03-114	6763

28120 7590 10/05/2010

ROPES & GRAY LLP
PATENT DOCKETING 39/41
ONE INTERNATIONAL PLACE
BOSTON, MA 02110-2624

EXAMINER	
GAMBEL, PHILLIP	

ART UNIT	PAPER NUMBER
1644	

MAIL DATE	DELIVERY MODE
10/05/2010	PAPER

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

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

Office Action Summary	Application No.	Applicant(s)	
	11/595,118	BELL ET AL.	
	Examiner	Art Unit	
	Phillip Gambel	1644	

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

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *1* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

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

Status

1)☒ Responsive to communication(s) filed on *20 September 2010*.

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

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

Disposition of Claims

4)☒ Claim(s) *1-191* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☐ Claim(s) _____ is/are rejected.

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

8)☒ Claim(s) *1-191* are subject to restriction and/or election requirement.

Application Papers

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

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

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

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

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

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

a)☐ All b)☐ Some * c)☐ None of:

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

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

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

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

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☒ Interview Summary (PTO-413) Paper No(s)/Mail Date. *09/20/2010* .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. Claims 1-191 are pending.

2. On 08/05/2010 and with reminders on 08/30/2010 and 09/20/2010,
Applicant's representative Xuqiong Wu requested that a new Restriction be set forth to clarify the discrepancies between the Restriction mailed 04/03/2009 and the Restriction mailed 07/07/2010 in order to clarify the Groups and the Election of Species.

The examiner agreed to issue a new Restriction to clarify the Groups and the Election of Species.

See attached Interview Summary.

3. The previous Restriction Requirements, mailed 04/03/2009 and 07/07/2010, have been withdrawn

From a review of the specification, it appears that all of the claims are drawn to methods of treating hemolytic diseases, which encompass various symptoms such as hemoglobinuria, anemia, dysphagia, fatigue, erectile dysfunction, recurrent abdominal pain and thrombosis (e.g., see pages 15-16 of the Detailed Description).
Therefore, setting forth the claimed invention in terms of Groups as done previously appears inconsistent with treating hemolytic diseases.

Claims 1-191 are pending and currently under Election of Species set forth herein.

The examiner apologizes for any inconvenience to applicant in this matter/

4. Restriction to one of the following inventions is required under 35 U.S.C. 121:

I. Claim 1-163 and 168-191, drawn to a method of reducing the occurrence of thrombosis in a subject, classified in class 424/130.1 and 514, subclass 2, for example.

From a review of the specification, it appears that all of the claims of this Group are drawn to methods of treating hemolytic diseases, which encompass various symptoms such as hemoglobinuria, anemia, dysphagia, fatigue, erectile dysfunction, recurrent abdominal pain and thrombosis (e.g., see pages 15-16 of the Detailed Description).

In turn, claims 1-163 and 168-191 are subject to an Election of Species set forth herein.

II. Claims 164-167, drawn to a method of determining whether a subject having a hemolytic disorder is susceptible to thrombosis by measuring PNH granulocyte size, classified in Class 435, subclass 7.1.

5. The inventions are distinct, each from the other because of the following reasons:

Inventions I and II are unrelated. Inventions are unrelated if it can be shown that they are not disclosed as capable of use together and they have different designs, modes of operation, and effects (MPEP § 802.01 and § 806.06).

In the instant case, the different inventions are drawn to methods of treatment in Group I and II and the method of diagnosing in Group II rely upon different ingredients, methods steps and endpoints.

The therapeutic / diagnostic methods do not require the practice of one another.

Also, each Group would require a separate search of the literature.

7. Restriction for examination purposes as indicated is proper because all these inventions listed in this action are independent or distinct for the reasons given above and there would be a serious search and examination burden if restriction were not required because one or more of the following reasons apply:

(a) the inventions have acquired a separate status in the art in view of their different classification;
(b) the inventions have acquired a separate status in the art due to their recognized divergent subject matter;
(c) the inventions require a different field of search (for example, searching different classes/subclasses or electronic resources, or employing different search queries);
(d) the prior art applicable to one invention would not likely be applicable to another invention;
(e) the inventions are likely to raise different non-prior art issues under 35 U.S.C. 101 and/or 35 U.S.C. 112, first paragraph.

Applicant is advised that the reply to this requirement to be complete must include (i) an election of a invention to be examined even though the requirement may be traversed (37 CFR 1.143) and (ii) identification of the claims encompassing the elected invention.

The election of an invention may be made with or without traverse. To reserve a right to petition, the election must be made with traverse. If the reply does not distinctly and specifically point out supposed errors in the restriction requirement, the election shall be treated as an election without traverse. Traversal must be presented at the time of election in order to be considered timely. Failure to timely traverse the requirement will result in the loss of right to petition under 37 CFR 1.144. If claims are added after the election, applicant must indicate which of these claims are readable on the elected invention.

If claims are added after the election, applicant must indicate which of these claims are readable upon the elected invention.

Should applicant traverse on the ground that the inventions are not patentably distinct, applicant should submit evidence or identify such evidence now of record showing the inventions to be obvious variants or clearly admit on the record that this is the case. In either instance, if the examiner finds one of the inventions unpatentable over the prior art, the evidence or admission may be used in a rejection under 35 U.S.C. 103(a) of the other invention.

8. Election of Species.

This application is directed to the following species.
A) administering a compound as set forth in claims 2 and 7 for example alone or
B) administering a compound as set forth in claims 2 and 7 for *example in combination with a second compound* as set forth in claim 31 for example.

The species are independent or distinct because claims to the different species recite the mutually exclusive characteristics of such species. In addition, these species are not obvious variants of each other based on the current record.

The species are distinct because they require different methods steps, ingredients and endpoints.

Further, these species of first and second compounds are distinct because their structures, physicochemical properties and modes of action differ action to such an extent and require non-coextensive searches to such an extent that they are considered patentable distinct. Further, these molecules do not share a substantial structural feature essential to a common utility do not have common structure to a common utility. Therefore, they are separate and patentably distinct species.

Applicant is required under 35 U.S.C. § 121 to elect a single disclosed species of (A) or (B) AND elect a specific ultimate species of
a first compound as set forth in (A) *(e.g., anti-C5 antibody or a specific RNA aptamer)* and
a specific ultimate species a second *compound of (B) (e.g., EPO, anti-lymphocyte globulin)* if elected herein
for prosecution on the merits to which the claims shall be restricted if no generic claim is finally held to be allowable.

Applicant is required under 35 U.S.C. 121 to elect a single disclosed species for prosecution on the merits to which the claims shall be restricted if no generic claim is finally held to be allowable. For example, claim 1 is generic.

There is an examination and search burden for these patentably distinct species due to their mutually exclusive characteristics. The species require a different field of search (e.g., searching different classes/subclasses or electronic resources, or employing different search queries); and/or the prior art applicable to one species would not likely be applicable to another species; and/or the species are likely to raise different non-prior art issues under 35 U.S.C. 101 and/or 35 U.S.C. 112, first paragraph.

9. In addition to the election of species from Section 8;
then applicant is required to elect a species from the following.

This application contains claims directed to the following patentably distinct species of the claimed invention by electing a specific hemolytic disease and/or a specific symptom of a hemolytic disease.

From a review of the specification, the only hemolytic disease described appears to be paroxysmal nocturnal hemoglobinuria (PNH).

If other hemolytic diseases are described, then applicant should elected a specific hemolytic disease.

In addition, particularly if the only hemolytic disease described is PNH,
then applicant should elect a specific symptom of a hemolytic disease such as hemoglobinuria, anemia, dysphagia, fatigue, erectile dysfunction, recurrent abdominal pain and thrombosis either claimed or disclosed in the instant specification (e.g., see pages 15-16 of the Detailed Descrption).

Alternatively, if applicant deems that all of the symptoms are inherent or obvious in treating patients with treating hemolytic diseases,
Then this aspect of the election of species may be withdrawn.

At this point, it is not clear whether applicant is treating different diseases or patient populations. Applicant is invited to clarify this issue in the interest of compact prosecution.

The species are independent or distinct because claims to the different species recite the mutually exclusive characteristics of such species. In addition, these species are not obvious variants of each other based on the current record.

These species are distinct because these targeted hemolytic diseases and/or symptoms differ in etiologies and therapeutic endpoints. Therefore, they are separate and patentably distinct species.

Applicant is required under 35 U.S.C. § 121 to elect a single disclosed species *(e.g., PNH if electing a hemolytic disease AND anemia, erectile dysfunction for a symptom)* for prosecution on the merits to which the claims shall be restricted if no generic claim is finally held to be allowable.

There is an examination and search burden for these patentably distinct species due to their mutually exclusive characteristics. The species require a different field of search (e.g., searching different classes/subclasses or electronic resources, or employing different search queries); and/or the prior art applicable to one species would not likely be applicable to another species; and/or the species are likely to raise different non-prior art issues under 35 U.S.C. 101 and/or 35 U.S.C. 112, first paragraph.

10. Applicant is advised that the reply to this requirement to be complete must include (i) an election of a species to be examined even though the requirement may be traversed (37 CFR 1.143) and (ii) identification of the claims encompassing the elected species, including any claims subsequently added. An argument that a claim is allowable or that all claims are generic is considered nonresponsive unless accompanied by an election.

The election of the species may be made with or without traverse. To preserve a right to petition, the election must be made with traverse. If the reply does not distinctly and specifically point out supposed errors in the election of species requirement, the election shall be treated as an election without traverse. Traversal must be presented at the time of election in order to be considered timely. Failure to timely traverse the requirement will result in the loss of right to petition under 37 CFR 1.144. If claims are added after the election, applicant must indicate which of these claims are readable on the elected species.

Should applicant traverse on the ground that the species are not patentably distinct, applicant should submit evidence or identify such evidence now of record showing the species to be obvious variants or clearly admit on the record that this is the case. In either instance, if the examiner finds one of the species unpatentable over the prior art, the evidence or admission may be used in a rejection under 35 U.S.C. 103(a) of the other species.

Upon the allowance of a generic claim, applicant will be entitled to consideration of claims to additional species which depend from or otherwise require all the limitations of an allowable generic claim as provided by 37 CFR 1.141.

11. Applicant is advised that the response to this requirement to be complete must include an election of the invention to be examined even though the requirement be traversed.

12. Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 C.F.R. 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a diligently-filed petition under 37 C.F.R. 1.48(b) and by the fee required under 37 C.F.R. 1.17(h).

13. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Phillip Gambel whose telephone number is (571) 272-0844. The examiner can normally be reached Monday through Thursday from 7:30 am to 6:00 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla can be reached on (571) 272-0735.

The fax number for the organization where this application or proceeding is assigned is 571-273-8300.

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

/Phillip Gambel/
Primary Examiner
Technology Center 1600
Art Unit 1644
September 29, 2010

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
11/595,118	11/08/2006	Leonard Bell	ALXN-P03-114	6763

28120 7590 07/07/2010

ROPES & GRAY LLP
PATENT DOCKETING 39/41
ONE INTERNATIONAL PLACE
BOSTON, MA 02110-2624

EXAMINER	
GAMBEL, PHILLIP	

ART UNIT	PAPER NUMBER
1644	

MAIL DATE	DELIVERY MODE
07/07/2010	PAPER

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

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

Office Action Summary	Application No.	Applicant(s)	
	11/595,118	BELL ET AL.	
	Examiner	Art Unit	
	Phillip Gambel	1644	

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

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *1* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

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

Status

1)☒ Responsive to communication(s) filed on *27 April 2009*.

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

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

Disposition of Claims

4)☒ Claim(s) *1-191* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☐ Claim(s) _____ is/are rejected.

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

8)☒ Claim(s) *1-191* are subject to restriction and/or election requirement.

Application Papers

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

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

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

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

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

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

a)☐ All b)☐ Some * c)☐ None of:

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

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

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

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

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. . The examiner of your application in the PTO has changed. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Technology Center 1600, Art Unit 1644

2. Applicant's Response to Restriction Requirement, filed 04/27/2009, is acknowledged.

However, upon a review of the instant specification, the previous Restriction Requirement, mailed 04/03/2009, has been withdrawn

From a review of the specification, it appears that all of the claims are drawn to methods of treating hemolytic diseases, which encompass various symptoms such as hemoglobinuria, anemia, dysphagia, fatigue, erectile dysfunction, recurrent abdominal pain and thrombosis (e.g., see pages 15-16 of the Detailed Description).

Therefore, setting forth the claimed invention in terms of Groups as done previously appears inconsistent with treating hemolytic diseases.

Claims 1-191 are pending and currently under Election of Species set forth herein.

The examiner apologizes for any inconvenience to applicant in this matter/

3. This application is directed to the following species.
   A) administering a compound as set forth in claims 2 and 7 for example alone or
   B) administering a compound as set forth in claims 2 and 7 for example *in combination with a second compound as set forth in claim 31 for example.*

The species are independent or distinct because claims to the different species recite the mutually exclusive characteristics of such species. In addition, these species are not obvious variants of each other based on the current record.

The species are distinct because they require different methods steps, ingredients and endpoints.

Further, these species of first and second compounds are distinct because their structures, physicochemical properties and modes of action differ action to such an extent and require non-coextensive searches to such an extent that they are considered patentable distinct. Further, these molecules do not share a substantial structural feature essential to a common utility do not have common structure to a common utility. Therefore, they are separate and patentably distinct species.

Applicant is required under 35 U.S.C. § 121 to elect a single disclosed species of (A) or (B) AND elect a specific ultimate species of a first compound as set forth in (A) *(e.g., anti-C5 antibody or a specific RNA aptamer)* and a specific ultimate species a second compound of (B) *(e.g., EPO, antilymphocyte globin)* if elected herein for prosecution on the merits to which the claims shall be restricted if no generic claim is finally held to be allowable.

Applicant is required under 35 U.S.C. 121 to elect a single disclosed species for prosecution on the merits to which the claims shall be restricted if no generic claim is finally held to be allowable. For example, claim 1 is generic.

There is an examination and search burden for these patentably distinct species due to their mutually exclusive characteristics. The species require a different field of search (e.g., searching different classes/subclasses or electronic resources, or employing different search queries); and/or the prior art applicable to one species would not likely be applicable to another species; and/or the species are likely to raise different non-prior art issues under 35 U.S.C. 101 and/or 35 U.S.C. 112, first paragraph.

4. In addition to the election of species from Section 3;
then applicant is required to elect a species from the following.

This application contains claims directed to the following patentably distinct species of the claimed invention by electing a specific hemolytic disease and/or a specific symptom of a hemolytic disease.

From a review of the specification, the only hemolytic disease described appears to be paroxysmal nocturnal hemoglobinuria (PNH).
If other hemolytic diseases are described, then applicant should elected a specific hemolytic disease.

In addition, particularly if the only hemolytic disease described is PNH,
then applicant should elect a specific symptom of a hemolytic disease such as hemoglobinuria, anemia, dysphagia, fatigue, erectile dysfunction, recurrent abdominal pain and thrombosis either claimed or disclosed in the instant specification (e.g., see pages 15-16 of the Detailed Descrption).

Alternatively, if applicant deems that all of the symptoms are inherent or obvious in treating patients with treating hemolytic diseases,
Then this aspect of the election of species may be withdrawn.

At this point, it is not clear whether applicant is treating different diseases or patient populations. Applicant is invited to clarify this issue in the interest of compact prosecution.

The species are independent or distinct because claims to the different species recite the mutually exclusive characteristics of such species. In addition, these species are not obvious variants of each other based on the current record.

These species are distinct because these targeted hemolytic diseases and/or symptoms differ in etiologies and therapeutic endpoints. Therefore, they are separate and patentably distinct species.

Applicant is required under 35 U.S.C. § 121 to elect a single disclosed *species (e.g., PNH if electing a hemolytic disease AND anemia, erectile dysfunction for a symptom)* for prosecution on the merits to which the claims shall be restricted if no generic claim is finally held to be allowable.

There is an examination and search burden for these patentably distinct species due to their mutually exclusive characteristics. The species require a different field of search (e.g., searching different classes/subclasses or electronic resources, or employing different search queries); and/or the prior art applicable to one species would not likely be applicable to another species; and/or the species are likely to raise different non-prior art issues under 35 U.S.C. 101 and/or 35 U.S.C. 112, first paragraph.

5. Applicant is advised that the reply to this requirement to be complete must include (i) an election of a species to be examined even though the requirement may be traversed (37 CFR 1.143) and (ii) identification of the claims encompassing the elected species, including any claims subsequently added. An argument that a claim is allowable or that all claims are generic is considered nonresponsive unless accompanied by an election.

The election of the species may be made with or without traverse. To preserve a right to petition, the election must be made with traverse. If the reply does not distinctly and specifically point out supposed errors in the election of species requirement, the election shall be treated as an election without traverse. Traversal must be presented at the time of election in order to be considered timely. Failure to timely traverse the requirement will result in the loss of right to petition under 37 CFR 1.144. If claims are added after the election, applicant must indicate which of these claims are readable on the elected species.

Should applicant traverse on the ground that the species are not patentably distinct, applicant should submit evidence or identify such evidence now of record showing the species to be obvious variants or clearly admit on the record that this is the case. In either instance, if the examiner finds one of the species unpatentable over the prior art, the evidence or admission may be used in a rejection under 35 U.S.C. 103(a) of the other species.

Upon the allowance of a generic claim, applicant will be entitled to consideration of claims to additional species which depend from or otherwise require all the limitations of an allowable generic claim as provided by 37 CFR 1.141.

6. Applicant is advised that the response to this requirement to be complete must include an election of the invention to be examined even though the requirement be traversed.

7. Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 C.F.R. 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a diligently-filed petition under 37 C.F.R. 1.48(b) and by the fee required under 37 C.F.R. 1.17(h).

8. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Phillip Gambel whose telephone number is (571) 272-0844. The examiner can normally be reached Monday through Thursday from 7:30 am to 6:00 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla can be reached on (571) 272-0735.

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/Phillip Gambel/
Primary Examiner
Technology Center 1600
Art Unit 1644
July 6, 2010

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
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www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
11/595,118	11/08/2006	Leonard Bell	ALXN-P03-114	6763

28120 7590 04/03/2009

ROPES & GRAY LLP
PATENT DOCKETING 39/41
ONE INTERNATIONAL PLACE
BOSTON, MA 02110-2624

EXAMINER	
VANDERVEGT, FRANCOIS P	
ART UNIT	**PAPER NUMBER**
1644	

MAIL DATE	DELIVERY MODE
04/03/2009	PAPER

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

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

Office Action Summary	Application No.	Applicant(s)	
	11/595,118	BELL ET AL.	
	Examiner	Art Unit	
	F. Pierre VanderVegt	1644	

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

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *1* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

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- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

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

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

Disposition of Claims

4)☒ Claim(s) *1-191* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☐ Claim(s) _____ is/are rejected.

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

8)☒ Claim(s) *1-191* are subject to restriction and/or election requirement.

Application Papers

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

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

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

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

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

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

a)☐ All b)☐ Some * c)☐ None of:

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

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

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

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

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

1. Restriction to one of the following inventions is required under 35 U.S.C. 121:

I. Claims 1-163, drawn to a method of reducing the occurrence of thrombosis in a subject, classified in class 514, subclass 2, for example.

II. Claims 164-167, drawn to a method of determining whether a subject having a hemolytic disorder is susceptible to thrombosis by measuring PNH granulocyte size, classified in class 435, subclass 7.1.

III. Claims 168-179, drawn to a method of increasing PNH red blood cell mass in a subject comprising inhibiting complement, classified in class 424, subclass 130.1, for example.

IV. Claims 180-191, drawn to a method for treating hemolytic anemia in a subject comprising inhibiting complement, classified in class 424, subclass 130.1 for example.

The inventions are distinct, each from the other because of the following reasons:

2. Inventions I, III, IV and II are unrelated. Inventions are unrelated if it can be shown that they are not disclosed as capable of use together and they have different designs, modes of operation, and effects (MPEP § 802.01 and § 806.06). In the instant case, the different inventions are drawn to methods of treatment in Groups I, III and IV, while Group II is drawn to a method of diagnosing a hemolytic disorder by measuring the size of the PNH granulocyte population in a subject. The diagnostic method does not require the practice of the treatment method and vice-versa.

3. Inventions I and III and IV are unrelated. Inventions are unrelated if it can be shown that they are not disclosed as capable of use together and they have different designs, modes of operation, and effects (MPEP § 802.01 and § 806.06). In the instant case, the different inventions are drawn to methods for the treatment of different conditions, each of which would require a separate search of the literature.

4. Restriction for examination purposes as indicated is proper because all these inventions listed in this action are independent or distinct for the reasons given above and there would be a serious search and examination burden if restriction were not required because one or more of the following reasons apply:

(a) the inventions have acquired a separate status in the art in view of their different classification;

(b) the inventions have acquired a separate status in the art due to their recognized divergent subject matter;

(c) the inventions require a different field of search (for example, searching different classes/subclasses or electronic resources, or employing different search queries);

(d) the prior art applicable to one invention would not likely be applicable to another invention;

(e) the inventions are likely to raise different non-prior art issues under 35 U.S.C. 101 and/or 35 U.S.C. 112, first paragraph.

Applicant is advised that the reply to this requirement to be complete must include (i) an election of a invention to be examined even though the requirement may be traversed (37 CFR 1.143) **and (ii) identification of the claims encompassing the elected invention**.

The election of an invention may be made with or without traverse. To reserve a right to petition, the election must be made with traverse. If the reply does not distinctly and specifically point out supposed errors in the restriction requirement, the election shall be treated as an election without traverse. Traversal must be presented at the time of election in order to be considered timely. Failure to timely traverse the requirement will result in the loss of right to petition under 37 CFR 1.144. If claims are added after the election, applicant must indicate which of these claims are readable on the elected invention.

If claims are added after the election, applicant must indicate which of these claims are readable upon the elected invention.

Should applicant traverse on the ground that the inventions are not patentably distinct, applicant should submit evidence or identify such evidence now of record showing the inventions to be obvious variants or clearly admit on the record that this is the case. In either instance, if the examiner finds one of the inventions unpatentable over the prior art, the evidence or admission may be used in a rejection under 35 U.S.C. 103(a) of the other invention.

5. **This application contains claims directed to the following patentably distinct species**:

IN GROUP I, there are three species elections required:

Applicant must elect a subject subset for search selected from the group consisting of patients with a higher than normal LDH level (claims 41-122) and patients with lower than normal nitric oxide level (123-163).

Applicant must further elect a complement inhibitor from the compounds enumerated in claims 7 OR 8.

Applicant must further elect a second compound for treatment of a subject selected from a compound that increases hematopoiesis and an anti-thrombotic compound.

6. The species are independent or distinct because claims to the different species recite the mutually exclusive characteristics of such species. In addition, these species are not obvious variants of each other based on the current record.

Should Applicant elect Group I, Applicant is further required under 35 U.S.C. 121 to elect a single disclosed species for prosecution on the merits to which the claims shall be restricted if no generic claim is finally held to be allowable. Currently, claims 11-6, 9-14 and 19-29 are generic.

There is an examination and search burden for these patentably distinct species due to their mutually exclusive characteristics. The species require a different field of search (e.g., searching different classes/subclasses or electronic resources, or employing different search queries); and/or the prior art applicable to one species would not likely be applicable to another species; and/or the species are likely to raise different non-prior art issues under 35 U.S.C. 101 and/or 35 U.S.C. 112, first paragraph.

Applicant is advised that the reply to this requirement to be complete must include (i) an election of a species to be examined even though the requirement may be traversed (37 CFR 1.143) **and (ii) identification of the claims encompassing the elected species**, including any claims subsequently added. An argument that a claim is allowable or that all claims are generic is considered nonresponsive unless accompanied by an election.

The election of the species may be made with or without traverse. To preserve a right to petition, the election must be made with traverse. If the reply does not distinctly and specifically point out supposed errors in the election of species requirement, the election shall be treated as an election without traverse. Traversal must be presented at the time of election in order to be considered timely. Failure to timely traverse the requirement will result in the loss of right to petition under 37 CFR 1.144. If claims are added after the election, applicant must indicate which of these claims are readable on the elected species.

Should applicant traverse on the ground that the species are not patentably distinct, applicant should submit evidence or identify such evidence now of record showing the species to be obvious variants or clearly admit on the record that this is the case. In either instance, if the examiner finds one of the species unpatentable over the prior art, the evidence or admission may be used in a rejection under 35 U.S.C. 103(a) of the other species.

Upon the allowance of a generic claim, applicant will be entitled to consideration of claims to additional species which depend from or otherwise require all the limitations of an allowable generic claim as provided by 37 CFR 1.141.

7. Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 CFR 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a request under 37 CFR 1.48(b) and by the fee required under 37 CFR 1.17(i).

8. Any inquiry concerning this communication or earlier communications from the examiner should be directed to F. Pierre VanderVegt whose telephone number is (571)272-0852. The examiner can normally be reached on M-F 9:00-5:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Eileen O'Hara can be reached on (571) 272-0878. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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F. Pierre VanderVegt, Ph.D. /PV/
Patent Examiner
March 27, 2009

/Eileen B. O'Hara/
Supervisory Patent Examiner
Art Unit 1644

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
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Alexandria, Virginia 22313-1450
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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
12/225,040	05/13/2009	Leonard Bell	ALXN-P04-114	5538

28120 7590 09/22/2011

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EXAMINER	
ROGERS, JAMES L	
ART UNIT	**PAPER NUMBER**
1644	

NOTIFICATION DATE	DELIVERY MODE
09/22/2011	ELECTRONIC

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

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

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

USPatentMail@ropesgray.com
USPatentMail2@ropesgray.com

Office Action Summary	Application No.	Applicant(s)	
	12/225,040	BELL ET AL.	
	Examiner	Art Unit	
	JAMES ROGERS	1644	

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

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

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

Status

1)☒ Responsive to communication(s) filed on *21 July 2011*.

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

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

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

Disposition of Claims

5)☒ Claim(s) *93-108* is/are pending in the application.

5a) Of the above claim(s) *103-108* is/are withdrawn from consideration.

6)☐ Claim(s) _____ is/are allowed.

7)☒ Claim(s) *93-102* is/are rejected.

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

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

Application Papers

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

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

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

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

12)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

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

a)☐ All b)☐ Some * c)☐ None of:

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

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

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

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

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *5/13/2009, 1/20/2010, 9/29/2010, 5/10/2010*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. Claims 93-108 are pending.

2. Applicant's election with traverse of Group I, claims 93-102, drawn to a pharmaceutical composition comprising a single unit dosage form of an anti-C5 antibody or a C5-binding fragment thereof, wherein the single unit dosage form comprises 300 mg of the anti-C5 antibody or C5-binding fragment thereof, and wherein the anti-C5 antibody or C5-binding fragment thereof inhibits cleavage of C5 into fragments C5a and C5b, filed on 07/21/11, is acknowledged.

Applicant's traversal is on the grounds that the cited reference of Hillmen et al. (N Engl J Med 2004; 350: 552-9) cited in the restriction requirement mailed on 6/1/2011 does not disclose or even suggest the instantly claimed pharmaceutical compositions or the use of the claimed compositions for treating patients afflicted with a hemolytic disease and thus Groups I and II are linked by a unifying inventive technical feature.

This argument was not found persuasive for the same reasons in the restriction requirement mailed 6/1/2011 and for the reasons in the obviousness rejection set forth below.

The requirement is still deemed proper and is therefore made FINAL.

3. Claims 103-108 (non-elected Groups II) are withdrawn from further consideration by the Examiner, 37 C.F.R. § 1.142(b) as being drawn to nonelected inventions/species.

4. Claims 93-102 are under consideration in the instant examination as they read on a method of pharmaceutical composition comprising a single unit dosage form of an anti-C5 antibody or a C5-binding fragment thereof, wherein the single unit dosage form comprises 300 mg of the anti-C5 antibody or C5-binding fragment thereof, and wherein the anti-C5 antibody or C5-binding fragment thereof inhibits cleavage of C5 into fragments C5a and C5b.

5. Applicant's IDSs, filed 5/13/2009, 1/20/2010, 9/29/2010 and 5/10/2010, are acknowledged. The foreign patent to Gotze EP0411306A1 listed on the information disclosure statement filed on 5/13/2009 fails to comply with 37 CFR 1.98(a)(3) because it does not include either a translation or a concise explanation of the relevance, as it is presently understood by the individual designated in 37 CFR 1.56(c) most knowledgeable about the content of the information. Applicant is invited to provide a copy of the English translation or a statement of relevance.

The Listed U.S. Patent to Bell et al. (2005/0191298) listed on the information disclosure statement filed on 5/13/2009 does not contain the correct Patent document number.

The reference has been considered by the examiner and the correct patent document number listed on the attached Form 892.

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The non-patent literature document, Hillmen et al., listed on the information disclosure statement filed 9/29/2010 fails to comply with 37 CFR 1.98(a)(2), which requires a legible copy of the non-patent literature publication or that portion which caused it to be listed; and all other information or that portion which caused it to be listed. Applicant is invited to provide a copy of the reference to the examiner.

6. The first line of the specification should be amended to reflect that the current application is a national stage application of PCT/US07/06606 which claims priority to US provisional application 60/783/070.

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

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

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

8. Claims 93, 95-97, and 99-100 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hillmen et al., (N Engl J Med 2004; 350: 552-9, IDS Ref of 5/13/09).

Hillmen et al. teaches a pharmaceutical composition comprising eculizumab (anti-C5 monoclonal antibody) which was administered to patients with PNH at 600 mg every week for four weeks, followed one week later by a 900-mg dose and then by 900 mg every other week through week 12. Hillmen et al. further discloses that the anti-C5 antibody binds specifically to the terminal complement protein C5, inhibiting its cleavage into C5a and C5b (p. 553, 3rd ¶)

Hillmen et al. differs from the claimed invention by not expressly reciting a single unit dosage form of 300 mg of the anti-C5 antibody, that the single unit dosage form has a volume of 30 mL and that the single unit dosage form comprises a 10 mg/mL solution of the anti-C5 antibody.

While the prior art reference is silent with respect to the limitations that the pharmaceutical composition comprise a single unit dosage form of 300 mg, that the single unit dosage form has a volume of 30 mL (claim 96) and comprises a 10 mg/mL solution of the anti-C5 antibody or C5-binding fragment thereof (claim 97), it has been held that where the general conditions of a claim are disclosed in the prior art, discovering the optimum or workable ranges involves only routine skill in the art. In re Aller, 220 F2d 454, 456, 105 USPQ 233; 235 (CCPA 1955). See MPE §§2144.05 part IIA.

In the instant case, given that Hillmen et al. teaches administration of a 600 mg and 900 mg doses which can both be obtained simply by administering two or three separate single unit dosage forms of 300 mg of the instant claimed invention, respectively, the claimed dosage forms are simply a matter of convenience based upon the needs of the patient and involves only routine skill in the art. Accordingly, it would have been obvious to one of ordinary skill in the art at the time Applicants' invention was made to supply the anti-C5 antibody or C5-binding fragment thereof in a composition comprising 300 mg single unit dosages as well as said dosages in a volume of 30 mL (i.e., 10 mg/mL).

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

9. Claims 101-102 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hillmen et al., (N Engl J Med 2004; 350: 552-9, IDS Ref of 5/13/09), as applied to claims 93, 95-97 and 99-100 above, in view of Kaplan (Curr. Opin. Investig. Drugs, 3(7): 1017-23 (2002), IDS Ref of 5/13/09).

The teachings of Hillmen et al. have been discussed supra.

Hillmen et al. differs from the claimed invention by not reciting a C5-binding fragment which is pexelizumab.

Kaplan teaches the humanized single chain anti-C5 monoclonal antibody fragment, pexeizumab (p. 1018, 4th ¶) which was designed to have the advantage of enhanced tissue penetration.

Those of skill in the art would have had reason to use the anti-C5 binding fragment pexelizumab as a substitute for the anti-C5 antibody eculizumab in the administration to patients with PNH as taught by Hillmen et al. because Kaplan teaches that the antibody fragment has the advantage of enhanced tissue penetration. Substituting a known

element for another, to yield the known result, is obvious. See KSR, 550 U.S. at 416, 421.

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

10. Claim 94 is rejected under 35 U.S.C. 103(a) as being unpatentable over Hillmen et al., (N Engl J Med 2004; 350: 552-9, IDS Ref of 5/13/09), as applied to claims 93, 95-97 and 99-100 above, and further in view of Tang et al. (Pharmaceutical Research, 21(2) (2004)).

The teachings of Hillmen et al. have been discussed supra.

Hillmen et al. differs from the claimed invention by not reciting that the pharmaceutical composition is lyophilized (claim 94).

Tang et al. teaches that lyophilization, also known as "freeze drying", is widely used for pharmaceuticals to improve the stability and long term storage stability of labile drugs, especially protein drugs (p. 191, 1st ¶).

It would have been obvious to one of ordinary skill in the art at the time Applicants' invention was made to combine the lyophilization procedure taught by Tang et al. with the anti-C5 antibody composition taught by Hillmen et al. One skilled in the art would be motivated to provide the single unit dosage form of anti-C5 antibody or a C5 binding fragment thereof in lyophilized form because Tang et al. teaches that lyophilization is commonly used to improve the stability and long term storage stability of labile drugs, especially protein drugs.

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

11. Claim 98 is rejected under 35 U.S.C. 103(a) as being unpatentable over Hillmen et al., (N Engl J Med 2004; 350: 552-9, IDS Ref of 5/13/09), as applied to claims 93, 95-97 and 99-100 above, and further in view of Garcia et al. (Biologicals (2002) 30, 143-151).

The teachings of Hillmen et al. have been discussed supra.

Hillmen et al. differs from the claimed invention by not reciting that the pharmaceutical composition is a preservative free formulation (claim 98).

Garci et al. teaches that the influence of preservatives on the safety and stability of antivenoms may be involved in adverse reactions to antivenoms and is an issue that deserves careful consideration (p. 144, 2nd ¶; p. 149, last ¶).

It would have been obvious to one of ordinary skill in the art at the time Applicants' invention was made to provide the composition taught by Hillmen et al. in a preservative free formulation. One skilled in the art would be motivated to provide the composition in a preservative free formulation because Garci et al. teaches that the presence of preservatives can be an important safety issue in that they may lead to adverse reactions when present in antibody compositions such as antivenoms.

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

12. No claim is allowed.

13. Any inquiry concerning this communication or earlier communications from the examiner should be directed to James Rogers whose telephone number is (571) 270-5374. The examiner can normally be reached Monday through Friday from 8:00 am to 5:30 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, **Ram Shukla** can be reached on (571) 272-0735. The fax number for the organization where this application or proceeding is assigned is 571-273-8300.

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

September 14, 2011

/JAMES ROGERS/
Examiner, Art Unit 1644

/Maher M. Haddad/
Primary Examiner, Art Unit 1644

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28120 7590 06/01/2011

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EXAMINER	
ROGERS, JAMES L	
ART UNIT	**PAPER NUMBER**
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NOTIFICATION DATE	DELIVERY MODE
06/01/2011	ELECTRONIC

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USPatentMail2@ropesgray.com

Office Action Summary	Application No.	Applicant(s)
	12/225,040	BELL ET AL.
	Examiner	Art Unit
	JAMES ROGERS	1644

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Period for Reply

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

Status

1)☒ Responsive to communication(s) filed on *10 May 2011*.

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

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

Disposition of Claims

4)☒ Claim(s) *93-108* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☐ Claim(s) _____ is/are rejected.

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

8)☒ Claim(s) *93-108* are subject to restriction and/or election requirement.

Application Papers

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

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

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

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

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

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

a)☐ All b)☐ Some * c)☐ None of:

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

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

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

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

Attachment(s)	
1) ☒ Notice of References Cited (PTO-892)	4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)	5) ☐ Notice of Informal Patent Application
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.	6) ☐ Other: _____.

DETAILED ACTION

1. Applicant's preliminary amendment, filed on May 10, 2011, is acknowledged. Claims 93-108 are pending and being acted upon presently.

Election/Restrictions

2. Restriction is required under 35 USC 121 and 372. This application contains the following inventions or groups of inventions which are not so linked as to form a single general inventive concept under PCT Rule 13.1.

3. In accordance with 37 CFR 1.499, applicant is required, in reply to this action, to elect a single invention to which the claims must be restricted.

I. Claims 93-102, drawn to a pharmaceutical composition comprising a single unit dosage form of an anti-C5 antibody or a C5-binding fragment thereof, wherein the single unit dosage form comprises 300 mg of the anti-C5 antibody or C5-binding fragment thereof, and wherein the anti-C5 antibody or C5-binding fragment thereof inhibits cleavage of C5 into fragments C5a and C5b.

II. Claims 103-108, drawn to a method for treating a patient afflicted with a hemolytic disease, the method comprising administering to the patient a pharmaceutical composition comprising a single unit dosage form of an anti-C5 antibody or a C5-binding fragment thereof, wherein the single unit dosage form comprises 300 mg of the anti-C5 antibody or C5-binding fragment thereof, and wherein the anti-C5 antibody or C5-binding fragment thereof inhibits cleavage of C5 into fragments C5a and C5b, in an amount and with a frequency effective to treat the hemolytic disease.

4. The inventions listed as Groups I-II do not relate to a single general inventive concept under PCT Rule 13.1, because under PCT Rule 132, they lack the same or corresponding special technical features for the following reasons:

The invention of Group II was found to have no special technical feature that defined the contribution over the prior art of Hillmen et al.: "Effect of Eculizumab on Hemolysis and Transfusion Requirements in Patients with Paroxysmal Nocturnal Hemoglobinuria" N Engl J Med 2004; 350: 552-9.

Hillmen et al. teaches treating patients with a hemolytic disease with infusions of eculizumab (600 mg) every week for four weeks, followed one week later by a 900-mg dose and then by 900 mg every other week through week 12 (Abstract).

Since Applicant's inventions do not contribute a special technical feature when viewed over the prior art they do not have a single general inventive concept and so lack unity of invention.

5. Applicant is advised that the reply to this requirement to be complete must include (i) an election of an invention to be examined even though the requirement may be traversed (37 CFR 1.143)**.**

6. The examiner has required restriction between product and process claims. Where applicant elects claims directed to the product, and the product claims are subsequently found allowable, withdrawn process claims that depend from or otherwise require all the limitations of the allowable product claim will be considered for rejoinder. All claims directed a nonelected process invention must require all the limitations of an allowable product claim for that process invention to be rejoined.

In the event of rejoinder, the requirement for restriction between the product claims and the rejoined process claims will be withdrawn, and the rejoined process claims will be fully examined for patentability in accordance with 37 CFR 1.104. Thus, to be allowable, the rejoined claims must meet all criteria for patentability including the requirements of 35 U.S.C. 101, 102, 103 and 112. Until all claims to the elected product are found allowable, an otherwise proper restriction requirement between product claims and process claims may be maintained. Withdrawn process claims that are not commensurate in scope with an allowable product claim will not be rejoined. See MPEP § 821.04(b). Additionally, in order to retain the right to rejoinder in accordance with the above policy, applicant is advised that the process claims should be amended during prosecution to require the limitations of the product claims. **Failure to do so may result in a loss of the right to rejoinder**. Further, note that the prohibition against double patenting rejections of 35 U.S.C. 121 does not apply where the restriction requirement is withdrawn by the examiner before the patent issues. See MPEP § 804.01.

7. Any inquiry concerning this communication or earlier communications from the examiner should be directed to James Rogers whose telephone number is (571) 270-5374. The examiner can normally be reached Monday through Friday from 8:00 am to 5:30 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla can be reached on (571) 272-0735. The fax number for the organization where this application or proceeding is assigned is 571-273-8300.

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May 24, 2011

/JAMES ROGERS/
Examiner, Art Unit 1644

/Maher M. Haddad/
Primary Examiner,
Art Unit 1644

UNITED STATES PATENT AND TRADEMARK OFFICE

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Status

1)☒ Responsive to communication(s) filed on *12 September 2008*.

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

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

Disposition of Claims

4)☒ Claim(s) *1-25, 44, 68-92* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☐ Claim(s) _____ is/are rejected.

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

8)☒ Claim(s) *1-25, 44, 68-92* are subject to restriction and/or election requirement.

Application Papers

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

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

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Priority under 35 U.S.C. § 119

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

a)☒ All b)☐ Some * c)☐ None of:

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

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

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. Applicant's preliminary amendment, filed on September 12, 2008, is acknowledged.

Claims 1-25, 44, and 68-92 are pending and being acted upon presently.

Species Election

2. Applicant is required under 35 US 121 (1) to elect a single disclosed species to which claims would be restricted if no generic claim is finally held to be allowable and (2) to list all claims readable thereon including those subsequently added.

A. Applicant is required to elect a particular assay for quality of life (e.g., FACIT-Fatigue score or EORTC QLQ-C30 score) such as one recited in claims 2 and 5. These species are distinct because the assays differ with respect to ingredients, method steps, and endpoints; thus each assay patentably distinct subject matter.

(i) If Applicant elects EORTC QLQ-C30 as an assay for quality of life, applicant is further required to elect a particular aspect of quality of life (e.g., global health status or insomnia) such as one recited in claims 7 and 8. These species are distinct because the pathological conditions differ in etiologies and therapeutic endpoints; thus each condition represents patentably distinct subject matter.

B. Applicant is required to elect a particular compound (e.g., CR1, K76 COOH, steroid, or antibody which blocks C5 cleavage) such as one recited in claims 9-17 and 80-85. These are distinct species because their structures and modes of action are different which, in turn, address different therapeutic endpoints.

C. Applicant is required to elect a particular type of disease (e.g., aplastic anemia, myelodysplastic syndrome, or paroxysmal nocturnal hemoglobinuria) such as one recited in claims 18, 74 and 90. These species are distinct because the pathological conditions differ in etiologies and therapeutic endpoints; thus each condition represents patentably distinct subject matter.

D. Applicant is required to elect a particular assay for health-adjusted life expectancy (e.g., Years of potential life lost or Years of healthy life) such as one recited in claim 75. These species are distinct because the pathological conditions differ in etiologies and therapeutic endpoints; thus each condition represents patentably distinct subject matter.

3. Applicant is required under 35 U.S.C. 121 to elect a single disclosed species for prosecution on the merits to which the claims shall be restricted if no generic claim is finally held to be allowable.

There is an examination and search burden for these patentably distinct species due to their mutually exclusive characteristics. The species require a different field of search (e.g., searching different classes/subclasses or electronic resources, or employing different search queries); and/or the prior art applicable to one species would not likely be applicable to another species; and/or the species are likely to raise different non-prior art issues under 35 U.S.C. 101 and/or 35 U.S.C. 112, first paragraph.

Applicant is advised that the reply to this requirement to be complete must include (i) an election of a species to be examined even though the requirement may be traversed (37 CFR 1.143) **and (ii) identification of the claims encompassing the elected species,** including any claims subsequently added. An argument that a claim is allowable or that all claims are generic is considered nonresponsive unless accompanied by an election.

The election of the species may be made with or without traverse. To preserve a right to petition, the election must be made with traverse. If the reply does not distinctly and specifically point out supposed errors in the election of species requirement, the election shall be treated as an election without traverse. Traversal must be presented at the time of election in order to be considered timely. Failure to timely traverse the requirement will result in the loss of right to petition under 37 CFR 1.144. If claims are added after the election, applicant must indicate which of these claims are readable on the elected species.

Should applicant traverse on the ground that the species are not patentably distinct, applicant should submit evidence or identify such evidence now of record showing the species to be obvious variants or clearly admit on the record that this is the case. In either instance, if the examiner finds one of the species unpatentable over the prior art, the evidence or admission may be used in a rejection under 35 U.S.C. 103(a) of the other species.

Upon the allowance of a generic claim, applicant will be entitled to consideration of claims to additional species which depend from or otherwise require all the limitations of an allowable generic claim as provided by 37 CFR 1.141.

4. Any inquiry concerning this communication or earlier communications from the examiner should be directed to James Rogers whose telephone number is (571) 270-5374. The examiner can normally be reached Monday through Friday from 8:00 am to 5:30 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla can be reached on (571) 272-0735. The fax number for the organization where this application or proceeding is assigned is 571-273-8300.

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

April 4, 2011

/JAMES ROGERS/
Examiner, Art Unit 1644

/Maher M. Haddad/
Primary Examiner, Art Unit 1644

UNITED STATES PATENT AND TRADEMARK OFFICE

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
12/621,792	11/19/2009	Leonard Bell	ALXN-P05-114	3142

28120 7590 09/30/2010

ROPES & GRAY LLP
PATENT DOCKETING 39/41
ONE INTERNATIONAL PLACE
BOSTON, MA 02110-2624

EXAMINER	
GAMBEL, PHILLIP	

ART UNIT	PAPER NUMBER
1644	

MAIL DATE	DELIVERY MODE
09/30/2010	PAPER

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

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

Office Action Summary	Application No.	Applicant(s)	
	12/621,792	BELL ET AL.	
	Examiner	Art Unit	
	Phillip Gambel	1644	

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

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

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

Status

1)☒ Responsive to communication(s) filed on *11/19/2009, 09/01/2010*.

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

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

Disposition of Claims

4)☒ Claim(s) *72-84* is/are pending in the application.

4a) Of the above claim(s) *75* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *72-74, 76-84* is/are rejected.

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

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

Application Papers

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

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

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

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

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

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

a)☐ All b)☐ Some * c)☐ None of:

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

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

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

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

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *01/21/2010*.
4) ☒ Interview Summary (PTO-413) Paper No(s)/Mail Date. *09/01/2010* .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. Applicant's amendment, filed 11/19/2009, has been entered
Claims 1-71 and 85-171 have been canceled.

Claims 72-84 are pending.

2. This application is directed to the following species of administering a "compound" as set forth in claims 73 and 74 or as disclosed on pages 11-16 of the specification.

The species are independent or distinct because claims to the different species recite the mutually exclusive characteristics of such species. In addition, these species are not obvious variants of each other based on the current record.

These species of "compounds" are distinct because their structures, physicochemical properties and modes of action differ action to such an extent and require non-coextensive searches to such an extent that they are considered patentable distinct. Further, these "compounds" do not share a substantial structural feature essential to a common utility do not have common structure to a common utility. Therefore, they are separate and patentably distinct species.

Applicant is required under 35 U.S.C. § 121 to elect a single disclosed species of "compound" (e.g., *anti-C5 antibody or anti-C5a receptor antibody)* if elected herein for prosecution on the merits to which the claims shall be restricted if no generic claim is finally held to be allowable.

Applicant is required under 35 U.S.C. 121 to elect a single disclosed species for prosecution on the merits to which the claims shall be restricted if no generic claim is finally held to be allowable. For example, claim 72 is generic.

There is an examination and search burden for these patentably distinct species due to their mutually exclusive characteristics. The species require a different field of search (e.g., searching different classes/subclasses or electronic resources, or employing different search queries); and/or the prior art applicable to one species would not likely be applicable to another species; and/or the species are likely to raise different non-prior art issues under 35 U.S.C. 101 and/or 35 U.S.C. 112, first paragraph.

3. Applicant is advised that the reply to this requirement to be complete must include (i) an election of a species to be examined even though the requirement may be traversed (37 CFR 1.143) and (ii) identification of the claims encompassing the elected species, including any claims subsequently added. An argument that a claim is allowable or that all claims are generic is considered nonresponsive unless accompanied by an election.

The election of the species may be made with or without traverse. To preserve a right to petition, the election must be made with traverse. If the reply does not distinctly and specifically point out supposed errors in the election of species requirement, the election shall be treated as an election without traverse. Traversal must be presented at the time of election in order to be considered timely. Failure to timely traverse the requirement will result in the loss of right to petition under 37 CFR 1.144. If claims are added after the election, applicant must indicate which of these claims are readable on the elected species.

Should applicant traverse on the ground that the species are not patentably distinct, applicant should submit evidence or identify such evidence now of record showing the species to be obvious variants or clearly admit on the record that this is the case. In either instance, if the examiner finds one of the species unpatentable over the prior art, the evidence or admission may be used in a rejection under 35 U.S.C. 103(a) of the other species.

Upon the allowance of a generic claim, applicant will be entitled to consideration of claims to additional species which depend from or otherwise require all the limitations of an allowable generic claim as provided by 37 CFR 1.141.

4. During a telephone conversation with Ryan Murphey on 09/01/2010, a provisional election was made with traverse to prosecute the species of "anti-C5a antibodies".

Affirmation of this election must be made by applicant in responding to this Office action.

Claims 72-74 and 76-84 are under consideration as they read on the elected species.

Claim 75 has been withdrawn from consideration as being drawn to a non-elected species.

5. Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 C.F.R. 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a diligently-filed petition under 37 C.F.R. 1.48(b) and by the fee required under 37 C.F.R. 1.17(h).

6. The title of the invention is not descriptive. A new title is required that is clearly indicative of the invention to which the claims are directed. Applicant should restrict the title to the claimed invention.

7. The application is required to be reviewed and all spelling, TRADEMARKS, and like errors corrected. Appropriate corrections are required.

Trademarks should be capitalized or accompanied by the ® or ™ symbol wherever they appear and be accompanied by the generic terminology. Although the use of trademarks is permissible in patent applications, the proprietary nature of the trademarks should be respected and every effort made to prevent their use in any manner, which might adversely affect their validity as trademarks.

Appropriate corrections are required

8. Claim 74 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 74 is indefinite in the recitation of "functional fragment of h5G1.1" in that while applicant's intent may be directed to "antigen-binding fragments thereof / C5-binding fragments thereof", the claims are no so limited and can read on any fragment.

For example, immunoglobulin Fc fragments comprised immunoglobulin effector function capabilities and often employed in therapeutic agents; however this does not appear to be applicant's intent for the claimed invention herein.

The claim is indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Applicant is invited to amend the claims to recite the appropriate "fragments thereof".

9. The following is a quotation of the first paragraph of 35 U.S.C. § 112:
The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

10. Claim 74: h5G1.1.

It is apparent that h5G1.1 antibody is required to practice the claimed invention. As a required element, it must be known and readily available to the public or obtainable by a repeatable method set forth in the specification. If it is not so obtainable or available, the enablement requirements of 35 USC 112, first paragraph, may be satisfied by a deposit of the pertinent cell line / hybridoma which produce this antibody. See 37 CFR 1.801-1.809.

Given the disclosure on pages 17-18 of the instant specification and the claims of U.S. Patent 6,355,245 (1449) encompassing the instant 5G1.1 antibody produced by the hybridoma designated ATCC HB 11625; the conditions for the deposit of biological materials under 35 USC 112, first paragraph, with respect to h5G1.1 has been satisfied.

Note that Kaplan (Curr. Opin. Investig. Drugs 3: 1017-1023, 2002) (1449) indicates that 5G1.1 and 5G1.1 are synonyms (see entire document, including page box on the top of page 1017, column 2).

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

A person shall be entitled to a patent unless --

(a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

(e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

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

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

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

13. Claims 72-74 and 76-84 are rejected under 35 U.S.C. § 102(a) as being anticipated by Hillmen et al. (Blood 102: 1858, 2003) (1449) (see entire document)
and in further evidence by Kaplan (Curr. Opin. Investig. Drugs 3: 1017-1023, 2002) (1449).

Hillmen et al. teach methods of treating paroxysmal nocturnal hemoglobulinuria (PNH), intravascular hemolysis and venous thrombosis, with an anti-C5 antibody (eculizumab) and in certain instances with erythropoietin as well, including improvement in biochemical / biological parameters associated with LDH and PNH type III cells (see entire document).

Eculizumab is derived from the h5G1.1 anti-C5 antibody, as evidenced by Kaplan.
Although the reference is silent about certain specific claimed limitations per se of a patient having paroxysmal nocturnal hemoglobulnuria (PNH) (e.g., see claims 76-84),
it does not appear that the claim language or limitations result in a manipulative difference in the method steps when compared to the prior art disclosure. See Bristol-Myers Squibb Company v. Ben Venue Laboratories 58 USPQ2d 1508 (CAFC 2001). "{i}t is a general rule that merely discovering and claiming a new benefit of an old process cannot render the process again patentable". In re Woodruff, 16 USPQ2d 1934, 1936 (Fed. Cir. 1990). The mechanism of action does not have a bearing on the patentability of the invention if the invention was already known or obvious. Mere recognition of latent properties in the prior art does not render nonobvious an otherwise known invention. In re Wiseman, 201 USPQ 658 (CCPA 1979). Granting a patent on the discovery of an unknown but inherent function would remove from the public that which is in the public domain by virtue of its inclusion in, or obviousness from, the prior art. In re Baxter Travenol Labs, 21 USPQ2d 1281 (Fed. Cir. 1991). See M.P.E.P. 2145.

On this record, it is reasonable to conclude that the same PNH patients are being administered the active agent anti-C5 antibodies by the same mode of administration in the same amount to achieve the same or nearly the same improvement in biochemical and biological parameters (e.g., reticulocyte numbers and PNH type III cells) in both the instant claims and the prior art reference. The fact that applicant may have discovered yet another beneficial effect from the method set forth in the prior art does not mean that they are entitled to receive a patent on that method.

Applicant is reminded that no more of the reference is required than that it sets forth the substance of the invention. The claimed functional limitations would be inherent properties of the referenced methods to administer anti-C5 antibodies to treat PNH patients.

14. Claims 72-74 and 76-84 are rejected under 35 U.S.C. § 102(b) as being anticipated by Alexion Pharmaceuticals Signs Agreement with Lonza Biologics for Commercial Manufacturing (01/06/2003) (1449) (see entire document)
and in further evidence by Kaplan (Curr. Opin. Investig. Drugs 3: 1017-1023, 2002) (1449).

Alexion Pharmaceuticals Signs Agreement with Lonza Biologics For Commercial Manufacturing describes the commercial manufacture, commercialization and clinical studies of evaluating and treating patients with paroxysmal nocturnal hemoglobinuria with eculizumab, an antibody that binds C5.

Note, too, that Alexion is treating patents with coronary artery bypass graft surgery patients undergoing cardiopulmonary bypass as well as patients with acute myocardial infarction patients with pexelizumab, a single chain antibody that binds C5.

Both eculizumab and pexelizumab are derived from the h5G1.1 anti-C5 antibody, as evidenced by Kaplan.

Although the reference is silent about certain specific claimed limitations per se of a patient having paroxysmal nocturnal hemoglobinuria (PNH) (e.g., see claims 76-84),
it does not appear that the claim language or limitations result in a manipulative difference in the method steps when compared to the prior art disclosure. See Bristol-Myers Squibb Company v. Ben Venue Laboratories 58 USPQ2d 1508 (CAFC 2001). "{i}t is a general rule that merely discovering and claiming a new benefit of an old process cannot render the process again patentable". In re Woodruff, 16 USPQ2d 1934, 1936 (Fed. Cir. 1990). The mechanism of action does not have a bearing on the patentability of the invention if the invention was already known or obvious. Mere recognition of latent properties in the prior art does not render nonobvious an otherwise known invention. In re Wiseman, 201 USPQ 658 (CCPA 1979). Granting a patent on the discovery of an unknown but inherent function would remove from the public that which is in the public domain by virtue of its inclusion in, or obviousness from, the prior art. In re Baxter Travenol Labs, 21 USPQ2d 1281 (Fed. Cir. 1991). See M.P.E.P. 2145.

On this record, it is reasonable to conclude that the same PNH patients are being administered the active agent anti-C5 antibodies by the same mode of administration in the same amount to achieve the same or nearly the same improvement in biochemical and biological parameters (e.g., platelet counts, reticulocyte counts and PNH type III cells) in both the instant claims and the prior art reference. The fact that applicant may have discovered yet another beneficial effect from the method set forth in the prior art does not mean that they are entitled to receive a patent on that method.

Applicant is reminded that no more of the reference is required than that it sets forth the substance of the invention. The claimed functional limitations would be inherent properties of the referenced methods to administer anti-C5 antibodies to treat PNH patients.

15. Claims 72-74 and 76-84 are rejected under 35 U.S.C. § 102(b) as being anticipated by Alexion Announces Results of Clinical Trial in Paroxysmal Nocturnal Hemoglobinuria Presented at the American Society of Hematology Annual Meeting (12/02/2002) (1449) (see entire document)
and in further evidence by Kaplan (Curr. Opin. Investig. Drugs 3: 1017-1023, 2002) (1449).

Alexion Announces Results of Clinical Trail in Paroxysmal Nocturnal Hemoglobinuria Presented at the American Society of Hematology Annual Meeting describes the use of eculizumab in the treatment of patients with paroxysmal nocturnal hemoglobinuria (PNH), showing a reduction in biochemical parameters of hemolysis, including the increase of Type III PNH red blood cells. Also, this announcement describes the complications of deficiencies of other blood cell types and inappropriate blood clotting known as thrombosis in patients with PNH.

Eculizumab is derived from the h5G1.1 anti-C5 antibody, as evidenced by Kaplan.

Although the reference is silent or not specific about certain specific claimed limitations per se of a patient having paroxysmal nocturnal hemoglobinuria (PNH) (e.g., see claims 76-84),
it does not appear that the claim language or limitations result in a manipulative difference in the method steps when compared to the prior art disclosure. See Bristol-Myers Squibb Company v. Ben Venue Laboratories 58 USPQ2d 1508 (CAFC 2001). "{i}t is a general rule that merely discovering and claiming a new benefit of an old process cannot render the process again patentable". In re Woodruff, 16 USPQ2d 1934, 1936 (Fed. Cir. 1990). The mechanism of action does not have a bearing on the patentability of the invention if the invention was already known or obvious. Mere recognition of latent properties in the prior art does not render nonobvious an otherwise known invention. In re Wiseman, 201 USPQ 658 (CCPA 1979). Granting a patent on the discovery of an unknown but inherent function would remove from the public that which is in the public domain by virtue of its inclusion in, or obviousness from, the prior art. In re Baxter Travenol Labs, 21 USPQ2d 1281 (Fed. Cir. 1991). See M.P.E.P. 2145.

On this record, it is reasonable to conclude that the same PNH patients are being administered the active agent anti-C5 antibodies by the same mode of administration in the same amount to achieve the same or nearly the same improvement in biochemical and biological parameters (e.g., platelet counts, reticulocyte counts and PNH type III cells) in both the instant claims and the prior art reference. The fact that applicant may have discovered yet another beneficial effect from the method set forth in the prior art does not mean that they are entitled to receive a patent on that method.

Applicant is reminded that no more of the reference is required than that it sets forth the substance of the invention. The claimed functional limitations would be inherent properties of the referenced methods to administer anti-C5 antibodies to treat PNH patients.

16. Claims 72-74 are rejected under 35 U.S.C. § 102(e) as being anticipated by Bell (U.S. Patent No. 7,361,339) (see entire document)
and in further evidence by Kaplan (Curr. Opin. Investig. Drugs 3: 1017-1023, 2002) (1449).

Bell teaches and claims methods of treat acute myocardial infarction, including reducing the mortality of patients as well as treating patients in connection with angioplasty with anti-C5 antibodies, including h5G1.1 anti-C5 antibodies (see entire document, including Background, Summary and Detailed Description of Preferred Embodiments and Claims).
Note that Bell describes the advent of thrombolysis and angioplasty to restore blood flow and the role of complement activation in the formation of pro-thrombotic microparticles in the Background of the Invention (e.g., see column 1, paragraph 3 and column 2, paragraph 1)

Eculizumab is derived from the h5G1.1 anti-C5 antibody, as evidenced by Kaplan.

Although the reference is not specific about reducing thrombosis per se,
it does not appear that the claim language or limitations result in a manipulative difference in the method steps when compared to the prior art disclosure. See Bristol-Myers Squibb Company v. Ben Venue Laboratories 58 USPQ2d 1508 (CAFC 2001). "{i}t is a general rule that merely discovering and claiming a new benefit of an old process cannot render the process again patentable". In re Woodruff, 16 USPQ2d 1934, 1936 (Fed. Cir. 1990). The mechanism of action does not have a bearing on the patentability of the invention if the invention was already known or obvious. Mere recognition of latent properties in the prior art does not render nonobvious an otherwise known invention. In re Wiseman, 201 USPQ 658 (CCPA 1979). Granting a patent on the discovery of an unknown but inherent function would remove from the public that which is in the public domain by virtue of its inclusion in, or obviousness from, the prior art. In re Baxter Travenol Labs, 21 USPQ2d 1281 (Fed. Cir. 1991). See M.P.E.P. 2145.

On this record, it is reasonable to conclude that the same patients with thrombotic conditions are being administered the active agent anti-C5 antibodies by the same mode of administration in the same amount to achieve the same or nearly the same improvement in biochemical and biological parameters associated with myocardial infarction in both the instant claims and the prior art reference. The fact that applicant may have discovered yet another beneficial effect from the method set forth in the prior art does not mean that they are entitled to receive a patent on that method.

Applicant is reminded that no more of the reference is required than that it sets forth the substance of the invention. The claimed functional limitations would be inherent properties of the referenced methods to administer anti-C5 antibodies to treat patients with myocardial infarction undergoing angioplasty.

17. Claims 72-74 and 76-84 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Hillmen et al. (Blood 102: 1858, 2003) (1449) AND/OR Alexion Announces Results of Clinical Trial in Paroxysmal Nocturnal Hemoglobinuria Presented at the American Society of ematology Annual Meeting (12/02/2002) (1449) in view of Meyers et al. (Int. J. Hematol. 77: 125-132, 2003) and Evans et al. (U.S. Patent No. 6,355,245) and in further evidence by Kaplan (Curr. Opin. Investig. Drugs 3: 1017-1023, 2002) (1449).

Hillmen et al. (2003) teach methods of treating paroxysmal nocturnal hemoglobulinuria (PNH), which is characterized by intravascular hemolysis and venous thrombosis with an anti-C5 antibody and in certain instances with erythropoietin as well, including improvement in biochemical / biological parameters associated with LDH and PNH type III cells (see entire document).

Alexion Announces Results of Clinical Trail in Paroxysmal Nocturnal Hemoglobinuria Presented at the American Society of Hematology Annual Meeting describes the use of eculizumab in the treatment of patients with paroxysmal nocturnal hemoglobinuria (PNH), showing a reduction in biochemical parameters of hemolysis, including the increase of Type III PNH red blood cells. Also, this announcement describes the complications of deficiencies of other blood cell types and inappropriate blood clotting known as thrombosis in patients with PNH.

Eculizumab is derived from the h5G1.1 anti-C5 antibody, as evidenced by Kaplan.

With respect to the 5G1.1 antibody itself,
Evans et al. teaches making and using the h5G1.1. anti-C5 antibody and antigen-binding fragments for therapeutic utilities associated with blocking the complement hemolytic activity and C5a generation associated undesirable inflammatory conditions (see entire document, including Field of the Invention, Background of the Invention, Summary of the Invention, Background Physiology and Pathology, Description of the Preferred "Embodiments, Examples and Claims.

It does not appear that the claim language or limitations result in a manipulative difference in the method steps when compared to the prior art disclosure

Meyers et al. teach management issues in the treatment of paroxysmal nocturnal hemoglobinuria (see entire document), including the hallmarks of hemolysis and anemia (e.g., see pages 125-128) as well as the treatment of this syndrome with complement inhibitors such as anti-C5 antibodies particularly for the hemolysis of PNH (see Section 2.5, Complement Inhibitors), erythropoietin (see Section 2.6, Management of Nonhemolytic Anemia) and Thrombosis (see Section 3) and Bone Marrow Failure (e.g., see Section 4).

Given the nature of the clinical manifestations of PNH such as hemolysis and anemia, one of ordinary skill in the art at the time the invention was made would have been motivated to select anti-C5 antibodies to address and manage the clinical manifestations of PNH over time with an expectation of success in increase type II red blood cells, platelet counts and reticulocytes. One would have been motivated to combine these therapies with a reasonable expectation of success because each treats a different aspect of the hemolytic disease in the patient and could be reasonably expected to improve the prognosis of the patient more rapidly than either therapy alone. From the teachings of the references, it was apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

"The test of obviousness is not express suggestion of the claimed invention in any or all of the references but rather what the references taken collectively would suggest to those of ordinary skill in the art presumed to be familiar with them." See In re Rosselet, 146 USPQ 183, 186 (CCPA 1965).

"There is no requirement (under 35 USC 103(a)) that the prior art contain an express suggestion to combine known elements to achieve the claimed invention. Rather, the suggestion to combine may come from the prior art, as filtered through the knowledge of one skilled in the art." Motorola, Inc. v. Interdiqital Tech. Corp., 43 USPQ2d 1481, 1489 (Fed. Cir. 1997).

An obviousness determination is not the result of a rigid formula disassociated from the consideration of the facts of a case. Indeed, the common sense of those skilled in the art demonstrates why some combinations would have been obvious where others would not. See KSR Int'l Co. v. Teleflex Inc., 82 USPQ2d 1385 (U.S. 2007) ("The combination of familiar elements according to known methods is likely to be obvious when it does no more than yield predictable results.").

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

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

19. Claims 72-74 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-23 of U.S. Patent No. 7,361,339.

Given that thrombosis is characteristic of treating patients with myocardial infarction undergoing angioplasty (e.g., see Background of U.S. Patent No. 7,361,339),
the patented claims of treating acute myocardial infarction, including reducing the mortality of patients as well as treating patients in connection with angioplasty with anti-C5 antibodies, including h5G1.1 anti-C5 antibodies, anticipate the instant claims.

20. Claims 72-74 are directed to an invention not patentably distinct from claims 1-23 of commonly assigned U.S. Patent No. 7,361,339 for the reasons above in Section 19.

The U.S. Patent and Trademark Office normally will not institute an interference between applications or a patent and an application of common ownership (see MPEP Chapter 2300). Commonly assigned U.S. Patent No., discussed above, would form the basis for a rejection of the noted claims under 35 U.S.C. 103(a) if the commonly assigned case qualifies as prior art under 35 U.S.C. 102(e), (f) or (g) and the conflicting inventions were not commonly owned at the time the invention in this application was made. In order for the examiner to resolve this issue, the assignee can, under 35 U.S.C. 103(c) and 37 CFR 1.78(c), either show that the conflicting inventions were commonly owned at the time the invention in this application was made, or name the prior inventor of the conflicting subject matter.
A showing that the inventions were commonly owned at the time the invention in this application was made will preclude a rejection under 35 U.S.C. 103(a) based upon the commonly assigned case as a reference under 35 U.S.C. 102(f) or (g), or 35 U.S.C. 102(e) for applications pending on or after December 10, 2004.

21. Claims 72-74 and 76-84 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-7, 9-48, 50-89, 91-129, 130, 132-163 and 168-191 of USSN 11/595,118.

The instant and copending claims are drawn to the same or nearly the same therapeutic endpoints of treating / reducing thrombosis encompassing the treatment of paroxysmal nocturnal hemoglobinuria (PNH) with the same anti-C5 antibodies to achieve the same or nearly same effects on hemopoietic elements.

While the copending claims include combination therapy, one of ordinary skill in the art would have employed conventional therapy to treat the same patients with thrombosis or PNH at the time the invention was made. Such combination therapy would anticipate the instant claims.

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

22. Given copending applications encompassing similar subject matter and the restriction set forth therein,
applicant is invited to clarify which applications should be subject to rejections under the judicially created doctrine of obviousness-type double patenting.

23. No claim is allowed.

24. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Phillip Gambel whose telephone number is (571) 272-0844. The examiner can normally be reached Monday through Thursday from 7:30 am to 6:00 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla can be reached on (571) 272-0735.

The fax number for the organization where this application or proceeding is assigned is 571-273-8300.

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

/Phillip Gambel/

Primary Examiner
Technology Center 1600
Art Unit 1644
September 20, 2010

UNITED STATES PATENT AND TRADEMARK OFFICE

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
12/902,617	10/12/2010	Leonard Bell	ALXN-P06-114	2376

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EXAMINER	
GAMBEL, PHILLIP	
ART UNIT	PAPER NUMBER
1644	

NOTIFICATION DATE	DELIVERY MODE
06/23/2011	ELECTRONIC

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

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

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

USPatentMail@ropesgray.com
USPatentMail2@ropesgray.com

Office Action Summary	Application No.	Applicant(s)
	12/902,617	BELL ET AL.
	Examiner	Art Unit
	PHILLIP GAMBEL	1644

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

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

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

Status

1)☒ Responsive to communication(s) filed on *04 May 2011*.

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

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

Disposition of Claims

4)☒ Claim(s) *131-145* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *131-145* is/are rejected.

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

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

Application Papers

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

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

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

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

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

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

a)☐ All b)☐ Some * c)☐ None of:

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

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

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

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

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *05/04/2011*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. Applicant's election of the species (B) (methods of administering anti-C5 antibody and one or more additional compounds that increase hematopoiesis) and the species erythropoietin with traverse in the Response to the Election of Species Requirement, filed 05/04/2011, is acknowledged.

The traversal is on the grounds the Groups (A) and (B) are closely related and both species rely upon the recitation of "comprising" and, in turn, that searching would not imnpose an undue or substantial burden since the search would overlap.

The species are independent or distinct because claims to the different species recite the mutually exclusive characteristics of such species. In addition, these species are not obvious variants of each other based on the current record.

The following is noted from the Election of Species, mailed 04/04/2011.

These species of (A) and (B) are distinct because they rely upon different ingredients, methods steps and endpoints.
In turn, the steps rely upon ingredients and compounds that differ in their structures, physicochemical properties and modes of action that differ action to such an extent and require non-coextensive searches to such an extent that they are considered patentable distinct. Further, these ingredients and compounds do not share a substantial structural feature essential to a common utility do not have common structure to a common utility. Therefore, they are separate and patentably distinct species

These species of compounds are distinct because their structures, physicochemical properties and modes of action differ action to such an extent and require non-coextensive searches to such an extent that they are considered patentable distinct. Further, these compounds do not share a substantial structural feature essential to a common utility do not have common structure to a common utility. Therefore, they are separate and patentably distinct species.

Applicant is required under 35 U.S.C. § 121 to elect a single disclosed species *(e.g., A or B and if B, then specific one or more compounds)* for prosecution on the merits to which the claims shall be restricted if no generic claim is finally held to be allowable. Currently, claims 131, 136 and 141 are generic, for example.
There is an examination and search burden for these patentably distinct species due to their mutually exclusive characteristics. The species require a different field of search (e.g., searching different classes/subclasses or electronic resources, or employing different search queries); and/or the prior art applicable to one species would not likely be applicable to another species; and/or the species are likely to raise different non-prior art issues under 35 U.S.C. 101 and/or 35 U.S.C. 112, first paragraph.

Should applicant traverse on the ground that the species are not patentably distinct, applicant should submit evidence or identify such evidence now of record showing the species to be obvious variants or clearly admit on the record that this is the case. In either instance, if the examiner finds one of the species unpatentable over the prior art, the evidence or admission may be used in a rejection under 35 U.S.C. 103(a) of the other species.

This, applicant has not done.

The election of species is maintained for the reasons of record, which are reiterated herein for applicant's convenience.

Claims 131-145 are pending.

Claims 1-130 have been canceled previously.

Claims 131-145 are under consideration in the instant application as they read on the elected invention / species, including the combination of anti-C5 antibodies and erythropoietin.

3. Applicant should update the status of the priority documents on page 1 of the specification.

USSN 11/050,543 is now abandoned.

4. The application is required to be reviewed and all spelling, TRADEMARKS, and like errors corrected. Appropriate corrections are required.

Trademarks should be capitalized or accompanied by the ® or ™ symbol wherever they appear and be accompanied by the generic terminology. Although the use of trademarks is permissible in patent applications, the proprietary nature of the trademarks should be respected and every effort made to prevent their use in any manner, which might adversely affect their validity as trademarks.

The disclosure is objected to because it contains an embedded hyperlink and/or other form of browser-executable code. Applicant is required to delete the embedded hyperlink and/or other form of browser-executable code. See MPEP 608.01.
For example, see page 40 of the specification.

Appropriate corrections are required

5. Claims 132, 137 and 142 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 132, 137 and 142 are indefinite in the recitation of "h5G1.1" because its characteristics are not known. The use of "h5G1.1" as the sole means of identifying the claimed antibody renders the claims indefinite because it is merely 1 laboratory designation which does not clearly define the claimed product, since different laboratories may use the same laboratory designation to define completely distinct antibodies or biological materials.

Amending the claims to recite the appropriate ATCC Accession Numbers would obviate this rejection.

Providing the entire amino acid sequence the "h5G1.1" antibody would obviate this rejection.

Alternatively, applicant is invited to make the record clear whether satisfaction of the requirements under 35 USC 112, second paragraph, for this particular biological material has been satisfied in current U.S. Patent 6,355,245 (1449), as described on page 19 of the specification in order to make the record of the instant application complete.

Note that if applicant is relying upon the sequence of h5G1.1, it is the entire amino acid sequence that encodes h5G1.1. that is required.

Applicant is reminded that the amendment must point to a basis in the specification so as not to add any new matter. See MPEP 714.02 and 2163.06

6. The following is a quotation of the first paragraph of 35 U.S.C. § 112:
The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

7. Claims 131-145 are rejected under 35 U.S.C. § 112, first paragraph, as the specification does not contain a written description of the claimed invention, in that the disclosure does not reasonably convey to one skilled in the relevant art that the inventor(s) had possession of the claimed invention at the time the application was filed.
The specification as originally filed does not provide support for the invention as now claimed:

The specification as originally filed does not provide support for the invention as now claimed:
"with a frequency effective to maintain a serum concentration of the antibody of about 35 μg/ml to thereby maintain serum complement activity in the patient at a level below 20% of the normal serum complement activity" and
"dosing schedule … at least once every 12 days".

Applicant's amendment, filed 10/12/2010, directs support for the newly added claims to page 19, lines 6-16; page 33, lines 20-23; page 36, lines 16 – page 37, line 9 and page 40, lines 1-7 and asserts no new matter has been filed.

However, with respect to the recitation of "with a frequency effective to maintain a serum concentration of the antibody of about 35 μg/ml to thereby maintain serum complement activity in the patient at a level below 20% of the normal serum complement activity",

applicant has relied upon the particulars of measuring the capacity of patient serum samples to lyse chicken erythrocytes in measuring serum hemolytic activity under certain conditions upon a particular dosage regimen(s) (e.g., see pages 39-40 of the specification).

In contrast, the claimed "frequency" is broader than that relied upon in the description of the specification as-filed.

In contrast, the claimed serum concentration is based upon any serum complement activity under any in vivo or in vitro conditions.

However, with respect to the recitation of "dosing schedule ... at least once every 12 days",
applicant has relied upon the particulars of "a reduction in the dosing interval from 14 to 12 days to maintain levels of eculizumab about 35 μg/ml and effectively and consistently blocked serum hemolytic activity for the remainder of the extension study for both patients" (E.g., see page 37, lines 2-9 of the specification),
in which the change in dosing to 12 days was limited to the particulars of the two patients in the study,
wherein the switch to 12 days was subsequent to a particular dosing regimen and for a fixed period of time.

In contrast, the claimed dosing regimen encompasses a broader dosing range of "at least once every 12 days", which includes a 12 day regimen and more than once during a 12 day regimen,
as well as a serum activity endpoints, which has addressed above.
The claims have broaden the claimed functional readout of the dosing regimen as well as the claimed dosing regimens from that described in the specification as-filed.

The specification does not provide sufficient blazemarks nor direction for the instant methods encompassing the above-mentioned "limitations" as currently recited. The instant claims now recite limitations which were not clearly disclosed in the specification as-filed, and now change the scope of the instant disclosure as-filed. Such limitations recited in the present claims, which did not appear in the specification, as filed, introduce new concepts and violate the description requirement of the first paragraph of 35 U.S.C. 112.

Applicant is required to cancel the new matter in the response to this Office Action.

Alternatively, applicant is invited to provide sufficient written support for the "limitations" indicated above.
See MPEP 714.02 and 2163.06.

8. Claims 132, 137 and 142 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled

in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention

It is apparent that the h5G1.1 antibody is required to practice the claimed invention. As a required element, it must be known and readily available to the public or obtainable by a repeatable method set forth in the specification. If it is not so obtainable or available, the enablement requirements of 35 USC 112, first paragraph, may be satisfied by a deposit of the appropriate cell line / hybridoma which produce this antibody. See 37 CFR 1.801-1.809.

In addition to the conditions under the Budapest Treaty, applicant is required to satisfy that all restrictions imposed by the depositor on the availability to the public of the deposited material will be irrevocably removed upon the granting of a patent in U.S. patent applications.

Amendment of the specification to recite the date of deposit and the complete name and address of the depository is required. As an additional means for completing the record, applicant may submit a copy of the contract with the depository for deposit and maintenance of each deposit.

If the original deposit is made after the effective filing date of an application for patent, the applicant should promptly submit a verified statement from a person in a position to corroborate the fact, and should state, that the biological material which is deposited is a biological material specifically identified in the application as filed, except if the person is an attorney or agent registered to practice before the Office, in which the case the statement need not be verified. See MPEP 1.804(b).

Alternatively, applicant is invited to make the record clear whether satisfaction of the requirements under 35 USC 112, first paragraph, enablement for biological materials has been satisfied in current U.S. Patent 6,355,245 (1449), as described on page 19 of the specification in order to make the record of the instant application complete.

Note that if applicant is relying upon the sequence of h5G1.1, it is the entire amino acid sequence that encodes h5G1.1. that is required.

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

A person shall be entitled to a patent unless --

(a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

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

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

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

11. Claims 131-140 are rejected under 35 U.S.C. § 102(a)(b) as being anticipated by Hillmen et al. (Blood 102: 1858, 2003) (1449) (see entire document).

Since the public availability of this document is not clear and given that certain claims are subject to a rejection under 35 USC 112, first paragraph, written description / new matter; this rejection is being applied under 35 U.S.C. § 102(a)(b).

Hillmen et al. teach methods of treating paroxysmal nocturnal hemoglobulinuria (PNH), intravascular hemolysis and venous thrombosis, with 900 mg eculizumab by i.v. infusion every other week for one year an anti-C5 antibody and completing 11 and 16 months of therapy and in certain instances with erythropoietin as well, including improvement in biochemical / biological parameters associated with LDH, PNH type III cells and complement activity (see entire document).

It does not appear that the claim language or limitations result in a manipulative difference in the method steps when compared to the prior art disclosure

Although the reference is silent about certain specific claimed limitations per se of a patient having paroxysmal nocturnal hemoglobulnuria (PNH) (e.g., see claims 133 and 138) or effective amounts to maintain serum complement activity at a certain range (e.g., see claims 131 and 136),
it does not appear that the claim language or limitations result in a manipulative difference in the method steps when compared to the prior art disclosure. See Bristol-Myers Squibb Company v. Ben Venue Laboratories 58 USPQ2d 1508 (CAFC 2001). "{i}t is a general rule that merely discovering and claiming a new benefit of an old process cannot render the process again patentable". In re Woodruff, 16 USPQ2d 1934, 1936 (Fed. Cir. 1990). The mechanism of action does not have a bearing on the patentability of the invention if the invention was already known or obvious. Mere recognition of latent properties in the prior art does not render nonobvious an otherwise known invention. In re Wiseman, 201 USPQ 658 (CCPA 1979). Granting a patent on the discovery of an unknown but inherent function would remove from the public that which is in the public domain by virtue of its inclusion in, or obviousness from, the prior art. In re Baxter Travenol Labs, 21 USPQ2d 1281 (Fed. Cir. 1991). See M.P.E.P. 2145.

Given the prior art teaching of treating with 900 mg of eculizumab (tradename for h5G1.1 antibody) every other week,
the prior art teaches effective amounts of treatment with the h5G1.1 anti-C5 antibody occurs in a dosing regimen at least once every 12 days.

On this record, it is reasonable to conclude that the same PNH patients are being administered the same active agent anti-C5 antibodies by the same mode of administration in the same amount to achieve the same or nearly the same improvement in biochemical and biological parameters (e.g., LDH, complement activity and PNH type III cells) in both the instant claims and the prior art reference. The fact that applicant may have discovered yet another beneficial effect from the method set forth in the prior art does not mean that they are entitled to receive a patent on that method.

Regarding the "frequencies to maintaining serum concentrations of antibodies" and "patient characterizations" recited in the claims,
it is noted that these limitations do not recite any additional active method steps, but simply states a characterization, an intended result or a conclusion of a process step or patient populations positively recited.

Applicant is reminded that no more of the reference is required than that it sets forth the substance of the invention. The claimed functional limitations would be inherent properties of the referenced methods to administer anti-C5 antibodies to treat PNH patients.

12. Claims 131-133, 136-139 and 141-143 are rejected under 35 U.S.C. § 102(b) as being anticipated by Hillmen (44th ASH Annual Meeting Abstract, Blood, Vol. 100, 2002) (1449) (see entire document).

Hillmen (2002) teaches that paroxysmal nocturnal hemoglubinuria (PNH) is characterized by intravascular hemolysis and venous thrombosis. Hillmen teaches that the hemolysis is complement-mediated and due to the deficiency of complement regulatory proteins on red cells, particularly the terminal complement inhibitor CD59 (see entire document). Hillmen teaches treating transfusion-dependent PNH patients with 600 mg weekly for four (4) dosea and 900 mg every other week of ECULIZUMAB, a humanized anti-C5 antibody (see entire publication). Hillmen teaches that the biological parameters of hemolysis dramatically improved or normalized for all patients within a week of starting therapy. Hillmen further teaches that mean LDH decreased greater than 50%, from 4494 +/- 3380 units/liter to 636 +/- 166 units/liter.

Although the reference is silent about certain specific claimed limitations per se of a patient having paroxysmal nocturnal hemoglobulnuria (PNH) (e.g., see claims 133, 138 and 143) or effective amounts to maintain serum complement activity at a certain range (e.g., see claims 131, 136 and 141),

it does not appear that the claim language or limitations result in a manipulative difference in the method steps when compared to the prior art disclosure. See Bristol-Myers Squibb Company v. Ben Venue Laboratories 58 USPQ2d 1508 (CAFC 2001). "{i}t is a general rule that merely discovering and claiming a new benefit of an old process cannot render the process again patentable". In re Woodruff, 16 USPQ2d 1934, 1936 (Fed. Cir. 1990). The mechanism of action does not have a bearing on the patentability of the invention if the invention was already known or obvious. Mere recognition of latent properties in the prior art does not render nonobvious an otherwise known invention. In re Wiseman, 201 USPQ 658 (CCPA 1979). Granting a patent on the discovery of an unknown but inherent function would remove from the public that which is in the public domain by virtue of its inclusion in, or obviousness from, the prior art. In re Baxter Travenol Labs, 21 USPQ2d 1281 (Fed. Cir. 1991). See M.P.E.P. 2145.

Given the prior art teaching of treating with 900 mg of eculizumab (tradename for h5G1.1 antibody) every other week,

the prior art teaches effective amounts of treatment with the h5G1.1 anti-C5 antibody occurs in a dosing regimen at least once every 12 days.

On this record, it is reasonable to conclude that the same PNH patients are being administered the same active agent anti-C5 antibodies by the same mode of administration in the same amount to achieve the same or nearly the same improvement in biochemical and biological parameters (e.g., LDH, complement activity and PNH type III cells) in both the instant claims and the prior art reference. The fact that applicant may have discovered yet another beneficial effect from the method set forth in the prior art does not mean that they are entitled to receive a patent on that method.

Regarding the "frequencies to maintaining serum concentrations of antibodies" and "patient characterizations" recited in the claims,

it is noted that these limitations do not recite any additional active method steps, but simply states a characterization, an intended result or a conclusion of a process step or patient populations positively recited.

Applicant is reminded that no more of the reference is required than that it sets forth the substance of the invention. The claimed functional limitations would be inherent properties of the referenced methods to administer anti-C5 antibodies to treat PNH patients.

13. Claims 131-145 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Hillmen et al. (Blood 102: 1858, 2003) (1449) AND/OR Hillmen (44th ASH Annual Meeting Abstract, Blood, Vol. 100, 2002) (1449) in view of Meyers et al. (Int. J. Hematol. 77: 125-132, 2003) (1449) and as evidenced by Garba et al. (Singapore Med. J. 46(11):632-634, 2005) (1449) with respect to normal LDH levels.

Hillmen et al. teach methods of treating paroxysmal nocturnal hemoglobulinuria (PNH), intravascular hemolysis and venous thrombosis, with 900 mg eculizumab by i.v. infusion every other week for one year an anti-C5 antibody and completing 11 and 16 months of therapy and in certain instances with erythropoietin as well, including improvement in biochemical / biological parameters associated with LDH, PNH type III cells and complement activity (see entire document).

Hillmen (2002) teaches that paroxysmal nocturnal hemoglubinuria (PNH) is characterized by intravascular hemolysis and venous thrombosis. Hillmen teaches that the hemolysis is complement-mediated and due to the deficiency of complement regulatory proteins on red cells, particularly the terminal complement inhibitor CD59 (see entire document). Hillmen teaches treating transfusion-dependent PNH patients with 600 mg weekly for four (4) dosea and 900 mg every other week of ECULIZUMAB, a humanized anti-C5 antibody (see entire publication). Hillmen teaches that the biological parameters of hemolysis dramatically improved or normalized for all patients within a week of starting therapy. Hillmen further teaches that mean LDH decreased greater than 50%, from 4494 +/- 3380 units/liter to 636 +/- 166 units/liter.
Hillmen (2002) does not teach treating a subject with EPO.

It does not appear that the claim language or limitations result in a manipulative difference in the method steps when compared to the prior art disclosure

Given the prior art teachings of treating with 900 mg of eculizumab (tradename for h5G1.1 antibody) every other week,
the prior art teaches effective amounts of treatment with the h5G1.1 anti-C5 antibody occurs in a dosing regimen at least once every 12 days.

On this record, it is reasonable to conclude that the same PNH patients are being administered the same active agent anti-C5 antibodies by the same mode of administration in the same amount to achieve the same or nearly the same improvement in biochemical and biological parameters

(e.g., LDH, complement activity and PNH type III cells) in both the instant claims and the prior art reference. The fact that applicant may have discovered yet another beneficial effect from the method set forth in the prior art does not mean that they are entitled to receive a patent on that method.

Regarding the "frequencies to maintaining serum concentrations of antibodies" and "patient characterizations" recited in the claims,
it is noted that these limitations do not recite any additional active method steps, but simply states a characterization, an intended result or a conclusion of a process step or patient populations positively recited.

Futher, the mean level of LDH in the PNH patients was more than 1.5 times the upper limit of a normal LDH level in a person, as evidenced by Garba, who discloses that normal LDH in a person is 247.10 +/- 19.0 units/liter (Abstract in particular). The prior art teaching clearly anticipates the claimed invention.

Regarding the "frequencies to maintaining serum concentrations of antibodies" and "patient characterizations" recited in the claims,
it is noted that these limitations do not recite any additional active method steps, but simply states a characterization, an intended result or a conclusion of a process step or patient populations positively recited.

Meyers et al. teach management issues in the treatment of paroxysmal nocturnal hemoglobinuria (see entire document), including the hallmarks of hemolysis and anemia (e.g., see pages 125-128) as well as the treatment of this syndrome with complement inhibitors such as anti-C5 antibodies particularly for the hemolysis of PNH (see Section 2.5, Complement Inhibitors) and erythropoietin (see Section 2.6, Management of Nonhemolytic Anemia).

In addition, as to the "frequencies to maintaining serum concentrations of antibodies" and "patient characterizations",
treating PNH patients characterized by the criteria of the proportion of type III red blood cells, platelet counts, type III granulocyte clone and serum complement activity are result effective variables of controlling hemolysis and reducing the risk of venous thrombosis with anti-C5 antibodies in the treatment of PNH patient populations who are characterized by intravascular hemolyisis, venous thrombosis and aplastic anemia.

It is well settled that "discovery of an optimum value of a result effective variable in a known process is ordinarily within the skill of the art." In re Boesch, 617 F.2d 272, 276, 205 USPQ 215, 219 (CCPA 1980). See also Merck & Co. v. Biocraft Labs. Inc., 874 F.2d 804, 809, 10 USPQ2d

1843, 1847-48 (Fed. Cir. 1989) (determination of suitable dosage amounts in diuretic compositions considered a matter of routine experimentation and therefore obvious).

As the nature of the dosing and therapeutic endpoints were known to the ordinary artisan, it would have been obvious to optimize the frequency of anti-C5 antibodies in order to control hemolysis and the risk of venous thrombosis in a variety of PNH patients.

Given the nature of the clinical manifestations of PNH such as hemolysis and anemia, one of ordinary skill in the art at the time the invention was made would have been motivated to select and combine both anti-C5 antibodies and erythropoietin to address and manage the clinical manifestations of PNH over time. One would have been motivated to combine these therapies with a reasonable expectation of success because each treats a different aspect of the hemolytic disease in the patient and could be reasonably expected to improve the prognosis of the patient more rapidly than either therapy alone. From the teachings of the references, it was apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

"The test of obviousness is not express suggestion of the claimed invention in any or all of the references but rather what the references taken collectively would suggest to those of ordinary skill in the art presumed to be familiar with them." See In re Rosselet, 146 USPQ 183, 186 (CCPA 1965).

"There is no requirement (under 35 USC 103(a)) that the prior art contain an express suggestion to combine known elements to achieve the claimed invention. Rather, the suggestion to combine may come from the prior art, as filtered through the knowledge of one skilled in the art." Motorola, Inc. v. Interdigital Tech. Corp., 43 USPQ2d 1481, 1489 (Fed. Cir. 1997).

An obviousness determination is not the result of a rigid formula disassociated from the consideration of the facts of a case. Indeed, the common sense of those skilled in the art demonstrates why some combinations would have been obvious where others would not. See KSR Int'l Co. v. Teleflex Inc., 82 USPQ2d 1385 (U.S. 2007) ("The combination of familiar elements according to known methods is likely to be obvious when it does no more than yield predictable results.").

14. Given copending applications encompassing similar subject matter and the restriction set forth herein, applicant is invited to clarify which applications should be subject to rejections under the judicially created doctrine of obviousness-type double patenting.

15. No claim is allowed.

16. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Phillip Gambel whose telephone number is (571) 272-0844. The examiner can normally be reached Monday through Thursday from 7:30 am to 6:00 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla can be reached on (571) 272-0735.

The fax number for the organization where this application or proceeding is assigned is 571-273-8300.

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

/Phillip Gambel/

Primary Examiner
Technology Center 1600
Art Unit 1644
June 16, 2011

UNITED STATES PATENT AND TRADEMARK OFFICE

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
12/902,617	10/12/2010	Leonard Bell	ALXN-P06-114	2376

28120 7590 04/04/2011

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EXAMINER	
GAMBEL, PHILLIP	
ART UNIT	PAPER NUMBER
1644	

NOTIFICATION DATE	DELIVERY MODE
04/04/2011	ELECTRONIC

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

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

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

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Office Action Summary	Application No.	Applicant(s)	
	12/902,617	BELL ET AL.	
	Examiner	Art Unit	
	PHILLIP GAMBEL	1644	

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

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 1 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

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

Status

1)☒ Responsive to communication(s) filed on *12 October 2010*.

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

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

Disposition of Claims

4)☒ Claim(s) *131-145* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☐ Claim(s) _____ is/are rejected.

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

8)☒ Claim(s) *131-145* are subject to restriction and/or election requirement.

Application Papers

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

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

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

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

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

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

a)☐ All b)☐ Some * c)☐ None of:

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

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

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

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

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. Applicant's amendment, filed 10/12/2010, has been entered.
Claims 1-130 have been canceled.
Claims 131-145 have been added.

Claims 131-145 are pending.

2. Applicant is required to elect
A) whether the claimed method do NOT comprise further administering one or more compounds that increase hematopoiesis OR
B) whether the claimed method do comprise further administering one or more compounds that increase hematopoiesis.

If applicant elects (B),
then applicant is required to elect a specific one or more compound that increase hematopoiesis from those recited in claims 135, 140 and 145 and more particularly from pages 8 and 12 of the instant specification.
If applicant elects *"one or more compounds"*, then applicant should clearly define the one or more compounds (e.g., cyclosporine, ATG, EPO derivatives, etc.).

The species are independent or distinct because claims to the different species recite the mutually exclusive characteristics of such species. In addition, these species are not obvious variants of each other based on the current record.

These species of (A) and (B) are distinct because they rely upon different ingredients, methods steps and endpoints.
In turn, the steps rely upon ingredients and compounds that differ in their structures, physicochemical properties and modes of action that differ action to such an extent and require non-coextensive searches to such an extent that they are considered patentable distinct. Further, these indgredients and compounds do not share a substantial structural feature essential to a common utility do not have common structure to a common utility. Therefore, they are separate and patentably distinct species

These species of compounds are distinct because their structures, physicochemical properties and modes of action differ action to such an extent and require non-coextensive searches to such an extent that they are considered patentable distinct. Further, these compounds do not share a substantial structural feature essential to a common utility do not have common structure to a common utility. Therefore, they are separate and patentably distinct species.

Applicant is required under 35 U.S.C. § 121 to elect a single disclosed species (e.g., A or B and if B, then specific one or more compounds) for prosecution on the merits to which the claims shall be restricted if no generic claim is finally held to be allowable. Currently, claims 131, 136 and 141 are generic, for example.

There is an examination and search burden for these patentably distinct species due to their mutually exclusive characteristics. The species require a different field of search (e.g., searching different classes/subclasses or electronic resources, or employing different search queries); and/or the prior art applicable to one species would not likely be applicable to another species; and/or the species are likely to raise different non-prior art issues under 35 U.S.C. 101 and/or 35 U.S.C. 112, first paragraph.

3. Applicant is advised that the reply to this requirement to be complete must include (i) an election of a species to be examined even though the requirement may be traversed (37 CFR 1.143) and (ii) identification of the claims encompassing the elected species, including any claims subsequently added. An argument that a claim is allowable or that all claims are generic is considered nonresponsive unless accompanied by an election.

The election of the species may be made with or without traverse. To preserve a right to petition, the election must be made with traverse. If the reply does not distinctly and specifically point out supposed errors in the election of species requirement, the election shall be treated as an election without traverse. Traversal must be presented at the time of election in order to be considered timely. Failure to timely traverse the requirement will result in the loss of right to petition under 37 CFR 1.144. If claims are added after the election, applicant must indicate which of these claims are readable on the elected species.

Should applicant traverse on the ground that the species are not patentably distinct, applicant should submit evidence or identify such evidence now of record showing the species to be obvious variants or clearly admit on the record that this is the case. In either instance, if the examiner finds one of the species unpatentable over the prior art, the evidence or admission may be used in a rejection under 35 U.S.C. 103(a) of the other species.

Upon the allowance of a generic claim, applicant will be entitled to consideration of claims to additional species which depend from or otherwise require all the limitations of an allowable generic claim as provided by 37 CFR 1.141.

4. Applicant is advised that the response to this requirement to be complete must include an election of the invention to be examined even though the requirement be traversed (37 CFR 1.143).

5. Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 C.F.R. § 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a diligently-filed petition under 37 C.F.R. § 1.48(b) and by the fee required under 37 C.F.R. § 1.17(h).

6. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Phillip Gambel whose telephone number is (571) 272-0844. The examiner can normally be reached Monday through Thursday from 7:30 am to 6:00 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla can be reached on (571) 272-0735.

The fax number for the organization where this application or proceeding is assigned is 571-273-8300.

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

/Phillip Gambel/
Primary Examiner
Technology Center 1600
Art Unit 1644
March 26, 2011

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
13/335,518	12/22/2011	Leonard Bell	AXJ-114CPCN2	4891

959 7590 09/12/2014

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EXAMINER	
GAMBEL, PHILLIP	
ART UNIT	PAPER NUMBER
1644	

NOTIFICATION DATE	DELIVERY MODE
09/12/2014	ELECTRONIC

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

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

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

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Office Action Summary	Application No. 13/335,518	Applicant(s) BELL ET AL.	
	Examiner PHILLIP GAMBEL	Art Unit 1644	AIA (First Inventor to File) Status No

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

Period for Reply

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

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

Status

1)☒ Responsive to communication(s) filed on *07/07/2014*.

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

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

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

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

Disposition of Claims*

5)☒ Claim(s) *131,133-136,138-141,143-147 and 149-153* is/are pending in the application.

5a) Of the above claim(s) *134, 135, 139, 140, 144, 145, 150 and 151* is/are withdrawn from consideration.

6)☐ Claim(s) _____ is/are allowed.

7)☒ Claim(s) *131,133,136,138,141,143,146,147,149,152 and 153* is/are rejected.

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

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

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

Application Papers

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

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

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

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

Priority under 35 U.S.C. § 119

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

Certified copies:

a)☐ All b)☐ Some** c)☐ None of the:

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

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

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

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

Attachment(s)

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

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

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

4) ☐ Other: _____.

DETAILED ACTION

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

2. Applicant's amendment, filed 07/07/2014, has been entered.

Claims 131, 136, 141 and 147 have been amended.

Claims 152-153 have been added.

Claims 132, 137, 142 and 148 have been canceled.
Claims 1-130 have been canceled previously.

Claims 131, 133-136, 138-141, 143-147 and 149-153 are pending.

As indicated previously, applicant's election of the species (A) (methods of administering anti-C5 antibody, where the claimed do not comprise further administering one or more compounds that increase hematopoiesis in the Response to Restriction Requirement, filed 12/09/2013, has been acknowledged.

Applicant's remarks concerning entitlement of claims to additional species upon allowance of a generic linking claim have been acknowledged.

Claims 131, 133, 136, 138, 141, 143, 146, 147, 149, 152 and 153 are under consideration in the instant application as they read on the elected species.

Claims 134, 135, 139, 140, 144, 145, 150 and 151 have been withdrawn as being drawn to the non-elected species.

3. The text of those sections of Title 35 USC not included in this Office Action can be found in a prior Office Action.

This Office Action will be in response to applicant's arguments and amendments, filed 07/07/2014).

The rejections of record can be found in the previous Office Action, mailed 02/06/2014.

4. Priority.

Note that not all claims may receive benefit of the priority applications.

The recitation of "the method comprising administering eculizumab to a patient who has experienced complement-related serum hemolytic activity breakthrough ...",
"a method for preventing complement-related serum hemolytic activity breakthrough in a patient",
"with a frequency effective to maintain a serum concentration of eculizumab of at least 35 µg/ml",
"at least once every 12 days to maintain in the patient a serum complement activity at a level below 20% of the normal serum complement activity"
broadly recited in the newly amended / added claims do not appear to have sufficient written support in the specification as filed.

Applicant's remarks, filed 07/07/2014, indicate that the support for the new and amended claims can be found throughout the specification and claims as originally filed.

Applicant also relies upon the following with respect to Priority.

Applicants respectfully note that literal support for an administration regimen that comprises administration of an anti-C5 antibody at least once every 12 days can be found at least, for example, at page 36 (line 16) through page 37 (line 9) of the specification as originally filed. For the Examiner's convenience, the relevant section is reproduced below:

Serum hemolytic activity in nine of the eleven patients was completely blocked throughout the 64 week treatment period with trough levels of eculizumab at equilibrium ranging from approximately 35 µg/ml to 350 µg/ml. During the extension study, 2 patients did not sustain levels of eculizumab necessary to consistently block complement. This breakthrough in serum hemolytic activity occurred in the last 2 days of the 14 day dosing interval, a pattern that was repeated between multiple doses. In one of the patients, as seen in FIG. 4, break-through of complement blockade resulted in hemoglobinuria, dysphagia, and increased LDH and AST, which correlated with the return of serum hemolytic activity. At the next dose, symptoms resolved (FIG. 5) and reduction in the dosing interval from 900 mg every 14 days to 900 mg every 12 days resulted in a regain of complement control which was maintained over the extension study to 64 weeks in both patients. This patient showed a 24 hour resolution of dysphagia and hemoglobinuria. A reduction in the dosing interval from 14 to 12 days was sufficient to maintain levels of eculizumab above 35 µg/ml and effectively and consistently blocked serum hemolytic activity for the remainder of the extension study for both patients (emphasis added).

Applicants also confirm that the present application is not a continuation-in- part of the prior application (USSN 12/902,617), but rather a continuation of USSN 12/902,617, which is a continuation of USSN 11/050,543, which is a continuation-in-part of USSN 10/771,552, as specified on the Application Data Sheet as filed with the application. Accordingly, the same support for "at least once every 12 days" that exists in the present specification can be found in each of the priority applications, including the earliest priority application, USSN 10/771,552 (see, e.g., paragraph [0078] of the corresponding published application, U.S. 2005/0169921).

Applicants, therefore, respectfully maintain that the presently pending claims are entitled to full priority.

Applicant's reliance on generic disclosure and possibly certain observations in the instant Example of eleven PNH patients who were transfusion-dependent and hemolytic in therapy trials and who were given a particular therapeutic regimen of eculizumab, including excerpt derived from pages 36-37 of the specification does not provide sufficient written description nor direction and guidance to the "currently claimed limitations".

Note that the explicit recitation of the "limitations" cited above are not readily apparent in the specification as filed.

Note that applicant has amended the claims or added new claims by relying upon certain observations of the eleven patients either in the treatment period or in an extension study under certain distinct dosing variable and time periods to broadly claim new limitations.

Again, the recitation of "comprising administering to a patient with PNH an anti-C5 antibody at least once every 12 days to thereby maintain in the patient a serum complement activation at a level below 20% of the normal serum complement activity", "at least once every 12 days" and "at least 35 μg/mg/ml" are setting forth new limitations based upon certain observations of the Examples, including setting forth limitations with no upper limit that departs from the instant disclosure as filed.

The limited disclosure of "a breakthrough in serum hemolytic activity" does not define nor set forth parameters for the "breakthrough" or provide for the metes and bounds of said "breakthrough".

The specification as filed does not provide sufficient written description of a separate category of patients who has experience complement-related serum hemolytic breakthrough, nor prevent PNH in such patients based upon certain observations in the clinical trials of the Example.

Obviousness is not the standard for the addition new limitations to the disclosure as filed. It is noted that entitlement to a filing date does not extend to subject matter which is not disclosed, but would be obvious over what is expressly disclosed. Lockwood v. American Airlines Inc., 41 USPQ2d 1961 (Fed. Cir. 1977).

It is noted that a generic or a sub-generic disclosure cannot support a species unless the species is specifically described. It cannot be said that a subgenus is necessarily described by a genus encompassing it and a species upon which it reads. See In re Smith 173 USPQ 679, 683 (CCPA 1972) and MPEP 2163.05.

The instant claims now recite limitations which were not clearly disclosed in the specification as-filed, and now change the scope of the instant disclosure as-filed. Applicant is claiming a subgenus not supported by the specification as-filed. Such limitations recited in the present claims, which did not appear in the specification, as filed, introduce new concepts and violate the description requirement of the first paragraph of 35 U.S.C. 112.

It is also true that the written description requirement must still be met in some way so as to "describe the claimed invention so that one skilled in the art can recognize what is claimed.

A patent specification should set forth enough detail to allow a person or ordinary skill in the art to understand what is claimed and to recognize that the inventor invented what is claimed.

If applicant desires priority for the above-mentioned limitation / current claims prior to filing date of the instant application (12/22/2011);
applicant is invited to point out and provide documentary support for the priority of the instant claims.

Applicant is reminded that such priority for the instant limitations requires written description and enablement under 35 U.S.C. 112(a) or 35 U.S.C. 112 (pre-AIA), first paragraph.

Therefore, this application repeats a substantial portion of prior USSN 12/902,617, filed 10/12/2010 and adds and claims additional disclosure not presented in the prior application, as indicated above.

Since this application names an inventor or inventors named in the prior application, it may constitute a continuation-in-part of the prior application.

Should applicant desire to obtain the benefit of the filing date of the prior application, attention is directed to 35 U.S.C. 120 and 37 CFR 1.78.

Therefore, applicant should amend the first line of the specification to indicate the status of the instant application as a continuation-in-part and file an Application Data Sheet reflecting the proper relationship of the instant application to its priority documents.

A claim as a whole has only one effective filing date.
See Studiengelsellschaft Kahle m.b.H. v. Shell Oil Co. 42 USPQ2d 1674, 1677 (Fed. Cir 1997).

Applicant's arguments, filed 07/14/2014, have been fully considered but have not been found convincing essentially for the reasons of record.

5. Upon reconsideration of applicant's amended claims, filed 07/07/2014, the previous rejection under 35 U.S.C. 112(b) or 35 U.S.C. 112 (pre-AIA), second paragraph, with respect to the "wherein clauses" have been withdrawn.

6. Claims 131, 133, 136, 138, 141, 143, 146, 149, 152 and 153 are rejected under 35 U.S.C. 112(b) or 35 U.S.C. 112 (pre-AIA), second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which the inventor or a joint inventor, or for pre-AIA the applicant regards as the invention.

Claims 131-133, 136-138, 141-143 and 146-149 are indefinite in the recitation of "a patient who has experienced complement-related serum hemolytic activity breakthrough" to maintain a serum concentration of eculizumab" because it is not clear as to what are the parameters that define specific patient populations (e.g., to be treated or have already been treated) or defines other characteristics of the claimed methods of elements recited within the claimed methods (e.g., amounts and frequency) of the claimed methods.

Applicant's reliance on generic disclosure and possibly certain observations in the instant Example of eleven PNH patients who were transfusion-dependent and hemolytic in therapy trials and who were given a particular therapeutic regimen of eculizumab, including excerpt derived from pages 36-37 of the specification does not particularly point out and distinctly claim the subject matter which the inventor or a joint inventor, or for pre-AIA the applicant regards as the invention to the "currently claimed limitations", as argued / asserted by applicant.

Other than relying upon the observations of the clinical and extend trails on pages 56-57 of the specification,
the specification does not define nor set forth the parameters of "a patient who has experienced complement-related serum hemolytic activity breakthrough".

Given the nature of the patients populations being treated (e.g., those with PNH or having symptoms associated with PNH) as well as applicant's reliance upon the Example for this limitation, wherein the Example describes certain patients undergoing treatment in clinical trials and extended trials,
it is unclear or indefinite as to the metes and bound of the claimed patient populations to be treated, that is, the broadest reasonable interpretation of the claims read on treating PNH patients, PNH patients undergoing treatment, who are PNH patients generally and/or patients with symptoms of PNH,
rather than being limited to patients identified as having experienced complement-related serum hemolytic activity breakthrough, as argued / asserted by applicant.

There is no positive step with regard to "identifying".

There is no clear definition, nor parameters as well as explicit recitation of "a patient who has experienced complement-related serum hemolytic activity breakthrough" or even "complement-related serum hemolytic activity breakthrough" in the specification as filed.

It is unclear whether the claimed methods necessarily limits the claimed patient population to a very well defined patient populations or simply states a characterization or conclusion of the results of those steps of patient populations being treated for PNH or having symptoms / manifestations such as hemolytic anemia associated with PNH with anti-C5 antibodies / eculizumab.

The claims are indefinite for failing to particularly point out and distinctly claim the subject matter which the inventor or a joint inventor, or for pre-AIA the applicant regards as the invention.

Applicant is reminded that the amendment must point to a basis in the specification so as not to add any new matter. See MPEP 714.02 and 2163.06

7. The specification is objected to as failing to provide proper antecedent basis for the claimed subject matter. See 37 C.F.R. § 1.75(d)(1) and M.P.E.P. § 608.01(o). Correction of the following is required:

The recitation of "comprising administering to a patient with PNH an anti-C5 antibody at least once every 12 days to thereby maintain in the patient a serum complement activation at a level below 20% of the normal serum complement activity" and "at least once every 12 days" (e.g., see claims 136 and dependent claims thereof, claims 141 and dependent claims thereof).

Applicant's arguments, filed 07/14/2014, have been fully considered but have not been found convincing essentially for the reasons of record.

In contrast to applicant's reliance upon pages 36-37 of the instant specification based upon the specifics of eleven patients participating in therapy and extended trials evaluating the effects of anti-C5 antibody / eculizumab on PNH and symptoms associated therewith,
the claims associated with the preliminary amendment, filed 12/22/2011, including the recitation of "at least once every 12 days" is not readily apparent in the specification as-filed and broadens the instant disclosure as-filed.

Applicant's preliminary amendment, filed 12/22/2011, directs support for the newly added claims to various pages of the specification but does not provide clear direct support for the above-mentioned limitations encompassing administration regimens that includes the recitation of "at least once every 12 days".

The written support of administration regimen that includes the recitation of "at least once every 12 days" is not readily apparent in the specification as-filed.

Applicant's arguments have not been found persuasive.

Applicant is required to amend the specification to provide proper antecedent basis of the current claims in the specification.

Alternatively, applicant is invited to identify the written support for instant claims in the specification as filed.

8. This is a written description rejection, new matter under 35 U.S.C. 112(a) or 35 U.S.C. 112 (pre-AIA), first paragraph.

Claims 131,133, 136, 138, 141, 143, 146, 147, 152 and 153 are rejected under 35 U.S.C. 112(a) or 35 U.S.C. 112 (pre-AIA), first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor or a joint inventor, or for pre-AIA the inventor(s), at the time the application was filed, had possession of the claimed invention.

Applicant's arguments, filed 07/14/2014, have been fully considered but have not been found convincing essentially for the reasons of record.

In contrast to applicant's reliance upon pages 36-37 of the instant specification based upon the specifics of eleven patients participating in therapy and extended trials evaluating the effects of anti-C5 antibody / eculizumab on PNH and symptoms associated therewith,
applicant's reliance on generic disclosure and possibly certain observations in the instant Example of eleven PNH patients who were transfusion-dependent and hemolytic in therapy trials and who were given a particular therapeutic regimen of eculizumab, including excerpt derived from pages 36-37 of the specification does not provide sufficient written description nor direction and guidance to the "currently claimed limitations".

Applicant relies upon the observations of treating a particular patient undergoing a particular dosing regimen on pages 36-37 of the specification to establish a new imitation.

A reduction in the dosing interval from 14 to 12 days was sufficient to maintain levels of eculizumab above 35 µg/ml and effectively and consistently blocked serum hemolytic activity for the remainder of the extension study for both patients.

Note that the explicit recitation of the "limitations" cited above are not readily apparent in the specification as filed.

Note that applicant has amended the claims or added new claims by relying upon certain observations of the eleven patients either in the treatment period or in an extension study under certain distinct dosing variable and time periods to broadly claim new limitations.

The specification as originally filed does not provide support for the invention as now claimed:

"at least 35 μg/ml" and "wherein the patient has experienced complement-related serum hemolytic activity breakthrough".

As indicated previously and consistent with current arguments,

applicant's amendment, filed 12/09/2013, directs support for the newly amended claims to paragraphs [0012], [0081], [0088] and [0093] of the corresponding US2012/0308559 and asserts no new matter has been filed.

Again, as noted previously, the specification as-filed appears to provide written description of "approximately 35 μg/ml to 50 μg/ml" and not an open-ended range of "at least 35 μg/ml" as currently recited (see pages 6-7, overlapping paragraph of the specification' paragraph [0088] of US2012/0308559).

Also, the specification as-filed appears to provide written description of "serum hemolytic activity" and not "complement-related serum hemolytic activity" as currently recited (see pages 6-7, overlapping paragraph of the specification' paragraph [0088] of US2012/0308559).

The newly amended "limitations" have broaden the written description of the Examples relied upon for the claimed "limitations" and, in turn, represent a departure of the specification / application as-filed.

The specification does not provide sufficient blazemarks nor direction for the instant methods encompassing the above-mentioned "limitations" as currently recited. The instant claims now recite limitations which were not clearly disclosed in the specification as-filed, and now change the scope of the instant disclosure as-filed. Such limitations recited in the present claims, which did not appear in the specification, as filed, introduce new concepts and violate the description requirement of the first paragraph of 35 U.S.C. 112.

Applicant is required to cancel the new matter in the response to this Office Action.

Alternatively, applicant is invited to provide sufficient written support for the "limitations" indicated above.

See MPEP 714.02 and 2163.06.

Applicant's arguments have not been found persuasive.

9. Claims 131, 133, 136, 138, 146, 147, 149, 152 and 153 are rejected under 35 U.S.C. § 102(a)(b) as being anticipated by Hillmen et al. (Blood 102: 1858, 2003) (1449) (see entire document).

Applicant's arguments in conjunction with certain legal citations, filed 07/14/2014, have been fully considered but have not been found convincing essentially for the reasons of record.

In contrast to applicant's arguments that the prior art fails to identify a patient who has experience a complement related serum hemolytic activity breakthrough on a particular dosing regimen schedule, the following is noted.

Under the broadest reasonable interpretation of the claims,
the claims read on treating PNH in patient populations who are patients in need of being treated such as those patients who have a complement-related serum hemolytic activity, who are PNH patients who are undergoing treatment (e.g., treatment with anti-C5 antibody / eculizumab) and/or patients who have been undergoing treatment and who are determined to have complement-related serum hemolytic activity.

Note that the claims do not recite a specific positive step of identifying a patient who has experienced complement-related serum hemolytic activity breakthrough.

Note that PNH is characterized by hemolytic anemia (a decreased number of red blood cells) (e.g., see page 2, paragraph 2 of the specification) and serum hemolytic activity (i.e., the percentage of cell lysis) (e.g., see page 40, paragraph 1 of the specification).

The specification does not define, nor set forth the parameters of "complement-related serum hemolytic activity breakthrough".

Given the description of "breakthrough" on pages 36-37, overlapping paragraphs of the specification,
a breakthrough could read on serum hemolytic activity or serum hemolytic activity that is not consistently block by treatment and/or treatment by eculizumab.

The following is reiterated for applicant's convenience.

Since the public availability of this document is not clear and given that certain claims are subject to a rejection under 35 USC 112, first paragraph, written description / new matter;
this rejection is being applied under 35 U.S.C. § 102(a)(b).

Hillmen et al. teach methods of treating paroxysmal nocturnal hemoglobulinuria (PNH), intravascular hemolysis and venous thrombosis, with 900 mg eculizumab by i.v. infusion every other week for one year an anti-C5 antibody and completing 11 and 16 months of therapy and in certain instances with erythropoietin as well, including improvement in biochemical / biological parameters associated with LDH, PNH type III cells and complement activity (see entire document).

The prior art dosage administration regimen reads on the claimed methods.

Consistent with the rejection under 35 U.S.C. 112(b) or 35 U.S.C. 112 (pre-AIA), second paragraph, above and with respect to claim construction for prior art rejections, the following is noted.

Although applicant has amended the claims to avoid the previously recited "wherein clauses", the claims do not necessarily recite any additional active method steps, but simply states a characterization or conclusion of the results of those steps or the patient populations that have been treated of or had symptoms / manifestations such as hemolytic anemia of PNH.

Therefore, under the broadest reasonable interpretation of the claims, the recitation a patient who has experienced complement-related serum hemolytic activity breakthrough" is not considered to further limit the method defined by the claim and has been given its proper weight in construing the claims of administering to a patient with PNH and/or manifestations of hemolytic anemia associated with PNH an anti-C5 antibody in an amount and with a frequency effective to maintain a serum concentration of at least 35 μg/ml.

It does not appear that the claim language or limitations result in a manipulative difference in the method steps when compared to the prior art disclosure

Although the reference is silent about certain specific claimed limitations per se of a patient having paroxysmal nocturnal hemoglobulnuria (PNH) or effective amounts to maintain serum complement activity at a certain range, it does not appear that the claim language or limitations result in a manipulative difference in the method steps when compared to the prior art disclosure. See Bristol-Myers Squibb Company v. Ben Venue Laboratories 58 USPQ2d 1508 (CAFC 2001). "{i}t is a general rule that merely discovering and claiming a new benefit of an old process cannot render the process again patentable". In re Woodruff, 16 USPQ2d 1934, 1936 (Fed. Cir. 1990). The mechanism of action does not have a bearing on the patentability of the invention if the invention was already known or obvious. Mere recognition of latent properties in the prior art does not render nonobvious an otherwise known invention. In re Wiseman, 201 USPQ 658 (CCPA 1979). Granting a patent on the discovery of an unknown but inherent function would remove from the public that which is in the public domain by virtue of its inclusion in, or obviousness from, the prior art. In re Baxter Travenol Labs, 21 USPQ2d 1281 (Fed. Cir. 1991). See M.P.E.P. 2145.

Given the prior art teaching of treating with 900 mg of eculizumab every other week, the prior art teaches effective amounts of treatment with the anti-C5 antibody eculizumab occurs in a dosing regimen at least once every 12 days.

On this record, it is reasonable to conclude that the same PNH patients are being administered the same active agent anti-C5 antibodies by the same mode of administration in the same amount to achieve the same or nearly the same improvement in biochemical and biological parameters (e.g., LDH, complement activity and PNH type III cells) in both the instant claims and the prior art reference. The fact that applicant may have discovered yet another beneficial effect from the method set forth in the prior art does not mean that they are entitled to receive a patent on that method.

Regarding the "frequencies to maintaining serum concentrations of antibodies" and "patient characterizations" recited in the claims,
it is noted that these limitations do not recite any additional active method steps, but simply states a characterization, an intended result or a conclusion of a process step or patient populations positively recited.

Applicant is reminded that no more of the reference is required than that it sets forth the substance of the invention. The claimed functional limitations would be inherent properties of the referenced methods to administer anti-C5 antibodies to treat PNH patients.

Applicant's arguments have not been found persuasive.

10. Claims 131, 133, 136, 138, 146, 147, 149, 152 and 153 are rejected under 35 U.S.C. § 102(b) as being anticipated by Hillmen (44th ASH Annual Meeting Abstract, Blood, Vol. 100, 2002) (1449) (see entire document).

Applicant's arguments in conjunction with certain legal citations, filed 07/14/2014, have been fully considered but have not been found convincing essentially for the reasons of record and that addressed above and reiterated herein.

In contrast to applicant's arguments that the prior art fails to identify a patient who has experience a complement related serum hemolytic activity breakthrough on a particular dosing regimen schedule, the following is noted.

Under the broadest reasonable interpretation of the claims,
the claims read on treating PNH in patient populations who are patients in need of being treated such as those patients who have a complement-related serum hemolytic activity, who are PNH patients who are undergoing treatment (e.g., treatment with anti-C5 antibody / eculizumab) and/or patients who have been undergoing treatment and who are determined to have complement-related serum hemolytic activity.

Note that the claims do not recite a specific positive step of identifying a patient who has experienced complement-related serum hemolytic activity breakthrough.

Note that PNH is characterized by hemolytic anemia (a decreased number of red blood cells) (e.g., see page 2, paragraph 2 of the specification) and serum hemolytic activity (i.e., the percentage of cell lysis) (e.g., see page 40, paragraph 1 of the specification).

The specification does not define, nor set forth the parameters of "complement-related serum hemolytic activity breakthrough".

Given the description of "breakthrough" on pages 36-37, overlapping paragraphs of the specification,
a breakthrough could read on serum hemolytic activity or serum hemolytic activity that is not consistently block by treatment and/or treatment by eculizumab.

The following of record is reiterated for applicant's convenience.

Hillmen (2002) teaches that paroxysmal nocturnal hemoglubinuria (PNH) is characterized by intravascular hemolysis and venous thrombosis. Hillmen teaches that the hemolysis is complement-mediated and due to the deficiency of complement regulatory proteins on red cells, particularly the terminal complement inhibitor CD59 (see entire document). Hillmen teaches treating transfusion-dependent PNH patients with 600 mg weekly for four (4) doses and 900 mg every other week of ECULIZUMAB, a humanized anti-C5 antibody (see entire publication). Hillmen teaches that the biological parameters of hemolysis dramatically improved or normalized for all patients within a week of starting therapy. Hillmen further teaches that mean LDH decreased greater than 50%, from 4494 +/- 3380 units/liter to 636 +/- 166 units/liter.
The prior art dosage administration regimen reads on the claimed methods

Consistent with the rejection under 35 U.S.C. 112(b) or 35 U.S.C. 112 (pre-AIA), second paragraph, above and with respect to claim construction for prior art rejections,
the following is noted.

Although applicant has amended the claims to avoid the previously recited "wherein clauses",
the claims do not necessarily recite any additional active method steps, but simply states a characterization or conclusion of the results of those steps or the patient populations that have been treated of or had symptoms / manifestations such as hemolytic anemia of PNH.

Therefore, under the broadest reasonable interpretation of the claims,
the recitation a patient who has experienced complement-related serum hemolytic activity breakthrough" is not considered to further limit the method defined by the claim and has been given its proper weight in construing the claims of administering to a patient with PNH and/or manifestations of hemolytic anemia associated with PNH an anti-C5 antibody in an amount and with a frequency effective to maintain a serum concentration of at least 35 μg/ml.

It does not appear that the claim language or limitations result in a manipulative difference in the method steps when compared to the prior art disclosure

Although the reference is silent about certain specific claimed limitations per se of a patient having paroxysmal nocturnal hemoglobulnuria (PNH) or effective amounts to maintain serum complement activity at a certain range,
it does not appear that the claim language or limitations result in a manipulative difference in the method steps when compared to the prior art disclosure. See Bristol-Myers Squibb Company v. Ben Venue Laboratories 58 USPQ2d 1508 (CAFC 2001). "{i}t is a general rule that merely discovering and claiming a new benefit of an old process cannot render the process again patentable". In re Woodruff, 16 USPQ2d 1934, 1936 (Fed. Cir. 1990). The mechanism of action does not have a bearing on the patentability of the invention if the invention was already known or obvious. Mere recognition of latent properties in the prior art does not render nonobvious an otherwise known invention. In re Wiseman, 201 USPQ 658 (CCPA 1979). Granting a patent on the discovery of an unknown but inherent function would remove from the public that which is in the public domain by virtue of its inclusion in, or obviousness from, the prior art. In re Baxter Travenol Labs, 21 USPQ2d 1281 (Fed. Cir. 1991). See M.P.E.P. 2145.

Given the prior art teaching of treating with 900 mg of eculizumab every other week,
the prior art teaches effective amounts of treatment with the anti-C5 antibody eculizumab occurs in a dosing regimen at least once every 12 days.

On this record, it is reasonable to conclude that the same PNH patients are being administered the same active agent anti-C5 antibodies by the same mode of administration in the same amount to achieve the same or nearly the same improvement in biochemical and biological parameters (e.g., LDH, complement activity and PNH type III cells) in both the instant claims and the prior art reference. The fact that applicant may have discovered yet another beneficial effect from the method set forth in the prior art does not mean that they are entitled to receive a patent on that method.

Regarding the "frequencies to maintaining serum concentrations of antibodies" and "patient characterizations" recited in the claims,
it is noted that these limitations do not recite any additional active method steps, but simply states a characterization, an intended result or a conclusion of a process step or patient populations positively recited.

Applicant is reminded that no more of the reference is required than that it sets forth the substance of the invention. The claimed functional limitations would be inherent properties of the referenced methods to administer anti-C5 antibodies to treat PNH patients.

Applicant's arguments have not been found persuasive.

11. Claims 131, 133, 136, 138, 141, 143, 146, 147, 149, 152 and 153 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Hillmen et al. (Blood 102: 1858, 2003) (1449) AND/OR Hillmen (44th ASH Annual Meeting Abstract, Blood, Vol. 100, 2002) (1449) in view of Meyers et al. (Int. J. Hematol. 77: 125-132, 2003) (1449) and as evidenced by Garba et al. (Singapore Med. J. 46(11):632-634, 2005) (1449) with respect to normal LDH levels.

Applicant's arguments, filed 07/14/2014, have been fully considered but have not been found convincing essentially for the reasons of record.

Applicant argues the following.

The pending claims are based, at least in part, on the surprising discovery that for a subset of patients afflicted with PNH, the original, established dosing regimen for eculizumab was insufficient to maintain the blockade of systemic complement activity in these patients. As described in the specification, this "[b]reakthrough of complement blockade resulted in hemoglobinuria, dysphagia, and increased LDH and AST, which correlated with a return of serum hemolytic activity" (page 36 (line 22) through page 37 (line 2)). These breakthrough patients were treated with a new dosing schedule - 900 mg of eculizumab every 12 days. Applicants further appreciated that, in order to more effectively treat PNH patients, eculizumab should be administered to the patients in an amount and with a frequency effective to maintain a serum concentration of eculizumab of at least 35 ug/ml (claim 131) or to maintain the hemolytic activity potential of the patient' s serum at a level below 20% of the hemolytic activity of their serum prior to treatment with eculizumab (claims 136, 141, and 147). The serum hemolytic activity was measured using the total human serum complement hemolytic assay described in the working examples. As

described in the specification, patients whose serum hemolytic activity (as measured using the assay) rose above 20% of the pretreatment serum hemolytic activity experienced breakthrough. In other words, Applicants determined a therapeutic threshold for more effective treatment of PNH using eculizumab.

Applicants also discovered that administration of eculizumab every 12 days, as presently claimed, is the optimum regimen for these particular patients. Specifically, as shown in Figure 4, at day 0, i.e., before administration of eculizumab, pharmacodynamic (PD) levels were consistently high, indicating high levels of complement activity in the patient's serum, which in turn correlates with high levels of hemolysis. PD levels again were measured on days 9, 12 and 13 after administration of eculizumab. The measured PD levels consistently show that no hemolysis was found until day 12. However, on day 13, PD levels surprisingly increased dramatically, thereby indicating an abrupt relapse of hemolytic activity in the PNH patients. In particular, the PD levels as shown in the below excerpt from Figure 4 demonstrate the dramatic increase of serum hemolytic activity from day 12 to day 13:

	Day 12	Day 13	Day 14 = day 0
PD	2	56	56

Accordingly, the optimal time window for administration of eculizumab is very narrow and a 12 day dosing interval, as recited in claims 136 and 141, is ideal.

None of the cited references teaches or suggests any particular therapeutic threshold for eculizumab, let alone a serum concentration of eculizumab of at least 35 µg/ml (claim 131) or a level which maintains in the patient a serum complement activity below 20% of the normal serum complement activity (claims 136, 141, and 147). Nor do the cited references teach or suggest any optimal window for administering eculizumab, let alone every 12 days (claims 136 and 141). Therefore, contrary to the Examiner's assertion, one of ordinary skill in the art would not have been motivated to have selected the particularly claimed treatment regimens based on the cited references. Specifically, Hillmen 2002, does not teach PNH breakthrough patients. While Hillmen 2003, mentions breakthrough patients, it does not teach the particularly claimed population of patients, as presently claimed (i. e., who experienced complement-related serum hemolytic activity breakthrough on the particular dosing schedule of eculizumab). Neither Hillmen 2002 nor Hillmen 2003 teach or suggest the 20% serum hemolytic activity threshold, the threshold serum concentration of eculizumab of at least 35 ug/ml, or the particular 12 day dosing schedule, as presently claimed.

Myers et al. and Garba et al., fail to cure the deficiencies of Hillmen 2002 and Hillmen 2002. Specifically neither of these references even discusses breakthrough of PNH patients, let alone a particular serum hemolytic activity threshold (e.g., 20%) or a threshold serum concentration of eculizumab (e.g., at least 35 ug/ml) or the optimal 12 day dosing schedule, as presently claimed.

In sum, none of the cited references would have provided motivation to have selected the presently claimed dosage regimens for preventing PNH breakthrough. Accordingly, the presently claimed methods are patentable over the cited references and Applicants respectfully request that the Examiner reconsider and withdraw the rejection.

Also, note the rebuttal above in terms of the broadest reasonable interpretation of the claims as follows.

In contrast to applicant's arguments that the prior art fails to identify a patient who has experience a complement related serum hemolytic activity breakthrough on a particular dosing regimen schedule, the following is noted.

Under the broadest reasonable interpretation of the claims,
the claims read on treating PNH in patient populations who are patients in need of being treated such as those patients who have a complement-related serum hemolytic activity, who are PNH patients who are undergoing treatment (e.g., treatment with anti-C5 antibody / eculizumab) and/or patients who have been undergoing treatment and who are determined to have complement-related serum hemolytic activity.

Note that the claims do not recite a specific positive step of identifying a patient who has experienced complement-related serum hemolytic activity breakthrough.

Note that PNH is characterized by hemolytic anemia (a decreased number of red blood cells) (e.g., see page 2, paragraph 2 of the specification) and serum hemolytic activity (i.e., the percentage of cell lysis) (e.g., see page 40, paragraph 1 of the specification).

The specification does not define, nor set forth the parameters of "complement-related serum hemolytic activity breakthrough".

Given the description of "breakthrough" on pages 36-37, overlapping paragraphs of the specification,
a breakthrough could read on serum hemolytic activity or serum hemolytic activity that is not consistently block by treatment and/or treatment by eculizumab.

Also, note that the prior art teach the same or nearly the same dosages and regimen consistent in the same or nearly the same clinical trials to treat PNH.

While applicant relies upon the instant Example, particularly pages 56-57 of the specification to assert unexpected results,
note that serum hemolytic activity of nine of the eleven patients was completely blocked by eculizumab at equilibrium ranging from approximately 35 µg/ml to 350 µg/ml and
that modifying the dosing interval was sufficient to active equilibrium and blocking hemolytic activity of administering eculizumab,
consistent with the result-effective variables of the prior art rejection relying upon treating the same or nearly the same patients with the same or nearly the same dosing /frequency at the time the invention was made.

The following is reiterated for applicant's convenience.

Hillmen et al. (2003) teach methods of treating paroxysmal nocturnal hemoglobulinuria (PNH), intravascular hemolysis and venous thrombosis, with 900 mg eculizumab by i.v. infusion every other week for one year an anti-C5 antibody and completing 11 and 16 months of therapy and in certain instances with erythropoietin as well, including improvement in biochemical / biological parameters associated with LDH, PNH type III cells and complement activity (see entire document).

Hillmen (2002) teaches that paroxysmal nocturnal hemoglubinuria (PNH) is characterized by intravascular hemolysis and venous thrombosis. Hillmen teaches that the hemolysis is complement-mediated and due to the deficiency of complement regulatory proteins on red cells, particularly the terminal complement inhibitor CD59 (see entire document). Hillmen teaches treating transfusion-dependent PNH patients with 600 mg weekly for four (4) doses and 900 mg every other week of ECULIZUMAB, a humanized anti-C5 antibody (see entire publication). Hillmen teaches that the biological parameters of hemolysis dramatically improved or normalized for all patients within a week of starting therapy. Hillmen further teaches that mean LDH decreased greater than 50%, from 4494 +/- 3380 units/liter to 636 +/- 166 units/liter.

It does not appear that the claim language or limitations result in an unobvious manipulative difference in the method steps when compared to the prior art disclosure of providing 600 mg weekly for four (4) doses and 900 mg every other week of eculizumab a humanized anti-C5 antibody and maintenance doses in the treatment of patients with PNH at the time the invention was made.

Given the prior art teachings of treating with 900 mg of eculizumab every other week, the prior art teaches effective amounts of treatment with the anti-C5 antibody eculizumab occurs in a dosing regimen at least once every 12 days to achieve effective treatment or blocking of hemolytic activity in PNH patients at the time the invention was made.

On this record, it is reasonable to conclude that the same PNH patients are being administered the same active agent anti-C5 antibodies by the same mode of administration in the same amount to achieve the same or nearly the same improvement in biochemical and biological parameters (e.g., LDH, complement activity and PNH type III cells) in both the instant claims and the prior art reference. The fact that applicant may have discovered yet another beneficial effect from the method set forth in the prior art does not mean that they are entitled to receive a patent on that method.

Regarding the "frequencies to maintaining serum concentrations of antibodies" and "patient characterizations" recited in the claims,
it is noted that these limitations do not recite any additional active method steps, but simply states a characterization, an intended result or a conclusion of a process step or patient populations positively recited.

Further, the mean level of LDH in the PNH patients was more than 1.5 times the upper limit of a normal LDH level in a person, as evidenced by Garba, who discloses that normal LDH in a person is 247.10 +/- 19.0 units/liter (Abstract in particular). The prior art teaching clearly anticipates the claimed invention.

Regarding the "frequencies to maintaining serum concentrations of antibodies" and "patient characterizations" recited in the claims,
it is noted that these limitations do not recite any additional active method steps, but simply states a characterization, an intended result or a conclusion of a process step or patient populations positively recited.

Meyers et al. teach management issues in the treatment of paroxysmal nocturnal hemoglobinuria (see entire document), including the hallmarks of hemolysis and anemia (e.g., see pages 125-128) as well as the treatment of this syndrome with complement inhibitors such as anti-C5 antibodies particularly for the hemolysis of PNH (see Section 2.5, Complement Inhibitors) and erythropoietin (see Section 2.6, Management of Nonhemolytic Anemia).

In addition, as to the "frequencies to maintaining serum concentrations of antibodies" and "patient characterizations",
treating PNH patients characterized by the criteria of the proportion of type III red blood cells, platelet counts, type III granulocyte clone and serum complement activity are result effective variables of controlling hemolysis and reducing the risk of venous thrombosis with anti-C5 antibodies in the treatment of PNH patient populations who are characterized by intravascular hemolyisis, venous thrombosis and aplastic anemia.

It is well settled that "discovery of an optimum value of a result effective variable in a known process is ordinarily within the skill of the art." In re Boesch, 617 F.2d 272, 276, 205 USPQ 215, 219 (CCPA 1980). See also Merck & Co. v. Biocraft Labs. Inc., 874 F.2d 804, 809, 10 USPQ2d 1843, 1847-48 (Fed. Cir. 1989) (determination of suitable dosage amounts in diuretic compositions considered a matter of routine experimentation and therefore obvious).

As the nature of the dosing and therapeutic endpoints were known to the ordinary artisan, it would have been obvious to optimize the frequency of anti-C5 antibodies in order to control hemolysis and the risk of venous thrombosis in a variety of PNH patients.

Given the nature of the clinical manifestations of PNH such as hemolysis and anemia, one of ordinary skill in the art at the time the invention was made would have been motivated to select and combine both anti-C5 antibodies and erythropoietin to address and manage the clinical manifestations of PNH over time. One would have been motivated to combine these therapies with a reasonable expectation of success because each treats a different aspect of the hemolytic disease in the patient and could be reasonably expected to improve the prognosis of the patient more rapidly than either therapy alone. From the teachings of the references, it was apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

"The test of obviousness is not express suggestion of the claimed invention in any or all of the references but rather what the references taken collectively would suggest to those of ordinary skill in the art presumed to be familiar with them." See In re Rosselet, 146 USPQ 183, 186 (CCPA 1965).

"There is no requirement (under 35 USC 103(a)) that the prior art contain an express suggestion to combine known elements to achieve the claimed invention. Rather, the suggestion to combine may come from the prior art, as filtered through the knowledge of one skilled in the art." Motorola, Inc. v. Interdigital Tech. Corp., 43 USPQ2d 1481, 1489 (Fed. Cir. 1997).

An obviousness determination is not the result of a rigid formula disassociated from the consideration of the facts of a case. Indeed, the common sense of those skilled in the art demonstrates why some combinations would have been obvious where others would not. See KSR Int'l Co. v. Teleflex Inc., 82 USPQ2d 1385 (U.S. 2007) ("The combination of familiar elements according to known methods is likely to be obvious when it does no more than yield predictable results.").

Applicant's arguments have not been found persuasive.

11. Given copending applications encompassing similar subject matter and the restriction set forth herein, applicant is invited to clarify which applications should be subject to rejections under the judicially created doctrine of obviousness-type double patenting.

Applicant's submission of an Information Disclosure Statement to make of record related appliations as wella s Office Actions is acknowledged.

12. No claim is allowed.

13. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, THIS ACTION IS MADE FINAL. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

14. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Phillip Gambel whose telephone number is (571) 272-0844. The examiner can normally be reached Monday through Thursday from 7:30 am to 6:00 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Daniel Kolker can be reached on (571) 272-3181.

The fax number for the organization where this application or proceeding is assigned is 571-273-8300.

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

/Phillip Gambel/
Primary Examiner
Technology Center 1600
Art Unit 1644
September 8, 2014

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
13/335,518	12/22/2011	Leonard Bell	ALXN-P07-114	4891

959 7590 02/06/2014

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EXAMINER	
GAMBEL, PHILLIP	
ART UNIT	PAPER NUMBER
1644	

MAIL DATE	DELIVERY MODE
02/06/2014	PAPER

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

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

Office Action Summary	Application No. 13/335,518	Applicant(s) BELL ET AL.	
	Examiner PHILLIP GAMBEL	Art Unit 1644	AIA (First Inventor to File) Status No

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

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

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

Status

1)☒ Responsive to communication(s) filed on *131-151*.

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

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

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

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

Disposition of Claims

5)☒ Claim(s) *131-151* is/are pending in the application.

5a) Of the above claim(s) *134,135,139,140,144,145,150 and 151* is/are withdrawn from consideration.

6)☐ Claim(s) _____ is/are allowed.

7)☒ Claim(s) *131-133,136-138,141-143 and 146-149* is/are rejected.

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

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

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

Application Papers

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

11)☒ The drawing(s) filed on *12/22/2011* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

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

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

Priority under 35 U.S.C. § 119

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

Certified copies:

a)☐ All b)☐ Some * c)☐ None of the:

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

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

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

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

Attachment(s)

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

2) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.

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

4) ☐ Other: _____.

DETAILED ACTION

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

2. Applicant's amendment, filed 12/09/2013, has been entered.

Claims 131-133, 136, 137, 141, 142 and 146-149 have been amended.

Claims 131-151 are pending.

Claims 1-130 have been canceled previously.

3. Applicant's election of the species (A) (methods of administering anti-C5 antibody, where the claimed do not comprise further administering one or more compounds that increase hematopoiesis in the Response to Restriction Requirement, filed 12/09/2013, is acknowledged.

Applicant's remarks concerning entitlement of claims to additional species upon allowance of a generic linking claim are acknowledged.

Claims 131-133, 136-138, 141-143 and 146-149 are under consideration in the instant application as they read on the elected species.

Claims 134, 135, 139, 140, 144, 145, 150 and 151 have been withdrawn as being drawn to the non-elected species.

4. Priority.

A) Applicant should update the status of the priority documents on page 1 of the specification.

USSN 12/902,617 is now abandoned.

B) Note that not all claims may receive benefit of the priority applications.

The recitation of "comprising administering to a patient with PNH an anti-C5 antibody at least once every 12 days to thereby maintain in the patient a serum complement activation at a level below 20% of the normal serum complement activity" and "at least once every 12 days" (e.g., see claims 136 and dependent claims thereof, claims 141 and dependent claims thereof).

Applicant's preliminary amendment filed 12/22/2011, directs support for the newly added claims to various pages of the specification but does not provide clear direct support for the above-mentioned limitations encompassing administration regimens that includes the recitation of "at least once every 12 days".

The written support of administration regimen that includes the recitation of "at least once every 12 days" is not readily apparent in the specification as-filed.

It is noted that a generic or a sub-generic disclosure cannot support a species unless the species is specifically described. It cannot be said that a subgenus is necessarily described by a genus encompassing it and a species upon which it reads. See In re Smith 173 USPQ 679, 683 (CCPA 1972) and MPEP 2163.05.

If applicant desires priority for the above-mentioned limitation / current claims prior to filing date of the instant application (12/22/2011);
applicant is invited to point out and provide documentary support for the priority of the instant claims.

Applicant is reminded that such priority for the instant limitations requires written description and enablement under 35 U.S.C. 112(a) or 35 U.S.C. 112 (pre-AIA), first paragraph.

Therefore, this application repeats a substantial portion of prior USSN 12/902,617, filed 10/12/2010 and adds and claims additional disclosure not presented in the prior application, as indicated above.
Since this application names an inventor or inventors named in the prior application, it may constitute a continuation-in-part of the prior application.

Should applicant desire to obtain the benefit of the filing date of the prior application, attention is directed to 35 U.S.C. 120 and 37 CFR 1.78.

Therefore, applicant should amend the first line of the specification to indicate the status of the instant application as a continuation-in-part and file an Application Data Sheet reflecting the proper relationship of the instant application to its priority documents.

A claim as a whole has only one effective filing date.
See Studiengelsellschaft Kahle m.b.H. v. Shell Oil Co. 42 USPQ2d 1674, 1677 (Fed. Cir 1997).

5. The application is required to be reviewed and all spelling, TRADEMARKS, and like errors corrected. Appropriate corrections are required.

Trademarks should be capitalized or accompanied by the ® or ™ symbol wherever they appear and be accompanied by the generic terminology. Although the use of trademarks is permissible in patent applications, the proprietary nature of the trademarks should be respected and every effort made to prevent their use in any manner, which might adversely affect their validity as trademarks.

The disclosure is objected to because it contains an embedded hyperlink and/or other form of browser-executable code. Applicant is required to delete the embedded hyperlink and/or other form of browser-executable code. See MPEP 608.01.

For example, see page 40 of the specification.

Appropriate corrections are required

6. The following is a quotation of 35 U.S.C. 112(b):

(B) CONCLUSION.—The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the inventor or a joint inventor regards as the invention.

The following is a quotation of 35 U.S.C. 112 (pre-AIA), second paragraph:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

7. Claims 131-133, 136-138, 141-143 and 146-149 are rejected under 35 U.S.C. 112(b) or 35 U.S.C. 112 (pre-AIA), second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which the inventor or a joint inventor, or for pre-AIA the applicant regards as the invention.

Claims 131-133, 136-138, 141-143 and 146-149 are indefinite in the recitation of the "wherein clause" in the independent claims ("wherein the patient has experienced complement activity breakthrough on a dosing schedule of eculizumab comprising: (i) 600 mg of eculizumab each week for four weeks; (ii) 900 mg of eculizumab on the fifth week; and thereafter, (iii) 900 mg of eculizumab once every two weeks, and wherein the anti-C5 antibody inhibits the cleavage of complement component C5 into fragments C5a and C5b") because it is not clear as to whether the wherein clause defines positive steps in the claimed methods, defines specific patient populations (e.g., to be treated or have already been treated) or defines other characteristics of the claimed methods of elements recited within the claimed methods (e.g., characteristics of the anti-C5 antibody or eculizumab, capabilities / possibilities of the claimed methods).

Given the recitation of "wherein the patient has experienced complement activity breakthrough on a dosing schedule",

it is unclear whether the "wherein clause" necessarily recites any additional active method steps, but simply states a characterization or conclusion of the results of those steps or the patient populations that have been treated of possibly the characterization of the anti-C5 antibodies / eculizumab.

Note that the claim recites "wherein the patient has experienced complement activity breakthrough on a dosing schedule" in the past tense.

It is not clear whether or how the "wherein clause" further limits the claimed methods of treating PNH.

The intent, meaning and the metes and bounds of the claimed methods in view of the "wherein clause" are ambiguous and ill-defined.

The claims are indefinite for failing to particularly point out and distinctly claim the subject matter which the inventor or a joint inventor, or for pre-AIA the applicant regards as the invention.

Applicant is reminded that the amendment must point to a basis in the specification so as not to add any new matter. See MPEP 714.02 and 2163.06

8. The following is a quotation of 35 U.S.C. 112(a):
(a) IN GENERAL.—The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same, and shall set forth the best mode contemplated by the inventor or joint inventor of carrying out the invention.

The following is a quotation of 35 U.S.C. 112 (pre-AIA), first paragraph:
The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

9. The specification is objected to as failing to provide proper antecedent basis for the claimed subject matter. See 37 C.F.R. § 1.75(d)(1) and M.P.E.P. § 608.01(o). Correction of the following is required:

The recitation of "comprising administering to a patient with PNH an anti-C5 antibody at least once every 12 days to thereby maintain in the patient a serum complement activation at a level below 20% of the normal serum complement activity" and "at least once every 12 days" (e.g., see claims 136 and dependent claims thereof, claims 141 and dependent claims thereof).

Applicant's preliminary amendment filed 12/22/2011, directs support for the newly added claims to various pages of the specification but does not provide clear direct support for the above-mentioned limitations encompassing administration regimens that includes the recitation of "at least once every 12 days".

The written support of administration regimen that includes the recitation of "at least once every 12 days" is not readily apparent in the specification as-filed.

Applicant is required to amend the specification to provide proper antecedent basis of claims 136 and dependent claims thereof and claims 141 and dependent claims thereof in the specification.

Alternatively, applicant is invited to identify the written support for instant claims in the specification as filed.

10. This is a written description rejection, new matter under 35 U.S.C. 112(a) or 35 U.S.C. 112 (pre-AIA), first paragraph.

Claims 131-133, 136-138, 141-143 and 146-149 are rejected under 35 U.S.C. 112(a) or 35 U.S.C. 112 (pre-AIA), first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor or a joint inventor, or for pre-AIA the inventor(s), at the time the application was filed, had possession of the claimed invention.

The specification as originally filed does not provide support for the invention as now claimed:

The specification as originally filed does not provide support for the invention as now claimed:
"at least 35 μg/ml" and "wherein the patient has experienced complement activity breakthrough on a dosing schedule".

Applicant's amendment, filed 12/09/2013, directs support for the newly amended claims to paragraphs [0012], [0081], [0088] and [0093] of the corresponding US2012/0308559 and asserts no new matter has been filed.

However the specification as-filed appears to provide written description of "approximately 35 μg/ml to 50 μg/ml" and not an open-ended range of "at least 35 μg/ml" as currently recited (see pages 6-7, overlapping paragraph of the specification' paragraph [0088] of US2012/0308559).

Also, the specification as-filed appears to provide written description of "serum hemolytic activity" and not any/all "complement activity" as currently recited (see pages 6-7, overlapping paragraph of the specification' paragraph [0088] of US2012/0308559).

The newly amended "limitations" have broaden the written description of the Examples relied upon for the claimed "limitations" and, in turn, represent a departure of the specification / application as-filed.

The specification does not provide sufficient blazemarks nor direction for the instant methods encompassing the above-mentioned "limitations" as currently recited. The instant claims now recite limitations which were not clearly disclosed in the specification as-filed, and now change the scope of the instant disclosure as-filed. Such limitations recited in the present claims, which did not appear in the specification, as filed, introduce new concepts and violate the description requirement of the first paragraph of 35 U.S.C. 112.

Applicant is required to cancel the new matter in the response to this Office Action.

Alternatively, applicant is invited to provide sufficient written support for the "limitations" indicated above.
See MPEP 714.02 and 2163.06.

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

A person shall be entitled to a patent unless --

(a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

12. The following is a quotation of 35 U.S.C. § 103(a) which forms the basis for all obviousness rejections set forth in this Office Action:
(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

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

13. Claims 131-133, 136-138 and 146-149 are rejected under 35 U.S.C. § 102(a)(b) as being anticipated by Hillmen et al. (Blood 102: 1858, 2003) (1449) (see entire document).

Since the public availability of this document is not clear and given that certain claims are subject to a rejection under 35 USC 112, first paragraph, written description / new matter; this rejection is being applied under 35 U.S.C. § 102(a)(b).

Hillmen et al. teach methods of treating paroxysmal nocturnal hemoglobulinuria (PNH), intravascular hemolysis and venous thrombosis, with 900 mg eculizumab by i.v. infusion every other week for one year an anti-C5 antibody and completing 11 and 16 months of therapy and in certain instances with erythropoietin as well, including improvement in biochemical / biological parameters associated with LDH, PNH type III cells and complement activity (see entire document).

The prior art dosage administration regimen reads on the claimed methods.

Consistent with the rejection under 35 U.S.C. 112(b) or 35 U.S.C. 112 (pre-AIA), second paragraph, above and with respect to claim construction for prior art rejections, the following is noted.

Regarding the interpretive "wherein" clause recited in independent claims, the wherein clause does not necessarily recite any additional active method steps, but simply states a characterization or conclusion of the results of those steps or the patient populations that have been treated of possibly the characterization of the anti-C5 antibodies / eculizumab.

Therefore, the "wherein clause" is not considered to further limit the method defined by the claim and has been given its proper weight in construing the claims of administering to a patient with PNH an anti-C5 antibody in an amount and with a frequency effective to maintain a serum concentration of at least 35 μg/ml.
It does not appear that the claim language or limitations result in a manipulative difference in the method steps when compared to the prior art disclosure

Although the reference is silent about certain specific claimed limitations per se of a patient having paroxysmal nocturnal hemoglobulnuria (PNH) (e.g., see claims 133, 138, 149) or effective amounts to maintain serum complement activity at a certain range (e.g., see claims 131, 136, 146), it does not appear that the claim language or limitations result in a manipulative difference in the method steps when compared to the prior art disclosure. See Bristol-Myers Squibb Company v. Ben Venue Laboratories 58 USPQ2d 1508 (CAFC 2001). "{i}t is a general rule that merely discovering and claiming a new benefit of an old process cannot render the process again patentable". In re Woodruff, 16 USPQ2d 1934, 1936 (Fed. Cir. 1990). The mechanism of action does not have a bearing on the patentability of the invention if the invention was already known or obvious. Mere recognition of latent properties in the prior art does not render nonobvious an otherwise known invention. In re Wiseman, 201 USPQ 658 (CCPA 1979).

Granting a patent on the discovery of an unknown but inherent function would remove from the public that which is in the public domain by virtue of its inclusion in, or obviousness from, the prior art. In re Baxter Travenol Labs, 21 USPQ2d 1281 (Fed. Cir. 1991). See M.P.E.P. 2145.

Given the prior art teaching of treating with 900 mg of eculizumab every other week, the prior art teaches effective amounts of treatment with the anti-C5 antibody eculizumab occurs in a dosing regimen at least once every 12 days.

On this record, it is reasonable to conclude that the same PNH patients are being administered the same active agent anti-C5 antibodies by the same mode of administration in the same amount to achieve the same or nearly the same improvement in biochemical and biological parameters (e.g., LDH, complement activity and PNH type III cells) in both the instant claims and the prior art reference. The fact that applicant may have discovered yet another beneficial effect from the method set forth in the prior art does not mean that they are entitled to receive a patent on that method.

Regarding the "frequencies to maintaining serum concentrations of antibodies" and "patient characterizations" recited in the claims,
it is noted that these limitations do not recite any additional active method steps, but simply states a characterization, an intended result or a conclusion of a process step or patient populations positively recited.

Applicant is reminded that no more of the reference is required than that it sets forth the substance of the invention. The claimed functional limitations would be inherent properties of the referenced methods to administer anti-C5 antibodies to treat PNH patients.

14. Claims 131-133, 136-138 and 146-149 are rejected under 35 U.S.C. § 102(b) as being anticipated by Hillmen (44th ASH Annual Meeting Abstract, Blood, Vol. 100, 2002) (1449) (see entire document).

Hillmen (2002) teaches that paroxysmal nocturnal hemoglubinuria (PNH) is characterized by intravascular hemolysis and venous thrombosis. Hillmen teaches that the hemolysis is complement-mediated and due to the deficiency of complement regulatory proteins on red cells, particularly the terminal complement inhibitor CD59 (see entire document). Hillmen teaches treating transfusion-dependent PNH patients with 600 mg weekly for four (4) doses and 900 mg every other week of ECULIZUMAB, a humanized anti-C5 antibody (see entire publication). Hillmen teaches that the biological parameters of hemolysis dramatically improved or normalized for all patients within a week of starting therapy. Hillmen further teaches that mean LDH decreased greater than 50%, from 4494 +/- 3380 units/liter to 636 +/- 166 units/liter.

The prior art dosage administration regimen reads on the claimed methods

Consistent with the rejection under 35 U.S.C. 112(b) or 35 U.S.C. 112 (pre-AIA), second paragraph, above and with respect to claim construction for prior art rejections,
the following is noted.

Regarding the interpretive "wherein" clause recited in independent claims,
the wherein clause does not necessarily recite any additional active method steps, but simply states a characterization or conclusion of the results of those steps or the patient populations that have been treated of possibly the characterization of the anti-C5 antibodies / eculizumab.

Therefore, the "wherein clause" is not considered to further limit the method defined by the claim and has been given its proper weight in construing the claims of administering to a patient with PNH an anti-C5 antibody in an amount and with a frequency effective to maintain a serum concentration of at least 35 μg/ml.
It does not appear that the claim language or limitations result in a manipulative difference in the method steps when compared to the prior art disclosure

Although the reference is silent about certain specific claimed limitations per se of a patient having paroxysmal nocturnal hemoglobulnuria (PNH) (e.g., see claims 133, 138 and 149) or effective amounts to maintain serum complement activity at a certain range (e.g., see claims 131, 136 and 146),
it does not appear that the claim language or limitations result in a manipulative difference in the method steps when compared to the prior art disclosure. See Bristol-Myers Squibb Company v. Ben Venue Laboratories 58 USPQ2d 1508 (CAFC 2001). "{i}t is a general rule that merely discovering and claiming a new benefit of an old process cannot render the process again patentable". In re Woodruff, 16 USPQ2d 1934, 1936 (Fed. Cir. 1990). The mechanism of action does not have a bearing on the patentability of the invention if the invention was already known or obvious. Mere recognition of latent properties in the prior art does not render nonobvious an otherwise known invention. In re Wiseman, 201 USPQ 658 (CCPA 1979). Granting a patent on the discovery of an unknown but inherent function would remove from the public that which is in the public domain by virtue of its inclusion in, or obviousness from, the prior art. In re Baxter Travenol Labs, 21 USPQ2d 1281 (Fed. Cir. 1991). See M.P.E.P. 2145.

Given the prior art teaching of treating with 900 mg of eculizumab every other week,
the prior art teaches effective amounts of treatment with the anti-C5 antibody eculizumab occurs in a dosing regimen at least once every 12 days.

On this record, it is reasonable to conclude that the same PNH patients are being administered the same active agent anti-C5 antibodies by the same mode of administration in the same amount to achieve the same or nearly the same improvement in biochemical and biological parameters (e.g., LDH, complement activity and PNH type III cells) in both the instant claims and the prior art reference. The fact that applicant may have discovered yet another beneficial effect from the method set forth in the prior art does not mean that they are entitled to receive a patent on that method.

Regarding the "frequencies to maintaining serum concentrations of antibodies" and "patient characterizations" recited in the claims,

it is noted that these limitations do not recite any additional active method steps, but simply states a characterization, an intended result or a conclusion of a process step or patient populations positively recited.

Applicant is reminded that no more of the reference is required than that it sets forth the substance of the invention. The claimed functional limitations would be inherent properties of the referenced methods to administer anti-C5 antibodies to treat PNH patients.

15. Claims 131-133, 136-138, 141-143 and 146-149 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Hillmen et al. (Blood 102: 1858, 2003) (1449) AND/OR Hillmen (44th ASH Annual Meeting Abstract, Blood, Vol. 100, 2002) (1449) in view of Meyers et al. (Int. J. Hematol. 77: 125-132, 2003) (1449) and as evidenced by Garba et al. (Singapore Med. J. 46(11):632-634, 2005) (1449) with respect to normal LDH levels.

Hillmen et al. (2003) teach methods of treating paroxysmal nocturnal hemoglobulinuria (PNH), intravascular hemolysis and venous thrombosis, with 900 mg eculizumab by i.v. infusion every other week for one year an anti-C5 antibody and completing 11 and 16 months of therapy and in certain instances with erythropoietin as well, including improvement in biochemical / biological parameters associated with LDH, PNH type III cells and complement activity (see entire document).

Hillmen (2002) teaches that paroxysmal nocturnal hemoglubinuria (PNH) is characterized by intravascular hemolysis and venous thrombosis. Hillmen teaches that the hemolysis is complement-mediated and due to the deficiency of complement regulatory proteins on red cells, particularly the terminal complement inhibitor CD59 (see entire document). Hillmen teaches treating transfusion-dependent PNH patients with 600 mg weekly for four (4) doses and 900 mg every other week of ECULIZUMAB, a humanized anti-C5 antibody (see entire publication). Hillmen teaches that the biological parameters of hemolysis dramatically improved or normalized for all patients within a week of starting therapy. Hillmen further teaches that mean LDH decreased greater than 50%, from 4494 +/- 3380 units/liter to 636 +/- 166 units/liter.

It does not appear that the claim language or limitations result in an unobvious manipulative difference in the method steps when compared to the prior art disclosure of providing 600 mg weekly for four (4) doses and 900 mg every other week of eculizumab a humanized anti-C5 antibody and maintenance doses in the treatment of patients with PNH at the time the invention was made.

Given the prior art teachings of treating with 900 mg of eculizumab every other week,

the prior art teaches effective amounts of treatment with the anti-C5 antibody eculizumab occurs in a dosing regimen at least once every 12 days.

On this record, it is reasonable to conclude that the same PNH patients are being administered the same active agent anti-C5 antibodies by the same mode of administration in the same amount to achieve the same or nearly the same improvement in biochemical and biological parameters (e.g., LDH, complement activity and PNH type III cells) in both the instant claims and the prior art reference. The fact that applicant may have discovered yet another beneficial effect from the method set forth in the prior art does not mean that they are entitled to receive a patent on that method.

Regarding the "frequencies to maintaining serum concentrations of antibodies" and "patient characterizations" recited in the claims,
it is noted that these limitations do not recite any additional active method steps, but simply states a characterization, an intended result or a conclusion of a process step or patient populations positively recited.

Further, the mean level of LDH in the PNH patients was more than 1.5 times the upper limit of a normal LDH level in a person, as evidenced by Garba, who discloses that normal LDH in a person is 247.10 +/- 19.0 units/liter (Abstract in particular). The prior art teaching clearly anticipates the claimed invention.

Regarding the "frequencies to maintaining serum concentrations of antibodies" and "patient characterizations" recited in the claims,
it is noted that these limitations do not recite any additional active method steps, but simply states a characterization, an intended result or a conclusion of a process step or patient populations positively recited.

Meyers et al. teach management issues in the treatment of paroxysmal nocturnal hemoglobinuria (see entire document), including the hallmarks of hemolysis and anemia (e.g., see pages 125-128) as well as the treatment of this syndrome with complement inhibitors such as anti-C5 antibodies particularly for the hemolysis of PNH (see Section 2.5, Complement Inhibitors) and erythropoietin (see Section 2.6, Management of Nonhemolytic Anemia).

In addition, as to the "frequencies to maintaining serum concentrations of antibodies" and "patient characterizations",
treating PNH patients characterized by the criteria of the proportion of type III red blood cells, platelet counts, type III granulocyte clone and serum complement activity are result effective variables of controlling hemolysis and reducing the risk of venous thrombosis with anti-C5 antibodies in the treatment of PNH patient populations who are characterized by intravascular hemolyisis, venous thrombosis and aplastic anemia.

It is well settled that "discovery of an optimum value of a result effective variable in a known process is ordinarily within the skill of the art." In re Boesch, 617 F.2d 272, 276, 205 USPQ 215, 219 (CCPA 1980). See also Merck & Co. v. Biocraft Labs. Inc., 874 F.2d 804, 809, 10 USPQ2d 1843, 1847-48 (Fed. Cir. 1989) (determination of suitable dosage amounts in diuretic compositions considered a matter of routine experimentation and therefore obvious).

As the nature of the dosing and therapeutic endpoints were known to the ordinary artisan, it would have been obvious to optimize the frequency of anti-C5 antibodies in order to control hemolysis and the risk of venous thrombosis in a variety of PNH patients.

Given the nature of the clinical manifestations of PNH such as hemolysis and anemia, one of ordinary skill in the art at the time the invention was made would have been motivated to select and combine both anti-C5 antibodies and erythropoietin to address and manage the clinical manifestations of PNH over time. One would have been motivated to combine these therapies with a reasonable expectation of success because each treats a different aspect of the hemolytic disease in the patient and could be reasonably expected to improve the prognosis of the patient more rapidly than either therapy alone. From the teachings of the references, it was apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

"The test of obviousness is not express suggestion of the claimed invention in any or all of the references but rather what the references taken collectively would suggest to those of ordinary skill in the art presumed to be familiar with them." See In re Rosselet, 146 USPQ 183, 186 (CCPA 1965).

"There is no requirement (under 35 USC 103(a)) that the prior art contain an express suggestion to combine known elements to achieve the claimed invention. Rather, the suggestion to combine may come from the prior art, as filtered through the knowledge of one skilled in the art." Motorola, Inc. v. Interdigital Tech. Corp., 43 USPQ2d 1481, 1489 (Fed. Cir. 1997).

An obviousness determination is not the result of a rigid formula disassociated from the consideration of the facts of a case. Indeed, the common sense of those skilled in the art demonstrates why some combinations would have been obvious where others would not. See KSR Int'l Co. v. Teleflex Inc., 82 USPQ2d 1385 (U.S. 2007) ("The combination of familiar elements according to known methods is likely to be obvious when it does no more than yield predictable results.").

16. Given copending applications encompassing similar subject matter and the restriction set forth herein, applicant is invited to clarify which applications should be subject to rejections under the judicially created doctrine of obviousness-type double patenting.

17. No claim is allowed.

18. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Phillip Gambel whose telephone number is (571) 272-0844. The examiner can normally be reached Monday through Thursday from 7:30 am to 6:00 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Daniel Kolker can be reached on (571) 272-3181.

The fax number for the organization where this application or proceeding is assigned is 571-273-8300.

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

/Phillip Gambel/

Primary Examiner
Technology Center 1600
Art Unit 1644
February 4, 2014

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
13/335,518	12/22/2011	Leonard Bell	ALXN-P07-114	4891

28120 7590 11/07/2013

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EXAMINER	
GAMBEL, PHILLIP	
ART UNIT	PAPER NUMBER
1644	

NOTIFICATION DATE	DELIVERY MODE
11/07/2013	ELECTRONIC

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

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

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

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USPatentMail2@ropesgray.com

Office Action Summary	Application No. 13/335,518	Applicant(s) BELL ET AL.	
	Examiner PHILLIP GAMBEL	Art Unit 1644	AIA (First Inventor to File) Status No

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

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *1* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

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

Status

1)☒ Responsive to communication(s) filed on *12/22/2011, 10/03/2012*.

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

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

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

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

Disposition of Claims

5)☒ Claim(s) *131-151* is/are pending in the application.

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

6)☐ Claim(s) _____ is/are allowed.

7)☐ Claim(s) _____ is/are rejected.

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

9)☒ Claim(s) *131-151* are subject to restriction and/or election requirement.

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

Application Papers

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

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

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

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

Priority under 35 U.S.C. § 119

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

Certified copies:

a)☐ All b)☐ Some * c)☐ None of the:

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

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

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

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

Attachment(s)

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

2) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.

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

4) ☐ Other: _____.

DETAILED ACTION

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

2. Applicant's amendment, filed 12/22/2011, has been entered.
Claims 1-130 have been canceled.
Claims 131-145 have been added.

Applicant's amendment, filed 10/03/2012, has been entered.
Claim 131 has been amended.
Claims 146-151 have been added.

Claims 131-151 are pending.

3. Applicant is required to elect
A) whether the claimed method do NOT comprise further administering one or more compounds that increase hematopoiesis **OR**
B) whether the claimed method do comprise further administering one or more compounds that increase hematopoiesis.

If applicant elects (B),
then applicant is required to elect a specific one or more compound that increase hematopoiesis from those recited in claims 135, 140 and 145 and more particularly from pages 8-9, 12 and 21-22 of the instant specification.
If applicant elects "one or more compounds", then applicant should clearly define the one or more compounds *(e.g., iron, antithymocyte globulin, cyclosporine, ATG, EPO derivatives, etc.).*

The species are independent or distinct because claims to the different species recite the mutually exclusive characteristics of such species. In addition, these species are not obvious variants of each other based on the current record.

These species of (A) and (B) are distinct because they rely upon different ingredients, methods steps and endpoints.

In turn, the steps rely upon ingredients and compounds that differ in their structures, physicochemical properties and modes of action that differ action to such an extent and require non-coextensive searches to such an extent that they are considered patentable distinct. Further, these ingredients and compounds do not share a substantial structural feature essential to a common utility do not have common structure to a common utility. Therefore, they are separate and patentably distinct species

These species of compounds are distinct because their structures, physicochemical properties and modes of action differ action to such an extent and require non-coextensive searches to such an extent that they are considered patentable distinct. Further, these compounds do not share a substantial structural feature essential to a common utility do not have common structure to a common utility. Therefore, they are separate and patentably distinct species.

Applicant is required under 35 U.S.C. § 121 to elect a single disclosed species (*e.g., A or B and if B, then specify one or more compounds)* for prosecution on the merits to which the claims shall be restricted if no generic claim is finally held to be allowable. Currently, claims 131, 136 and 141 are generic, for example.

There is an examination and search burden for these patentably distinct species due to their mutually exclusive characteristics. The species require a different field of search (e.g., searching different classes/subclasses or electronic resources, or employing different search queries); and/or the prior art applicable to one species would not likely be applicable to another species; and/or the species are likely to raise different non-prior art issues under 35 U.S.C. 101 and/or 35 U.S.C. 112, first paragraph.

4. Applicant is advised that the reply to this requirement to be complete must include (i) an election of a species to be examined even though the requirement may be traversed (37 CFR 1.143) and (ii) identification of the claims encompassing the elected species, including any claims subsequently added. An argument that a claim is allowable or that all claims are generic is considered nonresponsive unless accompanied by an election.

The election of the species may be made with or without traverse. To preserve a right to petition, the election must be made with traverse. If the reply does not distinctly and specifically point out supposed errors in the election of species requirement, the election shall be treated as an election without traverse. Traversal must be presented at the time of election in order to be considered timely. Failure to timely traverse the requirement will result in the loss of right to petition under 37 CFR 1.144. If claims are added after the election, applicant must indicate which of these claims are readable on the elected species.

Should applicant traverse on the ground that the species are not patentably distinct, applicant should submit evidence or identify such evidence now of record showing the species to be obvious variants or clearly admit on the record that this is the case. In either instance, if the examiner finds one of the species unpatentable over the prior art, the evidence or admission may be used in a rejection under 35 U.S.C. 103(a) of the other species.

Upon the allowance of a generic claim, applicant will be entitled to consideration of claims to additional species which depend from or otherwise require all the limitations of an allowable generic claim as provided by 37 CFR 1.141.

5. Applicant is advised that the response to this requirement to be complete must include an election of the invention to be examined even though the requirement be traversed (37 CFR 1.143).

6. Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 C.F.R. § 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a diligently-filed petition under 37 C.F.R. § 1.48(b) and by the fee required under 37 C.F.R. § 1.17(h).

7. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Phillip Gambel whose telephone number is (571) 272-0844. The examiner can normally be reached Monday through Thursday from 7:30 am to 6:00 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Daniel Kolker can be reached on (571) 272-3181.

The fax number for the organization where this application or proceeding is assigned is 571-273-8300.

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/Phillip Gambel/
Primary Examiner
Technology Center 1600
Art Unit 1644
November 4, 2013

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
13/426,973	03/22/2012	Leonard Bell	ALXN-P08-114	8851

28120 7590 01/27/2014

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EXAMINER	
ROGERS, JAMES L	
ART UNIT	**PAPER NUMBER**
1644	

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01/27/2014	ELECTRONIC

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

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

USPatentMail@ropesgray.com
USPatentMail2@ropesgray.com

Office Action Summary	Application No. 13/426,973	Applicant(s) BELL ET AL.	
	Examiner JAMES ROGERS	Art Unit 1644	AIA (First Inventor to File) Status No

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Period for Reply

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

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

Status

1)☒ Responsive to communication(s) filed on *10/23/2013*.

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

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

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

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

Disposition of Claims*

5)☒ Claim(s) *91,98,100-106,110-113 and 115* is/are pending in the application.

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

6)☐ Claim(s) _____ is/are allowed.

7)☒ Claim(s) *91,98,100-106,110-113 and 115* is/are rejected.

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

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

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

Application Papers

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

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

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

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

Priority under 35 U.S.C. § 119

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

Certified copies:

a)☐ All b)☐ Some** c)☐ None of the:

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

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

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

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

Attachment(s)

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

2) ☒ Information Disclosure Statement(s) (PTO/SB/08a and/or PTO/SB/08b) Paper No(s)/Mail Date *05/14/2013, 10/23/2013, and 01/08/2014*.

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

4) ☐ Other: _____.

RESPONSE TO APPLICANT'S AMENDMENT

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

2. Claims 91, 98, 100-106, 110-113 and 115 are pending.

3. Applicant's IDSs, filed 05/14/2013, 10/23/2013, and 01/08/2014, are acknowledged. The references on the two IDSs submitted on 05/14/2013 have been striked-through because the references are duplicates of the references listed on the IDS, also filed on 05/14/2013 and previously considered in the prior 05/31/2013 OA.

In view of the Response filed 10/23/2013, the following rejections are maintained.

Response to Arguments

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

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

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

5. Claims 91, 98, 100-106, and 112-113 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Hillmen et al. (N Engl J Med 2004; 350: 552-9, of record in the prior 08/20/2012 office action) and Hill et al. (Haematologica 2005, of record in the prior 08/20/2012 office action), in view of Evans et al. (US 6,355,245 B1, issued 3/12/2002) and Wang (US 2005/0271660), as is evidenced by the current specification at p. 16, lines 20-25.

Applicant's arguments filed 10/23/2013 were fully considered but were not considered persuasive.

Applicant asserts that the genus of potential dosage forms for eculizumab vary widely in volume, concentration and quantity whereas the instant claims are drawn to a distinct species in which the volume, concentration, and quantity are defined. Applicant further asserts that the examiner has relied nearly exclusively on general knowledge to supply the requisite reasons for the obviousness finding which is, in essence, “convenience” (p. 3 of the response). Applicant further asserts that weekly or biweekly injections of the 154, 210 or 350 mg doses of eculizumab would require the use of multiple 300 mg vials of the instantly claimed formulation or multiple uses of the same via which would be contrary to best practices for safe injection (p. 4 of the response).

This argument was not considered persuasive because while the examiner acknowledges that the ‘245 patent does not recite the specific species claimed by applicant (i.e., a single unit dosage form comprising 300 mg of the anti-C5 antibody, wherein the single unit dosage form comprises a 10 mg/mL solution of the anti-C5 antibody in a volume of 30 mL), the ‘245 patent does teach low doses of eculizumab which is the anti-C5 antibody are therapeutically effective (see p. 5 of the prior OA). The primary art reference Hill also teaches treating the same patient population afflicted with the same disease which is PNH by administering the same anti-C5 antibody, albeit at a higher dose of 600 mg (see p.3 of the prior OA). Those of skill in the art would look to the ‘245 patent for guidance in arriving at lower dosage amounts such as a single unit 300 mg or 10 mg/ml solution wherein the single unit dosage form has a volume of 30 mL as currently recited by applicant because the '245 teaches that lower dosages are also therapeutically effective. Where the general conditions of a claim are disclosed in the prior art, discovering the optimum or workable ranges involves only routine skill in the art. In re Aller, 220 F2d 454, 456, 105 USPQ 233; 235 (CCPA 1955). See MPE §§2144.05 part IIA. It remains the examiners position that given the teachings of Hill with respect to treating the exact same patient population and the same disease with the same antibody, that arriving at applicants' dosage would have amounted to no more than routine skill in the art in light of the ‘245 patent teachings that eculizumab is also effective at lower concentrations than the 600 mg dose taught by Hill.

In short, applicant is attempting to remove from the public domain methods of treating a specific disease with a specific therapeutic at a specific dose. The only difference between what is now claimed and what was known in the prior art is the single unit dosage size recited in the claims. The same therapeutic (eculizumab) was already known to be effective for treating the same disease (PNH). While the reference by Hillmen discloses methods of administering higher doses than are now claimed, Hill indicates that it would be effective at a range of doses including those now claimed. Applicant is requesting a 20-year right to exclude others from practicing the invention as claimed, on the theory that putting the therapeutic antibody in 30 ml at 10 mg/ml represents a non-obvious contribution over the art. The examiner is of the position that this difference could have easily been arrived at by one of ordinary skill in the art and does not merit a 20-year right to exclude others.

6. Claims 91, 98, 100-106, 110 and 112-113 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Hillmen et al. (N Engl J Med 2004; 350: 552-9, of record in the prior 08/20/2012 office action) and Hill et al. (Haematologica 2005, of record in the prior 08/20/2012 office action), in view of Evans et al. (US 6,355,245 B1, issued 3/12/2002) and Wang (US 2005/0271660), as applied to claims 91, 98, 100-106, and 112-113 above, in further view of Garcia et al. (Biologicals (2002) 30, 143-151, of record in the prior 08/20/2012 office action).

As applicant has not made any arguments with respect to the claimed difference that the composition is preservative free as in claim 110, the rejection from the prior OA is maintained.

7. Claims 91, 98, 100-106, 111-113 and 115 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Hillmen et al. (N Engl J Med 2004; 350: 552-9, of record in the prior 08/20/2012 office action) and Hill et al. (Haematologica 2005, of record in the prior 08/20/2012 office action), in view of Evans et al. (US 6,355,245 B1, issued 3/12/2002) and Wang (US 2005/0271660), as applied to claims 91,98, 100-106, and 112-113 above, in further view of Rosse et al. (Hematology Am Soc Hematol Edc. Program, 2004, 48-62, of record in the prior 08/20/2012 office action).

As applicant has not made any arguments with respect to the claimed difference concerning the treatment schedule set forth in claim 111, the rejection from the prior OA is maintained.

8. **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

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

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

January 17, 2014

/JAMES ROGERS/
Examiner, Art Unit 1644

/DANIEL E. KOLKER/
Supervisory Patent Examiner, Art Unit 1644
January 21, 2014

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
13/426,973	03/22/2012	Leonard Bell	ALXN-P08-114	8851

28120 7590 05/31/2013

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EXAMINER	
ROGERS, JAMES L	

ART UNIT	PAPER NUMBER
1644	

NOTIFICATION DATE	DELIVERY MODE
05/31/2013	ELECTRONIC

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

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

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

USPatentMail@ropesgray.com
USPatentMail2@ropesgray.com

Office Action Summary	Application No. 13/426,973	Applicant(s) BELL ET AL.	
	Examiner JAMES ROGERS	Art Unit 1644	AIA (First Inventor to File) Status No

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

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

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

Status

1)☒ Responsive to communication(s) filed on *22 January 2013*.

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

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

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

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

Disposition of Claims

5)☒ Claim(s) *91,98,100-106,110-113 and 115* is/are pending in the application.

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

6)☐ Claim(s) _____ is/are allowed.

7)☒ Claim(s) *91,98,100-106,110-113 and 115* is/are rejected.

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

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

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

Application Papers

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

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

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

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

Priority under 35 U.S.C. § 119

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

Certified copies:

a)☐ All b)☐ Some * c)☐ None of the:

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

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

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

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

Interim copies:

a)☐ All b)☐ Some c)☐ None of the: Interim copies of the priority documents have been received.

Attachment(s)

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

2) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *1/22/2013, 5/14/2013*.

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

4) ☐ Other: _____.

DETAILED ACTION

1. Applicant's amendment filed 01/22/2013 is acknowledged.

Claims 91, 98, 100-106, 110-113, and 115 are pending and under consideration in the instant examination as they read on a method for treating a patient that (i) is afflicted with a hemolytic disease and (ii) has been vaccinated against Neisseria meningitides, the method comprising administering to the patient an effective amount of an anti-C5 antibody that inhibits cleavage of C5 into C5a and C5b.

2. The examiner acknowledges a conversation with Anita Varma on May 14, 2013 about the possible allowance of claims 91, 98, 100-106, 110 and 112-113. Upon further consideration, however, a new rejection under 35 USC 103 is set forth infra.

3. Applicant's amendment, filed 01/22/2013, has overcome the enablement rejection under 35 USC 112, 1st paragraph and the rejections under 35 USC 102(b) which were of the previous office action mailed on 08/20/2012.

4. Applicant's IDSs, filed on 01/22/2013 and 05/14/2013, are acknowledged and have been considered.

5. Applicant's claim for the benefit of a prior-filed application under 35 U.S.C. 119(e) or under 35 U.S.C. 120, 121, or 365(c) is acknowledged. Applicant has not complied with one or more conditions for receiving the benefit of an earlier filing date under 35 U.S.C. 119(e) as follows:

The later-filed application must be an application for a patent for an invention which is also disclosed in the prior application (the parent or original nonprovisional application or provisional application). The disclosure of the invention in the parent application and in the later-filed application must be sufficient to comply with the requirements of 35 U.S.C. 112(a) or the first paragraph of 35 U.S.C. 112 (pre-AIA). See *Transco Products, Inc. v. Performance Contracting, Inc.*, 38 F.3d 551, 32 USPQ2d 1077 (Fed. Cir. 1994).

The disclosure of the prior-filed application, US Provisional Application No. 60/783,070, fails to provide adequate support or enablement in the manner provided by 35 U.S.C. 112(a) or 35 U.S.C. 112 (pre-AIA), first paragraph for one or more claims of this application. In particular, the claims as currently amended recite administration of "a pharmaceutical composition comprising a single unit dosage form ... wherein the single unit dosage form comprises 300 mg of the anti-C5 antibody, wherein the single unit dosage form comprises a 10 mg/mL solution of the anti-C5 antibody, wherein the single unit dosage form has a volume of 30 mL, and wherein the anti-C5 antibody is eculizumab".

Accordingly, the priority date of the instant claims of the current application is considered to be 3/15/2007, the filing date of PCT/US2007/006606.

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

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

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

7. Claims 91, 98, 100-106, and 112-113 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hillmen et al. (N Engl J Med 2004; 350: 552-9, of record in the prior 08/20/2012 office action) and Hill et al. (Haematologica 2005, of record in the prior 08/20/2012 office action), in view of Evans et al. (US 6,355,245 B1, issued 3/12/2002) and Wang (US 2005/0271660), as is evidenced by the current specification at p. 16, lines 20-25.

With respect to claims 91, 112-113 and 115, Hillmen teaches a method for treating a patient that suffers from paroxysmal nocturnal hemoglobinuria (PNH) by administering to the patient an effective amount of eculizumab (p. 552, "methods") which specifically binds to the terminal complement protein C5, inhibiting its cleavage into C5a and C5b (p. 553, 3rd ¶). Hillmen further teaches that patients were vaccinated against N. meningitides before treatment (p. 554, lines 2-4).

In a particular embodiment, Hillmen further teaches a pharmaceutical composition comprising eculizumab (anti-C5 monoclonal antibody) which was administered to patients with PNH at 600 mg every week for four weeks, followed one week later by a 900-mg dose and then by 900 mg every other week through week 12.

While Hillmen does not specifically recite that the patient afflicted with PNH is "due to a C3b-mediated vascular clearance of PNH erythrocytes through the reticuloendothelial system" as in claim 103, the prior art of treating the same PNH populations with the same composition (anti-C5 antibody) to achieve the same therapeutic effect does not differ from the claimed methods. The mechanism of action does not have a bearing on the patentability of the invention if the invention was already known or obvious. Mere recognition of latent properties in the prior art does not render nonobvious an otherwise known invention. In re Wiseman, 201 USPQ 658 (CCPA 1979). Granting a patent on the discovery of an unknown but inherent function would remove from the public that which is in the public domain by virtue of its inclusion in, or obviousness from, the prior art. In re Baxter Travenol Labs, 21 USPQ2d 1281 (Fed. Cir. 1991). See M.P.E.P. 2145. As is further evidenced by Jasinski, moreover, mice studies indicate that the shortened survival of PIGA negative RBCs which causes PNH is mediated by macrophage clearance (clearance of PNH erythrocytes through the reticuloendothelial system) (abstract).

With respect to claim 104, Hillmen teaches that PNH is characterized by hemolytic anemia which renders the patient transfusion dependent and that patients continued to receive transfusion when they had symptoms of anemia (p. 554, 1st¶ under "Investigations" and p. 557, 1st ¶ under "Discussion"). Hillmen further teaches that Type III erythrocytes increased significantly but less than 100% ("from a mean of 36.7 +5.9 to 59.2+8.0 percent") (p. 556, 3rd ¶). Thus the recitation "wherein the patient is anemic and the anemia results at least in part from extravascular hemolysis, and wherein the patient remains anemic following treatment with the anti-C5 antibody" is considered to be inherently taught by Hillmen.

With respect to claim 105, Hillmen teaches that the patient population included men and women of 18 years of age and older who had received a diagnosis of PNH at least 6 months earlier and had received at least 4 red cell transfusions in the preceding 12 months (p. 553, last ¶) and that the percentage of type III erythrocytes increased from a mean of 36.7 +5.9 percent before treatment to 49.2 +8.0 percent at the end of 12 weeks of treatment (the patient is at least 18 years of age and has (i) a PNH type III erythrocyte population of greater than 10%) (p. 556, 2nd ¶).

Hill also teaches treating patients afflicted with PNH by administering eculizumab that specifically targets C5 (anti-C5 antibody), blocking the generation of C5a and the formation of C5b-9 (inhibits cleavage of C5 into fragments C5a and C5b) (abstract; p. 2559, 3rd l[) .

With respect to claim 98, Hill teaches that sustained efficacy and safety of eculizamab in a 1 -year study (anti-C5 antibody is administered to the patient for at least 6 months) (p. 2564, 1st ¶).

With respect to claims 100-102, Hill teaches a hemoglobin level of 10.0 + 0.4 prior to treatment with eculizumab (patient has a hemoglobin level less than 12-14 g/dL if a man or 10-12 g/dL is a woman).

With respect to claim 106, Hill (I) teaches a patient with a history of PNH and aplastic anemia (p. 2563, last I[).

The prior art references differ from the claimed invention in the recitation that the pharmaceutical composition of eculizumab comprises a single unit dosage form of 300 mg comprising 30 mL at 10 mg/mL.

However, the '245 patent teaches antibody 5G1.1, which is the same as eculizumab (see present specification, p. 16 lines 20-25), is effective at doses of 2.2, 3, or 5 mg per kg body weight; this corresponds to 154, 210, or 350 mg of antibody for a 70kg adult human ('245 patent, column 16 lines 10-30). '245 patent also teaches that eculizumab is therapeutically effective when as little as 210 mg are present (column 16 lines 10-15). '245 teaches that the antibodies are particularly advantageous in that they are highly active even when administered in low doses (col 8 lines 25-32), providing a reasonable expectation of success in treating PHN with a dose less than what was disclosed by Hillmen. The reference teaches that it is within the skill of an artisan, particularly a physician, to determine the optimal dose (column 18 lines 15-30). The reference teaches sterile formulations are known in the art and can include various pharmaceutical excipients, etc. (col 18 lines 30-45).

However neither Hillmen nor '245 teaches a 300 mg single unit dosage as recited in the claims.

Nevertheless it would have been obvious to one of ordinary skill in the art to modify the teachings of Hillmen and Hill to administer 300 mg single unit dosages. Hillmen teaches that both 600 and 900 mg dosages can be used, and since '245 patent teaches that 210 or 350 mg of antibody would be expected to be therapeutically effective, arriving at the 300 mg dosage would be routine, convenient and obvious. One of ordinary skill in the art would have a reasonable expectation of success, as '245 teaches that the antibody exerts its effect at low doses.

Finally, US 2005/0271660 teaches that eculizumab is highly soluble, including at up to 30 mg per ml (paragraph 0171, Figure 10). Therefore the artisan of ordinary skill would have had a reasonable expectation of success in making a 10 mg / ml solution of the antibody.

From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was prima facie obvious to one of

ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

Applicant's arguments filed at pgs. 8-9 of the 01/22/2013 response have been fully considered but were not deemed persuasive.

Applicant asserts that it is well known in the art that the dose of an antibody will vary depending on such factors as the manner of administration, the particular symptoms of the patient being treated, the overall health, condition, size, and age of the patient and the judgment of the prescribing physician. Applicant further asserts that in order to produce a solution of eculizumab at 10 mg/mL, the inventors had to know that eculizumab was sufficiently soluble for a 10 mg/mL formulation.

This argument was not considered persuasive because the '245 patent teaches that optimal dosing of eculizumab is within the skill of an artisan, particularly a physician, as noted above. In addition, the '660 publication teaches that eculizumab is highly soluble, including at up to 30 mg per ml providing a reasonable expectation of success in making a 10 mg/ml solution of the antibody as is also noted above. Given the additional teachings of the '245 patent that eculizumab is effective at lower doses, it would have been obvious to a person of ordinary skill in the art at the time the invention was made to arrive at the lower single unit dosage form as currently claimed.

8. Claims 91, 98, 100-106, 110 and 112-113 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hillmen et al. (N Engl J Med 2004; 350: 552-9, of record in the prior 08/20/2012 office action) and Hill et al. (Haematologica 2005, of record in the prior 08/20/2012 office action), in view of Evans et al. (US 6,355,245 B1, issued 3/12/2002) and Wang (US 2005/0271660), as applied to claims 91, 98, 100-106, and 112-113 above, in further view of Garcia et al. (Biologicals (2002) 30, 143-151, of record in the prior 08/20/2012 office action).

The prior art teachings of Hillmen, Hill, the '245 patent and the '660 publication are discussed supra.

The reference teachings differ from the claimed invention by not reciting that the pharmaceutical composition is a preservative free formulation as in claim 110.

Garci et al. teaches that the influence of preservatives on the safety and stability of antivenoms may be involved in adverse reactions to antivenoms and is an issue that deserves careful consideration (p. 144, 2nd ¶; p. 149, last ¶).

It would have been obvious to one of ordinary skill in the art at the time applicant's invention was made to provide the composition taught by the primary references in a preservative free formulation. One skilled in the art would be motivated to provide the composition in a preservative free formulation because Garci teaches that the presence

of preservatives can be an important safety issue in that they may lead to adverse reactions when present in antibody compositions such as antivenoms.

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

9. Claims 91, 98, 100-106, 111-113 and 115 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hillmen et al. (N Engl J Med 2004; 350: 552-9, of record in the prior 08/20/2012 office action) and Hill et al. (Haematologica 2005, of record in the prior 08/20/2012 office action), in view of Evans et al. (US 6,355,245 B1, issued 3/12/2002) and Wang (US 2005/0271660), as applied to claims 91, 98, 100-106, and 112-113 above, in further view of Rosse et al. (Hematology Am Soc Hematol Edc. Program, 2004, 48-62, of record in the prior 08/20/2012 office action).

The prior art teachings of Hillmen, Hill, the '245 patent and the '660 publication are discussed supra.

The reference teachings differs from the claimed invention by not reciting the specific treatment schedule set forth in claim 111, "(i) 600 mg of the antibody every 7 ±2 days for the first 4 weeks, (ii) 900 mg of the antibody for the fifth dose 7 ± days after 9i), and (iii) 900 mg of the antibody every 14 ± 2 days thereafter, wherein the administration occurs via 25 to 45 minute intravenous infusion" as in claims 111 and 115.

Nevertheless, it would have been obvious to one of ordinary skill in the art to administer eculizumab according to the claimed recited treatment schedule above because, as stated supra, Hillman teaches a pharmaceutical composition comprising eculizumab (anti-C5 monoclonal antibody) which was administered to patients with PNH at 600 mg every week for four weeks, followed one week later by a 900-mg dose and then by 900 mg every other week through week 12.

Rosse also teaches therapeutic treatment of patients with transfusion-dependent paroxysmal nocturnal hemoglobinuria (PNH), by administering to the patients an effective amount of eculizumab, which blocks cleavage of C5 into C5a and C5b (Fig. 4; p. 48, 1 st ¶; p. 53, 2nd column, lines 16-18).

In a specific treatment schedule, Rosse further teaches the exact same treatment regimen where eculizumab (anti-C5 antibody) was given at a dose of 600 mg every week for 4 weeks (600 mg of the antibody every 7 + 2 days for the first 4 weeks) and then at a dose of 900 mg every other week (900 mg of the antibody for the fifth dose 7 + 2 days after and 900 mg of the antibody every 14 + 2 days thereafter). Rosse further

teaches that the drug is given by intravenous infusion over 30 minutes (administration of the antibody to the patient is to occur via 25 to 45 minutes intravenous infusion).

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

10. No claim is allowed.

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

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May 20, 2013

/JAMES ROGERS/
Examiner, Art Unit 1644

/DANIEL E. KOLKER/
Supervisory Patent Examiner, Art Unit 1644
May 24, 2013

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
13/426,973	03/22/2012	Leonard Bell	ALXN-P08-114	8851

28120 7590 08/20/2012

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EXAMINER	
ROGERS, JAMES L	

ART UNIT	PAPER NUMBER
1644	

NOTIFICATION DATE	DELIVERY MODE
08/20/2012	ELECTRONIC

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

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

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

USPatentMail@ropesgray.com
USPatentMail2@ropesgray.com

Office Action Summary	Application No.	Applicant(s)	
	13/426,973	BELL ET AL.	
	Examiner	Art Unit	
	JAMES ROGERS	1644	

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

Period for Reply

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- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
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Status

1)☒ Responsive to communication(s) filed on *22 March 2012*.

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

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

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

Disposition of Claims

5)☒ Claim(s) *91-115* is/are pending in the application.

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

6)☐ Claim(s) _____ is/are allowed.

7)☒ Claim(s) *91-115* is/are rejected.

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

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

Application Papers

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

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

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

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

12)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

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

a)☐ All b)☐ Some * c)☐ None of:

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

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

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

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

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *8/13/2012*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. Claims 91-115 are pending.

2. Claims 91-115 are under consideration in the instant examination as they read on a method for treating a patient that (i) is afflicted with a hemolytic disease and (ii) has been vaccinated against Neisseria meningitides, the method comprising administering to the patient an effective amount of an anti-C5 antibody that inhibits cleavage of C5 into C5a and C5b.

3. Applicant's IDS, filed 8/13/2012, is acknowledged and has been considered.

4. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> *The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.*

5. Claims 91-98 and 106-115 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method for treatment of paroxysmal nocturnal hemoglobinuria (PNH) by administering to a patient an effective amount of an anti-C5 antibody, does not reasonably provide enablement for a method for treatment of **any hemolytic disease** by administering an anti-C5 antibody. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

Factors to be considered in determining whether undue experimentation is required to practice the claimed invention are summarized *In re Wands* (858 F2d 731,737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)). The factors most relevant to this rejection are the scope of the claim, the amount of direction or guidance provided, the lack of sufficient working examples, the unpredictability in the art and the amount of experimentation required to enable one of skill in the art to practice the claimed invention.

Claims 91-98 and 106-115 are genus claims which encompass a method for treating a patient who suffers from **any type of hemolytic disease** by administering to the patient an effective amount of an anti-C5 antibody.

While the claims encompass treating a patient suffering from any type of hemolytic disease, the specification discloses a phase III study which evaluated the effect of eculizumab (an anti-C5 antibody) on a cohort of 87 transfusion dependent patients suffering from a single type of hemolytic disease, paroxysmal nocturnal hemoglobinuria (PNH) (p. 2, 1st ¶)

As evidenced by the specification, PNH is a disease which is characterized by hemolysis due to the absence of the GPI-anchored complement regulatory protein CD59 which blocks the formation of the terminal complement complex on the cell surface (p. 2, 2nd ¶). However, other hemolytic diseases do not share the same etiology as PNH. For example, sickle cell disease, which is also characterized by intravascular hemolysis" is caused by a mutation in the β-globin chain of hemoglobin (Kato, Blood Reviews, 2007, p. 38, 1st ¶Fig. 1), and at least one study has not identified any complement abnormality in sickle cell disease (Strauss, Pediat. Res. 11(4), 1997, abstract). In addition, as is stated by Stuart et al., sickle cell disease "is a systemic disease of monumental complexity" (Lancet, 364, 2004, p. 1357, last ¶)

In re Fisher, 166 USPQ 18 indicates that the more unpredictable an area is, the more specific enablement is necessary in order to satisfy the statute. Because the current claims encompass a large number of different hemolytic diseases, each with potentially different pathophysiological mechanisms, it is not clear that reliance upon a method for treating a single type of hemolytic disease (i.e., PNH) accurately reflects the relative mammal efficacy of the claimed therapeutic strategy for any type of hemolytic disease.

Reasonable correlation must exist between the scope of the claims and scope of the enablement set forth. In view on the quantity of experimentation necessary the limited working examples, the nature of the invention, the state of the prior art, the unpredictability of the art and the breadth of the claims, it would take undue trials and errors to practice the claimed invention.

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

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

7. Claims 113-115 are rejected under 35 U.S.C. 102(b) as being anticipated by Rosse et al. (hematology Am Soc Hematol Edc. Program, 2004, 48-62).

Rosse teaches therapeutic treatment of patients with transfusion-dependent paroxysmal nocturnal hemoglobinuria (PNH), which is characterized by chronic intravascular hemolysis (method for treating a patient that is afflicted with a hemolytic disease) by administering to the patients an effective amount of eculizumab, which is a humanized chimeric anti-C5 antibody (whole antibody) which blocks cleavage of C5 into C5a and C5b (Fig. 4; p. 48, 1st ¶; p. 53, 2nd column, lines 16-18).

Rosse further teaches that eculizumab (anti-C5 antibody) has a completely nonfunctional Fc domain (p. 53, lines 10-13). Because the constant region is nonfunctional, eculizumab would necessarily have decreased effector function with respect to antibody-dependent cell mediated cytotoxity (ADCC) and complement dependent cytotoxicity (CDC) relative to the corresponding native constant region.

With respect to claim 115, Rosse further teaches that eculizumab (anti-C5 antibody) was given at a dose of 600 mg every week for 4 weeks (600 mg of the antibody every 7 ± 2 days for the first 4 weeks) and then at a dose of 900 mg every other week (900 mg of the antibody for the fifth dose 7 ± 2 days after and 900 mg of the antibody every 14 ± 2 days thereafter). Rosse further teaches that the drug is given by intravenous infusion over 30 minutes (administration of the antibody to the patient is to occur via 25 to 45 minutes intravenous infusion).

The reference teachings anticipate the claimed invention.

8. Claims 91-93, 96-97, 99, 103-105, and 112-115 are rejected under 35 U.S.C. 102(b) as being anticipated by Hillmen et al. (N Engl J Med 2004; 350: 552-9), as is evidenced by Jasinski (Blood, 103, 2004, 2827-2834) and Rosse et al. (hematology Am Soc Hematol Edc. Program, 2004, 48-62).

With respect to claims 91-93, 99, and 112-115, Hillmen teaches a method for treating a patient that suffers from paroxysmal nocturnal hemoglobinuria (PNH) which is a disease characterized by hemolytic anemia (patient afflicted with a hemolytic disease) (p. 557, 2nd ¶) by administering to the patient an effective amount of eculizumab (whole antibody) (p. 552, “methods”) which specifically binds to the terminal complement protein C5, inhibiting its cleavage into C5a and C5b (p. 553, 3rd ¶). Hillmen further teaches that patients were vaccinated against *N. meningitides* before treatment (p. 554, lines 2-4). As is evidenced by Rosse, eculizumab (anti-C5 antibody) has a completely nonfunctional Fc domain (p. 53, lines 10-13). Because the constant region is nonfunctional, eculizumab would necessarily have decreased effector function with respect to antibody-dependent cell mediated cytotoxity (ADCC) and complement dependent cytotoxicity (CDC) relative to the corresponding native constant region.

Claim 103 is included because while Hillmen does not specifically recite that the patient afflicted with PNH is “due to a C3b-mediated vascular clearance of PNH erythrocytes through the reticuloendothelial system”, the prior art of treating the same PNH populations with the same composition (anti-C5 antibody) to achieve the same therapeutic effect does not differ from the claimed methods. The mechanism of action does not have a bearing on the patentability of the invention if the invention was already known or obvious. Mere recognition of latent properties in the prior art does not render nonobvious an otherwise known invention. In re Wiseman, 201 USPQ 658 (CCPA 1979). Granting a patent on the discovery of an unknown but inherent function would remove from the public that which is in the public domain by virtue of its inclusion in, or

obviousness from, the prior art. In re Baxter Travenol Labs, 21 USPQ2d 1281 (Fed. Cir. 1991). See M.P.E.P. 2145. As is further evidenced by Jasinski, moreover, mice studies indicate that the shortened survival of PIGA negative RBCs which causes PNH is mediated by macrophage clearance (clearance of PNH erythrocytes through the reticuloendothelial system) (abstract).

Claim 104 is included because Hillmen teaches that PNH is characterized by hemolytic anemia which renders the patient transfusion dependent and that patients continued to receive transfusion when they had symptoms of anemia (p. 554, 1st under "Investigations" and p. 557, 1st ¶ under "Discussion"). Hillmen further teaches that Type III erythrocytes increased significantly but less than 100% ("from a mean of 36.7 ±5.9 to 59.2±8.0 percent") (p. 556, 3rd ¶). Thus the recitation "wherein the patient is anemic and the anemia results at least in part from extravascular hemolysis, and wherein the patient remains anemic following treatment with the anti-C5 antibody" is considered to be inherently taught by Hillmen.

Claim 105 is included because Hillmen teaches that the patient population included men and women of 18 years of age and older who had received a diagnosis of PNH at least 6 months earlier and had received at least 4 red cell transfusions in the preceding 12 months (p. 553, last ¶) and that the percentage of type III erythrocytes increased from a mean of 36.7 ±5.9 percent before treatment to 49.2 ±8.0 percent at the end of 12 weeks of treatment (the patient is at least 18 years of age and has (i) a PNH type III erythrocyte population of greater than 10%) (p. 556, 2nd ¶).

The reference teachings anticipate the claimed invention.

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

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

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

10. Claims 91-93, 96-106 and 111-115 are rejected under 35 U.S.C. 103(a) as being unpatentable over Rosse et al. (Hematology 2004) OR Hill (Blood, 2005, hereafter "Hill (I)") OR Hill et al. ((Haematologica 2005, hereafter "Hill (II)"), each in view of Hillmen et al. (N Engl J Med 2004; 350: 552-9), as is evidenced by Jasinski (Blood, 103, 2004, 2827-2834).

With respect to claims 91-93, 99, and 112, Rosse teaches therapeutic treatment of patients with transfusion-dependent paroxysmal nocturnal hemoglobinuria (PNH), which is characterized by chronic intravascular hemolysis (method for treating a patient that is afflicted with a hemolytic disease) by administering to the patients an effective amount of eculizumab, which is a humanized chimeric anti-C5 antibody (whole antibody) which blocks cleavage of C5 into C5a and C5b (Fig. 4; p. 48, 1st ¶; p. 53, 2nd column, lines 16-18).

With respect to claims 96-97, 113 and 114, Rosse further teaches that eculizumab (anti-C5 antibody) has a completely nonfunctional Fc domain (p. 53, lines 10-13). Because the constant region is nonfunctional, eculizumab would necessarily have decreased effector function with respect to antibody-dependent cell mediated cytotoxity (ADCC) and complement dependent cytotoxicity (CDC) relative to the corresponding native constant region.

With respect to claims 111 and 115, Rosse teaches that eculizumab (anti-C5 antibody) was given at a dose of 600 mg every week for 4 weeks (600 mg of the antibody every 7 ± 2 days for the first 4 weeks) and then at a dose of 900 mg every other week (900 mg of the antibody for the fifth dose 7 ± 2 days after and 900 mg of the antibody every 14 ± 2 days thereafter). Rosse further teaches that the drug is given by intravenous infusion over 30 minutes (administration of the antibody to the patient is to occur via 25 to 45 minutes intravenous infusion).

Rosse further teaches that deficiency of complement molecules after C5 remarkably have little phenotype with the exception of an increased risk by encapsulated organisms such as *Neisseria meningitides* (p. 53, lines 1-3).

With respect to claims 91-93, Hill (I) teaches treating patients afflicted with PNH by administering eculizumab which is a humanized monoclonal antibody (whole antibody) that specifically targets C5 (anti-C5 antibody), blocking the generation of C5a and the formation of C5b-9 (inhibits cleavage of C5 into fragments C5a and C5b) (abstract; p. 2559, 3rd ¶)

With respect to claim 98, Hill (I) teaches that sustained efficacy and safety of eculizamab in a 1-year study (anti-C5 antibody is administered to the patient for at least 6 months) (p. 2564, 1st ¶).

With respect to claims 100-102, Hill (I) teaches a hemoglobin level of 10.0 ± 0.4 prior to treatment with eculizumab (patient has a hemoglobin level less than 12-14 g/dL if a man or 10-12 g/dL is a woman).

Claim 104 is included because Hill(I) teaches that the trigger for transfusion before and during the study remained unchanged for each patient and was based on the occurrence of symptoms resulting from anemia, hemolysis, or both (p. 2560 under "clinical investigations"). Thus the recitation "wherein the patient is anemic and the anemia results at least in part from extravascular hemolysis, and wherein the patient remains anemic following treatment with the anti-C5 antibody" is considered to be inherently taught by Hill(I).

With respect to claim 106, Hill (I) teaches a patient with a history of PNH and aplastic anemia (p. 2563, last ¶).

With respect to claim 99, and 101, Hill II teaches treatment of two PNH patients (patient afflicted with a hemolytic disease) by administering eculizumab (anti-C5 antibody) (abstract).

With respect to claim 105, Hill II further teaches that the first 27 year old (patient is at least 18 years of age) during the one year period prior to eculizumab treatment hematological parameters including 47% type III PNH RBCs at baseline (a PNH type II erythrocyte population of greater than 10 %) and that since being diagnosed with PNH in 1998 to treatment in July 2002, the patient was transfusion dependent receiving about 1-2 units/month (received at least 4 transfusion during the 12 months immediately preceding the first treatment with the anti-C5 antibody) (p. e111, 3rd ¶).

Claim 103 is included because while the prior art references do not specifically recite that the patient afflicted with PNH is "due to a C3b-mediated vascular clearance of PNH erythrocytes through the reticuloendothelial system", the prior art of treating the same PNH populations with the same composition (anti-C5 antibody) to achieve the same therapeutic effect does not differ from the claimed methods. The mechanism of action does not have a bearing on the patentability of the invention if the invention was already known or obvious. Mere recognition of latent properties in the prior art does not render nonobvious an otherwise known invention. In re Wiseman, 201 USPQ 658 (CCPA 1979). Granting a patent on the discovery of an unknown but inherent function would remove from the public that which is in the public domain by virtue of its inclusion in, or obviousness from, the prior art. In re Baxter Travenol Labs, 21 USPQ2d 1281 (Fed. Cir. 1991). See M.P.E.P. 2145. As is further evidenced by Jasinski, moreover, mice studies indicate that the shortened survival of PIGA negative RBCs which causes PNH is mediated by macrophage clearance (clearance of PNH erythrocytes through the reticuloendothelial system) (abstract).

The prior art references differ from the claimed invention by the recitation that the patient has been vaccinated against Neisseria meningitides.

With respect to claims 91-93, 99, and 112, Hillmen teaches a method for treating a patient that suffers from paroxysmal nocturnal hemoglobinuria (PNH) which is a disease characterized by hemolytic anemia (patient afflicted with a hemolytic disease) (p. 557, 2nd ¶) by administering to the patient an effective amount of eculizumab (whole antibody) (p. 552, "methods") which specifically binds to the terminal complement protein C5, inhibiting its cleavage into C5a and C5b (p. 553, 3rd ¶). Hillmen further teaches that patients were vaccinated against *N. meningitides* before treatment (p. 554, lines 2-4).

It would be obvious and within the skill of one in the art at the time the invention was made to vaccinate against *Neisseria meningitides* as taught by Hillmen in a method of treating PNH by administration of an anti-C5 antibody such as eculizamab as taught by either Rosse, Hill I or Hill II.

One of ordinary skill in the art at the time the invention was made would have been motivated to because eculizamab targets C5 thereby preventing cleavage of C5, and Rosse teaches that deficiency of complement molecules after C5 result in an increased risk by encapsulated organisms such as *Neisseria meningitides* (p. 53, lines 1-3). Thus, vaccination against *N. meningitides* prior to administration of eculizamab (anti-C5 antibody) for the treatment of PNH as taught by Hillmen would be a prudent measure against the risk of infection from *N. meningitides* in any method where an anti-C5 antibody is administered to a patient.

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

11. Claims 107-110 are rejected under 35 U.S.C. 103(a) as being unpatentable over Rosse et al. (Hematology 2004) OR Hill (Blood, 2005, hereafter "Hill (I)") OR Hill et al. ((Haematologica 2005, hereafter "Hill (II)") in view of Hillmen et al. (N Engl J Med 2004; 350: 552-9), as applied to claims 91-93, 96-102, 105-106 and 111-115 above, and further in view of Garcia et al. (Biologicals (2002) 30, 143-151).

The teachings of Rosse, Hill(I), Hill(II) and Hillmen have been discussed supra.

Hillmen further teaches a pharmaceutical composition comprising eculizumab (anti-C5 monoclonal antibody) which was administered to patients with PNH at 600 mg every week for four weeks, followed one week later by a 900-mg dose and then by 900 mg every other week through week 12.

The prior art references differ from the claimed invention by not expressly reciting a single unit dosage form of 300 mg of the anti-C5 antibody, that the single unit dosage form has a volume of 30 mL and that the single unit dosage form comprises a 10 mg/mL solution of the anti-C5 antibody as in claims 107-109.

The reference teachings also differ from the claimed invention by not reciting that the pharmaceutical composition is a preservative free formulation as in claim 110.

Garci et al. teaches that the influence of preservatives on the safety and stability of antivenoms may be involved in adverse reactions to antivenoms and is an issue that deserves careful consideration (p. 144, 2nd ¶; p. 149, last ¶).

It would have been obvious to one of ordinary skill in the art at the time applicant's invention was made to provide the composition taught by the primary references in a preservative free formulation. One skilled in the art would be motivated to provide the composition in a preservative free formulation because Garci teaches that the presence of preservatives can be an important safety issue in that they may lead to adverse reactions when present in antibody compositions such as antivenoms.

While the prior art references are silent with respect to the limitations that the pharmaceutical composition comprise a single unit dosage form of 300 mg, that the single unit dosage form has a volume of 30 mL (claim 96) and comprises a 10 mg/mL solution of the anti-C5 antibody or C5-binding fragment thereof (claim 97), it has been held that where the general conditions of a claim are disclosed in the prior art, discovering the optimum or workable ranges involves only routine skill in the art. In re Aller, 220 F2d 454, 456, 105 USPQ 233; 235 (CCPA 1955). See MPE §§2144.05 part IIA.

In the instant case, given that Hillmen teaches administration of a 600 mg and 900 mg doses which can both be obtained simply by administering two or three separate single unit dosage forms of 300 mg of the instant claimed invention, respectively, the claimed dosage forms are simply a matter of convenience based upon the needs of the patient and involves only routine skill in the art. Accordingly, it would have been obvious to one of ordinary skill in the art at the time Applicants' invention was made to supply the anti-C5 antibody or C5-binding fragment thereof in a composition comprising 300 mg single unit dosages as well as said dosages in a volume of 30 mL (i.e., 10 mg/mL).

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

12. Claims 94-95 are rejected under 35 U.S.C. 103(a) as being unpatentable over Rosse et al. (Hematology 2004) and Hill (Blood, 2005, hereafter "Hill (I)") and Hill et al. ((Haematologica 2005, hereafter "Hill (II)") and Hillmen et al. (N Engl J Med 2004; 350: 552-9), as applied to claims 91-93, 96-102, 105-106 and 111-115 above, and further in view of Kaplan (Curr. Opin. Investig. Drugs, 3(7): 1017-23 (2002), IDS Ref of 5/13/09).

The teachings of Rosse, Hill(I), Hill (II), and Hillmen have been discussed supra.

The prior art references differ from the claimed invention by not reciting that the anti-C5 antibody is a C5-binding fragment such as an scFv as in claim 94 and that the anti-C5 antibody is pexelizumab as in claim 95.

Kaplan teaches the humanized single chain (scFv) anti-C5 monoclonal antibody fragment, pexelizumab (p. 1018, 4th ¶) which was designed to have the advantage of enhanced tissue penetration.

Those of skill in the art would have had reason to use the anti-C5 binding fragment pexelizumab as a substitute for the anti-C5 antibody eculizumab in the administration to patients with PNH as taught by the prior art references because Kaplan teaches that the antibody fragment has the advantage of enhanced tissue penetration. Substituting a known element for another, to yield the known result, is obvious. See KSR, 550 U.S. at 416, 421.

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

13. No claim is allowed.

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

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you

have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

August 15, 2012

/JAMES ROGERS/
Examiner, Art Unit 1644

/Maher M. Haddad/
Primary Examiner, Art Unit 1644

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

Dated: May 6, 2016
Electronic Signature for Jill Gorny Sloper, Esq.: /Jill Gorny Sloper, Esq./

Docket No.: AXJ-114BUSCN2
(PATENT)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

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

Application No.: Not Yet Assigned

Confirmation No.: N/A

Filed: Concurrently Herewith

Art Unit: N/A

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

Examiner: Not Yet Assigned

INFORMATION DISCLOSURE STATEMENT (IDS)

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

Dear Sir:

In compliance with 37 C.F.R. § 1.56, 1.97 and 1.98, the attention of the Patent and Trademark Office is hereby directed to the documents listed on the attached PTO/SB/08.

For the Examiner's convenience in reviewing this continuation application, Applicant submits a consolidated PTO Form SB/08, listing all references cited during the prosecution of the parent application. The present application is a continuation of U.S. Application No. 13/426,973, filed March 22, 2012 (Atty. Docket No. AXJ-114BUSCN). In accordance with 37 C.F.R. §1.98(d), copies of the references previously cited by or submitted to the Office in the parent application are not enclosed, but will be provided upon request. In accordance with 37 C.F.R. § 1.98(a)(2)(i)-(iv), Applicant submits herewith copies of a non-patent literature references.

It is respectfully requested that the documents listed on the PTO/SB/08 be expressly considered by the Examiner during the prosecution of this application, and that the documents be made of record therein and appear among the "References Cited" on any patent to issue therefrom.

Applicants call to the attention of the Examiner the following Applications and Office Actions cited therein:

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

Office Actions (copies enclosed)			
Examiner's Initials	Serial No.	Date Mailed from USPTO	Examiner
	13/426,973	01-27-2014	J. Rogers
	13/426,973	05-31-2013	J. Rogers
	13/426,973	08-20-2012	J. Rogers
	12/225,040	09-22-2011	J. Rogers
	12/225,040	06-01-2011	J. Rogers
	12/225,040	04-11-2011	J. Rogers
	12/621,792	09-30-2010	P. Gambel
	10/771,552	12-22-2008	F. Vandervegt
	10/771,552	03-21-2008	F. Vandervegt
	10/771,552	08-10-2007	F. Vandervegt
	10/771,552	02-26-2007	F. Vandervegt
	10/771,552	09-26-2006	F. Vandervegt
	11/050,543	07-09-2010	P. Gambel
	11/050,543	04-02-2008	F. Vandervegt
	11/050,543	10-10-2007	F. Vandervegt
	11/050,543	06-11-2007	F. Vandervegt
	11/595,118	01-21-2011	P. Gambel
	11/595,118	10-05-2010	P. Gambel

	11/595,118	07-07-2010	P. Gambel
	11/595,118	04-03-2009	F. Vandervegt
	12/902,617	06-23-2011	P. Gambel
	12/902,617	04-04-2011	P. Gambel
	13/335,518	09-12-2014	P. Gambel
	13/335,518	02-06-2014	P. Gambel
	13/335,518	11-07-2013	P. Gambel

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

This Information Disclosure Statement accompanies the new patent application submitted herewith. Accordingly, no fees are due with this submission (37 C.F.R § 1.97(b)(3)). However, the Director is hereby authorized to charge any fee deficiency which should have been filed herewith (or with any paper hereafter filed in this application by this firm) to our Deposit Account No. 12-0080, under Order No. AXJ-114BUSCN2.

Dated: May 6, 2016

Respectfully submitted,

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PTO/SB/08a (03-15)
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U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

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INFORMATION DISCLOSURE STATEMENT BY APPLICANT
(Not for submission under 37 CFR 1.99)

Application Number	
Filing Date	
First Named Inventor	Leonard BELL
Art Unit	N/A
Examiner Name	Not Yet Assigned
Attorney Docket Number	AXJ-114BUSCN2

U.S.PATENTS Remove

Examiner Initial*	Cite No	Patent Number	Kind Code[1]	Issue Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear
	1	4686100		1987-08-11	Raffin et al.	
	2	5135916		1992-08-04	Sims et al.	
	3	5660825		1997-08-26	Sims et al.	
	4	6355245		2002-03-12	Evans et al.	
	5	7361339		2008-04-22	Bell	
	6	7482435		2009-01-27	Bowdish et al.	

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Examiner Initial*	Cite No	Publication Number	Kind Code[1]	Publication Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
	Application Number	
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	First Named Inventor	Leonard BELL
	Art Unit	N/A
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	1	0411306	EP	A1	1991-02-06	Goetze, Otto Prof. Dr. Med		
	2	2004/029207	WO	A2	2004-04-08	Xencor Inc		
	3	2005074607	WO	A2	2005-08-18	Alexion Pharmaceuticals, Inc		

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Signature	/Jill Gorny Sloper, Esq./	Date (YYYY-MM-DD)	2016-05-06
Name/Print	Jill Gorny Sloper, Esq.	Registration Number	60760

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Electronic Patent Application Fee Transmittal

Application Number:	
Filing Date:	
Title of Invention:	TREATMENT OF PAROXYSMAL NOCTURNAL HEMOGLOBINURIA PATIENTS BY AN INHIBITOR OF COMPLEMENT
First Named Inventor/Applicant Name:	Leonard BELL
Filer:	Jill R. Gorny Sloper/Carolyn Blake
Attorney Docket Number:	AXJ-114BUSCN2

Filed as Large Entity

Filing Fees for Utility under 35 USC 111(a)

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Basic Filing:				
Utility application filing	1011	1	280	280
Utility Search Fee	1111	1	600	600
Utility Examination Fee	1311	1	720	720
Pages:				
Claims:				
Miscellaneous-Filing:				
Late Filing Fee for Oath or Declaration	1051	1	140	140
Petition:				

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Patent-Appeals-and-Interference:				
Post-Allowance-and-Post-Issuance:				
Extension-of-Time:				
Miscellaneous:				
		Total in USD ($)		1740

Electronic Acknowledgement Receipt	
EFS ID:	25688668
Application Number:	15148839
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Confirmation Number:	3159
Title of Invention:	TREATMENT OF PAROXYSMAL NOCTURNAL HEMOGLOBINURIA PATIENTS BY AN INHIBITOR OF COMPLEMENT
First Named Inventor/Applicant Name:	Leonard BELL
Customer Number:	133485
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Attorney Docket Number:	AXJ-114BUSCN2
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Payment was successfully received in RAM	$1740
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Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Specification	AXJ-114BUSCN2_Specification.pdf	4591252 438a1bafcd0f36b0385034f014fa65ed7c8d4efa	no	45
Warnings:					
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2	Claims	AXJ-114BUSCN2_Claim.pdf	13322 e98bd2718bbed10ae396eb4c20fac1cdd61b1960	no	1
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3	Abstract	AXJ-114BUSCN2_Abstract.pdf	16322 5f9d0b2dc85355a9a87a9b86c6987bf0eace0756	no	1
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4	Drawings-only black and white line drawings	AXJ-114BUSCN2_Drawings.pdf	168940 54f57878bd8e61e713877134 27d96158267473c9	no	4
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5	Sequence Listing (Text File)	AXJ-114BUSCN2_Seq_Listing.txt	10493	no	0
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6	CRF Statement Paper and CRF are the same	AXJ-114BUSCN2_Seq_Listing_Statement.pdf	28034 54a65e245e9268a385d3b08a407f9ca86f09820d	no	2
Warnings:					
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7	Application Data Sheet	AXJ-114BUSCN2_ADS.pdf	1823044 bc6e23ac0593dd0e0bc59b0f8c84edc47f680dff	no	9
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8	Power of Attorney	AXJ-114BUSCN2_POA.pdf	1235610 45b1eafec744f7d6f96e5b3e8ce2a44de43d4803	no	2
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9	Petition to make special under Patent Prosecution Hwy	AXJ-114BUSCN2_PPH-Request.pdf	26425 bf64db3569fe62336c9dc34ea8b8365558718585	no	2
Warnings:					
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10	Non Patent Literature	CELLA.pdf	26534 ee671a2da07bc0da2fecbf7b3d90d76f394d98f5	no	1
Warnings:					
Information:					
11	Non Patent Literature	Corvini.pdf	148724 f64ce458a4383cfcc6fafc8af3cf1233b689d986	no	1
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12	Non Patent Literature	Morris.pdf	78106 117f214dfcd6e57607ae197c8d2b50f6aac3db69	no	1
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13	Non Patent Literature	Sierra.pdf	2272544 2700b5f73ca5cfa5331c9cf3127e6a9a0e580ccb	no	16
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14	Other Reference-Patent/App/Search documents	10771552.pdf	1115237 e3a89e9c3877787ada055bda3925f0f4d1f40a8a	no	26
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15	Other Reference-Patent/App/Search documents	11050543.pdf	1248587 4d4e8fa198834e1f4bdfc2e78ed07b6a89c5b493	no	27
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16	Other Reference-Patent/App/Search documents	11595118.pdf	1336578 138e6ad08e8059db9828fc3b209fc4fa6c083838	no	28
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17	Other Reference-Patent/App/Search documents	12225040.pdf	794072 fe79d9838d9718506cb151f86188c00c803c7a1c	no	17
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18	Other Reference-Patent/App/Search documents	12621792.pdf	831144 522897dd58c3e8bb9ecc869ef4e18034ae8d8dba	no	14
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19	Other Reference-Patent/App/Search documents	12902617.pdf	988774 ca5082bb6aa229b368848c9f9af2692cc5d427e8	no	19
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21	Other Reference-Patent/App/Search documents	13426973.pdf	1459620 f9f777145b54b47f770f50c521a65ebb31250c36	no	27
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22	Information Disclosure Statement (IDS) Form (SB08)	IDSTRANS_AXJ-114BUSCN2.pdf	32800 de50bab0ee8a9d17c67be8566eedd3591c3a1e86	no	3
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23	Information Disclosure Statement (IDS) Form (SB08)	SB01.pdf	1040147 70794589875db1fca9b95b5343f1e2bcf2ede768	no	10
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24	Information Disclosure Statement (IDS) Form (SB08)	SB02.pdf	1036917 2a4c8d90239739ddf9509ae11c20709cc9c4c739	no	5
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TREATMENT OF PAROXYSMAL NOCTURNAL HEMOGLOBINURIA PATIENTS BY AN INHIBITOR OF COMPLEMENT

BACKGROUND

Paroxysmal nocturnal hemoglobinuria (PNH) is an acquired hematologic disease that results from clonal expansion of hematopoietic stem cells with somatic mutations in the X-linked gene called PIG-A.[1,2] Mutations in PIG-A lead to an early block in the synthesis of glycosylphosphatidylinositol (GPI)-anchors, which are required to tether many proteins to the cell surface. Consequently, PNH blood cells have a partial (type II) or complete (type III) deficiency of GPI-anchored proteins.

Intravascular hemolysis is a prominent feature of PNH and a direct result of the absence of the GPI-anchored complement regulatory protein CD59.[3,4] Under normal circumstances, CD59 blocks the formation of the terminal complement complex (also called the membrane attack complex) on the cell surface, thereby preventing erythrocyte lysis and platelet activation.[5-8] Excessive or persistent intravascular hemolysis in PNH patients not only results in anemia (normal ranges of hemoglobin are 14-18 g/dL for men and 12-16 g/dL for women, and persons with lower levels are considered to be anemic), but also hemoglobinuria and clinical sequelae related to the release of the erythrocyte contents into the circulation: fatigue, thrombosis, abdominal pain, dysphagia, erectile dysfunction, and pulmonary hypertension.[9,10,21,22] Indeed, impaired quality of life in PNH is disproportionate to the degree of anemia. Many PNH patients depend on blood transfusions to maintain adequate erythrocyte hemoglobin levels. There have been no therapies that effectively reduce intravascular hemolysis and improve the associated clinical morbidities in PNH.

Eculizumab is a humanized monoclonal antibody directed against the terminal complement protein C5.[11] In a preliminary, 12-week, open-label clinical study in 11 PNH patients, eculizumab was shown to reduce intravascular hemolysis and transfusion requirements.[12] However, this unblinded study involved a small number of patients with no control arm and without protocol-driven transfusion standards.

SUMMARY

The present pivotal, phase III study, Transfusion Reduction Efficacy and Safety Clinical Investigation, Randomized, Multi-Center, Double-Blind, Placebo-Controlled, Using Eculizumab in Paroxysmal Nocturnal Hemoglobinuria (TRIUMPH), evaluated the effect of eculizumab on the stabilization of hemoglobin levels and transfusion requirements during 6 months of treatment in a cohort of 87 transfusion-dependent PNH patients. Measures of intravascular hemolysis and quality of life were also assessed. This is the first placebo controlled study of a PNH patient population to control hemolysis and to differentiate between the effects due to hemolysis and the effects due to anemia.

It has been surprisingly discovered that certain aspects of quality of life were unexpectedly improved by the treatment of PNH patients with eculizumab. Furthermore, these improvements in the quality of life were independent of transfusion. The improved aspects include, e.g., global health status, physical functioning, emotional functioning, cognitive functioning, role functioning, social functioning, fatigue, pain, dyspnea, appetite loss and insomnia. Improvement was also seen in nausea and vomiting, diarrhea, constipation, and financial difficulties but did not reach the level of statistical significance. Because the treated patients remained anemic throughout their treatment, it was unexpected that all of these improvements would have been seen because they were previously thought to be a result of the patient being anemic. Although not wishing to be bound by any theory, it appears that some of the symptoms are likely due, at least in part, to hemolysis and release of hemoglobin into the bloodstream and do not result solely from the patient being anemic. The treatment with eculizumab decreases the amount of lysis thereby limiting hemoglobin release into the bloodstream, thereby apparently resulting in the improvements seen in the treated patients' quality of life. The results presented herein indicate that any treatment that decreases hemolysis in a patient will result in an improvement in the quality of life of said patient.

In certain aspects, the application provides a method to improve at least one aspect of the quality of life of a patient suffering from paroxysmal nocturnal hemoglobinuria, said method comprising administering to said patient in need thereof a compound which inhibits complement or inhibits formation of C5b-9.

In certain aspects, the application provides a method to improve at least one aspect of the quality of life of a patient suffering from paroxysmal nocturnal hemoglobinuria, said method comprising administering to said patient in need thereof a compound which inhibits

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intravascular hemolysis. In certain embodiments, said method results in a greater than 30% reduction in LDH in said patient.

In certain aspects, the application provides a method to improve at least one aspect of the quality of life of an anemic patient whose anemia results at least in part from hemolysis, said method comprising administering to said patient in need thereof a compound which inhibits intravascular hemolysis, wherein said patient remains anemic. In certain embodiments, said method results in a greater than 30% reduction in LDH in said patient.

In certain aspects, the application provides a method of prolonging the health-adjusted life expectancy of a patient comprising administering to said patient in need thereof a compound which inhibits formation of C5b-9. In certain embodiments, said patient is anemic. In certain embodiments, said patient remains anemic following treatment. In certain embodiments, said patient has a hemoglobin level less than i) 14 g/dL if a man or ii) 12 g/dL if a woman. In certain embodiments, said patient has a hemoglobin level less than i) 13 g/dL if a man or ii) 11 g/dL if a woman. In certain embodiments, said patient has a hemoglobin level less than i) 12 g/dL if a man or ii) 10 g/dL if a woman. In certain embodiments, said patient suffers from paroxysmal nocturnal hemoglobinuria.

In certain aspects, the application provides a pharmaceutical composition comprising an antibody that binds C5 or an active antibody fragment thereof. In certain embodiments, the antibody that binds C5 or an active antibody fragment thereof is eculizumab. In certain embodiments, the antibody that binds C5 or an active antibody fragment thereof is pexelizumab. In certain embodiments, the pharmaceutical formulations of the application may be administered to a subject, particularly a subject having PNH.

In certain aspects, the application provides a method of treating a patient suffering from paroxysmal nocturnal hemoglobinuria by administering a pharmaceutical composition comprising an antibody that binds C5 or an active antibody fragment thereof. In certain embodiments, the antibody that binds C5 or an active antibody fragment thereof is eculizumab. In certain embodiments, the antibody that binds C5 or an active antibody fragment thereof is pexelizumab. In certain embodiments, the pharmaceutical formulations of the application may be administered to a subject, particularly a subject having PNH.

In certain aspects, the application provides kits comprising a pharmaceutical composition of the application. In some embodiments, the kit further comprises at least one component of a closed sterile system. Components of the closed sterile system

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include, but are not limited to, needles, syringes, catheter based syringes, needle based injection devices, needle-less injection devices, filters, tubing, valves and cannulas. In a related embodiment, the kit comprise components for the removal of a preservative from the composition. Such components include filters, syringes, vials, containers, tubing, etc.

In certain embodiments, said quality of life is measured by a FACIT-Fatigue score. In certain embodiments, the FACIT-Fatigue score increases by at least 3 points. In certain embodiments, the FACIT-Fatigue score increases by ≥ 4 points.

In certain embodiments, said quality of life is measured by an EORTC QLQ-C30 score. In certain embodiments, said EORTC QLQ-C30 score improves by $\geq 10\%$ of the pretreatment score. In certain embodiments, said aspect of the quality of life as measured by an EORTC QLQ-C30 score is selected from the group consisting of a) global health status, b) physical functioning, c) emotional functioning, d) cognitive functioning, e) role functioning, f) social functioning, g) fatigue, h) pain, i) dyspnea, j) appetite loss, and k) insomnia. In certain embodiments, said aspect of quality of life is fatigue.

In certain embodiments, said compound is selected from the group consisting of CR1, LEX-CR1, MCP, DAF, CD59, Factor H, cobra venom factor, FUT-175, complestatin, and K76 COOH. In certain embodiments, said compound is a steroid that suppresses complement.

In certain embodiments, said compound is selected from the group consisting of antibodies, active antibody fragments, soluble complement inhibitory compounds, proteins, soluble complement inhibitors with a lipid tail, protein fragments, peptides, small organic compounds, RNA aptamers, L-RNA aptamers, spiegelmers, antisense compounds, serine protease inhibitors, double stranded RNA, small interfering RNA, locked nucleic acid inhibitors, and peptide nucleic acid inhibitors. In certain embodiments, said compound is an antibody or an active antibody fragment. In certain embodiments, said antibody or active antibody fragment is selected from the group consisting of a) polyclonal antibodies, b) monoclonal antibodies, c) single chain antibodies, d) chimeric antibodies, e) humanized antibodies, f) Fabs, g) F(ab')s, h) $F(ab')_2$s, i) Fvs, j) diabodies, and k) human antibodies.

In certain embodiments, said antibody or an active antibody fragment thereof binds C5. In certain embodiments, said antibody or active antibody fragment blocks C5 cleavage. In certain embodiments, said antibody or active antibody fragment inhibits the formation of C5b-9. In certain embodiments, said antibody is eculizumab. In certain embodiments, said antibody or active antibody fragment is administered for at least 6

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months. In certain embodiments, said patient has aplastic anemia or myelodysplastic syndrome.

In certain embodiments, said antibody that binds C5 or an active antibody fragment thereof is administered in a single unit dosage form. In certain embodiments, the single unit dosage form is a 300 mg unit dosage form. In certain embodiments, the single unit dosage form is lyophilized. In certain embodiments, the single unit dosage form is a sterile solution. In certain embodiments, the single unit dosage form is a preservative free formulation. In certain embodiments, the 300 mg single-use dosage form comprises 30 ml of a 10 mg/ml sterile, preservative free solution.

In certain embodiments, the antibody that binds C5 or an active antibody fragment thereof comprises an altered constant region, wherein said antibody or antigen-binding fragment exhibits decreased effector function relative to an anti-CDCP1 antibody with a native constant region. In certain embodiments, decreased effector function comprises one or more properties of the following group: a) decreased antibody-dependent cell-mediated cytotoxicity (ADCC), and b) decreased complement dependent cytotoxicity (CDC), compared to an anti-CDCP1 antibody with a native constant region. In certain embodiments, the altered constant region comprises a G2/G4 construct in place of the G1 domain.

In certain embodiments, the antibody that binds C5 or an active antibody fragment thereof comprises a heavy chain variable region and a light chain variable region, wherein the heavy chain variable region comprises one or more CDR regions having an amino acid sequence selected from the group consisting of SEQ ID NO:5, SEQ ID NO:6, or SEQ ID NO:7, and wherein the light chain variable region comprises one or more CDR regions having an amino acid sequence selected from the group consisting of SEQ ID NO:8, SEQ ID NO:9, or SEQ ID NO:10. In certain embodiments, the antibody that binds C5 or an active antibody fragment thereof comprises a heavy chain variable region and a light chain variable region, wherein the heavy chain variable region consists of SEQ ID NO: 1 and the light chain variable region consists of SEQ ID NO: 3. In certain embodiments, the pharmaceutical composition comprises eculizumab. In certain embodiments, the pharmaceutical composition comprises pexelizumab. In certain embodiments, the antibody that binds C5 or an active antibody fragment thereof comprises a heavy chain and a light chain, wherein the heavy chain consists of SEQ ID NO: 2 and the light chain consists of SEQ ID NO: 4.

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In certain embodiments, said patient is anemic. In certain embodiments, said patient remains anemic following treatment. In certain embodiments, said patient has a hemoglobin level less than i) 14 g/dL if a man or ii) 12 g/dL if a woman. In certain embodiments, said patient has a hemoglobin level less than i) 13 g/dL if a man or ii) 11 g/dL if a woman. In certain embodiments, said patient has a hemoglobin level less than i) 12 g/dL if a man or ii) 10 g/dL if a woman.

In certain embodiments, said health-adjusted life expectancy is measured according to a unit selected from the group consisting of Years of potential life lost, Disability-free life expectancy, Health-adjusted life year, Quality adjusted life year, Healthy years equivalents, Healthy days gained, Episode-free day, Q-TWiST, Health Utilities Index, or Years of healthy life.

In certain embodiments, the health-adjusted life expectancy in a subject is prolonged by at least one day. In certain embodiments, the health-adjusted life expectancy in a subject is prolonged by at least week. In certain embodiments, the health-adjusted life expectancy in a subject is prolonged by at least one month. In certain embodiments, the health-adjusted life expectancy in a subject is prolonged by at least one year.

In certain embodiments, the pharmaceutical composition is in a single unit dosage form. In certain embodiments, the single unit dosage form is a 300 mg unit dosage form. In certain embodiments, the pharmaceutical composition is lyophilized. In certain embodiments, the pharmaceutical composition is a sterile solution. In certain embodiments, the pharmaceutical composition is a preservative free formulation. In certain embodiments, the pharmaceutical composition comprises a 300 mg single-use formulation of 30 ml of a 10 mg/ml sterile, preservative free solution. In certain embodiments, the pharmaceutical composition comprises an antibody that binds C5 or an active antibody fragment thereof.

BRIEF DESCRIPTION OF THE FIGURES

Figures 1A-B show that eculizumab treatment decreases intravascular hemolysis and increases PNH type III erythrocytes. Figure 1A shows the degree of intravascular hemolysis in PNH patients, demonstrated by mean lactate dehydrogenase (LDH) levels. Figure 1B shows the mean proportion of PNH type III erythrocytes assessed for placebo- and eculizumab-treated patients.

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Figure 2 shows the effect of eculizumab treatment on transfusion requirements in PNH patients. This is a Kaplan-Meier plot of time to first transfusion for eculizumab- and placebo-treated patients from baseline through week 26. The P value is from the log rank analysis.

Figure 3 shows the effect of eculizumab on fatigue assessed by the FACIT-Fatigue Instrument. Quality of Life scores were assessed using the Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-Fatigue) instrument. Values for change from baseline to 26 weeks represent least-square means. A positive change indicates an improvement and a negative change indicates deterioration in the FACIT-Fatigue measures of quality of life.

DETAILED DESCRIPTION

I. Definitions

The term "derived from" means "obtained from" or "produced by" or "descending from".

The term "genetically altered antibodies" means antibodies wherein the amino acid sequence has been varied from that of a native antibody. Because of the relevance of recombinant DNA techniques to this application, one need not be confined to the sequences of amino acids found in natural antibodies; antibodies can be redesigned to obtain desired characteristics. The possible variations are many and range from the changing of just one or a few amino acids to the complete redesign of, for example, the variable or constant region. Changes in the constant region will, in general, be made in order to improve or alter characteristics, such as complement fixation, interaction with membranes and other effector functions. Changes in the variable region will be made in order to improve the antigen binding characteristics.

The term "an antigen-binding fragment of an antibody" refers to any portion of an antibody that retains the binding utility to the antigen. An exemplary antigen-binding fragment of an antibody is the heavy chain and/or light chain CDR, or the heavy and/or light chain variable region.

The term "homologous," in the context of two nucleic acids or polypeptides refers to two or more sequences or subsequences that have at least about 85%, at least 90%, at least 95%, or higher nucleotide or amino acid residue identity, when compared and aligned for maximum correspondence, as measured using the following sequence comparison

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method and/or by visual inspection. In certain embodiments, the "homolog" exists over a region of the sequences that is about 50 residues in length, at least about 100 residues, at least about 150 residues, or over the full length of the two sequences to be compared.

Methods of determining percent identity are known in the art. "Percent (%) sequence identity" with respect to a specified subject sequence, or a specified portion thereof, may be defined as the percentage of nucleotides or amino acids in the candidate derivative sequence identical with the nucleotides or amino acids in the subject sequence (or specified portion thereof), after aligning the sequences and introducing gaps, if necessary to achieve the maximum percent sequence identity, as generated by the program WU-BLAST-2.0a19 (Altschul et al., J. Mol. Biol. 215:403-410 (1997); http://blast.wustl.edu/blast/README.htm- l) with search parameters set to default values. The HSP S and HSP S2 parameters are dynamic values and are established by the program itself depending upon the composition of the particular sequence and composition of the particular database against which the sequence of interest is being searched. A "% identity value" is determined by the number of matching identical nucleotides or amino acids divided by the sequence length for which the percent identity is being reported.

II. Overview

The present disclosure relates to a method of treating paroxysmal nocturnal hemoglobinuria ("PNH"), more specifically to improving certain aspects of quality of life which are impaired in PNH patients, and other hemolytic diseases in mammals. Specifically, the methods of treating hemolytic diseases, which are described herein, involve using compounds which bind to or otherwise block the generation and/or activity of one or more complement components. The present methods have been found to provide surprising results. For instance, hemolysis rapidly ceases upon administration of the compound which binds to or otherwise blocks the generation and/or activity of one or more complement components, with hemoglobinuria being significantly reduced after treatment. Also, hemolytic patients can be rendered less dependent on transfusions or transfusion-independent for extended periods (twelve months or more), well beyond the 120 day life cycle of red blood cells. In addition, type III red blood cell count can be increased dramatically in the midst of other mechanisms of red blood cell lysis (non-complement mediated and/or earlier complement component mediated e.g., Cb3). Another example of a surprising result is that symptoms resolved, indicating that NO serum levels were increased

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enough even in the presence of other mechanisms of red blood cell lysis. These and other results reported herein are unexpected and could not be predicted from prior treatments of hemolytic diseases.

III The Complement System

The complement system, useful complement inhibitors, and use of these inhibitors to treat PNH and other patients are more fully described in PCT Patent Application PCT/US2005/003225 filed February 3, 2005 and published as International Publication Number WO 2005/074607 A2 on August 18, 2005, the contents of which are incorporated herein by reference in their entirety.

The complement system acts in conjunction with other immunological systems of the body to defend against intrusion of cellular and viral pathogens. There are at least 25 complement proteins, which are found as a complex collection of plasma proteins and membrane cofactors. The plasma proteins make up about 10% of the globulins in vertebrate serum. Complement components achieve their immune defensive functions by interacting in a series of intricate but precise enzymatic cleavage and membrane binding events. The resulting complement cascade leads to the production of products with opsonic, immunoregulatory, and lytic functions.

The complement cascade progresses via the classical pathway or the alternative pathway. These pathways share many components and, while they differ in their initial steps, they converge and share the same "terminal complement" components (C5 through C9) responsible for the activation and destruction of target cells.

The classical complement pathway is typically initiated by antibody recognition of and binding to an antigenic site on a target cell. The alternative pathway is usually antibody independent and can be initiated by certain molecules on pathogen surfaces. Both pathways converge at the point where complement component C3 is cleaved by an active protease (which is different in each pathway) to yield C3a and C3b. Other pathways activating complement attack can act later in the sequence of events leading to various aspects of complement function.

C3a is an anaphylatoxin. C3b binds to bacterial and other cells, as well as to certain viruses and immune complexes, and tags them for removal from the circulation. C3b in this role is known as opsonin. The opsonic function of C3b is considered to be the most

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important anti-infective action of the complement system. Patients with genetic lesions that block C3b function are prone to infection by a broad variety of pathogenic organisms, while patients with lesions later in the complement cascade sequence, i.e., patients with lesions that block C5 functions, are found to be more prone only to Neisseria infection, and then only somewhat more prone (Fearon, 1983).

C3b also forms a complex with other components unique to each pathway to form classical or alternative C5 convertase, which cleaves C5 into C5a and C5b. C3 is thus regarded as the central protein in the complement reaction sequence since it is essential to both the alternative and classical pathways (Wurzner et al., 1991). This property of C3b is regulated by the serum protease Factor I, which acts on C3b to produce iC3b. While still functional as opsonin, iC3b cannot form an active C5 convertase.

C5 is a 190 kDa beta globulin found in normal serum at approximately 75 μg/mL (0.4 μM). C5 is glycosylated, with about 1.5-3 percent of its mass attributed to carbohydrate. Mature C5 is a heterodimer of a 999 amino acid 115 kDa alpha chain that is disulfide linked to a 656 amino acid 75 kDa beta chain. C5 is synthesized as a single chain precursor protein product of a single copy gene (Haviland et al., 1991). The cDNA sequence of the transcript of this gene predicts a secreted pro-C5 precursor of 1659 amino acids along with an 18 amino acid leader sequence.

The pro-C5 precursor is cleaved after amino acid 655 and 659, to yield the beta chain as an amino terminal fragment (amino acid residues +1 to 655) and the alpha chain as a carboxyl terminal fragment (amino acid residues 660 to 1658), with four amino acids deleted between the two.

C5a is cleaved from the alpha chain of C5 by either alternative or classical C5 convertase as an amino terminal fragment comprising the first 74 amino acids of the alpha chain (i.e., amino acid residues 660-733). Approximately 20 percent of the 11 kDa mass of C5a is attributed to carbohydrate. The cleavage site for convertase action is at or immediately adjacent to amino acid residue 733. A compound that would bind at or adjacent to this cleavage site would have the potential to block access of the C5 convertase enzymes to the cleavage site and thereby act as a complement inhibitor.

C5 can also be activated by means other than C5 convertase activity. Limited trypsin digestion (Minta and Man, 1977; Wetsel and Kolb, 1982) and acid treatment

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(Yamamoto and Gewurz, 1978; Vogt et al., 1989) can also cleave C5 and produce active C5b.

C5a is another anaphylatoxin. C5b combines with C6, C7, and C8 to form the C5b-8 complex at the surface of the target cell. Upon binding of several C9 molecules, the membrane attack complex (MAC, C5b-9, terminal complement complex-TCC) is formed. When sufficient numbers of MACs insert into target cell membranes the openings they create (MAC pores) mediate rapid osmotic lysis of the target cells. Lower, non-lytic concentrations of MACs can produce other effects. In particular, membrane insertion of small numbers of the C5b-9 complexes into endothelial cells and platelets can cause deleterious cell activation. In some cases activation may precede cell lysis.

As mentioned above, C3a and C5a are anaphylatoxins. These activated complement components can trigger mast cell degranulation, which releases histamine and other mediators of inflammation, resulting in smooth muscle contraction, increased vascular permeability, leukocyte activation, and other inflammatory phenomena including cellular proliferation resulting in hypercellularity. C5a also functions as a chemotactic peptide that serves to attract pro-inflammatory granulocytes to the site of complement activation.

The beneficial effect of anti-C5 mAb has previously been reported in several experimental models including myocardial reperfusion (Vakeva et al., 1998), systemic lupus erythematosus (Wang et al., 1996) and rheumatoid arthritis (Wang et al., 1995); as well as in human clinical trials (Kirschfink, 2001) of autoimmune disease, cardiopulmonary bypass and acute myocardial infarction.

IV Measures of Quality of Life

Various measurements exist to assess quality of life and the effect of medical interventions on quality of life for example the Mini-Mental State Examination (MMSE), the Short Test of Mental Status, the European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire, the FACIT questionnaires and subscales including fatigue and anemia, the Likert Scale, and Borg Scale (Tombaugh, et al., J. Am. Geriatr. Soc. 40:922, 1992; Cummings, JAMA. 269(18):2420, 1993; Crum, et al., JAMA. 269(18):2386, 1993; Folstein, et al., J. Psychiat. Res. 12:189,1975; Kokmen, et al., Mayo Clin. Proc. 62:281, 1987; Tang-Wai, et al., Arch. Neurol. 60:1777, 2003; Tamburini, Ann.

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Oncol. 12(Suppl. 3):S7, 2001; Webster et al., Health and Quality of Life Outcomes. 1:79, 2003, www.hqlo.com/content/I/I/79; Grant, et al., Chest. 116:1208, 1999; and www.qolid.org). Any of these measurements may be used to assess the change in quality of life due to administration of a compound which inhibits complement or inhibits formation of C5b-9.

In certain embodiments, improvement in quality of life due to administration of a compound which inhibits complement or inhibits formation of C5b-9 is measured by the Functional Assessment of Chronic Illness Therapy (FACIT) Measurement System. In certain embodiments, improvement in quality of life is measured by: a) full scales; b) stand-alone subscales; and c) symptom indices.

In certain embodiments, improvement in quality of life due to administration of a compound which inhibits complement or inhibits formation of C5b-9 is measured by a European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire. In certain embodiments, the EORTC questionnaire is the QLQ-C30.

In certain embodiments, improvement in quality of life is measured by the health-adjusted life expectancy (HALE) index as described in Wilkins, R. and Adams, OB., Am J Public Health, 73:1073-1080 (1983). Health-adjusted life expectancy is an average of the quality-adjusted life years (QALY) for a given population and can be used to evaluate the therapeutic value of a medical intervention. Quality-adjusted life years is a health index that weighs each year of life on a scale from 1 to 0 (Weinstein MC and Stason WB, N Engl J Med, 296:716-721 (1977)). Perfect health is rated as 1, death is rated as 0, and disability and pain are rated based on severity. QALY is determined by multiplying the number of years at each health status.

In certain embodiments, improvement in quality of life is measured by the following instruments: Years of potential life lost, Disability-free life expectancy, Health-adjusted life year, Quality adjusted life year, Healthy years equivalents, Healthy days gained, Episode-free day, Q-TWiST, Health Utilities Index, and Years of healthy life. These measurements account for both changes in mortality as well as changes in morbidity and disability. Any of these measurements may be used to assess the change in quality of life due to administration of a compound which inhibits complement or inhibits formation of C5b-9.

In one embodiment, the disclosed methods improve the quality of life of a patient for at least one day, at least one week, at least two weeks, at least three weeks, at least one

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month, at least two months, at least three months, at least 6 months, at least one year, at least 18 months, at least two years, at least 30 months, or at least three years, or the duration of treatment.

In certain embodiments, the symptoms used to measure quality of life are scaled for intensity. In certain embodiments, the symptoms are scaled for frequency. In certain embodiments, the symptoms are scaled for intensity and frequency.

In certain aspects, the application provides a method for prolonging the health-adjusted life expectancy of a subject comprising administering to the subject a compound which inhibits complement or inhibits formation of C5b-9. The above measurements account for both changes in mortality as well as changes in morbidity and disability. Any of these measurements may be used to assess the change in quality-adjusted life expectancy due to administration of a compound which inhibits complement or inhibits formation of C5b-9.

In one embodiment, the disclosed methods prolong the health-adjusted life expectancy in a subject by at least one day, at least one week, at least two weeks, at least three weeks, at least one month, at least two months, at least three months, at least 6 months, at least one year, at least 18 months, at least two years, at least 30 months, or at least three years as measured by the health-adjusted life expectancy (HALE) index as described in Wilkins et al. Am J Public Health, 73:1073-1080 (1983). Health-adjusted life expectancy is an average of the quality-adjusted life years (QALY) for a given population and can be used to evaluate the therapeutic value of a medical intervention. Quality-adjusted life years is a health index that weighs each year of life on a scale from 1 to 0 (Weinstein et al., N Engl J Med, 296:716-721 (1977)). Perfect health is rated as 1, death is rated as 0, and disability and pain are rated based on severity. QALY is determined by multiplying the number of years at each health status.

V Inhibitors of the Complement Cascade

In certain embodiments, any compound which binds to or otherwise blocks the generation and/or activity of one or more complement components can be used in the present methods. In certain embodiments, a complement inhibitor may be a small molecule (up to 6,000 Da in molecular weight), a nucleic acid or nucleic acid analog, a peptidomimetic, or a macromolecule that is not a nucleic acid, a serine protease inhibitor, or a protein. These agents include, but are not limited to, small organic molecules, RNA

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aptamers including ARC187 (which is commercially available from Archemix Corp., Cambridge, Mass.), L-RNA aptamers, Spiegelmers, antisense compounds, molecules which may be utilized in RNA interference (RNAi) such as double stranded RNA including small interfering RNA (siRNA), locked nucleic acid (LNA) inhibitors, peptide nucleic acid (PNA) inhibitors.

In certain embodiments, a complement inhibitor may be a protein or protein fragment. Proteins are known which inhibit the complement cascade, including CD59, CD55, CD46 and other inhibitors of C8 and C9 (see, e.g., U.S. Patent 6,100,443). Proteins known as complement receptors and which bind complement are also known (see, Published PCT Patent Application WO 92/10205 and U.S. Patent 6,057,131). Use of soluble forms of complement receptors, e.g., soluble CR1, can inhibit the consequences of complement activation such as neutrophil oxidative burst, complement mediated neural injury, and C3a and C5a production. In certain embodiments, a complement inhibitor may be naturally occurring or soluble forms of complement inhibitory compounds such as CR1, LEX-CR1, MCP, DAF, CD59, Factor H, cobra venom factor, FUT-175, complestatin, and K76 COOH. Those of skill in the art recognize the above as some, but not all, of the known methods of inhibiting complement and its activation.

In certain embodiments, a complement inhibitor may be an antibody capable of inhibiting complement, such as an antibody that can block the formation of MAC. For example, an antibody complement inhibitor may include an antibody that binds C5. Such anti-C5 antibodies may directly interact with C5 and/or C5b, so as to inhibit the formation of and/or physiologic function of C5b.

Suitable anti-C5 antibodies are known to those of skill in the art. Antibodies can be made to individual components of activated complement, e.g., antibodies to C7, C9, etc. (see, e.g., U.S. Patent 6,534,058; published U.S. patent application US 2003/0129187; and U.S. Patent 5,660,825). U.S. Patent 6,355,245 teaches an antibody which binds to C5 and inhibits cleavage into C5a and C5b thereby decreasing the formation not only of C5a but also the downstream complement components.

The concentration and/or physiologic activity of C5a and C5b in a body fluid can be measured by methods well known in the art. For C5a such methods include chemotaxis assays, RIAs, or ELISAs (see, for example, Ward and Zvaifler, J Clin Invest. 1971 Mar;50(3):606-16; Wurzner, et al., Complement Inflamm. 8:328-340, 1991). For C5b, hemolytic assays or assays for soluble C5b-9 as discussed herein can be used. Other assays

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known in the art can also be used. Using assays of these or other suitable types, candidate antibodies capable of inhibiting complement such as anti-C5 antibodies, now known or subsequently identified, can be screened in order to 1) identify compounds that are useful in the practice of the application and 2) determine the appropriate dosage levels of such compounds.

An antibody capable of inhibiting complement such as an antibody that binds C5 affecting C5b is preferably used at concentrations providing substantial reduction (i.e., reduction by at least about 25% as compared to that in the absence of the antibody that binds C5) in the C5b levels present in at least one blood-derived fluid of the patient following activation of complement within the fluid. Such concentrations can be conveniently determined by measuring the cell-lysing ability (e.g., hemolytic activity) of complement present in the fluid or the levels of soluble C5b-9 present in the fluid. Accordingly, a specific concentration for an antibody that affects C5b is one that results in a substantial reduction (i.e., a reduction by at least about 25%) in the cell-lysing ability of the complement present in at least one of the patient's blood-derived fluids. Reductions of the cell-lysing ability of complement present in the patient's body fluids can be measured by methods well known in the art such as, for example, by a conventional hemolytic assay such as the hemolysis assay described by Kabat and Mayer (eds), "Experimental Immunochemistry, 2d Edition", 135-240, Springfield, IL, CC Thomas (1961), pages 135-139, or a conventional variation of that assay such as the chicken erythrocyte hemolysis method described below.

Specific antibodies capable of inhibiting complement, such as an antibody that binds C5, are relatively specific and do not block the functions of early complement components. In particular, such specific agents will not substantially impair the opsonization functions associated with complement component C3b, which functions provide a means for clearance of foreign particles and substances from the body.

C3b is generated by the cleavage of C3, which is carried out by classical and/or alternative C3 convertases and results in the generation of both C3a and C3b. Therefore, in order not to impair the opsonization functions associated with C3b, specific antibodies capable of inhibiting complement such as an antibody that binds C5 do not substantially interfere with the cleavage of complement component C3 in a body fluid of the patient (e.g., serum) into C3a and C3b. Such interference with the cleavage of C3 can be detected by measuring body fluid levels of C3a and/or C3b, which are produced in equimolar ratios

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by the actions of the C3 convertases. Such measurements are informative because C3a and C3b levels will be reduced (compared to a matched sample without the antibody capable of inhibiting complement such as an antibody that binds C5) if cleavage is interfered with by an antibody capable of inhibiting complement such as an antibody that binds C5.

In practice, the quantitative measurement of such cleavage is generally more accurate when carried out by the measurement of body fluid C3a levels rather than of body fluid C3b levels, since C3a remains in the fluid phase whereas C3b is rapidly cleared. C3a levels in a body fluid can be measured by methods well known in the art such as, for example, by using a commercially available C3a EIA kit, e.g., that sold by Quidel Corporation, San Diego, Calif., according to the manufacturer's specifications. Particularly specific antibodies capable of inhibiting complement such as an antibody that binds C5 produce essentially no reduction in body fluid C3a levels following complement activation when tested in such assays.

Certain antibodies of the disclosure will prevent the cleavage of C5 to form C5a and C5b, thus preventing the generation of the anaphylatoxic activity associated with C5a and preventing the assembly of the membrane attack complex associated with C5b. As discussed above, in a particular embodiment, these anti-C5 antibodies will not impair the opsonization function associated with the action of C3b.

A preferred method of inhibiting complement activity is to use a monoclonal antibody which binds to complement C5 and inhibits cleavage. This decreases the formation of both C5a and C5b while at the same time allowing the formation of C3a and C3b which are beneficial to the recipient. Such antibodies which are specific to human complement are known (U.S. Patent 6,355,245). These antibodies disclosed in U.S. Patent 6,355,245 include a preferred whole antibody (now named eculizumab). A similar antibody against mouse C5 is called BB5.1 (Frei et al., Mol. Cell. Probes. 1:141-149 (1987)). Antibodies to inhibit complement activity need not be monoclonal antibodies. They can be, e.g., polyclonal antibodies. They may additionally be antibody fragments. An antibody fragment includes, but is not limited to, an Fab, F(ab'), $F(ab')_2$, single-chain antibody, and Fv. Furthermore, it is well known by those of skill in the art that antibodies can be humanized (Jones et al., Nature 321:522-5 (1986)), chimerized, or deimmunized. The antibodies to be used in the present disclosure may be any of these. It is preferable to use humanized antibodies.

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In specific embodiments, a therapeutic agent of the disclosure comprises an antibody or antibody fragment. Antibodies and fragments thereof may be made by any conventional method, such as those methods described herein. Antibodies are found in multiple forms, e.g., IgA, IgG, IgM, etc. Additionally, antibodies can be engineered in numerous ways. They can be made as single-chain antibodies (including small modular immunopharmaceuticals or SMIPs™), Fab and $F(ab')_2$ fragments, etc. Antibodies can be humanized, chimerized, deimmunized, or fully human. Numerous publications set forth the many types of antibodies and the methods of engineering such antibodies. For example, see U.S. Patent Nos. 6,355,245; 6,180,370; 5,693,762; 6,407,213; 6,548,640; 5,565,332; 5,225,539; 6,103,889; and 5,260,203.

This invention provides fragments of anti-C5 antibodies, which may comprise a portion of an intact antibody, preferably the antigen-binding or variable region of the intact antibody. Examples of antibody fragments include Fab, Fab', $F(ab')_2$, and Fv fragments; diabodies; linear antibodies (Zapata et al., Protein Eng. 8:1057-1062 (1995)); single-chain antibody molecules; and multispecific antibodies formed from antibody fragments.

Papain digestion of antibodies produces two identical antigen-binding fragments, called "Fab" fragments, each with a single antigen-binding site, and a residual "Fc" fragment, whose name reflects its ability to crystallize readily. Pepsin treatment of an antibody yields an $F(ab')_2$ fragment that has two antigen-combining sites and is still capable of cross-linking antigen.

"Fv" refers to the minimum antibody fragment that contains a complete antigen-recognition and -binding site. This region consists of a dimer of one heavy- and one light-chain variable domain in tight, non-covalent association. It is in this configuration that the three CDRs of each variable domain interact to define an antigen-binding site on the surface of the V_H-V_L dimer. Collectively, the six CDRs confer antigen-binding specificity to the antibody. However, even a single variable domain (or half of an Fv comprising only three CDRs specific for an antigen) has the ability to recognize and bind antigen, although likely at a lower affinity than the entire binding site.

The Fab fragment also contains the constant domain of the light chain and the first constant domain (CH1) of the heavy chain. Fab' fragments differ from Fab fragments by the addition of a few residues at the carboxy terminus of the heavy chain CH1 domain including one or more cysteines from the antibody hinge region. Fab'-SH is the designation herein for Fab' in which the cysteine residue(s) of the constant domains bear a

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free thiol group. $F(ab')_2$ antibody fragments originally were produced as pairs of Fab' fragments that have hinge cysteines between them. Other chemical couplings of antibody fragments are also known.

"Single-chain Fv" or "scFv" antibody fragments comprise the V_H and V_L domains of an antibody, wherein these domains are present in a single polypeptide chain. Preferably, the Fv polypeptide further comprises a polypeptide linker between the V_H and V_L domains that enables the scFv to form the desired structure for antigen binding. For a review of scFv see Pluckthun in The Pharmacology of Monoclonal Antibodies, vol. 113, Rosenburg and Moore, eds. (Springer-Verlag: New York, 1994), pp. 269-315.

SMIPs are a class of single-chain peptide engineered to include a target binding region, effector domain (CH2 and CH3 domains). *See, e.g.*, U.S. Patent Application Publication No. 20050238646. The target binding region may be derived from the variable region or CDRs of an antibody, e.g., an antibody that binds C5 of the application. Alternatively, the target binding region is derived from a protein that binds C5.

The term "diabodies" refers to small antibody fragments with two antigen-binding sites, which fragments comprise a heavy-chain variable domain (V_H) connected to a light-chain variable domain (V_L) in the same polypeptide chain (V_H-V_L). By using a linker that is too short to allow pairing between the two domains on the same chain, the domains are forced to pair with the complementary domains of another chain and create two antigen-binding sites. Diabodies are described more fully in, for example, EP 404,097; WO 93/11161; and Hollinger et al., Proc. Natl. Acad. Sci. USA, 90: 6444-6448 (1993).

It is well known that the binding to a molecule (or a pathogen) of antibodies with an Fc region assists in the processing and clearance of the molecule (or pathogen). The Fc portions of antibodies are recognized by specialized receptors expressed by immune effector cells. The Fc portions of IgG1 and IgG3 antibodies are recognized by Fc receptors present on the surface of phagocytic cells such as macrophages and neutrophils, which can thereby bind and engulf the molecules or pathogens coated with antibodies of these isotypes (C. A. Janeway et al., Immunobiology 5th edition, page 147, Garland Publishing (New York, 2001)).

This disclosure also provides monoclonal anti-C5 antibodies. A monoclonal antibody can be obtained from a population of substantially homogeneous antibodies, i.e., the individual antibodies comprising the population are identical except for possible naturally-occurring mutations that may be present in minor amounts. Monoclonal

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antibodies are highly specific, being directed against a single antigenic site. Furthermore, in contrast to conventional (polyclonal) antibody preparations that typically include different antibodies directed against different determinants (epitopes), each monoclonal antibody is directed against a single determinant on the antigen. In addition to their specificity, the monoclonal antibodies are advantageous in that they are often synthesized by the hybridoma culture, uncontaminated by other immunoglobulins. Monoclonal antibodies may also be produced in transfected cells, such as CHO cells and NS0 cells. The modifier "monoclonal" indicates the character of the antibody as being obtained from a substantially homogeneous population of antibodies and does not require production of the antibody by any particular method. For example, the monoclonal antibodies to be used in accordance with the present disclosure may be made by the hybridoma method first described by Kohler et al., Nature 256:495-497 (1975), or may be made by recombinant DNA methods (*see, e.g.*, U.S. Patent Nos. 4,816,567 and 6,331,415). The "monoclonal antibodies" may also be isolated from phage antibody libraries using the techniques described in Clackson et al., Nature 352:624-628 (1991) and Marks et al., J. Mol. Biol. 222:581-597 (1991), for example.

A description of the preparation of a mouse anti-human-C5 monoclonal antibody with specific binding characteristics is presented in U.S. Patent Application Publication No. 20050226870. Wurzner et al., Complement Inflamm. 8:328-340 (1991), describe the preparation of other mouse anti-human-C5 monoclonal antibodies referred to as N19-8 and N20-9.

Other antibodies specifically contemplated are "oligoclonal" antibodies. As used herein, the term "oligoclonal" antibodies" refers to a predetermined mixture of distinct monoclonal antibodies. *See, e.g.*, PCT publication WO 95/20401; U.S. Patent Nos. 5,789,208 and 6,335,163. In one embodiment, oligoclonal antibodies consisting of a predetermined mixture of antibodies against one or more epitopes are generated in a single cell. In other embodiments, oligoclonal antibodies comprise a plurality of heavy chains capable of pairing with a common light chain to generate antibodies with multiple specificities (*e.g.*, PCT publication WO 04/009618). Oligoclonal antibodies are particularly useful when it is desired to target multiple epitopes on a single target molecule (*e.g.*, C5). In view of the assays and epitopes disclosed herein, those skilled in the art can generate or select antibodies or mixtures of antibodies that are applicable for an intended purpose and desired need.

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In certain embodiments that include a humanized and/or chimeric antibody, one or more of the CDRs are derived from an anti-human C5 antibody. In a specific embodiment, all of the CDRs are derived from an anti-human C5 antibody. In another specific embodiment, the CDRs from more than one anti-human C5 antibody are mixed and matched in a chimeric antibody. For instance, a chimeric antibody may comprise a CDR1 from the light chain of a first anti-human C5 antibody combined with CDR2 and CDR3 from the light chain of a second anti-human C5 antibody, and the CDRs from the heavy chain may be derived from a third anti-human C5 antibody. Further, the framework regions may be derived from one of the same anti-human C5 antibodies, from one or more different antibodies, such as a human antibody, or from a humanized antibody. Human or humanized antibodies are specific for administration to human patients.

In certain embodiments, single chain antibodies, and chimeric, humanized or primatized (CDR-grafted) antibodies, as well as chimeric or CDR-grafted single chain antibodies, comprising portions derived from different species, are also encompassed by the present disclosure as antigen-binding fragments of an antibody. The various portions of these antibodies can be joined together chemically by conventional techniques, or can be prepared as a contiguous protein using genetic engineering techniques. For example, nucleic acids encoding a chimeric or humanized chain can be expressed to produce a contiguous protein. See, e.g., U.S. Pat. Nos. 4,816,567 and 6,331,415; U.S. Pat. No. 4,816,397; European Patent No. 0,120,694; WO 86/01533; European Patent No. 0,194,276 B1; U.S. Pat. No. 5,225,539; and European Patent No. 0,239,400 B1. See also, Newman et al., BioTechnology 10:1455-1460 (1992), regarding primatized antibody. See, e.g., Ladner et al., U.S. Pat. No. 4,946,778; and Bird et al., Science 242:423-426 (1988), regarding single chain antibodies.

In addition, functional fragments of antibodies, including fragments of chimeric, humanized, primatized or single chain antibodies, can also be produced. Functional fragments of the subject antibodies retain at least one binding function and/or modulation function of the full-length antibody from which they are derived. Preferred functional fragments retain an antigen-binding function of a corresponding full-length antibody (such as for example, ability of antibody that binds C5 to bind C5).

General methods for the immunization of animals (in this case with C5 and/or C5b, etc.), isolation of antibody producing cells, fusion of such cells with immortal cells (e.g., myeloma cells) to generate hybridomas secreting monoclonal antibodies, screening of

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hybridoma supernatants for reactivity of secreted monoclonal antibodies with a desired antigen (in this case the immunogen or a molecule containing the immunogen), the preparation of quantities of such antibodies in hybridoma supernatants or ascites fluids, and for the purification and storage of such monoclonal antibodies, can be found in numerous publications. These include: Coligan, et al., eds. Current Protocols In Immunology, John Wiley & Sons, New York, 1992; Harlow and Lane, Antibodies, A Laboratory Manual, Cold Spring Harbor Laboratory, New York, 1988; Liddell and Cryer, A Practical Guide To Monoclonal Antibodies, John Wiley & Sons, Chichester, West Sussex, England, 1991; Montz et al., Cellular Immunol. 127:337-351 (1990); Wurzner et al., Complement Inflamm. 8:328-340 (1991); and Mollnes et al., Scand. J. Immunol. 28:307-312 (1988).

VI Methods of Treatment

Methods of the application may be used to treat paroxysmal nocturnal hemoglobinuria associated symptoms. Methods of the application may be used to treat anemia associated symptoms. Treatment of paroxysmal nocturnal hemoglobinuria and/or anemia may be administered by standard means. Treatments of the application may be used in combination with other treatments of the application or known treatments for paroxysmal nocturnal hemoglobinuria and/or anemia. Treatments of the application may be co-administered with other treatments that treat symptoms of paroxysmal nocturnal hemoglobinuria and/or anemia.

VII Pharmaceutical Formulations and Uses

Methods of administration of small molecules, proteins, and nucleic acids are well-known to those of skill in the art. Methods of administration of antibodies are well-known to those of skill in the art. To achieve the desired inhibition, the antibodies can be administered in a variety of unit dosage forms. The dose will vary according to the particular antibody. For example, different antibodies may have different masses and/or affinities, and thus require different dosage levels. Antibodies prepared as Fab fragments will also require differing dosages than the equivalent intact immunoglobulins, as they are of considerably smaller mass than intact immunoglobulins, and thus require lower dosages to reach the same molar levels in the patient's blood. The dose will also vary depending on the manner of administration, the particular symptoms of the patient being treated, the overall health, condition, size, and age of the patient, and the judgment of the prescribing

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physician. Dosage levels of the antibodies for human subjects are generally between about 1 mg per kg and about 100 mg per kg per patient per treatment, and preferably between about 5 mg per kg and about 50 mg per kg per patient per treatment. In terms of plasma concentrations, the antibody concentrations are preferably in the range from about 25 μg/mL to about 500 μg/mL. However, greater amounts may be required for extreme cases and smaller amounts may be sufficient for milder cases.

In certain embodiments, the pharmaceutical composition is in a single unit dosage form. In certain embodiments, the single unit dosage form is a 300 mg unit dosage form. In certain embodiments, the pharmaceutical composition is lyophilized. In certain embodiments, the pharmaceutical composition is a sterile solution. In certain embodiments, the pharmaceutical composition is a preservative free formulation. In certain embodiments, the pharmaceutical composition comprises a 300 mg single-use formulation of 30 ml of a 10 mg/ml sterile, preservative free solution. In certain embodiments, the antibody is administered according to the following protocol:

600 mg via 25 to 45 minute IV infusion every 7 ± 2 days for the first 4 weeks, followed by 900 mg for the fifth dose 7 ± 2 days later, then 900 mg every 14 ± 2 days thereafter. Antibody is administered via IV infusion over 25 to 45 minute.

Administration of the anti-C5 antibodies will generally be performed by an intravascular route, e.g., via intravenous infusion by injection. Other routes of administration may be used if desired but an intravenous route will be the most preferable. Formulations suitable for injection are found in Remington's Pharmaceutical Sciences, Mack Publishing Company, Philadelphia, Pa., 17th ed. (1985). Such formulations must be sterile and non-pyrogenic, and generally will include a pharmaceutically effective carrier, such as saline, buffered (e.g., phosphate buffered) saline, Hank's solution, Ringer's solution, dextrose/saline, glucose solutions, and the like. The formulations may contain pharmaceutically acceptable auxiliary substances as required, such as, tonicity adjusting agents, wetting agents, bactericidal agents, preservatives, stabilizers, and the like. In certain embodiments, complement inhibitors such as eculizumab may be administered via IV infusion and diluted to a final concentration of 5 mg/ml prior to administration.

Administration of the antibodies capable of inhibiting complement such as an antibody that binds C5 will generally be performed by a parenteral route, typically via injection such as intra-articular or intravascular injection (e.g., intravenous infusion) or intramuscular injection. Other routes of administration, e.g., oral (p.o.), may be used if

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desired and practicable for the particular antibody capable of inhibiting complement to be administered. Antibodies capable of inhibiting complement such as an antibody that binds C5 can also be administered in a variety of unit dosage forms and their dosages will also vary with the size, potency, and in vivo half-life of the particular antibody capable of inhibiting complement being administered. Doses of antibodies capable of inhibiting complement such as an antibody that binds C5 will also vary depending on the manner of administration, the particular symptoms of the patient being treated, the overall health, condition, size, and age of the patient, and the judgment of the prescribing physician.

In certain embodiments, a typical therapeutic treatment includes a series of doses, which will usually be administered concurrently with the monitoring of clinical endpoints with the dosage levels adjusted as needed to achieve the desired clinical outcome. In certain embodiments, treatment is administered in multiple dosages over at least a week. In certain embodiments, treatment is administered in multiple dosages over at least a month. In certain embodiments, treatment is administered in multiple dosages over at least a year. In certain embodiments, treatment is administered in multiple dosages over the remainder of the patient's life.

The frequency of administration may also be adjusted according to various parameters. These include the clinical response, the plasma half-life of the therapeutic of the disclosure, and the levels of the antibody in a body fluid, such as, blood, plasma, serum, or synovial fluid. To guide adjustment of the frequency of administration, levels of the therapeutic of the disclosure in the body fluid may be monitored during the course of treatment.

In certain embodiments, the frequency of administration may be adjusted according to an assay measuring cell-lysing ability of complement present in one or more of the patient's body fluids. The cell-lysing ability can be measured as percent hemolysis in hemolytic assays of the types described herein. A 10% or 25% or 50% reduction in the cell-lysing ability of complement present in a body fluid after treatment with the antibody capable of inhibiting complement used in the practice of the application means that the percent hemolysis after treatment is 90, 75, or 50 percent, respectively, of the percent hemolysis before treatment.

For the treatment of hemolytic diseases such as PNH by systemic administration of an antibody capable of inhibiting complement such as an antibody that binds C5 (as opposed to local administration), administration of a large initial dose is specific, i.e., a

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single initial dose sufficient to yield a substantial reduction, and more preferably an at least about 50% reduction, in the hemolytic activity of the patient's serum. Such a large initial dose is preferably followed by regularly repeated administration of tapered doses as needed to maintain substantial reductions of serum hemolytic titer. In another embodiment, the initial dose is given by both local and systemic routes, followed by repeated systemic administration of tapered doses as described above.

Formulations particularly useful for antibody-based therapeutic agents are also described in U.S. Patent App. Publication Nos. 20030202972, 20040091490 and 20050158316. In certain embodiments, the liquid formulations of the application are substantially free of surfactant and/or inorganic salts. In another specific embodiment, the liquid formulations have a pH ranging from about 5.0 to about 7.0. In yet another specific embodiment, the liquid formulations comprise histidine at a concentration ranging from about 1 mM to about 100 mM. In still another specific embodiment, the liquid formulations comprise histidine at a concentration ranging from 1 mM to 100 mM. It is also contemplated that the liquid formulations may further comprise one or more excipients such as a saccharide, an amino acid (e.g., arginine, lysine, and methionine) and a polyol. Additional descriptions and methods of preparing and analyzing liquid formulations can be found, for example, in PCT publications WO 03/106644, WO 04/066957, and WO 04/091658.

Wetting agents, emulsifiers and lubricants, such as sodium lauryl sulfate and magnesium stearate, as well as coloring agents, release agents, coating agents, sweetening, flavoring and perfuming agents, preservatives and antioxidants can also be present in the pharmaceutical compositions of the application.

In certain embodiments, formulations of the subject antibodies are pyrogen-free formulations which are substantially free of endotoxins and/or related pyrogenic substances. Endotoxins include toxins that are confined inside microorganisms and are released when the microorganisms are broken down or die. Pyrogenic substances also include fever-inducing, thermostable substances (glycoproteins) from the outer membrane of bacteria and other microorganisms. Both of these substances can cause fever, hypotension and shock if administered to humans. Due to the potential harmful effects, it is advantageous to remove even low amounts of endotoxins from intravenously administered pharmaceutical drug solutions. The Food & Drug Administration ("FDA") has set an upper limit of 5 endotoxin units (EU) per dose per kilogram body weight in a

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single one hour period for intravenous drug applications (The United States Pharmacopeial Convention, Pharmacopeial Forum 26 (1):223 (2000)). When therapeutic proteins are administered in amounts of several hundred or thousand milligrams per kilogram body weight, as can be the case with monoclonal antibodies, it is advantageous to remove even trace amounts of endotoxin.

Formulations of the subject antibodies include those suitable for oral, dietary, topical, parenteral (e.g., intravenous, intraarterial, intramuscular, subcutaneous injection), ophthalmologic (e.g., topical or intraocular), inhalation (e.g., intrabronchial, intranasal or oral inhalation, intranasal drops), rectal, and/or intravaginal administration. Other suitable methods of administration can also include rechargeable or biodegradable devices and controlled release polymeric devices. Stents, in particular, may be coated with a controlled release polymer mixed with an agent of the application. The pharmaceutical compositions of this disclosure can also be administered as part of a combinatorial therapy with other agents (either in the same formulation or in a separate formulation).

The amount of the formulation which will be therapeutically effective can be determined by standard clinical techniques. In addition, *in vitro* assays may optionally be employed to help identify optimal dosage ranges. The precise dose to be employed in the formulation will also depend on the route of administration, and the seriousness of the disease or disorder, and should be decided according to the judgment of the practitioner and each patient's circumstances. Effective doses may be extrapolated from dose-response curves derived from in vitro or animal model test systems. The dosage of the compositions to be administered can be determined by the skilled artisan without undue experimentation in conjunction with standard dose-response studies. Relevant circumstances to be considered in making those determinations include the condition or conditions to be treated, the choice of composition to be administered, the age, weight, and response of the individual patient, and the severity of the patient's symptoms. For example, the actual patient body weight may be used to calculate the dose of the formulations in milliliters (mL) to be administered. There may be no downward adjustment to "ideal" weight. In such a situation, an appropriate dose may be calculated by the following formula: Dose (mL) = [patient weight (kg) x dose level (mg/kg)/ drug concentration (mg/mL)]

To achieve the desired treatment results, anti-C5 antibodies can be administered in a variety of unit dosage forms. The dose will vary according to the particular antibody. For example, different antibodies may have different masses and/or affinities, and thus require

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different dosage levels. Antibodies prepared as Fab' fragments or single chain antibodies will also require differing dosages than the equivalent native immunoglobulins, as they are of considerably smaller mass than native immunoglobulins, and thus require lower dosages to reach the same molar levels in the patient's blood.

Other therapeutics of the disclosure can also be administered in a variety of unit dosage forms and their dosages will also vary with the size, potency, and *in vivo* half-life of the particular therapeutic being administered.

Doses of therapeutics of the disclosure will also vary depending on the manner of administration, the particular symptoms of the patient being treated, the overall health, condition, size, and age of the patient, and the judgment of the prescribing physician.

The formulations of the application can be distributed as articles of manufacture comprising packaging material and a pharmaceutical agent which comprises the antibody capable of inhibiting complement and a pharmaceutically acceptable carrier as appropriate to the mode of administration. The packaging material may include a label which indicates that the formulation is for use in the treatment of hemolytic diseases such as PNH. Although antibodies are preferred, especially anti-C5 antibodies which have already been shown to be safe and effective at decreasing the accumulation of downstream complement components in persons, the use of other complement inhibitors is also contemplated by this disclosure. The pharmaceutical formulations and uses of the disclosure may be combined with any known complement inhibitors or hemolytic diseases treatments known in the art.

In certain aspects, the application provides kits comprising a pharmaceutical composition of the application. In some embodiments, the kit further comprises at least one component of a closed sterile system. Components of the closed sterile system include, but are not limited to, needles, syringes, catheter based syringes, needle based injection devices, needle-less injection devices, filters, tubing, valves and cannulas. In a related embodiment, the kit comprise components for the removal of a preservative from the composition. Such components include filters, syringes, vials, containers, tubing, etc.

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EXEMPLIFICATION

METHODS

Patient Selection

The TRIUMPH trial consisted of a 2-week screening period, an observation period of up to 3 months duration, and a 26-week treatment period.

During the screening period, patients were evaluated with respect to inclusion and exclusion criteria. Men and women, 18 years or older, diagnosed as having PNH with a type III erythrocyte population of ≥10%, and who had received at least 4 transfusions in the previous 12 months were eligible. Concomitant administration of erythropoietin, immunosuppressants, corticosteroids, coumadin, low molecular weight heparin, iron supplements, and folic acid were not reasons for exclusion, provided the doses were steady prior to the first visit and throughout the duration of the study. Because of the increased frequency of neisserial infections in individuals genetically deficient in terminal complement proteins, all patients were vaccinated against *Neisseria meningitides*. Patients were to avoid conception. The protocol was approved by an Investigational Review Board at each clinical site and written informed consent was obtained from all patients enrolled.

Patients transfused with a mean pre-transfusion hemoglobin level >10.5 g/dL over the previous 12 months, and those who showed evidence of having a suppressed immune response, complement deficiency, or active bacterial infection, including any history of meningococcal disease, were excluded from the study. Patients were also not eligible if they had previously received a bone marrow transplant or if they had participated in another trial or received another investigational drug within 30 days of the first visit. An individualized transfusion algorithm was calculated for each patient based on their prior 12-month transfusion history; the written algorithm documented the number of packed red blood cell (PRBC) units transfused for given hemoglobin values and served as a prospectively determined guide for transfusion during observation and treatment periods.

Each patient considered eligible entered an observation period of up to 13 weeks in order to confirm their PBRC transfusion dependence. At least one transfusion --termed the "qualifying" transfusion-- during the 13-week observation period at a hemoglobin value at or below 9 g/dL with symptoms, or at or below 7 g/dL with or without symptoms, in accordance with the transfusion algorithm indicated for each patient, was a requirement to

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proceed to randomization. The hemoglobin value at which each individual's qualifying transfusion was administered, was defined as the hemoglobin "set point" for that individual for the purpose of the primary efficacy variable. A platelet count ≥100,000/mL and a LDH level ≥1.5 times the upper limit of the normal range were also required either at screening or during the observation period for eligibility.

Study Design

Patients were randomly assigned on a one-on-one basis to receive either placebo or eculizumab (Soliris™, Alexion Pharmaceuticals, Inc.) within 10 days of the qualifying transfusion. Study medication was dosed in a blinded fashion as follows: 600 mg eculizumab for patients randomly assigned to active drug, or placebo for those patients randomly assigned to placebo, respectively via IV infusion every 7±1 days for 4 doses; followed by 900 mg eculizumab, or placebo, respectively, via IV infusion 7±1 day later; followed by a maintenance dose of 900 mg eculizumab, or placebo, respectively, via IV infusion every 14±2 days for a total of 26 weeks of treatment.

Measures of Clinical Efficacy

There were two co-primary endpoints in the study: (1) stabilization of hemoglobin levels, defined as a hemoglobin value maintained above the individual hemoglobin set point in the absence of transfusions for the entire 26-week treatment period, and (2) reduction in units of PRBCs transfused during the 26-week treatment phase of the study. The trigger for transfusion during the study period remained unchanged for each patient, as compared with their care before entry into the study: patients received blood transfusions when they had symptoms resulting from anemia and reached their individualized, pre-determined "set point". Pre-specified secondary endpoints included transfusion avoidance, hemolysis as measured by LDH area under the curve from baseline to 26 weeks, and QoL changes as measured from baseline to 26 weeks using the Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-Fatigue) instrument.[13] Pre-specified exploratory analyses included assessment of the EORTC QLQ-C30 instrument,[14] the change in LDH from baseline through week 26, and thrombosis. Other pre-specified measurements included pharmacokinetics, pharmacodynamics, and immunogenicity of eculizumab. Time to first transfusion during the 26-week treatment phase and the proportion of PNH type III blood cells were also assessed.

Safety Assessments

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Treatment-emergent adverse events, clinical laboratory tests (e.g., serum chemical analyses and complete blood counts), electrocardiogram data, and vital signs were assessed. Adverse events were defined using the MedDRA preferred terms and tabulated as incidence rates per treatment group.

Statistical Analysis

For co-primary endpoints, analyses were performed according to the intention to treat using the data from all patients who were randomized and received study drug; stabilization of hemoglobin levels was analyzed using the Fisher's exact test and total PRBC units transfused were analyzed with the Wilcoxon's rank sum test. For comparison of treatment effect on transfusion avoidance, the Fisher's exact test was used on the incidence and the log rank test was used for time to first transfusion. For LDH area under the curve the Wilcoxon's rank sum test was used.

Quality of life measure of fatigue was assessed using the scoring guidelines for the FACIT-Fatigue instrument.[15] Assessment of quality of life measures based on the EORTC QLQ-C30 instrument was conducted in accordance with the appropriate scoring guidelines.[16] The changes of FACIT-Fatigue and EORTC QLQ-C30 scores from baseline through 26 weeks were analyzed using a mixed model, with baseline as covariate, treatment and time as fixed effects, and patient as a random effect. Changes in LDH levels and PNH type III erythrocytes from baseline through 26 weeks were analyzed using the same mixed model. Two-sided tests were used for all analyses. The adverse events and long-term safety checklist were tabulated separately and compared between treatments using the Fisher's exact test. A p-value ≤ 0.05 was considered to be statistically significant.

RESULTS

Characteristics of Patients

A total of 115 PNH patients were screened. Six patients did not meet the inclusion/exclusion criteria during the screening period. Twenty-one other patients did not receive a qualifying transfusion and were not randomized into the treatment phase. One patient who did not meet the inclusion criteria was inadvertently randomized, but did not receive study medication. Thus 87 hemolytic PNH patients (35 men and 52 women) were enrolled and randomized to receive either eculizumab (N=43) or placebo (N=44), exceeding the original target of 75 randomized patients.

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Patient characteristics were similar in the eculizumab- and placebo-treated cohorts: median age, 41 (range 20-85) and 35 (range 18-78) years; median duration of PNH, 4.2 (range 0.8 to 29.7) and 9.2 (range 0.4 to 38.3) years; patients with history of aplastic anemia, 4 and 11; history of myelodysplastic syndrome, 1 and 0; and history of thrombosis, 9 (16 events) and 8 (11 events). Stable usage of concomitant medications at baseline in the eculizumab- and placebo-treated groups included the following: erythropoietin, 3 patients and 0 patients; cyclosporine, 1 and 1; anticoagulants (coumarins or heparins) 21 and 11; and steroids (glucocorticoids or androgenic steroids), 12 and 12, respectively.

Of the 87 patients randomized, 85 completed the trial. Two patients who did not complete the trial had been randomized to the eculizumab arm: one patient discontinued due to the inconvenience of travel to the study site and the second patient became pregnant. Ten patients in the placebo-treatment group discontinued infusions, in all cases due to perceived lack of efficacy, but they remained in the study for monitoring purposes.

Pharmacokinetics/Pharmacodynamics

In 42 of the 43 eculizumab-treated patients the levels of drug during the maintenance period (900 mg every 2 weeks±2 days) were sufficient to completely block serum hemolytic activity (mean trough value at week 26 of 101.8 μg/mL). A single patient did not sustain therapeutic trough levels of eculizumab and demonstrated a breakthrough in complement blockade during the last few days of each dosing interval. These breakthroughs were clinically manageable and quickly resolved following the next dose.

Hemolytic Efficacy Variables

The impact of terminal complement inhibition with eculizumab on chronic intravascular hemolysis in PNH patients was demonstrated in this study by an immediate (one week) and sustained decrease in mean levels of LDH (Figure 1A). The median LDH area under the curve during the 26-week study period was reduced 85.8% in eculizumab-relative to placebo-treated patients ($P<0.001$). The mean LDH level decreased from 2199.7±157.7 IU/L at baseline to 327.3±67.6 IU/L by 26 weeks in eculizumab-treated patients while levels in placebo-treated patients remained consistently elevated with values of 2259.0±158.5 IU/L at baseline and 2418.9±140.3 IU/L at 26 weeks ($P<0.001$, for eculizumab versus placebo). A second biochemical measure of hemolysis, serum aspartate aminotransferase (AST), also showed a statistically significant improvement following eculizumab- versus placebo-treatment (data not shown). Haptoglobin levels were statistically significantly increased in eculizumab- as compared to placebo-treated patients

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but mean levels of haptoglobin were still below normal levels in eculizumab-treated patients (data not shown).

Figure 1A shows the degree of intravascular hemolysis in PNH patients, demonstrated by mean lactate dehydrogenase (LDH) levels (±standard error) from baseline (study week 0) to week 26 for both eculizumab- and placebo-treated patient populations. Screening occurred up to 3 months prior to study week 0. The upper limit of the normal range (103-223 IU/L) for LDH is indicated by a dashed line. LDH was reduced to a mean level just above the upper limit of normal at week 26 for eculizumab-treated patients; 15 of 41 patients who completed the study demonstrated LDH levels within the normal range. All placebo-treated patients remained at least 5 times above the upper limit of normal at week 26. The P value is based on a mixed model analysis from baseline through week 26. Figure 1B shows the mean proportion (±standard error) of PNH type III erythrocytes assessed for placebo- and eculizumab-treated patients. The screening visit occurred up to 3 months prior to study week 0. The P value is based on a mixed model analysis from baseline through week 26.

A corollary to the reduction in intravascular hemolysis during eculizumab treatment was an observed increase in the PNH type III erythrocyte population (Figure 1B). The mean proportions of type III erythrocytes increased from 28.1±2.0% at baseline to 56.9±3.6% by week 26 for eculizumab-treated patients while proportions in the placebo group remained constant with mean values of 35.7±2.8% before treatment to 35.5±2.8% at 26 weeks ($P<0.001$, for eculizumab versus placebo). By contrast, the proportions of PNH type III granulocytes and monocytes did not change significantly between the treatment groups during the treatment period and were greater than 90% at week 26.

CLINICAL EFFICACY

Co-primary endpoints

The co-primary efficacy endpoints in the TRIUMPH trial were stabilization of hemoglobin levels and reduction in PRBC units transfused. At the end of the treatment period, 48.8% of eculizumab-treated patients had maintained levels of hemoglobin above the pre-specified set-point (median set-point value of 7.7 g/dL for both treatment groups) in the absence of transfusions, whereas stabilization of hemoglobin did not occur in any of the patients in the placebo group ($P<0.001$; Table 1). By week 26, the median of PRBC units transfused per patient was 0 in the eculizumab group and 10.0 in the placebo cohort

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(P<0.001), while the mean of PRBC units transfused was 3.0 and 11.0 in the eculizumab and placebo cohorts, respectively. In the 6-month period prior to the study, the median of PRBC units transfused per patient was 9.0 in the eculizumab cohort and 8.5 in placebo patients while the mean of PRBC units transfused was 9.6±0.6 and 9.7±0.7, respectively. Mean hemoglobin levels were similar between the treatment groups at baseline (10.0±1.8 g/dL in eculizumab-treated patients and 9.7±1.8 g/dL in placebo-treated patients) and did not substantially change by week 26 (10.1±2.5 g/dL and 8.9±2.2 g/dL in eculizumab and placebo cohorts, respectively).

The median time to first transfusion was not reached during the study period in eculizumab-treated patients (it was greater than 26 weeks) while the placebo group reached the median time to first transfusion in only 4 weeks (P<0.001; Figure 2). Transfusion avoidance was achieved in 51.2% and 0% of the eculizumab and placebo cohorts, respectively (P<0.001). By the end of the 26-week treatment period, the total PRBC units transfused were 131 in eculizumab-treated patients versus 482 in the placebo group (Table 1). By contrast, in the 6-month period prior to the study, total PRBC units transfused in the eculizumab- and placebo-cohorts were 413 and 417, respectively.

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Table 1

Stabilization of Hemoglobin Levels and Reduction

in Transfusion Requirements during Eculizumab Treatment

	PRE-TREATMENT HISTORY*		TREATMENT PERIOD		
	Placebo	Eculizumab	Placebo	Eculizumab	P Value
†Stabilization of Hemoglobin Levels in the absence of transfusions (percent of patients)	NA	NA	0	48.8	<0.001‡
†Units Transfused per Patient					
Median	8.5	9.0	10	0	<0.001§
Mean±SE	9.7±0.7	9.6±0.6	11.0±0.83	3.0±0.67	
Total Units Transfused per Group	417	413	482	131	

*Twelve month historical transfusion data normalized to 6 months

†Co-primary endpoints

‡Base on 2-sided Fisher's exact test

§Based on Wilcoxon's rank sum test

NA, not applicable

Improvements in quality of life measures

Assessments of quality of life in PNH patients during eculizumab treatment were performed using two different instruments, FACIT-Fatigue and the EORTC QLQ-C30. Eculizumab-treated patients showed a mean increase (improvement) in the FACIT-Fatigue score of 6.4±1.2 points from baseline to 26-weeks while the mean score in placebo patients decreased by 4.0±1.7 points, a total difference between the treatment groups of 10.4 points (Figure 3). Mixed model analysis of covariance demonstrated a statistically significant difference between treatment groups (P<0.001).

For the EORTC instrument, improvements were observed with eculizumab-treatment in each subscale. Statistically significant improvements with eculizumab-compared with placebo-treated groups were observed in the following quality of life

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subscales (Table 2): global health status (P<0.001), physical functioning (P<0.001), emotional functioning (P=0.008), cognitive functioning (P=0.002), role functioning (P<0.001), social functioning (P=0.003), fatigue (P<0.001), pain (P=0.002), dyspnea (P<0.001), appetite loss (P<0.001), and insomnia (P=0.014). The improvements with eculizumab treatment in the other scales, including nausea and vomiting, diarrhea, constipation, and financial difficulties, did not reach statistical significance.

Table 2

Effect of Eculizumab Treatment on

Quality of Life Assessed by the EORTC QLQ-C30 Instrument

	Mean Change from Baseline to Week 26*			
	Placebo	Eculizumab	Absolute Difference	P Value†
Global Health Status	-8.5	10.9	19.4	<0.001
Functional				
Role	-6.9	17.9	24.8	<0.001
Social	2.0	16.7	14.6	=0.003
Cognitive	-6.1	7.9	14.0	=0.002
Physical	-3.5	9.4	13.0	<0.001
Emotional	-3.7	7.5	11.2	=0.008
Symptoms/Single Items				
Fatigue	10.0	-16.9	27.0	<0.001
Pain	5.3	-12.3	17.6	=0.002
Dyspnea	8.9	-7.9	16.9	<0.001
Appetite Loss	3.3	-10.3	13.6	<0.001
Insomnia	4.9	-7.9	12.8	=0.014

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Financial Difficulties	0.0	-10.3	10.3	=0.186
Constipation	0.0	-6.3	6.3	=0.199
Nausea/vomiting	2.8	-0.4	3.2	=0.056
Diarrhea	5.7	4.8	0.9	=0.147

*A positive change indicates an improvement in global health status and functional scales and a negative change indicates an improvement in symptom and single item scales.

†Based on a mixed analysis-of-covariance model with visit as a fixed effect, patient as a random effect and baseline as a covariate.

Relationship between FACIT-Fatigue quality of life and intravascular hemolysis

In order to determine if there was a treatment independent relationship between the FACIT-Fatigue quality of life instrument and intravascular hemolysis, an analysis was performed whereby the mean LDH level (through the 26 week study period) for each TRIUMPH patient was analyzed as a function of the patient's respective mean change in FACIT-Fatigue score from baseline (through the 26 week study period) (see Table 3). For this analysis, mean levels of LDH were divided into 4 groups that included: normal levels, 1-2 times the upper limit of normal (ULN), 2-10 times the upper limit of normal, and greater than 10 times the upper limit of normal. The analysis demonstrated that patients who maintained normal LDH levels throughout the study experienced significant improvements in fatigue when compared to patients who had incrementally higher levels of LDH throughout the study (p=0.0048). These data establish a clear link between increasing intravascular hemolysis as measured by LDH levels and decreased quality of life as measured by the FACIT-Fatigue quality of life instrument.

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Table 3

Relationship between FACIT-Fatigue and Intravascular Hemolysis

Treatment Group	LDH Category	Change of FACIT from Baseline		
		<4	>=4	P.Value
Combined	Normal	4 (30.77%)	9 (69.23%)	.0048
	1 - 2 X ULN	16 (61.54%)	10 (38.46%)	
	2 - 10 X ULN	18 (72.00%)	7 (28.00%)	
	> 10 X ULN	16 (80.00%)	4 (20.00%)	

Safety

There were no deaths in the study. Serious adverse events (SAEs) were reported for 13 patients, of which 4 occurred in the eculizumab-treated cohort and 9 were in the placebo-treated cohort (see Table 4). All patients recovered without sequelae.

The most common AEs reported for eculizumab-treated patients were headache, nasopharyngitis, back pain, and upper respiratory tract infection. Headache and back pain occurred more commonly in the eculizumab-treatment group compared with the placebo group. However, the increase in headaches was limited to the first 2 weeks of therapy and was mild to moderate. There were no statistically significant differences in incidents rates between treatment groups for any AEs reported.

One episode of thrombosis (Budd-Chiari) occurred in a placebo-treated patient. There were no thromboses in eculizumab-treated patients.

Only one patient showed a detectable level of anti-eculizumab antibodies in the eculizumab-treated cohort; this response was weak (did not titrate), occurred at only one time point and did not result in a disruption of complement blockade.

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Table 4

Adverse Event Reporting

SERIOUS ADVERSE EVENTS*	Placebo Patients n (percent)	Eculizumab Patients n (percent)
Total	9 (20.5)	4 (9.3)
Eculizumab treatment emergent		
Exacerbation of PNH	3 (6.8)	1 (2.3)
Renal colic	0	1 (2.3)
Lumbar sacral disc prolapse	0	1 (2.3)
Alpha streptococcal bacteremia	0	1 (2.3)
Central line infection and UTI	1 (2.3)	0 (0)
Upper respiratory tract infection	1 (2.3)	0 (0)
Probable viral infection	1 (2.3)	0 (0)
Neutropenia	1 (2.3)	0 (0)
Cellulitis / folliculitis / neutropenia	1 (2.3)	0 (0)
Anemia and pyrexia	1 (2.3)	0 (0)
MOST FREQUENT ADVERSE EVENTS*†		
Headache§	12 (27.3)	19‡ (44.2)
Nasopharyngitis	8 (18.2)	10 (23.3)
Upper respiratory tract infection	10 (22.7)	6 (14)
Back pain	4 (9.1)	8 (18.6)
Nausea	5 (11.4)	7 (16.3)
Cough	4 (9.1)	5 (11.6)
Diarrhea	5 (11.4)	4 (9.3)
Arthralgia	5 (11.4)	3 (7.0)
Abdominal pain	5 (11.4)	2 (4.7)
Dizziness	5 (11.4)	2 (4.7)
Vomiting	5 (11.4)	2 (4.7)
Fatigue	1 (2.3)	5 (11.6)

Viral infection	5 (11.4)	1 (2.3)

*By preferred terms

†Occurring in 10% or more of patients

‡Sixteen of 19 patients experienced headache within 48 hours of infusion

§Following the first 2 weeks of dosing, 20.9% of eculizumab- and 22.7% of placebo-treated patients experienced headache

DISCUSSION

Chronic intravascular hemolysis with periods of acute exacerbation are the classical manifestations of PNH, frequently resulting in anemia, the need for transfusions to sustain hemoglobin levels, and deterioration in quality of life. In the phase III pivotal TRIUMPH study, we examined the effect of terminal complement inhibition with eculizumab on hemoglobin levels and transfusion requirements in patients with PNH. Forty-nine percent of patients treated with eculizumab over the 6-month period demonstrated stabilization of hemoglobin in the absence of transfusions compared to no patients in the placebo arm of the trial. Over 50% of eculizumab-treated patients were transfusion independent during the entire study compared to none in the placebo arm, and the overall mean transfusion rate was reduced by 73%. Moreover, even in patients who did not achieve transfusion independence, eculizumab treatment was associated with a 44% reduction in the rate of transfusion (data now shown).

Lactate dehydrogenase, a biochemical marker of hemolysis in PNH,[9] was immediately and consistently decreased in all eculizumab-treated patients, while patients in the placebo cohort continued to hemolyze with levels of LDH exceeding 5 times the upper limit of the normal range in all patients at the study end. Levels of LDH were reduced into the normal range in approximately one-third of eculizumab-treated patients, while the remainder stabilized at a level just above the upper limit of normal suggesting residual low level hemolysis in some patients. Levels of haptoglobin, a more sensitive marker of the presence of cell free hemoglobin in the circulation, were undetectable in most patients. Low level hemolysis in a subset of eculizumab-treated patients is possibly due to an inherent decrease in survival of these cells or C3b-mediated, extravascular clearance of PNH erythrocytes through the reticuloendothelial system.[17]

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Before eculizumab treatment, hemoglobin levels in study patients were artificially maintained by frequent transfusion. Therefore, stabilization of hemoglobin levels with a concomitant cessation of or reduction in transfusions represents a net increase in endogenous hemoglobin levels. Our data suggest that resolution of hemolysis with eculizumab results in a new steady state hemoglobin level determined by a balance between the extent of the underlying bone marrow dysfunction, the number of PNH erythrocytes that are preserved by eculizumab therapy and the new level (if any) of transfusion requirement.

Patients with PNH generally experience markedly impaired quality of life characterized by fatigue, anemia, thrombosis, and pulmonary hypertension as well as smooth muscle dystonia including abdominal pain, dysphagia, and erectile dysfunction.[9,10,18] These symptoms have been attributed to both excessive intravascular hemolysis and downstream scavenging of nitric oxide by cell free hemoglobin in plasma. The reduction of intravascular hemolysis in eculizumab-treated patients in the current study was associated with significant improvements in the fatigue component of quality of life relative to placebo-treated patients as assessed via the FACIT-Fatigue instrument. Further, eculizumab therapy was associated with a median increase of 6.4 points over baseline values established before treatment. It has previously been demonstrated that an increase of 3 or more points from baseline represents a clinically important difference in this quality of life instrument.[19] Patients who received eculizumab also experienced a significant improvement in most domains of the EORTC QLQ-30 relative to the placebo-treated cohort including global health status, physical functioning, emotional functioning, cognitive functioning, role functioning, social functioning, fatigue, pain, dyspnea, appetite loss, and insomnia. Improvement in the fatigue component of the EORTC QLQ-30 provides support for the improvement demonstrated in the FACIT-Fatigue instrument during eculizumab therapy. Importantly, these improvements in quality of life in the eculizumab-treated patients occurred despite similar levels of erythrocyte hemoglobin in the two treatment groups, further supporting the contribution of hemolysis per se, as opposed to anemia, in mediating the poor quality of life in PNH patients. Clinical assessment of additional life quality-related symptoms of PNH, including abdominal pain, dysphagia, and erectile dysfunction, have also been reported to improve during eculizumab therapy.[20]

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Eculizumab was safe and well-tolerated. There were no deaths in the study and only a single thrombotic event which occurred in a placebo patient in a site (the hepatic veins) which is typical of the thrombosis in PNH. The relative brief duration of this study was not sufficient to address the relevant issue of a possible protection from thrombosis by terminal complement inhibition with eculizumab.

Adverse events were generally mild with headache occurring at increased frequency in the eculizumab-treated patients; however, this increased frequency did not persist following the first two doses of therapy. There were 4 SAEs in the eculizumab treatment group and 9 SAEs in the placebo group. There was no evidence of increased infection risk in eculizumab-treated patients during the study period. One eculizumab-treated patient showed a low level of anti-eculizumab antibodies at one time point during the study which did not persist and did not result in a disruption of complement blockade. There were no AEs associated with eculizumab withdrawal in the 2 eculizumab-treated patients who did not complete the trial. Additional safety assessments, as well as efficacy measures, are being examined in an ongoing multi-center, open-label Phase III safety trial of eculizumab (SHEPHERD) in approximately 95 patients with PNH.

Results from the current randomized, double-blind, placebo-controlled, global study show that terminal complement inhibition with eculizumab appears to be a safe and effective therapy for patients with the rare disorder PNH. Treatment with eculizumab reduced intravascular hemolysis, and stabilized hemoglobin levels despite a reduction of transfusions, to the point where most PNH patients were rendered transfusion independent. Substantial and clinically meaningful improvements in fatigue and other key quality of life parameters were also demonstrated. All of the 85 patients who completed the study elected to receive eculizumab in an open-label extension study and all currently remain on drug. The results of the TRIUMPH study indicate that terminal complement inhibition with eculizumab safely and effectively addresses an important consequence of the underlying genetic defect in PNH hematopoietic stem cells by providing a therapeutic replacement for the terminal complement inhibitor deficiency.

The present invention provides among other things treatment with an inhibitor of complement. Many variations of the invention will become apparent to those skilled in the art upon review of this specification. The full scope of the invention should be determined by reference to the claims, along with their full scope of equivalents, and the specification, along with such variations.

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All publications and patents mentioned herein, including those items listed below, are hereby incorporated by reference in their entirety as if each individual publication or patent was specifically and individually indicated to be incorporated by reference. In case of conflict, the present application, including any definitions herein, will control.

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17. Jasinski M, Pantazopoulos P, Rother RP et al. A novel mechanism of complement-independent clearance of red cells deficient in glycosyl phosphatidylinositol-linked proteins. Blood 2004;103:2827-34.

18. Hill A, Wang X, Sapsford RJ et al. Nitric oxide Consumption and Pulmonary Hypertension in Patients with Paroxysmal Nocturnal Hemoglobinuria. Blood 106[11]. 2005.
Ref Type: Abstract

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SEQUENCES

SEQ ID NO: 1 – Eculizumab V_H

QVQLVQSGAEVKKPGASVKVSCKASGYIFSNYWIQWVRQAPGQGLEWMGEILPG
SGSTEYTENFKDRVTMTRDTSTSTVYMELSSLRSEDTAVYYCARYFFGSSPNWYF
DVWGQGTLVTVSSA

SEQ ID NO: 2 – Eculizumab Heavy chain

QVQLVQSGAEVKKPGASVKVSCKASGYIFSNYWIQWVRQAPGQGLEWMGEILPG
SGSTEYTENFKDRVTMTRDTSTSTVYMELSSLRSEDTAVYYCARYFFGSSPNWYF
DVWGQGTLVTVSSASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNS
GALTSGVHTFPAVLQSSGLYSLSSVVTVPSSNFGTQTYTCNVDHKPSNTKVDKTVE
RKCCVECPPCPAPPVAGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQFN
WYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLP
SSIEKTISKAKGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQ
PENNYKTTPPVLDSDGSFFLYSRLTVDKSRWQEGNVFSCSVMHEALHNHYTQKSL
SLSLGK

SEQ ID NO: 3 – Eculizumab V_L

MDMRVPAQLLGLLLLWLRGARCDIQMTQSPSSLSASVGDRVTITCGASENIYGAL
NWYQQKPGKAPKLLIYGATNLADGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCQ
NVLNTPLTFGQGTKVEIKRT

SEQ ID NO: 4 – Eculizumab Light chain

MDMRVPAQLLGLLLLWLRGARCDIQMTQSPSSLSASVGDRVTITCGASENIYGAL
NWYQQKPGKAPKLLIYGATNLADGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCQ
NVLNTPLTFGQGTKVEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKV
QWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQG
LSSPVTKSFNRGEC

SEQ ID NO: 5 – Eculizumab CDRH1

NYWIQ

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SEQ ID NO: 6 – Eculizumab CDRH2
EILPGSGSTEYTENFKD

SEQ ID NO: 7 – Eculizumab CDRH3
YFFGSSPNWYFDV

SEQ ID NO: 8 – Eculizumab CDRL1
GASENIYGALN

SEQ ID NO: 9 – Eculizumab CDRL2
GATNLAD

SEQ ID NO: 10 – Eculizumab CDRL3
QNVLNTPLT

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WHAT IS CLAIMED IS:

1. A pharmaceutical composition for use in treating a patient afflicted with paroxysmal nocturnal hemoglobinuria (PNH), wherein the composition is a 300 mg eculizumab single-use dosage form comprising 30 ml of a 10 mg eculizumab/ml sterile, preservative free solution.

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TREATMENT OF PAROXYSMAL NOCTURNAL HEMOGLOBINURIA PATIENTS BY AN INHIBITOR OF COMPLEMENT

Eculizumab, a humanized monoclonal antibody against C5 that inhibits terminal complement activation, showed activity in a preliminary 12-week open-label trial in a small cohort of patients with paroxysmal nocturnal hemoglobinuria (PNH). The present study examined whether chronic eculizumab therapy could reduce intravascular hemolysis, stabilize hemoglobin levels, reduce transfusion requirements, and improve quality of life in a double-blind, randomized, placebo-controlled, multi-center global Phase III trial. It has been found that eculizumab stabilized hemoglobin levels, decreased the need for transfusions, and improved quality of life in PNH patients via reduced intravascular hemolysis. Chronic eculizumab treatment appears to be a safe and effective therapy for PNH.

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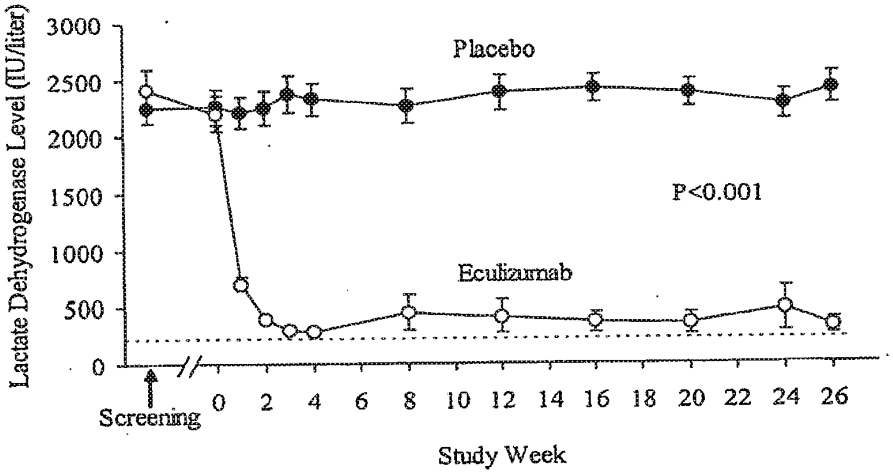

Lactate Dehydrogenase Level (IU/liter)
3000
2500
2000
1500
1000
500
0
Placebo
P<0.001
Eculizumab
Screening
0 2 4 6 8 10 12 14 16 18 20 22 24 26
Study Week

FIGURE 1A

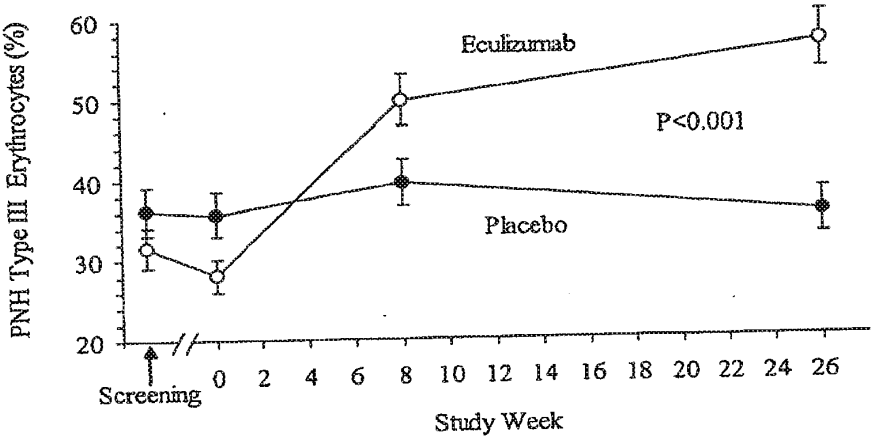

PNH Type III Erythrocytes (%)
60
50
40
30
20
Eculizumab
P<0.001
Placebo
Screening
0 2 4 6 8 10 12 14 16 18 20 22 24 26
Study Week

FIGURE 1B

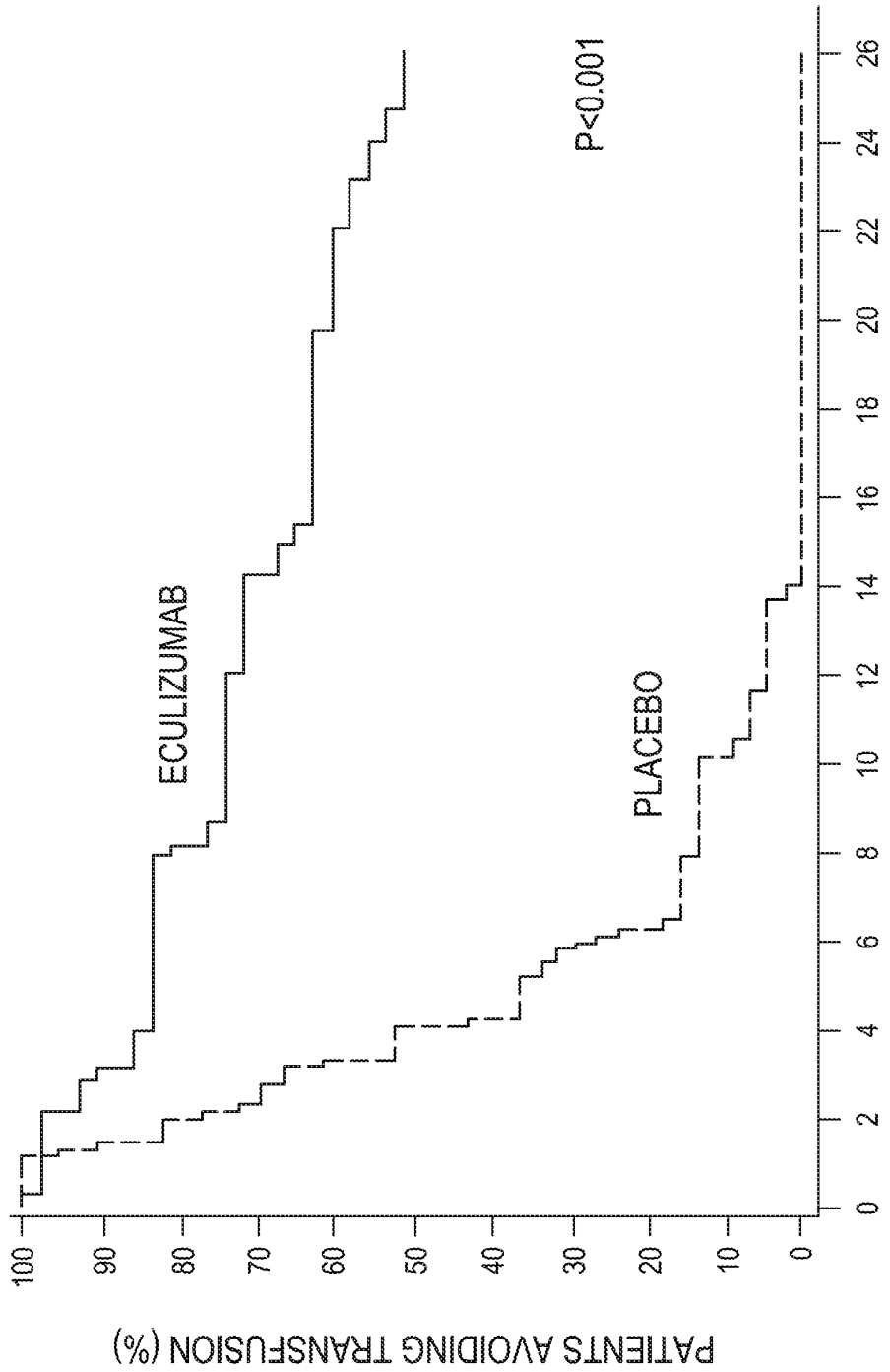

PATIENTS AVOIDING TRANSFUSION (%)
100
90
80
70
60
50
40
30
20
10
0
0
2
4
6
8
10
12
14
16
18
20
22
24
26
STUDY WEEK
ECULIZUMAB
PLACEBO
P<0.001

FIGURE 2

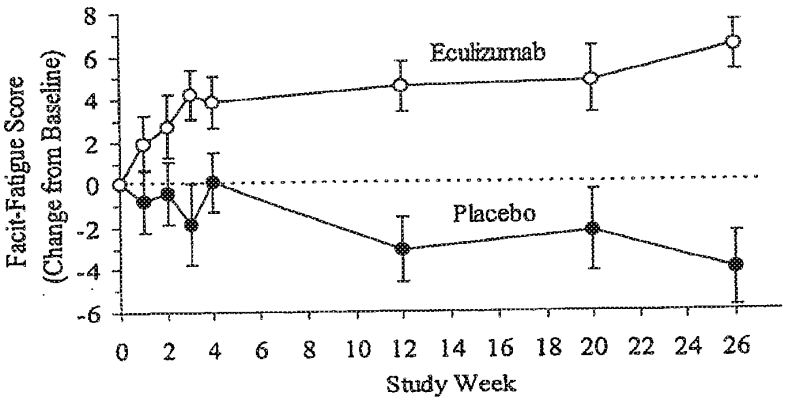

Facit-Fatigue Score
(Change from Baseline)
8
6
4
2
0
-2
-4
-6
0 2 4 6 8 10 12 14 16 18 20 22 24 26
Study Week
Eculizumab
Placebo

FIGURE 3

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

Dated: May 6, 2016
Electronic Signature for Jill Gorny Sloper, Esq.: /Jill Gorny Sloper, Esq./

Docket No.: AXJ-114BUSCN2
(PATENT)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

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

Application No.: Not Yet Assigned

Confirmation No.: N/A

Filed: Concurrently Herewith

Art Unit: N/A

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

Examiner: Not Yet Assigned

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

STATEMENT PURSUANT TO 37 CFR 1.821

Dear Sir:

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

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

Dated: May 6, 2016

Respectfully submitted,
Electronic signature: /Jill Gorny Sloper, Esq./
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Application Data Sheet 37 CFR 1.76	Attorney Docket Number	AXJ-114BUSCN2
	Application Number	
Title of Invention	TREATMENT OF PAROXYSMAL NOCTURNAL HEMOGLOBINURIA PATIENTS BY AN INHIBITOR OF COMPLEMENT	

The application data sheet is part of the provisional or nonprovisional application for which it is being submitted. The following form contains the bibliographic data arranged in a format specified by the United States Patent and Trademark Office as outlined in 37 CFR 1.76.
This document may be completed electronically and submitted to the Office in electronic format using the Electronic Filing System (EFS) or the document may be printed and included in a paper filed application.

Secrecy Order 37 CFR 5.2:

☐ Portions or all of the application associated with this Application Data Sheet may fall under a Secrecy Order pursuant to 37 CFR 5.2 (Paper filers only. Applications that fall under Secrecy Order may not be filed electronically.)

Inventor Information:

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Inventor 2 Remove

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Residence Information (Select One) ◉ US Residency Non US Residency Active US Military Service

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All Inventors Must Be Listed - Additional Inventor Information blocks may be generated within this form by selecting the **Add** button. Add

Correspondence Information:

Enter either Customer Number or complete the Correspondence Information section below.
For further information see 37 CFR 1.33(a).

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Application Data Sheet 37 CFR 1.76	Attorney Docket Number	AXJ-114BUSCN2
	Application Number	
Title of Invention	TREATMENT OF PAROXYSMAL NOCTURNAL HEMOGLOBINURIA PATIENTS BY AN INHIBITOR OF COMPLEMENT	

☐ **An Address is being provided for the correspondence Information of this application.**

Customer Number	133485		
Email Address	IPBoston.Docketing@nelsonmullins.com	Add Email	Remove Email

Application Information:

Title of the Invention	TREATMENT OF PAROXYSMAL NOCTURNAL HEMOGLOBINURIA PATIENTS BY AN INHIBITOR OF COMPLEMENT		
Attorney Docket Number	AXJ-114BUSCN2	**Small Entity Status Claimed**	☐
Application Type	Nonprovisional		
Subject Matter	Utility		
Total Number of Drawing Sheets (if any)	4	**Suggested Figure for Publication (if any)**	

Filing By Reference:

Only complete this section when filing an application by reference under 35 U.S.C. 111(c) and 37 CFR 1.57(a). Do not complete this section if application papers including a specification and any drawings are being filed. Any domestic benefit or foreign priority information must be provided in the appropriate section(s) below (i.e., "Domestic Benefit/National Stage Information" and "Foreign Priority Information").

For the purposes of a filing date under 37 CFR 1.53(b), the description and any drawings of the present application are replaced by this reference to the previously filed application, subject to conditions and requirements of 37 CFR 1.57(a).

Application number of the previously filed application	Filing date (YYYY-MM-DD)	Intellectual Property Authority or Country

Publication Information:

☐ Request Early Publication (Fee required at time of Request 37 CFR 1.219)

☐ **Request Not to Publish.** I hereby request that the attached application not be published under 35 U.S.C. 122(b) and certify that the invention disclosed in the attached application **has not and will not** be the subject of an application filed in another country, or under a multilateral international agreement, that requires publication at eighteen months after filing.

Representative Information:

Representative information should be provided for all practitioners having a power of attorney in the application. Providing this information in the Application Data Sheet does not constitute a power of attorney in the application (see 37 CFR 1.32).
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Application Data Sheet 37 CFR 1.76	Attorney Docket Number	AXJ-114BUSCN2
	Application Number	
Title of Invention	TREATMENT OF PAROXYSMAL NOCTURNAL HEMOGLOBINURIA PATIENTS BY AN INHIBITOR OF COMPLEMENT	

Domestic Benefit/National Stage Information:

This section allows for the applicant to either claim benefit under 35 U.S.C. 119(e), 120, 121, 365(c), or 386(c) or indicate National Stage entry from a PCT application. Providing benefit claim information in the Application Data Sheet constitutes the specific reference required by 35 U.S.C. 119(e) or 120, and 37 CFR 1.78.
When referring to the current application, please leave the "Application Number" field blank.

Prior Application Status	Pending		Remove
Application Number	Continuity Type	Prior Application Number	Filing or 371(c) Date (YYYY-MM-DD)
	Continuation of	13/426973	2012-03-22
Prior Application Status	Abandoned		Remove
Application Number	Continuity Type	Prior Application Number	Filing or 371(c) Date (YYYY-MM-DD)
13/426973	Continuation of	12/225040	2009-05-13
Prior Application Status			Remove
Application Number	Continuity Type	Prior Application Number	Filing or 371(c) Date (YYYY-MM-DD)
12/225040	a 371 of international	PCT/US2007/006606	2007-03-15
Prior Application Status			Remove
Application Number	Continuity Type	Prior Application Number	Filing or 371(c) Date (YYYY-MM-DD)
PCT/US2007/006606	Claims benefit of provisional	60/783070	2006-03-15

Additional Domestic Benefit/National Stage Data may be generated within this form by selecting the **Add** button. Add

Foreign Priority Information:

This section allows for the applicant to claim priority to a foreign application. Providing this information in the application data sheet constitutes the claim for priority as required by 35 U.S.C. 119(b) and 37 CFR 1.55. When priority is claimed to a foreign application that is eligible for retrieval under the priority document exchange program (PDX)[i] the information will be used by the Office to automatically attempt retrieval pursuant to 37 CFR 1.55(i)(1) and (2). Under the PDX program, applicant bears the ultimate responsibility for ensuring that a copy of the foreign application is received by the Office from the participating foreign intellectual property office, or a certified copy of the foreign priority application is filed, within the time period specified in 37 CFR 1.55(g)(1).

Remove

Application Number	Country[i]	Filing Date (YYYY-MM-DD)	Access Code[i] (if applicable)

Additional Foreign Priority Data may be generated within this form by selecting the **Add** button. Add

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Application Data Sheet 37 CFR 1.76		Attorney Docket Number	AXJ-114BUSCN2
		Application Number	
Title of Invention	TREATMENT OF PAROXYSMAL NOCTURNAL HEMOGLOBINURIA PATIENTS BY AN INHIBITOR OF COMPLEMENT		

Statement under 37 CFR 1.55 or 1.78 for AIA (First Inventor to File) Transition Applications

☐ This application (1) claims priority to or the benefit of an application filed before March 16, 2013 and (2) also contains, or contained at any time, a claim to a claimed invention that has an effective filing date on or after March 16, 2013.
NOTE: By providing this statement under 37 CFR 1.55 or 1.78, this application, with a filing date on or after March 16, 2013, will be examined under the first inventor to file provisions of the AIA.

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Application Data Sheet 37 CFR 1.76	Attorney Docket Number	AXJ-114BUSCN2
	Application Number	
Title of Invention	TREATMENT OF PAROXYSMAL NOCTURNAL HEMOGLOBINURIA PATIENTS BY AN INHIBITOR OF COMPLEMENT	

Authorization or Opt-Out of Authorization to Permit Access:

When this Application Data Sheet is properly signed and filed with the application, applicant has provided written authority to permit a participating foreign intellectual property (IP) office access to the instant application-as-filed (see paragraph A in subsection 1 below) and the European Patent Office (EPO) access to any search results from the instant application (see paragraph B in subsection 1 below).

Should applicant choose not to provide an authorization identified in subsection 1 below, applicant **must opt-out** of the authorization by checking the corresponding box A or B or both in subsection 2 below.

NOTE: This section of the Application Data Sheet is **ONLY** reviewed and processed with the **INITIAL** filing of an application. After the initial filing of an application, an Application Data Sheet cannot be used to provide or rescind authorization for access by a foreign IP office(s). Instead, Form PTO/SB/39 or PTO/SB/69 must be used as appropriate.

1. Authorization to Permit Access by a Foreign Intellectual Property Office(s)

A. Priority Document Exchange (PDX) - Unless box A in subsection 2 (opt-out of authorization) is checked, the undersigned hereby **grants the USPTO authority** to provide the European Patent Office (EPO), the Japan Patent Office (JPO), the Korean Intellectual Property Office (KIPO), the State Intellectual Property Office of the People's Republic of China (SIPO), the World Intellectual Property Organization (WIPO), and any other foreign intellectual property office participating with the USPTO in a bilateral or multilateral priority document exchange agreement in which a foreign application claiming priority to the instant patent application is filed, access to: (1) the instant patent application-as-filed and its related bibliographic data, (2) any foreign or domestic application to which priority or benefit is claimed by the instant application and its related bibliographic data, and (3) the date of filing of this Authorization. See 37 CFR 1.14(h)(1).

B. Search Results from U.S. Application to EPO - Unless box B in subsection 2 (opt-out of authorization) is checked, the undersigned hereby **grants the USPTO authority** to provide the EPO access to the bibliographic data and search results from the instant patent application when a European patent application claiming priority to the instant patent application is filed. See 37 CFR 1.14(h)(2).

The applicant is reminded that the EPO's Rule 141(1) EPC (European Patent Convention) requires applicants to submit a copy of search results from the instant application without delay in a European patent application that claims priority to the instant application.

2. Opt-Out of Authorizations to Permit Access by a Foreign Intellectual Property Office(s)

☐ A. Applicant **DOES NOT** authorize the USPTO to permit a participating foreign IP office access to the instant application-as-filed. If this box is checked, the USPTO will not be providing a participating foreign IP office with any documents and information identified in subsection 1A above.

☐ B. Applicant **DOES NOT** authorize the USPTO to transmit to the EPO any search results from the instant patent application. If this box is checked, the USPTO will not be providing the EPO with search results from the instant application.

NOTE: Once the application has published or is otherwise publicly available, the USPTO may provide access to the application in accordance with 37 CFR 1.14.

PTO/AIA/14 (11-15)
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Application Data Sheet 37 CFR 1.76	Attorney Docket Number	AXJ-114BUSCN2
	Application Number	
Title of Invention	TREATMENT OF PAROXYSMAL NOCTURNAL HEMOGLOBINURIA PATIENTS BY AN INHIBITOR OF COMPLEMENT	

Applicant Information:

Providing assignment information in this section does not substitute for compliance with any requirement of part 3 of Title 37 of CFR to have an assignment recorded by the Office.

Applicant 1 — Remove

If the applicant is the inventor (or the remaining joint inventor or inventors under 37 CFR 1.45), this section should not be completed. The information to be provided in this section is the name and address of the legal representative who is the applicant under 37 CFR 1.43; or the name and address of the assignee, person to whom the inventor is under an obligation to assign the invention, or person who otherwise shows sufficient proprietary interest in the matter who is the applicant under 37 CFR 1.46. If the applicant is an applicant under 37 CFR 1.46 (assignee, person to whom the inventor is obligated to assign, or person who otherwise shows sufficient proprietary interest) together with one or more joint inventors, then the joint inventor or inventors who are also the applicant should be identified in this section.

Clear

● Assignee	Legal Representative under 35 U.S.C. 117	Joint Inventor
Person to whom the inventor is obligated to assign.	Person who shows sufficient proprietary interest	

If applicant is the legal representative, indicate the authority to file the patent application, the inventor is:

Name of the Deceased or Legally Incapacitated Inventor:

If the Applicant is an Organization check here. ☒

Organization Name	Alexion Pharmaceuticals, Inc.		
Mailing Address Information For Applicant:			
Address 1	100 College St.		
Address 2			
City	New Haven	**State/Province**	CT
Country	US	Postal Code	06510
Phone Number		Fax Number	
Email Address			

Additional Applicant Data may be generated within this form by selecting the Add button. Add

Assignee Information including Non-Applicant Assignee Information:

Providing assignment information in this section does not substitute for compliance with any requirement of part 3 of Title 37 of CFR to have an assignment recorded by the Office.

PTO/AIA/14 (11-15)
Approved for use through 04/30/2017. OMB 0651-0032
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it contains a valid OMB control number.

Application Data Sheet 37 CFR 1.76	Attorney Docket Number	AXJ-114BUSCN2
	Application Number	
Title of Invention	TREATMENT OF PAROXYSMAL NOCTURNAL HEMOGLOBINURIA PATIENTS BY AN INHIBITOR OF COMPLEMENT	

Assignee 1

Complete this section if assignee information, including non-applicant assignee information, is desired to be included on the patent application publication. An assignee-applicant identified in the "Applicant Information" section will appear on the patent application publication as an applicant. For an assignee-applicant, complete this section only if identification as an assignee is also desired on the patent application publication.

Remove

If the Assignee or Non-Applicant Assignee is an Organization check here. ☐

Prefix	**Given Name**	Middle Name	**Family Name**	Suffix

Mailing Address Information For Assignee including Non-Applicant Assignee:

Address 1			
Address 2			
City		**State/Province**	
Country i		Postal Code	
Phone Number		Fax Number	
Email Address			

Additional Assignee or Non-Applicant Assignee Data may be generated within this form by selecting the Add button. Add

Signature:

Remove

NOTE: This Application Data Sheet must be signed in accordance with 37 CFR 1.33(b). **However, if this Application Data Sheet is submitted with the INITIAL filing of the application and either box A or B is not checked in subsection 2 of the "Authorization or Opt-Out of Authorization to Permit Access" section, then this form must also be signed in accordance with 37 CFR 1.14(c).**

This Application Data Sheet **must** be signed by a patent practitioner if one or more of the applicants is a **juristic entity** (e.g., corporation or association). If the applicant is two or more joint inventors, this form must be signed by a patent practitioner, **all** joint inventors who are the applicant, or one or more joint inventor-applicants who have been given power of attorney (e.g., see USPTO Form PTO/AIA/81) on behalf of **all** joint inventor-applicants.

See 37 CFR 1.4(d) for the manner of making signatures and certifications.

Signature	/Jill Gorny Sloper, Esq./			Date (YYYY-MM-DD)	2016-05-06
First Name	Jill Gorny	Last Name	Sloper	Registration Number	60760

Additional Signature may be generated within this form by selecting the Add button. Add

PTO/AIA/14 (11-15)
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U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it contains a valid OMB control number.

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	Application Number	
Title of Invention	TREATMENT OF PAROXYSMAL NOCTURNAL HEMOGLOBINURIA PATIENTS BY AN INHIBITOR OF COMPLEMENT	

This collection of information is required by 37 CFR 1.76. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 23 minutes to complete, including gathering, preparing, and submitting the completed application data sheet form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

Privacy Act Statement

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

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

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

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

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

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

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

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

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

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

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

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Sequence Listing was accepted.
See attached Validation Report.
If you need help call the Patent Electronic Business Center at (866)
217-9197 (toll free).
Reviewer: Saleem, Syed (ASRC)
Timestamp: [year=2016; month=5; day=12; hr=13; min=50; sec=42; ms=843; ]
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Validated By CRFValidator v 1.0.5

Application No: 15148839 Version No: 1.0

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Total Warnings: 10
Total Errors: 1
No. of SeqIDs Defined: 10
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ROTHER, RUSSELL P.

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BY AN INHIBITOR OF COMPLEMENT

<130> AXJ-114BUSCN2

<140> US 15/148,839
<141> 2016-05-06

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

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

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

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

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

Ala Arg Tyr Phe Phe Gly Ser Ser Pro Asn Trp Tyr Phe Asp Val Trp
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Gly Gln Gly Thr Leu Val Thr Val Ser Ser Ala
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            20                  25                  30

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Pro Pro Ser Gln Glu Glu Met Thr Lys Asn Gln Val Ser Leu Thr Cys
        355                 360                 365
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Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser
    370                 375                 380

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

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

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

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

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

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

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

Ile Ser Ser Leu Gln Pro Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Asn
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            100                 105                 110

Val Leu Asn Thr Pro Leu Thr Phe Gly Gln Gly Thr Lys Val Glu Ile
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Lys Arg Thr
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            20                  25                  30

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

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

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

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

Ile Ser Ser Leu Gln Pro Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Asn
            100                 105                 110

Val Leu Asn Thr Pro Leu Thr Phe Gly Gln Gly Thr Lys Val Glu Ile
        115                 120                 125

Lys Arg Thr Val Ala Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp
    130                 135                 140
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Glu Gln Leu Lys Ser Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn
145                 150                 155                 160

Phe Tyr Pro Arg Glu Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu
                165                 170                 175

Gln Ser Gly Asn Ser Gln Glu Ser Val Thr Glu Gln Asp Ser Lys Asp
            180                 185                 190

Ser Thr Tyr Ser Leu Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr
        195                 200                 205

Glu Lys His Lys Val Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser
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Ser Pro Val Thr Lys Ser Phe Asn Arg Gly Glu Cys
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<210> 7
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<211> 13
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Gly Ala Thr Asn Leu Ala Asp
1 5

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<400> 10
Gln Asn Val Leu Asn Thr Pro Leu Thr
1 5

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NUMBER	FILING or 371(c) DATE	GRP ART UNIT	FIL FEE REC'D	ATTY.DOCKET.NO	TOT CLAIMS	IND CLAIMS
15/148,839	05/06/2016	1677	1740	AXJ-114BUSCN2	1	1

CONFIRMATION NO. 3159

FILING RECEIPT

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

OC000000082939289

Date Mailed: 05/17/2016

Receipt is acknowledged of this non-provisional patent application. The application will be taken up for examination in due course. Applicant will be notified as to the results of the examination. Any correspondence concerning the application must include the following identification information: the U.S. APPLICATION NUMBER, FILING DATE, NAME OF APPLICANT, and TITLE OF INVENTION. Fees transmitted by check or draft are subject to collection. Please verify the accuracy of the data presented on this receipt. **If an error is noted on this Filing Receipt, please submit a written request for a Filing Receipt Correction. Please provide a copy of this Filing Receipt with the changes noted thereon. If you received a "Notice to File Missing Parts" for this application, please submit any corrections to this Filing Receipt with your reply to the Notice. When the USPTO processes the reply to the Notice, the USPTO will generate another Filing Receipt incorporating the requested corrections**

Inventor(s)

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

Applicant(s)

Alexion Pharmaceuticals, Inc., New Haven, CT;

Power of Attorney: The patent practitioners associated with Customer Number 133485

Domestic Priority data as claimed by applicant

This application is a CON of 13/426,973 03/22/2012
which is a CON of 12/225,040 05/13/2009 ABN
which is a 371 of PCT/US2007/006606 03/15/2007
which claims benefit of 60/783,070 03/15/2006

Foreign Applications for which priority is claimed (You may be eligible to benefit from the **Patent Prosecution Highway** program at the USPTO. Please see http://www.uspto.gov for more information.) - None.
Foreign application information must be provided in an Application Data Sheet in order to constitute a claim to foreign priority. See 37 CFR 1.55 and 1.76.

Permission to Access Application via Priority Document Exchange: Yes

Permission to Access Search Results: Yes

Applicant may provide or rescind an authorization for access using Form PTO/SB/39 or Form PTO/SB/69 as appropriate.

If Required, Foreign Filing License Granted: 05/16/2016

The country code and number of your priority application, to be used for filing abroad under the Paris Convention, is **US 15/148,839**

Projected Publication Date: 08/25/2016

Non-Publication Request: No

Early Publication Request: No

Title

TREATMENT OF PAROXYSMAL NOCTURNAL HEMOGLOBINURIA PATIENTS BY AN INHIBITOR OF COMPLEMENT

Preliminary Class

435

Statement under 37 CFR 1.55 or 1.78 for AIA (First Inventor to File) Transition Applications: No

PROTECTING YOUR INVENTION OUTSIDE THE UNITED STATES

Since the rights granted by a U.S. patent extend only throughout the territory of the United States and have no effect in a foreign country, an inventor who wishes patent protection in another country must apply for a patent in a specific country or in regional patent offices. Applicants may wish to consider the filing of an international application under the Patent Cooperation Treaty (PCT). An international (PCT) application generally has the same effect as a regular national patent application in each PCT-member country. The PCT process **simplifies** the filing of patent applications on the same invention in member countries, but **does not result** in a grant of "an international patent" and does not eliminate the need of applicants to file additional documents and fees in countries where patent protection is desired.

Almost every country has its own patent law, and a person desiring a patent in a particular country must make an application for patent in that country in accordance with its particular laws. Since the laws of many countries differ in various respects from the patent law of the United States, applicants are advised to seek guidance from specific foreign countries to ensure that patent rights are not lost prematurely.

Applicants also are advised that in the case of inventions made in the United States, the Director of the USPTO must issue a license before applicants can apply for a patent in a foreign country. The filing of a U.S. patent application serves as a request for a foreign filing license. The application's filing receipt contains further information and guidance as to the status of applicant's license for foreign filing.

Applicants may wish to consult the USPTO booklet, "General Information Concerning Patents" (specifically, the section entitled "Treaties and Foreign Patents") for more information on timeframes and deadlines for filing foreign patent applications. The guide is available either by contacting the USPTO Contact Center at 800-786-9199, or it can be viewed on the USPTO website at http://www.uspto.gov/web/offices/pac/doc/general/index.html.

For information on preventing theft of your intellectual property (patents, trademarks and copyrights), you may wish to consult the U.S. Government website, http://www.stopfakes.gov. Part of a Department of Commerce initiative, this website includes self-help "toolkits" giving innovators guidance on how to protect intellectual property in specific countries such as China, Korea and Mexico. For questions regarding patent enforcement issues, applicants may call the U.S. Government hotline at 1-866-999-HALT (1-866-999-4258).

LICENSE FOR FOREIGN FILING UNDER

Title 35, United States Code, Section 184

Title 37, Code of Federal Regulations, 5.11 & 5.15

GRANTED

The applicant has been granted a license under 35 U.S.C. 184, if the phrase "IF REQUIRED, FOREIGN FILING LICENSE GRANTED" followed by a date appears on this form. Such licenses are issued in all applications where the conditions for issuance of a license have been met, regardless of whether or not a license may be required as set forth in 37 CFR 5.15. The scope and limitations of this license are set forth in 37 CFR 5.15(a) unless an earlier license has been issued under 37 CFR 5.15(b). The license is subject to revocation upon written notification. The date indicated is the effective date of the license, unless an earlier license of similar scope has been granted under 37 CFR 5.13 or 5.14.

This license is to be retained by the licensee and may be used at any time on or after the effective date thereof unless it is revoked. This license is automatically transferred to any related applications(s) filed under 37 CFR 1.53(d). This license is not retroactive.

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NOT GRANTED

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PATENT APPLICATION FEE DETERMINATION RECORD

Substitute for Form PTO-875

Application or Docket Number: 15/148,839

APPLICATION AS FILED - PART I

FOR	(Column 1) NUMBER FILED	(Column 2) NUMBER EXTRA	SMALL ENTITY RATE($)	SMALL ENTITY FEE($)	OR	OTHER THAN SMALL ENTITY RATE($)	OTHER THAN SMALL ENTITY FEE($)
BASIC FEE (37 CFR 1.16(a), (b), or (c))	N/A	N/A	N/A			N/A	280
SEARCH FEE (37 CFR 1.16(k), (i), or (m))	N/A	N/A	N/A			N/A	600
EXAMINATION FEE (37 CFR 1.16(o), (p), or (q))	N/A	N/A	N/A			N/A	720
TOTAL CLAIMS (37 CFR 1.16(i))	1 minus 20 =	*			OR	x 80 =	0.00
INDEPENDENT CLAIMS (37 CFR 1.16(h))	1 minus 3 =	*				x 420 =	0.00
APPLICATION SIZE FEE (37 CFR 1.16(s))	If the specification and drawings exceed 100 sheets of paper, the application size fee due is $310 ($155 for small entity) for each additional 50 sheets or fraction thereof. See 35 U.S.C. 41(a)(1)(G) and 37 CFR 1.16(s).						0.00
MULTIPLE DEPENDENT CLAIM PRESENT (37 CFR 1.16(j))							0.00
* If the difference in column 1 is less than zero, enter "0" in column 2.			TOTAL			TOTAL	1600

APPLICATION AS AMENDED - PART II

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

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

* If the entry in column 1 is less than the entry in column 2, write "0" in column 3.

** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 20, enter "20".

*** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 3, enter "3".

The "Highest Number Previously Paid For" (Total or Independent) is the highest found in the appropriate box in column 1.

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United States Patent and Trademark Office
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P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NUMBER	FILING OR 371(C) DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO./TITLE
15/148,839	05/06/2016	Leonard BELL	AXJ-114BUSCN2

CONFIRMATION NO. 3159

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

INFORMAL NOTICE

OC000000082939290

Date Mailed: 05/17/2016

INFORMATIONAL NOTICE TO APPLICANT

Applicant is notified that the above-identified application contains the deficiencies noted below. No period for reply is set forth in this notice for correction of these deficiencies. However, if a deficiency relates to the inventor's oath or declaration, the applicant must file an oath or declaration in compliance with 37 CFR 1.63, or a substitute statement in compliance with 37 CFR 1.64, executed by or with respect to each actual inventor no later than the expiration of the time period set in the "Notice of Allowability" to avoid abandonment. See 37 CFR 1.53(f).

The item(s) indicated below are also required and should be submitted with any reply to this notice to avoid further processing delays.

- A properly executed inventor's oath or declaration has not been received for the following inventor(s):
  Leonard BELL
  Russell P. ROTHER

Questions about the contents of this notice and the requirements it sets forth should be directed to the Office of Data Management, Application Assistance Unit, at **(571) 272-4000** or **(571) 272-4200** or **1-888-786-0101**.

/tpetros/

To: chris.schlauch@nelsonmullins.com,ipqualityassuranceboston@nelsonmullins.com,ipboston.docketing@nel
From: PAIR_eOfficeAction@uspto.gov
Cc: PAIR_eOfficeAction@uspto.gov
Subject: Private PAIR Correspondence Notification for Customer Number 133485

May 17, 2016 05:37:19 AM

Dear PAIR Customer:

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

The following USPTO patent application(s) associated with your Customer Number, 133485 , have new outgoing correspondence. This correspondence is now available for viewing in Private PAIR.

The official date of notification of the outgoing correspondence will be indicated on the form PTOL-90 accompanying the correspondence.

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Application	Document	Mailroom Date	Attorney Docket No.
15148839	APP.FILE.REC	05/17/2016	AXJ-114BUSCN2
	M327	05/17/2016	AXJ-114BUSCN2

To view your correspondence online or update your email addresses, please visit us anytime at https://sportal.uspto.gov/secure/myportal/privatepair.

If you have any questions, please email the Electronic Business Center (EBC) at EBC@uspto.gov with 'e-Office Action' on the subject line or call 1-866-217-9197 during the following hours:

Monday - Friday 6:00 a.m. to 12:00 a.m.

Thank you for prompt attention to this notice,

UNITED STATES PATENT AND TRADEMARK OFFICE

PATENT APPLICATION INFORMATION RETRIEVAL SYSTEM

PTO/AIA/01 (06-12)
Approved for use through 01/31/2014. OMB 0651-0032
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Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number.

DECLARATION (37 CFR 1.63) FOR UTILITY OR DESIGN APPLICATION USING AN APPLICATION DATA SHEET (37 CFR 1.76)

Title of Invention	TREATMENT OF PAROXYSMAL NOCTURNAL HEMOGLOBINURIA PATIENTS BY AN INHIBITOR OF COMPLEMENT

As the below named inventor, I hereby declare that:

This declaration is directed to:
- [ ] The attached application, or
- [x] United States application or PCT international application number 15/148,839 filed on 05/06/2016

The above-identified application was made or authorized to be made by me.

I believe that I am the original inventor or an original joint inventor of a claimed invention in the application.

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

WARNING:

Petitioner/applicant is cautioned to avoid submitting personal information in documents filed in a patent application that may contribute to identity theft. Personal information such as social security numbers, bank account numbers, or credit card numbers (other than a check or credit card authorization form PTO-2038 submitted for payment purposes) is never required by the USPTO to support a petition or an application. If this type of personal information is included in documents submitted to the USPTO, petitioners/applicants should consider redacting such personal information from the documents before submitting them to the USPTO. Petitioner/applicant is advised that the record of a patent application is available to the public after publication of the application (unless a non-publication request in compliance with 37 CFR 1.213(a) is made in the application) or issuance of a patent. Furthermore, the record from an abandoned application may also be available to the public if the application is referenced in a published application or an issued patent (see 37 CFR 1.14). Checks and credit card authorization forms PTO-2038 submitted for payment purposes are not retained in the application file and therefore are not publicly available.

LEGAL NAME OF INVENTOR

Inventor: Leonard Bell Date (Optional): _____

Signature: _____

Note: An application data sheet (PTO/SB/14 or equivalent), including naming the entire inventive entity, must accompany this form or must have been previously filed. Use an additional PTO/AIA/01 form for each additional inventor.

Doc code: Oath
Document Description: Oath or declaration filed

PTO/AIA/02 (07-13)
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SUBSTITUTE STATEMENT IN LIEU OF AN OATH OR DECLARATION FOR UTILITY OR DESIGN PATENT APPLICATION (35 U.S.C. 115(d) AND 37 CFR 1.64)

Title of Invention	TREATMENT OF PAROXYSMAL NOCTURNAL HEMOGLOBINURIA PATIENTS BY AN INHIBITOR OF COMPLEMENT

This statement is directed to:

[ ] The attached application,

OR

[X] United States application or PCT international application number 15/148,839 filed on 05/06/2016.

LEGAL NAME of inventor to whom this substitute statement applies:

(*E.g.*, Given Name (first and middle (if any)) and Family Name or Surname)

Russell P. ROTHER

Residence (except for a deceased or legally incapacitated inventor):

Oklahoma City	OK	United States of America
City	State	Country

Mailing Address (except for a deceased or legally incapacitated inventor):

10325 Forest Meadow Drive

Oklahoma City	OK	73151	United States of America
City	State	Zip	Country

I believe the above-named inventor or joint inventor to be the original inventor or an original joint inventor of a claimed invention in the application.

The above-identified application was made or authorized to be made by me.

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

Relationship to the inventor to whom this substitute statement applies:

[ ] Legal Representative (for deceased or legally incapacitated inventor only),

[X] Assignee,

[ ] Person to whom the inventor is under an obligation to assign,

[ ] Person who otherwise shows a sufficient proprietary interest in the matter (petition under 37 CFR 1.46 is required), or

[ ] Joint Inventor.

PTO/SB/AIA02 (07-13)
Approved for use through 01/31/2014. OMB 0651-0032
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SUBSTITUTE STATEMENT

Circumstances permitting execution of this substitute statement:

- [ ] Inventor is deceased,
- [ ] Inventor is under legal incapacity,
- [ ] Inventor cannot be found or reached after diligent effort, or
- [x] Inventor has refused to execute the oath or declaration under 37 CFR 1.63.

If there are joint inventors, please check the appropriate box below:

- [x] An application data sheet under 37 CFR 1.76 (PTO/AIA/14 or equivalent) naming the entire inventive entity has been or is currently submitted.

OR

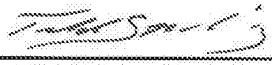
- [ ] An application data sheet under 37 CFR 1.76 (PTO/AIA/14 or equivalent) has not been submitted. Thus, a Substitute Statement Supplemental Sheet (PTO/AIA/11 or equivalent) naming the entire inventive entity and providing inventor information is attached. See 37 CFR 1.64(b).

WARNING:

Petitioner/applicant is cautioned to avoid submitting personal information in documents filed in a patent application that may contribute to identity theft. Personal information such as social security numbers, bank account numbers, or credit card numbers (other than a check or credit card authorization form PTO-2038 submitted for payment purposes) is never required by the USPTO to support a petition or an application. If this type of personal information is included in documents submitted to the USPTO, petitioners/applicants should consider redacting such personal information from the documents before submitting them to the USPTO. Petitioner/applicant is advised that the record of a patent application is available to the public after publication of the application (unless a non-publication request in compliance with 37 CFR 1.213(a) is made in the application) or issuance of a patent. Furthermore, the record from an abandoned application may also be available to the public if the application is referenced in a published application or an issued patent (see 37 CFR 1.14). Checks and credit card authorization forms PTO-2038 submitted for payment purposes are not retained in the application file and therefore are not publicly available.

PERSON EXECUTING THIS SUBSTITUTE STATEMENT:

Name: Todd Spalding	Date (Optional):

Signature: 

APPLICANT NAME AND TITLE OF PERSON EXECUTING THIS SUBSTITUTE STATEMENT:

If the applicant is a juristic entity, list the applicant name and the title of the signer:

Applicant Name: Alexion Pharmaceuticals, Inc.

Title of Person Executing This Substitute Statement: Vice President, Head of Intellectual Property

The signer, whose title is supplied above, is authorized to act on behalf of the applicant.

Residence of the signer (unless provided in an application data sheet, PTO/AIA/14 or equivalent):

City	State	Country

Mailing Address of the signer (unless provided in an application data sheet, PTO/AIA/14 or equivalent)

100 College St.

City	State	Zip	Country
New Haven	CT	06510	US

Note: Use an additional PTO/AIA/02 form for each inventor who is deceased, legally incapacitated, cannot be found or reached after diligent effort, or has refused to execute the oath or declaration under 37 CFR 1.63.

Electronic Acknowledgement Receipt

EFS ID:	25864926
Application Number:	15148839
International Application Number:	
Confirmation Number:	3159
Title of Invention:	TREATMENT OF PAROXYSMAL NOCTURNAL HEMOGLOBINURIA PATIENTS BY AN INHIBITOR OF COMPLEMENT
First Named Inventor/Applicant Name:	Leonard BELL
Customer Number:	133485
Filer:	Jill R. Gorny Sloper/Danielle Gamache
Filer Authorized By:	Jill R. Gorny Sloper
Attorney Docket Number:	AXJ-114BUSCN2
Receipt Date:	24-MAY-2016
Filing Date:	06-MAY-2016
Time Stamp:	13:54:37
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	no

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Oath or Declaration filed	AXJ_114BUSCN2_Declarations.pdf	2627453 611f9dd6532afb737fd2b8b738fffb3c7782add2	no	3

Warnings:	
Information:	

Total Files Size (in bytes):	2627453

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

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

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

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

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
15/148,839	05/06/2016	Leonard BELL	AXJ-114BUSCN2	3159

133485 7590 06/16/2016

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

EXAMINER
ROGERS, JAMES L

ART UNIT	PAPER NUMBER
1644	

NOTIFICATION DATE	DELIVERY MODE
06/16/2016	ELECTRONIC

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

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

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

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

UNITED STATES PATENT AND TRADEMARK OFFICE

Commissioner for Patents
United States Patent and Trademark Office
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Alexandria, VA 22313-1450
www.uspto.gov

In re Application of
Leonard Bell et al.
Application No.: 15/148,839
Filed: 06 May 2016
Attorney Docket No.: AXJ-114BUSCN2
For: TREATMENT OF PAROXYSMAL NOCTURNAL HEMOGLOBINURIA PATIENTS BY AN INHIBITOR OF COMPLEMENT

: DECISION ON REQUEST TO
: PARTICIPATE IN THE PATENT
: PROSECUTION HIGHWAY
: PROGRAM AND PETITION
: TO MAKE SPECIAL UNDER
: 37 CFR 1.102(a)

This is a decision on the request to participate in the Patent Prosecution Highway (PPH) program and the petition under 37 CFR 1.102(a), filed 06 May 2016, to make the above-identified application special.

The request and petition are **GRANTED**.

DISCUSSION

A grantable request to participate in the PPH pilot program and petition to make special require:

1. The U.S. application for which participation in the Global/IP5 PPH pilot program is requested must have the same earliest date, whether this is the priority date or filing date, as that of a corresponding national or regional application filed with another Global/IP5 PPH participating office or a corresponding PCT international application for which one of the Global/IP5 PPH participating offices was the International Searching Authority (ISA) or the International Preliminary Examining Authority (IPEA).

2. Applicant must:
    a. Ensure all the claims in the U.S. application must sufficiently correspond or be amended to sufficiently correspond to the allowable/patentable claim(s) in the corresponding Office of Earlier Examination (OEE) application and
    b. Submit a claims correspondence table in English;
3. Examination of the U.S. application has not begun;
4. Applicant must submit:
    a. Documentation of prior office action:

i. a copy of the office action(s) just prior to the "Decision to Grant a Patent" from each of the Global/IP5 PPH participating office application(s) containing the allowable/patentable claim(s) or
ii. if the allowable/patentable claims(s) are from a "Notification of Reasons for Refusal" then the Notification of Reasons for Refusal or
iii. if the Global/IP5 PPH participating office application is a first action allowance then no office action from the Global/IP5 PPH participating office is necessary should be indicated on the request/petition form or
iv. the latest work product in the international phase of the OEE PCT application;

b. An English language translation of the Global/IP5 PPH participating office action or work product from (4)(a)(i)-(ii) or (iv) above;

5. Applicant must submit:
   a. An IDS listing the documents cited by the Global/IP5 PPH participating office examiner in the Global/IP5 PPH participating office action or work product (unless already submitted in this application)
   b. Copies of the documents except U.S. patents or U.S. patent application publications (unless already submitted in this application);

The request to participate in the PPH pilot program and petition comply with the above requirements. Accordingly, the above-identified application has been accorded "special" status.

Telephone inquiries concerning this decision should be directed to JoAnne Burke at (571) 272-4584

All other inquiries concerning the examination or status of the application is accessible in the PAIR system at http://www.uspto.gov/ebc.index.html.

This application will be forwarded to the examiner for action on the merits commensurate with this decision once this application's formality reviews have been completed.

/JoAnne Burke/
JoAnne Burke
Paralegal Specialist
Office of Petitions

Office of Petitions: Routing Sheet



Application No. 15/148,839

This application is being forwarded to your office for further processing. A decision has been rendered on a petition filed in this application, as indicated below. For details of this decision, please see the document PET.OP.DEC filed on the same date as this document.

- [X] **GRANTED**
- [ ] **DISMISSED**
- [ ] **DENIED**

Office of Petitions: Decision Count Sheet

Mailing Month

Application No. 15148839

15148839

For US serial numbers: enter number only, no slashes or commas. Ex: 10123456

For PCT: enter "51+single digit of year of filing+last 5 numbers", Ex. for PCT/US05/12345, enter 51512345

Deciding Official: BURKE, JOANNE

Count (1) - Palm Credit 15/148,839

Decision: GRANT

FINANCE WORK NEEDED

☐ Select Check Box for YES

GRANT

Decision Type: 652 - Petition to make special-PPH

652

Notes:

Count (2)

Decision: n/a

FINANCE WORK NEEDED

☐ Select Check Box for YES

Decision Type: NONE

Notes:

Count (3)

Decision: n/a

FINANCE WORK NEEDED

☐ Select Check Box for YES

Decision Type: NONE

Notes:

Initials of Approving Official (if required)

If more than 3 decisions, attach 2nd count sheet & mark this box ☐

Printed on:

Office of Petitions Internal Document - Ver. 5.0

To: chris.schlauch@nelsonmullins.com,ipqualityassuranceboston@nelsonmullins.com,ipboston.docketing@nel
From: PAIR_eOfficeAction@uspto.gov
Cc: PAIR_eOfficeAction@uspto.gov
Subject: Private PAIR Correspondence Notification for Customer Number 133485

Jun 16, 2016 05:30:01 AM

Dear PAIR Customer:

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Alexion
One Post Office Square
30th Floor
Boston, MA 02109-2127
UNITED STATES

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Application	Document	Mailroom Date	Attorney Docket No.
15148839	PET.OP.DEC	06/16/2016	AXJ-114BUSCN2
	PPH.DECISION	06/16/2016	AXJ-114BUSCN2

To view your correspondence online or update your email addresses, please visit us anytime at https://sportal.uspto.gov/secure/myportal/privatepair.

If you have any questions, please email the Electronic Business Center (EBC) at EBC@uspto.gov with 'e-Office Action' on the subject line or call 1-866-217-9197 during the following hours:

Monday - Friday 6:00 a.m. to 12:00 a.m.

Thank you for prompt attention to this notice,

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PATENT APPLICATION INFORMATION RETRIEVAL SYSTEM

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United States Patent and Trademark Office
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www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
15/148,839	05/06/2016	Leonard BELL	AXJ-114BUSCN2	3159

133485 7590 08/16/2016

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

EXAMINER
ROGERS, JAMES L

ART UNIT	PAPER NUMBER
1644	

NOTIFICATION DATE	DELIVERY MODE
08/16/2016	ELECTRONIC

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

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

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

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

Office Action Summary	Application No. 15/148,839	Applicant(s) BELL ET AL.	
	Examiner JAMES ROGERS	Art Unit 1644	AIA (First Inventor to File) Status No

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

Period for Reply

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

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

Status

1)☒ Responsive to communication(s) filed on *5/6/2016*.

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

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

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

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

Disposition of Claims*

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

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

6)☐ Claim(s) _____ is/are allowed.

7)☒ Claim(s) *1* is/are rejected.

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

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

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

Application Papers

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

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

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

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

Priority under 35 U.S.C. § 119

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

Certified copies:

a)☐ All b)☐ Some** c)☐ None of the:

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

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

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

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

Attachment(s)

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

2) ☒ Information Disclosure Statement(s) (PTO/SB/08a and/or PTO/SB/08b) Paper No(s)/Mail Date *5/6/2016*.

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

4) ☐ Other: _____.

DETAILED ACTION

1. Claim 1 is pending and under consideration in the instant examination and reads on a compositions which is a 300 mg eculizumab single-use dosage form comprising 30 ml of a 10 mg eculizumab/ml sterile, preservative free solution.

2. Applicant's IDSs, filed on 05/06/2016, are acknowledged and have been considered.

Priority

3. Applicant's claim for the benefit of a prior-filed application under 35 U.S.C. 119(e) or under 35 U.S.C. 120, 121, or 365(c) is acknowledged. Applicant has not complied with one or more conditions for receiving the benefit of an earlier filing date under 35 U.S.C. 119(e) as follows:

The later-filed application must be an application for a patent for an invention which is also disclosed in the prior application (the parent or original nonprovisional application or provisional application). The disclosure of the invention in the parent application and in the later-filed application must be sufficient to comply with the requirements of 35 U.S.C. 112(a) or the first paragraph of 35 U.S.C. 112 (pre-AIA). See *Transco Products, Inc. v. Performance Contracting, Inc.*, 38 F.3d 551, 32 USPQ2d 1077 (Fed. Cir. 1994).

The disclosure of the prior-filed application, US Provisional Application No. 60/783,070, fails to provide adequate support or enablement in the manner provided by 35 U.S.C. 112(a) or 35 U.S.C. 112 (pre-AIA), first paragraph for one or more claims of this application. In particular, the claim recites a composition which is a 300 mg eculizumab single-use dosage comprising 30 ml of a 10 mg eculizumab/ml steril, preservative free solution.

Accordingly, the priority date of the instant claims of the current application is considered to be **3/15/2007**, the filing date of PCT/US2007/006606.

Claim Rejections - 35 USC § 103

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

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

pertains. Patentability shall not be negatived by the manner in which the invention was made.

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

5. Claim 1 is rejected under 35 U.S.C. 103(a) as being unpatentable over Hillmen et al. (N Engl J Med 2004; 350: 552-9), in view of Evans et al. (US 6,355,245 B1, issued 3/12/2002), Wang (US 2005/0271660), as is evidenced by the parent specification of US Patent Application No. 13/426,973 at p. 16, lines 20-25.

Hillmen teaches a method for treating a human patient that suffers from paroxysmal nocturnal hemoglobinuria (PNH) by administering to the patient an effective amount of eculizumab (p. 552, "methods") which specifically binds to the terminal complement protein C5, inhibiting its cleavage into C5a and C5b (p. 553, 3rd ¶). Hillmen teaches that patients received infusions of eculizumab weekly for four weeks, followed one week later by a 900 mg dose and then by a dose of 900 mg every other week through week 12 (p. 554 under “treatment schedule”).

The prior art references differ from the claimed invention in the recitation that the composition is a 300 mg eculizumab single-use dosage form comprising 30 ml of a 10 mg eculizumab/ml steril, preservative free solution.

However, Evans teaches antibody 5G1.1, which is the same as eculizumab (see parent specification US Patent Application No. 13/426,973, p. 16 lines 20-25), is effective at doses of 2.2, 3, or 5 mg per kg body weight; this corresponds to 154, 210, or 350 mg of antibody for a 70kg adult human (‘245 patent, column 16 lines 10-30). Evans also teaches that eculizumab is therapeutically effective when as little as 210 mg are present (column 16 lines 10-15). Evans teaches that the antibodies are particularly advantageous in that they are highly active even when administered in low doses (col 8 lines 25-32), providing a reasonable expectation of success in treating PHN with a dose less than what was disclosed by Hillmen. The reference teaches that it is within the skill of an artisan, particularly a physician, to determine the optimal dose (column 18 lines 15-30). Evans teaches formulations of the anti-C5 antibodies may be formulated in a pharmaceutically effective carrier such saline, which is considered to be a "preservative free solution". (col 18 lines 30-45).

However neither Hillmen nor '245 teaches a 300 mg single unit dosage as recited in the claims.

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

Finally, Wang teaches that eculizumab is highly soluble, including at up to 30 mg per ml (paragraph 0171, Figure 10). Wang further teaches that pharmaceutically acceptable carriers include pyrogen-free water may be used in formulation of the antibody (¶71) (sterile, preservative free solution). Therefore the artisan of ordinary skill would have had a reasonable expectation of success in making a 10 mg / ml solution of the antibody sterile, preservative free solution.

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

6. No claim is allowed.

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

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

August 9, 2016

/JAMES ROGERS/

Examiner, Art Unit 1644

/SHARON WEN/
Primary Examiner, Art Unit 1644

Notice of References Cited	Application/Control No. 15/148,839	Applicant(s)/Patent Under Reexamination BELL ET AL.	
	Examiner JAMES ROGERS	Art Unit 1644	Page 1 of 1

U.S. PATENT DOCUMENTS

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

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

NON-PATENT DOCUMENTS

*		Include as applicable: Author, Title Date, Publisher, Edition or Volume, Pertinent Pages)
	U	hILLMEN ET AL. "eFFECT OF eCULIZUMAB ON hEMOLYSIS AND TRANSFUSION REQUIREMENTS IN PATIENTS WITH PAROXYSMAL NOCTURNAL HEMOGLOBINURIA" nejm 350(6), 2004, PP. 552-559
	V	
	W	
	X	

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

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BIB DATA SHEET

CONFIRMATION NO. 3159

SERIAL NUMBER	FILING or 371(c) DATE RULE	CLASS	GROUP ART UNIT	ATTORNEY DOCKET NO.
15/148,839	05/06/2016	424	1644	AXJ-114BUSCN2

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

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

**** CONTINUING DATA ***************************
This application is a CON of 13/426,973 03/22/2012
which is a CON of 12/225,040 05/13/2009 ABN
which is a 371 of PCT/US2007/006606 03/15/2007
which claims benefit of 60/783,070 03/15/2006

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

**** IF REQUIRED, FOREIGN FILING LICENSE GRANTED ****
05/16/2016

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

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

TITLE
TREATMENT OF PAROXYSMAL NOCTURNAL HEMOGLOBINURIA PATIENTS BY AN INHIBITOR OF COMPLEMENT

FILING FEE RECEIVED		
1740	FEES: Authority has been given in Paper No._____ to charge/credit DEPOSIT ACCOUNT No._____ for following:	☐ All Fees ☐ 1.16 Fees (Filing) ☐ 1.17 Fees (Processing Ext. of time) ☐ 1.18 Fees (Issue) ☐ Other _____ ☐ Credit

Doc code: IDS
Doc description: Information Disclosure Statement (IDS) Filed

PTO/SB/08a (03-15)
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INFORMATION DISCLOSURE STATEMENT BY APPLICANT (**Not for submission under 37 CFR 1.99**)		
	Application Number	
	Filing Date	
	First Named Inventor	Leonard BELL
	Art Unit	N/A
	Examiner Name	Not Yet Assigned
	Attorney Docket Number	AXJ-114BUSCN2

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

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
	Application Number	
	Filing Date	
	First Named Inventor	Leonard BELL
	Art Unit	N/A
	Examiner Name	Not Yet Assigned
	Attorney Docket Number	AXJ-114BUSCN2

	1	Mortazavi et al., "The spectrum of PIG-A gene mutations in a plastic anemia/paroxysmal nocturnal hemoglobinuria (AAIPNH): a high incidence of multiple mutations and evidence of a mutational hot spot," Blood 101 2833-2841 (2003).	
	2	Moyo et al., "Natural history of paroxysmal nocturnal haemoglobinuria using modern diagnostic assays," British J Haematology 126, 133-138 (2004).	
	3	Notice of Opposition for EP Patent No. 1720571, dated 3/18/2013.	
	4	Parker et al., Diagnosis and management of paroxysmal nocturnal hemoglobinuria, Blood, 106(12):3699-3709 (2005).	
	5	Paroxysmal nocturnal hemoglobinuria, included; PNH, included phosphatidylinositol glycan, class A, pseudogene 1, included; pigap1, included piga-related processed gene, included [online]. OM 1M-Online Medelian Inheritance in Man; John Hopkins University; [Retrieved on 2003-06-18]. Retrieved from the world wide web at ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=OMIM&dopt=detailed ...	
	6	Reiter et al., "Cell-free hemoglobin limits nitric oxide bioavailability in sickle-cell disease," Nature Medicine 8 (12):1383-1389 (2002).	
	7	Richards et al., "Evolution of GPI-Deficient Clones Predicts Clinical Course in Paroxysmal Nocturnal Haemoglobinuria," Blood, 104:Abstract 172 (2004).	
	8	Rodary et al., "Patient preference for either the EORTC QLQ-C30 or the FACIT Quality of Life (QOL) measures: a study performed in patient suffering from carcinoma of an unknown primary site (CUP)," European Journal of Cancer, Vol. 40, pp. 521-528 (2004).	
	9	Rosse et al., Immune-mediated hemolytic anemia, Hematology Am Soc Hematol Educ. Program, 48-62 (2004) XP002497825.	
	10	ROTHER et al., Eculizumab, a C5 complement-blocking antibody, abolishes hemolysis and reduces transfusion dependency in patients with paroxysmal nocturnal hemoglobinuria (PNH), Molecular Immunology, Vol. 40(2-4), page 197; XP009163498, (2003).	
	11	Rother et al., The clinical sequelae of intravascular hemolysis and extracellular plasma hemoglobin, JAMA 293 (13):1653-1662 (2005).	

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

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
	Application Number	
	Filing Date	
	First Named Inventor	Leonard BELL
	Art Unit	N/A
	Examiner Name	Not Yet Assigned
	Attorney Docket Number	AXJ-114BUSCN2

	12	Stebler et al., High-dose recombinant human erythropoietin for treatment of anemia in myelodysplastic syndromes and paroxysmal nocturnal hemoglobinuria: a pilot study, Exp. Hematol. 18:1204-1208 (1990).	
	13	Strauss et al. "Alternative pathway of complement in sickle cell disease," Pediat. Res., vol. 11:285-289 (1977)	
	14	Stuart et al., "Sickle-cell disease," Lancet, vol. 364:1343-60 (2004)	
	15	Tang and Pikal, Design of Freeze-Drying Processes for Pharmaceuticals: Practical Advice, Pharmaceutical Research, Vol. 21 (2):191-200 (2004).	
	16	Thomas et al., Inhibition of complement activity by humanized anti-C5 antibody and single chain Fv, Mol.Imm. 33 (17-18):1389-1401, XP002262113 (1996).	
	17	Vakeva, et al., "Myocardial infarction and apoptosis after myocardial ischemia and reperfusion," Circulation 97:2259-2267 (1998).	

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EXAMINER SIGNATURE

Examiner Signature	/JAMES L ROGERS/	Date Considered	08/08/2016

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

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

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INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
	Application Number	
	Filing Date	
	First Named Inventor	Leonard BELL
	Art Unit	N/A
	Examiner Name	Not Yet Assigned
	Attorney Docket Number	AXJ-114BUSCN2

CERTIFICATION STATEMENT

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

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

OR

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

See attached certification statement.

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

A certification statement is not submitted herewith.

SIGNATURE

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

Signature	/Jill Gorny Sloper, Esq./	Date (YYYY-MM-DD)	2016-05-06
Name/Print	Jill Gorny Sloper, Esq.	Registration Number	60760

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

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

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

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

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

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

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

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

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

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

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

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

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

supplemental STN search

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L44            0 FILE USPATOLD
L45            7 FILE USPAT2
L46            0 FILE VETB
L47            0 FILE VETU
L48            7 FILE IPA
L49            0 FILE NAPRALERT
     TOTAL FOR ALL FILES
```

supplemental STN search

```
L50         755 S (DOSE OR DOSAGE) (10A) (ECULIZUMAB OR SOLIRIS)
L51           0 FILE DISSABS
L52           0 FILE 1MOBILITY
L53           0 FILE AGRICOLA
L54           0 FILE BIOTECHNO
L55           0 FILE COMPENDEX
L56           0 FILE EMBASE
L57           0 FILE INSPEC
L58           0 FILE PASCAL
L59           0 FILE PQSCITECH
L60           0 FILE ADISCTI
L61           0 FILE ADISINSIGHT
L62           0 FILE ADISNEWS
L63           0 FILE ANABSTR
L64           0 FILE BIOSIS
L65           0 FILE BIOTECHDS
L66           0 FILE CABA
L67           0 FILE CAPLUS
L68           0 FILE CEABA-VTB
L69           0 FILE CIN
L70           0 FILE CROPB
L71           0 FILE CROPU
L72           0 FILE DDFB
L73           0 FILE DGENE
L74           0 FILE DRUGB
L75           0 FILE DRUGU
L76           0 FILE EMBAL
L77           0 FILE ESBIOBASE
L78           0 FILE FOMAD
L79           0 FILE FROSTI
L80           0 FILE FSTA
L81           0 FILE GENBANK
L82           0 FILE IFIALL
L83           0 FILE IMSRESEARCH
L84           0 FILE KOSMET
L85           0 FILE MEDLINE
L86           0 FILE NTIS
L87           0 FILE PCTGEN
L88           0 FILE PS
L89           0 FILE RDISCLOSURE
L90           0 FILE SCISEARCH
L91           0 FILE TOXCENTER
L92           0 FILE USGENE
L93           0 FILE USPATFULL
L94           0 FILE USPATOLD
L95           0 FILE USPAT2
L96           0 FILE VETB
L97           0 FILE VETU
L98           0 FILE IPA
L99           0 FILE NAPRALERT
     TOTAL FOR ALL FILES
L100          0 S L50 (20A) (SINGLE (2A) UNIT)
L101          0 FILE DISSABS
L102          0 FILE 1MOBILITY
L103          0 FILE AGRICOLA
L104          0 FILE BIOTECHNO
L105          0 FILE COMPENDEX
L106          0 FILE EMBASE
L107          0 FILE INSPEC
```

supplemental STN search

```
L108          0 FILE PASCAL
L109          0 FILE PQSCITECH
L110          0 FILE ADISCTI
L111          0 FILE ADISINSIGHT
L112          0 FILE ADISNEWS
L113          0 FILE ANABSTR
L114          0 FILE BIOSIS
L115          0 FILE BIOTECHDS
L116          0 FILE CABA
L117          0 FILE CAPLUS
L118          0 FILE CEABA-VTB
L119          0 FILE CIN
L120          0 FILE CROPB
L121          0 FILE CROPU
L122          0 FILE DDFB
L123          0 FILE DGENE
L124          0 FILE DRUGB
L125          0 FILE DRUGU
L126          0 FILE EMBAL
L127          0 FILE ESBIOBASE
L128          0 FILE FOMAD
L129          0 FILE FROSTI
L130          0 FILE FSTA
L131          0 FILE GENBANK
L132          0 FILE IFIALL
L133          0 FILE IMSRESEARCH
L134          0 FILE KOSMET
L135          0 FILE MEDLINE
L136          0 FILE NTIS
L137          0 FILE PCTGEN
L138          0 FILE PS
L139          0 FILE RDISCLOSURE
L140          0 FILE SCISEARCH
L141          0 FILE TOXCENTER
L142          0 FILE USGENE
L143          0 FILE USPATFULL
L144          0 FILE USPATOLD
L145          0 FILE USPAT2
L146          0 FILE VETB
L147          0 FILE VETU
L148          0 FILE IPA
L149          0 FILE NAPRALERT
     TOTAL FOR ALL FILES
L150          0 S L50 (20A) (10 (2A) MG/ML)
L151          0 FILE DISSABS
L152          0 FILE 1MOBILITY
L153          0 FILE AGRICOLA
L154          0 FILE BIOTECHNO
L155          0 FILE COMPENDEX
L156          5 FILE EMBASE
L157          0 FILE INSPEC
L158          0 FILE PASCAL
L159          0 FILE PQSCITECH
L160          0 FILE ADISCTI
L161          0 FILE ADISINSIGHT
L162          0 FILE ADISNEWS
L163          0 FILE ANABSTR
L164          0 FILE BIOSIS
L165          0 FILE BIOTECHDS
```

supplemental STN search

```
L166           0 FILE CABA
L167           1 FILE CAPLUS
L168           0 FILE CEABA-VTB
L169           0 FILE CIN
L170           0 FILE CROPB
L171           0 FILE CROPU
L172           0 FILE DDFB
L173           0 FILE DGENE
L174           0 FILE DRUGB
L175           6 FILE DRUGU
L176           0 FILE EMBAL
L177           1 FILE ESBIOBASE
L178           0 FILE FOMAD
L179           0 FILE FROSTI
L180           0 FILE FSTA
L181           0 FILE GENBANK
L182           1 FILE IFIALL
L183           0 FILE IMSRESEARCH
L184           0 FILE KOSMET
L185           1 FILE MEDLINE
L186           0 FILE NTIS
L187           0 FILE PCTGEN
L188           0 FILE PS
L189           0 FILE RDISCLOSURE
L190           1 FILE SCISEARCH
L191           0 FILE TOXCENTER
L192           0 FILE USGENE
L193           5 FILE USPATFULL
L194           0 FILE USPATOLD
L195           1 FILE USPAT2
L196           0 FILE VETB
L197           0 FILE VETU
L198           0 FILE IPA
L199           0 FILE NAPRALERT
     TOTAL FOR ALL FILES
L200          22 S L50 (20A) (300 (2A) MG)
L201          15 DUP REM L200 (7 DUPLICATES REMOVED)
L202           0 FILE DISSABS
L203           0 FILE 1MOBILITY
L204           0 FILE AGRICOLA
L205           0 FILE BIOTECHNO
L206           0 FILE COMPENDEX
L207           0 FILE EMBASE
L208           0 FILE INSPEC
L209           0 FILE PASCAL
L210           0 FILE PQSCITECH
L211           0 FILE ADISCTI
L212           0 FILE ADISINSIGHT
L213           0 FILE ADISNEWS
L214           0 FILE ANABSTR
L215           0 FILE BIOSIS
L216           0 FILE BIOTECHDS
L217           0 FILE CABA
L218           0 FILE CAPLUS
L219           0 FILE CEABA-VTB
L220           0 FILE CIN
L221           0 FILE CROPB
L222           0 FILE CROPU
L223           0 FILE DDFB
```

supplemental STN search

```
L224            0 FILE DGENE
L225            0 FILE DRUGB
L226            0 FILE DRUGU
L227            0 FILE EMBAL
L228            0 FILE ESBIOBASE
L229            0 FILE FOMAD
L230            0 FILE FROSTI
L231            0 FILE FSTA
L232            0 FILE GENBANK
L233            0 FILE IFIALL
L234            0 FILE IMSRESEARCH
L235            0 FILE KOSMET
L236            0 FILE MEDLINE
L237            0 FILE NTIS
L238            0 FILE PCTGEN
L239            0 FILE PS
L240            0 FILE RDISCLOSURE
L241            0 FILE SCISEARCH
L242            0 FILE TOXCENTER
L243            0 FILE USGENE
L244            3 FILE USPATFULL
L245            0 FILE USPATOLD
L246            0 FILE USPAT2
L247            0 FILE VETB
L248            0 FILE VETU
L249            0 FILE IPA
L250            0 FILE NAPRALERT
     TOTAL FOR ALL FILES
L251            3 S L50 AND (SINGLE (2A) UNIT)
L252            3 DUP REM L251 (0 DUPLICATES REMOVED)
L253            0 FILE DISSABS
L254            0 FILE 1MOBILITY
L255            0 FILE AGRICOLA
L256            0 FILE BIOTECHNO
L257            0 FILE COMPENDEX
L258            8 FILE EMBASE
L259            0 FILE INSPEC
L260            0 FILE PASCAL
L261            0 FILE PQSCITECH
L262            0 FILE ADISCTI
L263            0 FILE ADISINSIGHT
L264            0 FILE ADISNEWS
L265            0 FILE ANABSTR
L266            1 FILE BIOSIS
L267            0 FILE BIOTECHDS
L268            0 FILE CABA
L269            1 FILE CAPLUS
L270            0 FILE CEABA-VTB
L271            0 FILE CIN
L272            0 FILE CROPB
L273            0 FILE CROPU
L274            0 FILE DDFB
L275            0 FILE DGENE
L276            0 FILE DRUGB
L277            8 FILE DRUGU
L278            1 FILE EMBAL
L279            1 FILE ESBIOBASE
L280            0 FILE FOMAD
L281            0 FILE FROSTI
```

supplemental STN search

```
L282          0 FILE FSTA
L283          0 FILE GENBANK
L284          1 FILE IFIALL
L285          0 FILE IMSRESEARCH
L286          0 FILE KOSMET
L287          2 FILE MEDLINE
L288          0 FILE NTIS
L289          0 FILE PCTGEN
L290          0 FILE PS
L291          0 FILE RDISCLOSURE
L292          2 FILE SCISEARCH
L293          0 FILE TOXCENTER
L294          0 FILE USGENE
L295         12 FILE USPATFULL
L296          0 FILE USPATOLD
L297          1 FILE USPAT2
L298          0 FILE VETB
L299          0 FILE VETU
L300          0 FILE IPA
L301          0 FILE NAPRALERT
     TOTAL FOR ALL FILES
L302         38 S L50 AND (300 (2A) MG)
L303          0 FILE DISSABS
L304          0 FILE 1MOBILITY
L305          0 FILE AGRICOLA
L306          0 FILE BIOTECHNO
L307          0 FILE COMPENDEX
L308          0 FILE EMBASE
L309          0 FILE INSPEC
L310          0 FILE PASCAL
L311          0 FILE PQSCITECH
L312          0 FILE ADISCTI
L313          0 FILE ADISINSIGHT
L314          0 FILE ADISNEWS
L315          0 FILE ANABSTR
L316          0 FILE BIOSIS
L317          0 FILE BIOTECHDS
L318          0 FILE CABA
L319          0 FILE CAPLUS
L320          0 FILE CEABA-VTB
L321          0 FILE CIN
L322          0 FILE CROPB
L323          0 FILE CROPU
L324          0 FILE DDFB
L325          0 FILE DGENE
L326          0 FILE DRUGB
L327          0 FILE DRUGU
L328          0 FILE EMBAL
L329          0 FILE ESBIOBASE
L330          0 FILE FOMAD
L331          0 FILE FROSTI
L332          0 FILE FSTA
L333          0 FILE GENBANK
L334          0 FILE IFIALL
L335          0 FILE IMSRESEARCH
L336          0 FILE KOSMET
L337          0 FILE MEDLINE
L338          0 FILE NTIS
L339          0 FILE PCTGEN
```

supplemental STN search

```
L340            0 FILE PS
L341            0 FILE RDISCLOSURE
L342            0 FILE SCISEARCH
L343            0 FILE TOXCENTER
L344            0 FILE USGENE
L345            0 FILE USPATFULL
L346            0 FILE USPATOLD
L347            0 FILE USPAT2
L348            0 FILE VETB
L349            0 FILE VETU
L350            0 FILE IPA
L351            0 FILE NAPRALERT
     TOTAL FOR ALL FILES
L352            0 S L302 AND (10 (2A) MG/ML)
L353            0 FILE DISSABS
L354            0 FILE 1MOBILITY
L355            0 FILE AGRICOLA
L356            0 FILE BIOTECHNO
L357            0 FILE COMPENDEX
L358            0 FILE EMBASE
L359            0 FILE INSPEC
L360            0 FILE PASCAL
L361            0 FILE PQSCITECH
L362            0 FILE ADISCTI
L363            0 FILE ADISINSIGHT
L364            0 FILE ADISNEWS
L365            0 FILE ANABSTR
L366            0 FILE BIOSIS
L367            0 FILE BIOTECHDS
L368            0 FILE CABA
L369            0 FILE CAPLUS
L370            0 FILE CEABA-VTB
L371            0 FILE CIN
L372            0 FILE CROPB
L373            0 FILE CROPU
L374            0 FILE DDFB
L375            0 FILE DGENE
L376            0 FILE DRUGB
L377            0 FILE DRUGU
L378            0 FILE EMBAL
L379            0 FILE ESBIOBASE
L380            0 FILE FOMAD
L381            0 FILE FROSTI
L382            0 FILE FSTA
L383            0 FILE GENBANK
L384            0 FILE IFIALL
L385            0 FILE IMSRESEARCH
L386            0 FILE KOSMET
L387            0 FILE MEDLINE
L388            0 FILE NTIS
L389            0 FILE PCTGEN
L390            0 FILE PS
L391            0 FILE RDISCLOSURE
L392            0 FILE SCISEARCH
L393            0 FILE TOXCENTER
L394            0 FILE USGENE
L395            0 FILE USPATFULL
L396            0 FILE USPATOLD
L397            0 FILE USPAT2
```

supplemental STN search

```
L398          0 FILE VETB
L399          0 FILE VETU
L400          0 FILE IPA
L401          0 FILE NAPRALERT
     TOTAL FOR ALL FILES
L402          0 S L352 AND PY<2008
L403         19 FILE DISSABS
L404          0 FILE 1MOBILITY
L405         13 FILE AGRICOLA
L406        176 FILE BIOTECHNO
L407          9 FILE COMPENDEX
L408        977 FILE EMBASE
L409          1 FILE INSPEC
L410        146 FILE PASCAL
L411        212 FILE PQSCITECH
L412         15 FILE ADISCTI
L413         18 FILE ADISINSIGHT
L414         11 FILE ADISNEWS
L415          4 FILE ANABSTR
L416        619 FILE BIOSIS
L417         71 FILE BIOTECHDS
L418         45 FILE CABA
L419        786 FILE CAPLUS
L420          6 FILE CEABA-VTB
L421         35 FILE CIN
L422          0 FILE CROPB
L423          0 FILE CROPU
L424          4 FILE DDFB
L425       2828 FILE DGENE
L426          4 FILE DRUGB
L427         71 FILE DRUGU
L428          7 FILE EMBAL
L429        235 FILE ESBIOBASE
L430          0 FILE FOMAD
L431          0 FILE FROSTI
L432          2 FILE FSTA
L433       1292 FILE GENBANK
L434        277 FILE IFIALL
L435          8 FILE IMSRESEARCH
L436          0 FILE KOSMET
L437        601 FILE MEDLINE
L438          4 FILE NTIS
L439        864 FILE PCTGEN
L440          0 FILE PS
L441          0 FILE RDISCLOSURE
L442        523 FILE SCISEARCH
L443        376 FILE TOXCENTER
L444       3290 FILE USGENE
L445       1467 FILE USPATFULL
L446          1 FILE USPATOLD
L447        554 FILE USPAT2
L448          0 FILE VETB
L449          1 FILE VETU
L450         17 FILE IPA
L451          0 FILE NAPRALERT
     TOTAL FOR ALL FILES
L452      15589 S (C5 (10A) ANTIBOD?)
L453          0 FILE DISSABS
L454          0 FILE 1MOBILITY
```

supplemental STN search

```
L455          0 FILE AGRICOLA
L456          0 FILE BIOTECHNO
L457          0 FILE COMPENDEX
L458          8 FILE EMBASE
L459          0 FILE INSPEC
L460          0 FILE PASCAL
L461          0 FILE PQSCITECH
L462          1 FILE ADISCTI
L463          0 FILE ADISINSIGHT
L464          0 FILE ADISNEWS
L465          0 FILE ANABSTR
L466          1 FILE BIOSIS
L467          0 FILE BIOTECHDS
L468          0 FILE CABA
L469          0 FILE CAPLUS
L470          0 FILE CEABA-VTB
L471          0 FILE CIN
L472          0 FILE CROPB
L473          0 FILE CROPU
L474          0 FILE DDFB
L475          0 FILE DGENE
L476          0 FILE DRUGB
L477          1 FILE DRUGU
L478          0 FILE EMBAL
L479          0 FILE ESBIOBASE
L480          0 FILE FOMAD
L481          0 FILE FROSTI
L482          0 FILE FSTA
L483          0 FILE GENBANK
L484          2 FILE IFIALL
L485          0 FILE IMSRESEARCH
L486          0 FILE KOSMET
L487          1 FILE MEDLINE
L488          0 FILE NTIS
L489          0 FILE PCTGEN
L490          0 FILE PS
L491          0 FILE RDISCLOSURE
L492          1 FILE SCISEARCH
L493          0 FILE TOXCENTER
L494          0 FILE USGENE
L495        310 FILE USPATFULL
L496          0 FILE USPATOLD
L497        105 FILE USPAT2
L498          0 FILE VETB
L499          0 FILE VETU
L500          0 FILE IPA
L501          0 FILE NAPRALERT
     TOTAL FOR ALL FILES
L502        430 S L452 AND (300 (2A) MG)
L503          0 FILE DISSABS
L504          0 FILE 1MOBILITY
L505          0 FILE AGRICOLA
L506          0 FILE BIOTECHNO
L507          0 FILE COMPENDEX
L508          0 FILE EMBASE
L509          0 FILE INSPEC
L510          0 FILE PASCAL
L511          0 FILE PQSCITECH
L512          0 FILE ADISCTI
```

supplemental STN search

```
L513           0 FILE ADISINSIGHT
L514           0 FILE ADISNEWS
L515           0 FILE ANABSTR
L516           0 FILE BIOSIS
L517           0 FILE BIOTECHDS
L518           0 FILE CABA
L519           0 FILE CAPLUS
L520           0 FILE CEABA-VTB
L521           0 FILE CIN
L522           0 FILE CROPB
L523           0 FILE CROPU
L524           0 FILE DDFB
L525           0 FILE DGENE
L526           0 FILE DRUGB
L527           0 FILE DRUGU
L528           0 FILE EMBAL
L529           0 FILE ESBIOBASE
L530           0 FILE FOMAD
L531           0 FILE FROSTI
L532           0 FILE FSTA
L533           0 FILE GENBANK
L534           0 FILE IFIALL
L535           0 FILE IMSRESEARCH
L536           0 FILE KOSMET
L537           0 FILE MEDLINE
L538           0 FILE NTIS
L539           0 FILE PCTGEN
L540           0 FILE PS
L541           0 FILE RDISCLOSURE
L542           0 FILE SCISEARCH
L543           0 FILE TOXCENTER
L544           0 FILE USGENE
L545           0 FILE USPATFULL
L546           0 FILE USPATOLD
L547           0 FILE USPAT2
L548           0 FILE VETB
L549           0 FILE VETU
L550           0 FILE IPA
L551           0 FILE NAPRALERT
     TOTAL FOR ALL FILES
L552           0 S L502 AND (10 (2A) MG/ML)
L553           0 FILE DISSABS
L554           0 FILE 1MOBILITY
L555           0 FILE AGRICOLA
L556           0 FILE BIOTECHNO
L557           0 FILE COMPENDEX
L558           0 FILE EMBASE
L559           0 FILE INSPEC
L560           0 FILE PASCAL
L561           0 FILE PQSCITECH
L562           0 FILE ADISCTI
L563           0 FILE ADISINSIGHT
L564           0 FILE ADISNEWS
L565           0 FILE ANABSTR
L566           0 FILE BIOSIS
L567           0 FILE BIOTECHDS
L568           0 FILE CABA
L569           0 FILE CAPLUS
L570           0 FILE CEABA-VTB
```

supplemental STN search

```
L571          0 FILE CIN
L572          0 FILE CROPB
L573          0 FILE CROPU
L574          0 FILE DDFB
L575          0 FILE DGENE
L576          0 FILE DRUGB
L577          0 FILE DRUGU
L578          0 FILE EMBAL
L579          0 FILE ESBIOBASE
L580          0 FILE FOMAD
L581          0 FILE FROSTI
L582          0 FILE FSTA
L583          0 FILE GENBANK
L584          1 FILE IFIALL
L585          0 FILE IMSRESEARCH
L586          0 FILE KOSMET
L587          0 FILE MEDLINE
L588          0 FILE NTIS
L589          0 FILE PCTGEN
L590          0 FILE PS
L591          0 FILE RDISCLOSURE
L592          0 FILE SCISEARCH
L593          0 FILE TOXCENTER
L594          0 FILE USGENE
L595          2 FILE USPATFULL
L596          0 FILE USPATOLD
L597          0 FILE USPAT2
L598          0 FILE VETB
L599          0 FILE VETU
L600          0 FILE IPA
L601          0 FILE NAPRALERT
     TOTAL FOR ALL FILES
L602          3 S L452 (20A) (SINGLE (2A) UNIT)
L603          2 DUP REM L602 (1 DUPLICATE REMOVED)
L604          0 FILE DISSABS
L605          0 FILE 1MOBILITY
L606          0 FILE AGRICOLA
L607          0 FILE BIOTECHNO
L608          0 FILE COMPENDEX
L609          1 FILE EMBASE
L610          0 FILE INSPEC
L611          0 FILE PASCAL
L612          0 FILE PQSCITECH
L613          0 FILE ADISCTI
L614          0 FILE ADISINSIGHT
L615          0 FILE ADISNEWS
L616          0 FILE ANABSTR
L617          0 FILE BIOSIS
L618          0 FILE BIOTECHDS
L619          0 FILE CABA
L620          0 FILE CAPLUS
L621          0 FILE CEABA-VTB
L622          0 FILE CIN
L623          0 FILE CROPB
L624          0 FILE CROPU
L625          0 FILE DDFB
L626          0 FILE DGENE
L627          0 FILE DRUGB
L628          1 FILE DRUGU
```

supplemental STN search

```
L629           0 FILE EMBAL
L630           0 FILE ESBIOBASE
L631           0 FILE FOMAD
L632           0 FILE FROSTI
L633           0 FILE FSTA
L634           0 FILE GENBANK
L635           2 FILE IFIALL
L636           0 FILE IMSRESEARCH
L637           0 FILE KOSMET
L638           0 FILE MEDLINE
L639           0 FILE NTIS
L640           0 FILE PCTGEN
L641           0 FILE PS
L642           0 FILE RDISCLOSURE
L643           0 FILE SCISEARCH
L644           0 FILE TOXCENTER
L645           0 FILE USGENE
L646           5 FILE USPATFULL
L647           0 FILE USPATOLD
L648           0 FILE USPAT2
L649           0 FILE VETB
L650           0 FILE VETU
L651           0 FILE IPA
L652           0 FILE NAPRALERT
     TOTAL FOR ALL FILES
L653           9 S L452 (20A) (300 (2A) MG)
L654           6 DUP REM L653 (3 DUPLICATES REMOVED)
L655           0 FILE DISSABS
L656           0 FILE 1MOBILITY
L657           0 FILE AGRICOLA
L658           0 FILE BIOTECHNO
L659           0 FILE COMPENDEX
L660          16 FILE EMBASE
L661           0 FILE INSPEC
L662           1 FILE PASCAL
L663           0 FILE PQSCITECH
L664           1 FILE ADISCTI
L665           0 FILE ADISINSIGHT
L666           0 FILE ADISNEWS
L667           0 FILE ANABSTR
L668           2 FILE BIOSIS
L669           0 FILE BIOTECHDS
L670           0 FILE CABA
L671           2 FILE CAPLUS
L672           0 FILE CEABA-VTB
L673           0 FILE CIN
L674           0 FILE CROPB
L675           0 FILE CROPU
L676           0 FILE DDFB
L677           0 FILE DGENE
L678           0 FILE DRUGB
L679          11 FILE DRUGU
L680           0 FILE EMBAL
L681           1 FILE ESBIOBASE
L682           0 FILE FOMAD
L683           0 FILE FROSTI
L684           0 FILE FSTA
L685           0 FILE GENBANK
L686           1 FILE IFIALL
```

supplemental STN search

```
L687          0 FILE IMSRESEARCH
L688          0 FILE KOSMET
L689          3 FILE MEDLINE
L690          0 FILE NTIS
L691          0 FILE PCTGEN
L692          0 FILE PS
L693          0 FILE RDISCLOSURE
L694          3 FILE SCISEARCH
L695          1 FILE TOXCENTER
L696          0 FILE USGENE
L697          7 FILE USPATFULL
L698          0 FILE USPATOLD
L699          1 FILE USPAT2
L700          0 FILE VETB
L701          0 FILE VETU
L702          0 FILE IPA
L703          0 FILE NAPRALERT
     TOTAL FOR ALL FILES
L704         50 S (300 (2A) MG) (10A) (ECULIZUMAB OR SOLIRIS)
L705         34 DUP REM L704 (16 DUPLICATES REMOVED)
L706          0 S L705
L707          0 FILE DISSABS
L708          0 S L705
L709          0 FILE 1MOBILITY
L710          0 S L705
L711          0 FILE AGRICOLA
L712          0 S L705
L713          0 FILE BIOTECHNO
L714          0 S L705
L715          0 FILE COMPENDEX
L716         16 S L705
L717          0 FILE EMBASE
L718          0 S L705
L719          0 FILE INSPEC
L720          0 S L705
L721          0 FILE PASCAL
L722          0 S L705
L723          0 FILE PQSCITECH
L724          1 S L705
L725          0 FILE ADISCTI
L726          0 S L705
L727          0 FILE ADISINSIGHT
L728          0 S L705
L729          0 FILE ADISNEWS
L730          0 S L705
L731          0 FILE ANABSTR
L732          2 S L705
L733          0 FILE BIOSIS
L734          0 S L705
L735          0 FILE BIOTECHDS
L736          0 S L705
L737          0 FILE CABA
L738          0 S L705
L739          0 FILE CAPLUS
L740          0 S L705
L741          0 FILE CEABA-VTB
L742          0 S L705
L743          0 FILE CIN
L744          0 S L705
```

supplemental STN search

```
L745          0 FILE CROPB
L746          0 S L705
L747          0 FILE CROPU
L748          0 S L705
L749          0 FILE DDFB
L750          0 S L705
L751          0 FILE DGENE
L752          0 S L705
L753          0 FILE DRUGB
L754          7 S L705
L755          0 FILE DRUGU
L756          0 S L705
L757          0 FILE EMBAL
L758          0 S L705
L759          0 FILE ESBIOBASE
L760          0 S L705
L761          0 FILE FOMAD
L762          0 S L705
L763          0 FILE FROSTI
L764          0 S L705
L765          0 FILE FSTA
L766          0 S L705
L767          0 FILE GENBANK
L768          1 S L705
L769          0 FILE IFIALL
L770          0 S L705
L771          0 FILE IMSRESEARCH
L772          0 S L705
L773          0 FILE KOSMET
L774          0 S L705
L775          0 FILE MEDLINE
L776          0 S L705
L777          0 FILE NTIS
L778          0 S L705
L779          0 FILE PCTGEN
L780          0 S L705
L781          0 FILE PS
L782          0 S L705
L783          0 FILE RDISCLOSURE
L784          0 S L705
L785          0 FILE SCISEARCH
L786          0 S L705
L787          0 FILE TOXCENTER
L788          0 S L705
L789          0 FILE USGENE
L790          6 S L705
L791          0 FILE USPATFULL
L792          0 S L705
L793          0 FILE USPATOLD
L794          1 S L705
L795          0 FILE USPAT2
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supplemental STN search

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supplemental STN search

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supplemental STN search

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     TOTAL FOR ALL FILES
L953            6 S (300 (2A) MG) (10A) (C5 (10A) ANTIBOD?)
L954            4 DUP REM L953 (2 DUPLICATES REMOVED)
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I hereby certify that this paper (along with any paper referred to as being attached or enclosed) is being transmitted via the Office electronic filing system in accordance with 37 CFR § 1.6(a)(4).

Dated: May 6, 2016
Electronic Signature for Jill Gorny Sloper, Esq.: /Jill Gorny Sloper, Esq./

Docket No.: AXJ-114BUSCN2
(PATENT)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

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

Application No.: Not Yet Assigned

Confirmation No.: N/A

Filed: Concurrently Herewith

Art Unit: N/A

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

Examiner: Not Yet Assigned

INFORMATION DISCLOSURE STATEMENT (IDS)

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

Dear Sir:

In compliance with 37 C.F.R. § 1.56, 1.97 and 1.98, the attention of the Patent and Trademark Office is hereby directed to the documents listed on the attached PTO/SB/08.

For the Examiner's convenience in reviewing this continuation application, Applicant submits a consolidated PTO Form SB/08, listing all references cited during the prosecution of the parent application. The present application is a continuation of U.S. Application No. 13/426,973, filed March 22, 2012 (Atty. Docket No. AXJ-114BUSCN). In accordance with 37 C.F.R. §1.98(d), copies of the references previously cited by or submitted to the Office in the parent application are not enclosed, but will be provided upon request. In accordance with 37 C.F.R. § 1.98(a)(2)(i)-(iv), Applicant submits herewith copies of a non-patent literature references.

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

It is respectfully requested that the documents listed on the PTO/SB/08 be expressly considered by the Examiner during the prosecution of this application, and that the documents be made of record therein and appear among the "References Cited" on any patent to issue therefrom.

Applicants call to the attention of the Examiner the following Applications and Office Actions cited therein:

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

Office Actions (copies enclosed)			
Examiner's Initials	Serial No.	Date Mailed from USPTO	Examiner
	13/426,973	01-27-2014	J. Rogers
	13/426,973	05-31-2013	J. Rogers
	13/426,973	08-20-2012	J. Rogers
	12/225,040	09-22-2011	J. Rogers
	12/225,040	06-01-2011	J. Rogers
	12/225,040	04-11-2011	J. Rogers
	12/621,792	09-30-2010	P. Gambel
	10/771,552	12-22-2008	F. Vandervegt
	10/771,552	03-21-2008	F. Vandervegt
	10/771,552	08-10-2007	F. Vandervegt
	10/771,552	02-26-2007	F. Vandervegt
	10/771,552	09-26-2006	F. Vandervegt
	11/050,543	07-09-2010	P. Gambel
	11/050,543	04-02-2008	F. Vandervegt
	11/050,543	10-10-2007	F. Vandervegt
	11/050,543	06-11-2007	F. Vandervegt
	11/595,118	01-21-2011	P. Gambel
	11/595,118	10-05-2010	P. Gambel

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

	11/595,118	07-07-2010	P. Gambel
	11/595,118	04-03-2009	F. Vandervegt
	12/902,617	06-23-2011	P. Gambel
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	13/335,518	09-12-2014	P. Gambel
	13/335,518	02-06-2014	P. Gambel
	13/335,518	11-07-2013	P. Gambel

/JAMES L ROGERS/ 08/08/2016

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

This Information Disclosure Statement accompanies the new patent application submitted herewith. Accordingly, no fees are due with this submission (37 C.F.R § 1.97(b)(3)). However, the Director is hereby authorized to charge any fee deficiency which should have been filed herewith (or with any paper hereafter filed in this application by this firm) to our Deposit Account No. 12-0080, under Order No. AXJ-114BUSCN2.

Dated: May 6, 2016

Respectfully submitted,

Electronic signature: /Jill Gorny Sloper, Esq./
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Search Notes	Application/Control No.	Applicant(s)/Patent Under Reexamination
	15148839	BELL ET AL.
	Examiner	Art Unit
	JAMES ROGERS	1644

CPC- SEARCHED		
Symbol	Date	Examiner

CPC COMBINATION SETS - SEARCHED		
Symbol	Date	Examiner

US CLASSIFICATION SEARCHED			
Class	Subclass	Date	Examiner

SEARCH NOTES		
Search Notes	Date	Examiner
STN: DISSABS MEETINGS BIOSCI CAPLUS MEDICINE	8/8/2016	JR
EAST: PGPUB, USPAT, JPO, EPO, INVENTOR SEARCH	8/8/2016	JR

INTERFERENCE SEARCH			
US Class/ CPC Symbol	US Subclass / CPC Group	Date	Examiner

	/James Rogers/ Examiner Art Unit 1644

ORIGINAL ARTICLE

Effect of Eculizumab on Hemolysis and Transfusion Requirements in Patients with Paroxysmal Nocturnal Hemoglobinuria

Peter Hillmen, M.B., Ph.D., Claire Hall, M.B., Ch.B., Judith C.W. Marsh, M.B., M.D., Modupe Elebute, M.B., M.D., Michael P. Bombara, B.S., Beth E. Petro, B.S., Matthew J. Cullen, B.Sc., Stephen J. Richards, Ph.D., Scott A. Rollins, Ph.D., Christopher F. Mojcik, M.D., Ph.D., and Russell P. Rother, Ph.D.

ABSTRACT

BACKGROUND

Paroxysmal nocturnal hemoglobinuria (PNH) arises from a somatic mutation of the *PIG-A* gene in a hematopoietic stem cell and the subsequent production of blood cells with a deficiency of surface proteins that protect the cells against attack by the complement system. We tested the clinical efficacy of eculizumab, a humanized antibody that inhibits the activation of terminal complement components, in patients with PNH.

METHODS

Eleven transfusion-dependent patients with PNH received infusions of eculizumab (600 mg) every week for four weeks, followed one week later by a 900-mg dose and then by 900 mg every other week through week 12. Clinical and biochemical indicators of hemolysis were measured throughout the trial.

RESULTS

Mean lactate dehydrogenase levels decreased from 3111 IU per liter before treatment to 594 IU per liter during treatment (P=0.002). The mean percentage of PNH type III erythrocytes increased from 36.7 percent of the total erythrocyte population to 59.2 percent (P=0.005). The mean and median transfusion rates decreased from 2.1 and 1.8 units per patient per month to 0.6 and 0.0 units per patient per month, respectively (P=0.003 for the comparison of the median rates). Episodes of hemoglobinuria were reduced by 96 percent (P<0.001), and measurements of the quality of life improved significantly.

CONCLUSIONS

Eculizumab is safe and well tolerated in patients with PNH. This antibody against terminal complement protein C5 reduces intravascular hemolysis, hemoglobinuria, and the need for transfusion, with an associated improvement in the quality of life in patients with PNH.

From the Department of Haematology, Leeds Teaching Hospitals National Health Science Trust, Leeds, United Kingdom (P.H., C.H., M.J.C., S.J.R.); the Department of Haematology, St. George's Hospital Medical School, London (J.C.W.M., M.E.); and Alexion Pharmaceuticals, Cheshire, Conn. (M.P.B., B.E.P., S.A.R., C.F.M., R.P.R.). Address reprint requests to Dr. Hillmen at the Department of Haematology, Leeds General Infirmary, Great George St., Leeds LS1 3EX, United Kingdom, or at peter.hillmen@panp-tr.northy.nhs.uk.

N Engl J Med 2004;350:552-9.

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THE MAJOR CLINICAL SIGNS OF PAROXysmal nocturnal hemoglobinuria (PNH) are intravascular hemolysis, venous thrombosis, and hemoglobinuria.[1] The disease arises from a somatic mutation of the *PIG-A* gene in a pluripotent hematopoietic stem cell. *PIG-A* encodes a protein that is essential for the synthesis of glycosylphosphatidylinositol (GPI), a lipid moiety that is embedded in the plasma membrane, where it serves to anchor a wide variety of proteins to the cell surface. The mutant stem cell subsequently expands to form a hematopoietic clone with a deficiency in proteins that are normally attached to the cell surface by the GPI anchor.[2,3] The mature blood cells derived from the hematopoietic clone can have a complete deficiency (type III) or a partial deficiency (type II) of GPI-linked proteins and almost always coexist with residual cells with a normal expression of these proteins (previously identified as type I).

The clinical features of PNH result from the lack of one or more GPI-linked proteins that protect cells from complement-mediated attack. Two such proteins — CD55 and CD59 — are absent from PNH type III erythrocytes, platelets, and other blood cells.[4-6] CD55 regulates early complement activation by inhibiting C3 convertases,[7] whereas CD59 inhibits the assembly of the membrane-attack complex C5b–C9 by interacting with C8 and C9.[4,5] The lack of CD59 is probably responsible for the increased sensitivity of PNH erythrocytes and platelets to complement.[4,8-13]

Eculizumab is a recombinant humanized monoclonal antibody that was designed to block the activation of terminal complement components.[14,15] It binds specifically to the terminal complement protein C5, inhibiting its cleavage into C5a and C5b, thereby preventing the release of the inflammatory mediator C5a and the formation of the cytolytic-pore C5b–C9. Blockade of the complement cascade at C5 preserves the early components of complement that are essential for the opsonization of microorganisms and clearance of immune complexes.[16] In this trial, we investigated whether eculizumab could reduce the incidence of intravascular hemolysis, hemoglobinuria, and transfusion requirements in patients with PNH.

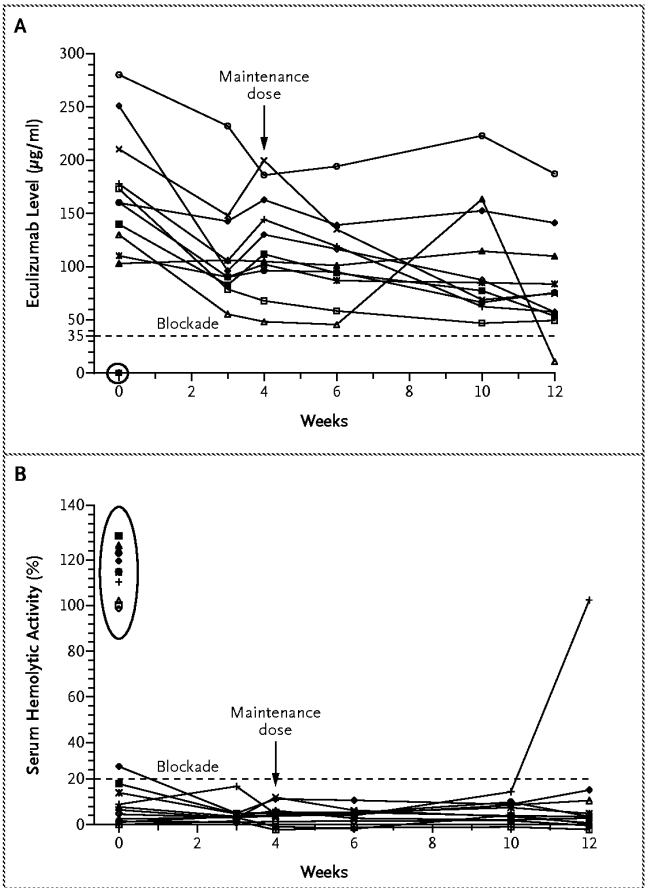


Figure 1. Pharmacokinetic and Pharmacodynamic Analysis of Eculizumab in 11 Patients with Paroxysmal Nocturnal Hemoglobinuria (PNH).

Panel A depicts serum levels of eculizumab during the 12-week treatment period. Eculizumab levels just before a patient's first dose of eculizumab are circled on the x axis. Also shown at time zero are levels of eculizumab one hour after the initial dose. Other data points indicate trough levels of eculizumab for each patient at weeks 3, 4, 6, 10, and 12. The beginning of the 900-mg maintenance dose is indicated by an arrow. The level of eculizumab required to block complement activity (≥35 μg per milliliter) is indicated by a dashed line. Panel B shows hemolytic activity in serum during the 12-week treatment period, as assessed in a presensitized chicken-erythrocyte hemolytic assay. Pretreatment serum hemolytic activity values are circled at time zero. Also shown at time zero are values for hemolytic activity one hour after the initial dose. Other data points indicate trough hemolytic activity at weeks 3, 4, 6, 10, and 12. The dashed line indicates the level of hemolytic activity that is considered to represent complete complement blockade (≤20 percent).

METHODS

PATIENTS

The study was conducted from May through December 2002. Men and women (18 years of age and older) who had received a diagnosis of PNH at least six months earlier, had a detectable GPI-deficient hematopoietic clone, and had received at least four red-cell transfusions in the preceding 12 months were

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eligible. Patients were required to have a negative throat culture for *Neisseria meningitidis* and *N. gonorrhoeae*. All patients were vaccinated against *N. meningitidis* (Mengivac (A+C), Aventis Pasteur) before treatment. One patient had a stroke after consent but never received eculizumab and was excluded. Patients who were taking stable doses of immunosuppressive drugs (e.g., cyclosporine), warfarin, and iron supplements were permitted to continue them.

The trial was approved by the local research ethics committee and was performed according to the International Conference on Harmonisation and Good Clinical Practice Standards. Eleven patients gave written informed consent and were treated with eculizumab.

TREATMENT SCHEDULE

Patients received infusions of 600 mg of eculizumab weekly for four weeks, followed one week later by a 900-mg dose and then by a dose of 900 mg every other week through week 12.

INVESTIGATIONS

In this open-label pilot study, we obtained data on the pharmacokinetics, pharmacodynamics, and immunogenicity of eculizumab and observed its clinical effects by measuring the following: lactate dehydrogenase, haptoglobin, bilirubin, and hemoglobin levels; reticulocyte counts; the proportion of GPI-deficient cells, as assessed by flow cytometry[17]; the rate of transfusion with packed red cells; the rate of occurrence of hemoglobinuria (assessed by daily comparison of the first morning urine sample with a standardized color chart before and during treatment); and the quality of life, as reflected by the scores on the European Organization for Research and Treatment of Cancer (EORTC) QLQ-C30 instrument. The trigger for transfusion during the study period remained unchanged for each patient, as compared with their care before entry into the study: patients received blood transfusions when they had symptoms resulting from anemia.

Assessment of the safety of eculizumab included ascertainment of treatment-related adverse events, electrocardiography, and routine laboratory tests (e.g., serum chemical analyses and complete blood counts).

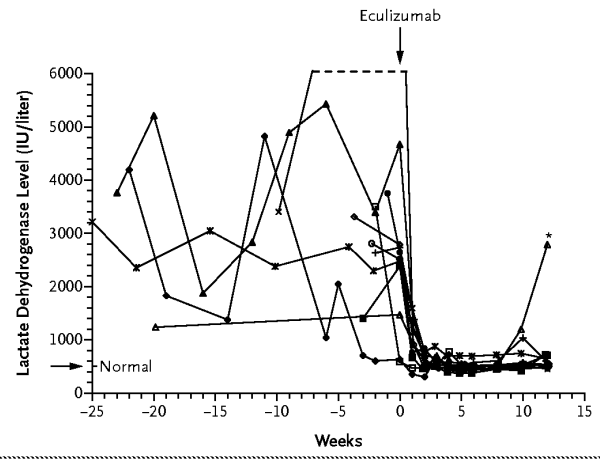


Figure 2. Analysis of Lactate Dehydrogenase Levels, a Biochemical Indicator of Hemolysis, in 11 Patients with Paroxysmal Nocturnal Hemoglobinuria up to 25 Weeks before and during 12 Weeks of Eculizumab Treatment.

The first dose of eculizumab is indicated by an arrow, as is the upper limit of the normal range of lactate dehydrogenase at the Leeds Teaching Hospital. The data point identified at week 12 by the asterisk represents a reading that was obtained from a duplicate serum sample since the original sample was lost. The dashed line represents off-scale points from one patient with a peak value of 12,100 IU per liter.

ASSAY METHODS

The pharmacokinetics of eculizumab were determined with an enzyme-linked immunosorbent assay that detects both free and C5-bound eculizumab.[15] The pharmacodynamics of eculizumab were determined by measuring the capacity of the patient's serum to lyse chicken erythrocytes in a standard total human serum-complement hemolytic assay.[18] The presence or absence of antibodies against eculizumab was assessed by an enzyme-linked immunosorbent assay.[19]

STATISTICAL ANALYSIS

Biochemical values were compared with the use of a paired Student's t-test, quality-of-life measurements with the use of a mixed-effect analysis of covariance, the median rate of transfusions with the use of a Wilcoxon signed-rank test, and the comparison of the number of days with paroxysms with the use of Fisher's exact test.

The corresponding author and the sponsor were jointly responsible for the design of this trial and the development of the protocol. Data were collected and analyzed by a clinical research organization, Kendle International, which maintained the trial data base and provided statistical support. The manuscript was prepared by the corresponding author, with substantial review and comments by the other authors and the sponsor. Final decisions on

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the content of the manuscript rested with the corresponding author in consultation with the other authors. All authors had access to the primary data.

RESULTS

DEMOGRAPHIC CHARACTERISTICS

Six men and five women (median age, 48 years; range, 21 to 67) with a median duration of PNH of 8.6 years (range, 1.7 to 37.4) participated in the trial. Five of the patients had platelet counts at base line of less than 150,000 per cubic millimeter. Eight patients had previously received a diagnosis of aplastic anemia, two were concomitantly receiving cyclosporine for aplastic anemia, and six were receiving warfarin.

SAFETY

All patients completed the 12-week study. There were no deaths or thrombotic events, and all patients subsequently entered a 12-month extension study. Each patient reported one or more adverse events during the trial. Events reported by three patients included headache and upper respiratory tract infection. Events reported by two patients included influenza-like symptoms, rigors, dizziness, nausea, nasal congestion, and joint aches. None of these events were attributed to the study medication. Serious adverse events occurred in two patients. The first was hospitalized with a viral chest infection. The second reported nausea, vomiting, and headache after the first infusion, with dizziness and shivering the following day. The patient was hospitalized overnight, and subsequent infusions were well tolerated.

PHARMACOKINETICS, PHARMACODYNAMICS, AND IMMUNOGENICITY OF ECULIZUMAB

Peak and trough levels of eculizumab were well above 35 μg per milliliter from one hour after the first dose through the completion of the 600-mg weekly dose period (Fig. 1A). In 10 patients, serum trough levels of eculizumab remained above 35 μg per milliliter for the entire study.

The hemolytic activity of serum from these 10 patients was completely blocked (less than 20 percent in the chicken–red-cell assay) for essentially the entire treatment period (Fig. 1B). In 1 of the 11 patients, the trough level of eculizumab fell below 35 μg per milliliter at week 12 and serum hemolytic activity returned. In no case were antibodies against eculizumab detected.

BIOCHEMICAL INDICATORS OF HEMOLYSIS

Levels of lactate dehydrogenase in serum were markedly elevated in all patients before eculizumab treatment. Mean (±SD) lactate dehydrogenase levels fell from 3111±598 IU per liter during the 12 months before enrollment to 594±32 IU per liter (normal range, 150 to 480) during treatment ($P=0.002$) (Fig. 2).

The decrease in lactate dehydrogenase began after a single dose of eculizumab in all patients. Lactate dehydrogenase levels remained within or just above the normal range for the duration of the study (Fig. 2). In the one patient in whom eculizumab levels fell below 35 μg per milliliter at week 12 (Fig. 1A), hemolytic activity returned (Fig. 1B) and lactate dehydrogenase levels increased transiently (Fig. 2).

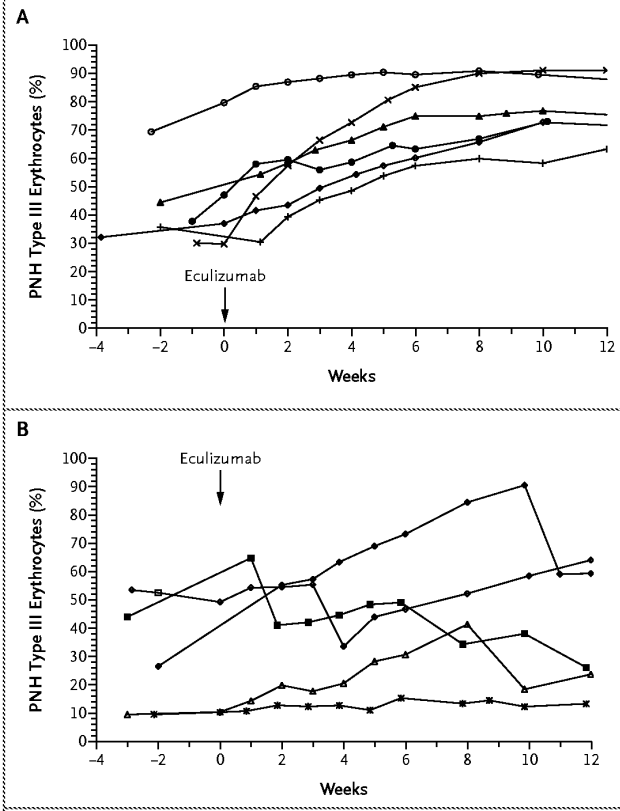


Figure 3. Changes in the Percentage of Paroxysmal Nocturnal Hemoglobinuria (PNH) Type III Erythrocytes during Eculizumab Treatment in Six Patients Who Received No Transfusions during Treatment (Panel A) and Five Patients Who Received at Least One Transfusion after Starting Treatment (Panel B).
The initial dose of eculizumab is indicated by the arrow in each panel.

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The dosing frequency was increased from 900 mg every 14 days to 900 mg every 12 days, reestablishing complete complement blockade during the ongoing 12-month extension study (data not shown).

Haptoglobin became detectable in the serum of 5 of the 11 patients after two weeks of eculizumab treatment but returned to undetectable levels soon thereafter (data not shown). Bilirubin levels were also elevated in most patients at base line and did not change significantly during treatment (data not shown).

EFFECT ON PNH CLONES

Type III erythrocytes are highly sensitive to lysis by complement and as a result have a short life span. In our study, the percentage of type III erythrocytes increased significantly from a mean of 36.7±5.9 percent before treatment to 59.2±8.0 percent at the end of 12 weeks of treatment (P=0.005) (Fig. 3). The increase was particularly consistent in six patients who remained transfusion-independent during the study (Fig. 3A). In patients who received transfusions during the study, sudden drops in the proportion of type III cells were seen as the transfused red cells diluted the type III population (Fig. 3B). There were no significant changes in the percentages of PNH type III neutrophils, monocytes, or platelets during treatment with eculizumab; in most cases, these percentages were 90 to 100 percent before the study (data not shown).

TRANSFUSION REQUIREMENTS, HEMOGLOBIN LEVELS, AND RETICULOCYTE COUNTS

During the year preceding enrollment, the range of red-cell transfusions received by the 11 patients was 12 to 55 units, whereas during the three months of the study, the range was 0 to 8 units. Before eculizumab treatment, the mean and median transfusion rates were 2.1 and 1.8 units per patient per month, respectively (Table 1). These transfusion rates decreased to 0.6 and 0.0 unit per patient per month, respectively, during the three months of treatment with eculizumab (P=0.003). Hemoglobin levels did not increase significantly during the treatment period, although hemoglobin values in six patients stabilized without transfusions (Table 1). Similarly, the numbers of reticulocytes remained relatively constant during eculizumab treatment.

HEMOGLOBINURIA

Our patients recorded the color of their urine each morning using a color chart designed to assess the

Table 1. **Transfusion Rates, Hemoglobin Levels, and Reticulocyte Counts 12 Months before and after 3 Months of Eculizumab Treatment.**

Patient No.	12 Mo before Eculizumab Treatment				After 3 Mo of Eculizumab Treatment			
	Transfusions		Hemoglobin	Reticulocytes	Transfusions		Hemoglobin	Reticulocytes
	no. of units	*rate**	*g/dl*	*×10⁻³/mm³*	*no. of units*	*rate†*	*g/dl*	*×10⁻³/mm³*
1	22	1.8	10.3	77.5	2	0.7	10.0	100.7
2	23	1.9	8.3	200.0	8	2.9	8.8	182.6
3	20	1.6	10.1	169.5	0	0.0	10.7	175.9
4	28	2.3	9.3	282.0	0	0.0	9.4	333.3
5	12	1.0	11.9	96.3	2	0.7	10.6	121.8
6	14	1.2	9.8	346.8	0	0.0	10.6	259.0
7	34	2.8	12.8	100.6	0	0.0	13.5	166.8
8	21	1.7	9.5	164.5	0	0.0	9.8	239.6
9	55	4.5	10.7	138.0	3	1.1	11.4	285.8
10	41	3.4	8.5	108.7	5	1.8	8.8	140.1
11	14	1.2	8.5	91.4	0	0.0	10.0	97.4
Median‡		1.8				0.0		
Mean		2.1	10.0	161.4		0.6	10.3	191.2

* The rate (in units per month) was calculated as (number of units÷365 days)×30.
† The rate (in units per month) was calculated as (number of units÷84 days)×30.
‡ P=0.003 for the change in the median rate of transfusion by the Wilcoxon signed-rank test.

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degree of hemoglobinuria (Fig. 4A) during both the 2-to-4-week screening period and the 12-week treatment period. Paroxysms of hemoglobinuria were prospectively defined as dark-colored urine with a colorimetric level of 6 or more. In nine patients for whom urine scores were assessed, the mean incidence of paroxysms was reduced from 2.9 days to 0.12 day per patient per month ($P<0.001$) (Fig. 4B).

QUALITY OF LIFE

The quality of life was assessed with the use of the EORTC QLQ-C30 instrument. When responses at base line were compared with responses during 12 weeks of eculizumab treatment, there were significant improvements in the domains of global health status ($P=0.02$), physical functioning ($P<0.001$), emotional functioning ($P<0.001$), cognitive functioning ($P=0.002$), fatigue ($P<0.001$), dyspnea ($P=0.002$), and insomnia ($P=0.049$) (Table 2).

DISCUSSION

Patients with PNH have chronic, often disabling symptoms of fatigue and intermittent episodes of dysphagia, abdominal pain, and hemoglobinuria. These symptoms are thought to be related to the intravascular destruction of PNH type III erythrocytes, which are deficient in complement inhibitors, by autologous complement. The hemolytic anemia frequently renders the patients transfusion-dependent. In addition, patients have an extremely high risk of potentially life-threatening thrombosis, particularly thrombosis of the hepatic and cerebral veins. Approximately 50 percent of patients with PNH die of the disease; the median duration of survival after diagnosis is 10 years.[1]

We found that the defect in the membrane-bound inhibitor of terminal complement components in PNH was ameliorated by the administration of eculizumab. This antibody specifically prevents cleavage of C5, which is necessary for assembly of the membrane-attack complex. Blockade of terminal complement components presumably prolongs the survival of type III erythrocytes (since there was no simultaneous increase in reticulocytes), which are highly sensitive to lysis by complement, thereby increasing the proportion of these cells in the blood and reducing signs of hemolysis in most patients. In some patients, the percentage of type III erythrocytes increased to more than 80 percent of the total erythrocyte population. This interpretation of the mechanism of action of eculizumab is consistent with the report of an asymptomatic patient with PNH who had more than 80 percent type III erythrocytes and a concomitant deficiency in the terminal complement protein C9.[20] Thus, inhibition of the assembly of C5b–C9 by an antibody or by a congenital deficiency of a terminal component of the complement system can protect type III erythrocytes from complement-mediated lysis.

The long-term effects of protecting PNH type III erythrocytes from complement are not known. For example, will removing the negative pressure

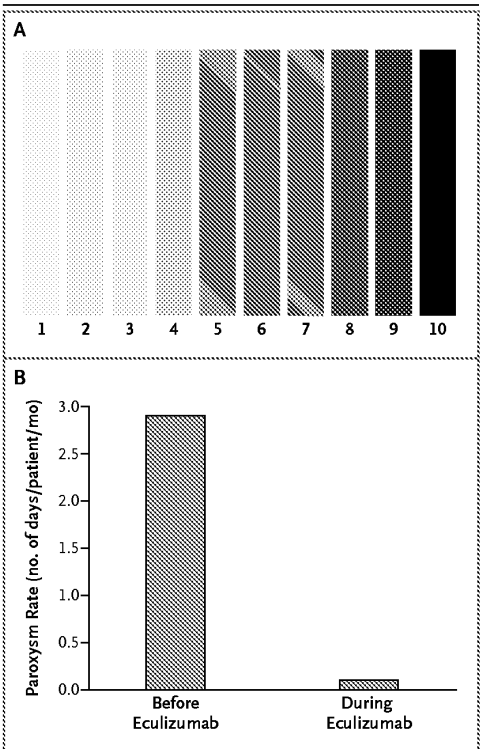


Figure 4. **Incidence of Paroxysms during Eculizumab Treatment.**

Panel A shows a urine color scale devised to monitor the incidence of paroxysms of hemoglobinuria in patients with paroxysmal nocturnal hemoglobinuria before and during treatment. A paroxysm was prospectively defined as a urine score of 6 or greater in this study. Panel B depicts the change in the paroxysm rate (defined as the mean number of days in paroxysm per patient per month) in nine patients 1 month before and during 12 weeks of eculizumab therapy. Pretreatment data on paroxysms were inadvertently not collected for two patients, and these two were therefore excluded from the analysis.

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Table 2. **Change in the Quality of Life during Eculizumab Treatment.***

Domain	Mean Base-Line Score†	Change from Base Line‡§	P Value§
Global health status	56.1	13.7	0.02
Physical functioning	70.9	13.0	<0.001
Emotional functioning	70.5	12.7	<0.001
Cognitive functioning	77.3	11.8	0.002
Fatigue	47.5	−15.3	<0.001
Dyspnea	39.4	−12.4	0.002
Insomnia	30.3	−10.8	0.049

* The quality of life was assessed with the European Organization for Research and Treatment of Cancer QLQ-C30 instrument.
† Numbers represent mean values of linearly transformed scores.
‡ Values for change from base line represent least-square means. A positive value indicates an improvement in the score for global health status, physical functioning, emotional functioning, and cognitive functioning, whereas a negative value indicates an improvement in the score for fatigue, dyspnea, and insomnia.
§ Values are from a mixed analysis-of-covariance model with visit as a fixed effect, patient as a random effect, and base line as a covariate.

on type III hematopoietic cells alter the rate of expansion of the PNH clone? What might occur in a patient with an increased population of PNH type III erythrocytes if treatment with eculizumab is stopped? Two of the patients who entered the eculizumab extension study had transient breakthroughs (lasting two to three days) in complement blockade until the dosing interval was adjusted. Both patients had hemoglobinuria with mild symptoms, but the episodes were not life threatening and were easily managed (data not shown). Definitive answers to these questions will require further study.

In this trial, lactate dehydrogenase levels declined rapidly and remained reduced as long as the serum level of eculizumab exceeded 35 μg per milliliter. The importance of maintaining this level of antibody was demonstrated in a single patient, in whom the eculizumab level transiently dropped below 35 μg per milliliter at week 12, resulting in a return of serum complement activity and an increase in lactate dehydrogenase levels. Subsequent administration of eculizumab reestablished complement blockade and rapidly reduced lactate dehydrogenase levels. Interestingly, lactate dehydrogenase levels were reduced in most patients to just above the upper limit of normal. The slightly elevated levels of this enzyme during treatment with eculizumab could reflect persistent, low-level C3b-mediated extravascular hemolysis or, possibly, undefined mechanisms of hemolysis that are unrelated to complement.

We also found that eculizumab treatment significantly reduced transfusion requirements, even though the levels of hemoglobin did not change significantly. However, the hemoglobin level in an individual patient before study entry was artificially maintained as a result of the transfusion of normal red cells. The transfused red cells survive far longer than PNH cells. Therefore, the stabilization of hemoglobin levels with a reduced need or no need for transfusion is a result of the protection of PNH red cells from complement-mediated lysis by eculizumab.

The decrease in transfusion requirements was most apparent in the six patients without a clinically significant degree of bone marrow failure (as defined by a normal platelet count). All but one of these patients were transfusion-independent during the study and remained so during an extension study. The remaining patient received a single 3-unit transfusion during the study, as compared with the receipt of 55 units in the 12 months preceding enrollment.

There was a rapid improvement in the quality of life during eculizumab therapy, as measured by the EORTC QLQ-C30. These clinical observations support the hypothesis that many of the important coexisting clinical conditions in patients with PNH are directly related to chronic and acute episodes of hemolysis, possibly through the scavenging of nitric oxide by plasma free hemoglobin.[21-25]

Eculizumab was safe and well tolerated during this open-label pilot study. The adverse events reported by patients were similar in type and frequency to those reported with either eculizumab or placebo in other controlled trials. All patients are currently participating in a one-year extension study in which the drug continues to be well tolerated. Furthermore, the rates of intravascular hemolysis, as measured by lactate dehydrogenase levels and hemoglobinuria, remain reduced in all patients, with 5 of 11 patients having been transfusion-independent for at least one year since starting eculizumab treatment.

The *PIG-A* mutation in patients with PNH causes deficiencies in the membrane-bound complement inhibitors CD55 and CD59, resulting in intravascular hemolysis.[2,3] However, patients who have genetic deficiencies in the surface expression of CD55 (Inab phenotype) with normal levels of CD59 have no clinical signs of hemolysis.[8,9] Conversely, a pa-

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tient with a genetic deficiency in the expression of CD59 but normal levels of CD55 had symptoms indistinguishable from those of PNH.[10,11] Therefore, the somatic mutation in the *PIG-A* gene that causes the deficiency of the membrane-bound terminal complement inhibitor CD59 is critical to the pathogenesis of PNH. We found that terminal complement inhibition with eculizumab ameliorated the untoward effects of this deficiency.

In summary, eculizumab appears to enhance the survival of type III PNH erythrocytes, improving the quality of life and reducing the extent of hemolysis, hemoglobinuria (the clinical hallmark of PNH), and the need for blood transfusions in patients with PNH. This study confirms that terminal complement activation is the key mediator of erythrocyte destruction in PNH.

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Dr. Hillmen reports serving as a consultant to Alexion Pharmaceuticals and receiving grant support from the company; Drs. Rollins, Mojcik, and Rother, Mr. Bombara, and Ms. Petro report having equity ownership in Alexion Pharmaceuticals; and Drs. Rollins and Rother have assigned to Alexion Pharmaceuticals their inventions made as employees of the company and have received no royalties from Alexion for these inventions. Dr. Rollins receives royalties for inventions he made before becoming an employee of Alexion.

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EAST Search History

EAST Search History (Prior Art)

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L3	0	(61/199764).APP.	US-PGPUB; USPAT; USOCR	OR	OFF	2016/08/08 15:34
L4	0	(61/199562).APP.	US-PGPUB; USPAT; USOCR	OR	OFF	2016/08/08 15:34
L5	13	("10" near2 mg/ml) near10 (eculizumab or soliris)	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2016/08/08 15:37
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EAST Search History (Interference)

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S18	3	(purified of purification or purifying or isolate or isolating or isolated Or separate or separated or separating).clm. and S12	US-PGPUB; USPAT	OR	ON	2016/08/08 09:16
S19	110	(purified of purification or purifying or isolate or isolating or isolated Or separate or separated or separating).clm. and S13	US-PGPUB; USPAT	OR	ON	2016/08/08 09:17
S20	91	S19 and (antibody or antibodies or IgG).clm.	US-PGPUB; USPAT	OR	ON	2016/08/08 09:18

S21	110	(purified of purification or purifying or isolate or isolating or isolated Or separate or separated or separating).clm. and S13	US-PGPUB; USPAT	OR	ON	2016/08/08 09:25
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	Art Unit	N/A
	Examiner Name	Not Yet Assigned
	Attorney Docket Number	AXJ-114BUSCN2

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	2	5135916		1992-08-04	Sims et al.	
	3	5660825		1997-08-26	Sims et al.	
	4	6355245		2002-03-12	Evans et al.	
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	Art Unit	N/A
	Examiner Name	Not Yet Assigned
	Attorney Docket Number	AXJ-114BUSCN2

	1	20030049683	A1	2003-03-13	Bowdish et al.	
	2	20050191298	A1	2005-09-01	Bell et al.	
	3	20050221382	A1	2005-10-06	Rother	
	4	20050169921	A1	2005-08-04	Bell et al.	
	5	20050271660	A1	2005-12-08	Wang	
	6	20070116710	A1	2007-05-24	Bell et al.	
	7	20090220508	A1	2009-09-03	Bell et al.	
	8	20100068202	A1	2010-03-18	Bell et al.	
	9	20110086040	A1	2011-04-14	Bell et al.	
	10	20120308559	A1	2012-12-06	Bell et al.	
	11	20120237515	A1	2012-09-20	Bell et al.	

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	Art Unit	N/A
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	Attorney Docket Number	AXJ-114BUSCN2

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	1	0411306	EP	A1	1991-02-06	Goetze, Otto Prof. Dr. Med		
	2	2004/029207	WO	A2	2004-04-08	Xencor Inc		
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Application	Document	Mailroom Date	Attorney Docket No.
15148839	CTNF	08/16/2016	AXJ-114BUSCN2
	892	08/16/2016	AXJ-114BUSCN2
	1449	08/16/2016	AXJ-114BUSCN2
	1449	08/16/2016	AXJ-114BUSCN2
	1449	08/16/2016	AXJ-114BUSCN2

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Subject: Private PAIR Correspondence Notification for Customer Number 133485

Aug 16, 2016 05:37:59 AM

Dear PAIR Customer:

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Application	Document	Mailroom Date	Attorney Docket No.
15148839	CTNF	08/16/2016	AXJ-114BUSCN2
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United States Patent and Trademark Office
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Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NUMBER	FILING OR 371(C) DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO./TITLE
15/148,839	05/06/2016	Leonard BELL	AXJ-114BUSCN2

CONFIRMATION NO. 3159

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

PUBLICATION NOTICE

OC000000085354308

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

Publication No.US-2016-0244516-A1
Publication Date:08/25/2016

NOTICE OF PUBLICATION OF APPLICATION

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

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

The publication process established by the Office does not provide for mailing a copy of the publication to applicant. A copy of the publication may be obtained from the Office upon payment of the appropriate fee set forth in 37 CFR 1.19(a)(1). Orders for copies of patent application publications are handled by the USPTO's Office of Public Records. The Office of Public Records can be reached by telephone at (703) 308-9726 or (800) 972-6382, by facsimile at (703) 305-8759, by mail addressed to the United States Patent and Trademark Office, Office of Public Records, Alexandria, VA 22313-1450 or via the Internet.

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

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

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

To: chris.schlauch@nelsonmullins.com,ipqualityassuranceboston@nelsonmullins.com,ipboston.docketing@nel
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Subject: Private PAIR Correspondence Notification for Customer Number 133485

Aug 26, 2016 05:40:30 AM

Dear PAIR Customer:

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Boston, MA 02109-2127
UNITED STATES

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Application	Document	Mailroom Date	Attorney Docket No.
15148839	NTC.PUB	08/25/2016	AXJ-114BUSCN2

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UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
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Alexandria, Virginia 22313-1450
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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
15/148,839	05/06/2016	Leonard BELL	AXJ-114BUSCN2	3159

133485 7590 09/14/2016

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

EXAMINER	
ROGERS, JAMES L	

ART UNIT	PAPER NUMBER
1644	

NOTIFICATION DATE	DELIVERY MODE
09/14/2016	ELECTRONIC

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

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

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

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

Applicant-Initiated Interview Summary	**Application No.** 15/148,839	**Applicant(s)** BELL ET AL.	
	Examiner JAMES ROGERS	**Art Unit** 1644	

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

(1) *JAMES ROGERS*.

(2) *SHARON WEN*.

(3) *JANE REMILLARD*.

(4) *DARRELL FONTENOT*.

Date of Interview: *07 September 2016*.

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

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

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

Claim(s) discussed: *1*.

Identification of prior art discussed: _____.

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

Proposed amendments to the outstanding rejection of record was discussed. No agreement was reached.

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

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

☐ Attachment

/SHARON WEN/ Primary Examiner, Art Unit 1644	/James Rogers/ Examiner, Art Unit 1644

Summary of Record of Interview Requirements

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

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

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

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

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

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

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

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

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

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

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

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

Examiner to Check for Accuracy

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

To: chris.schlauch@nelsonmullins.com,ipqualityassuranceboston@nelsonmullins.com,ipboston.docketing@nel
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Sep 14, 2016 08:52:42 AM

Dear PAIR Customer:

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UNITED STATES

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Application	Document	Mailroom Date	Attorney Docket No.
15148839	INTV.SUM.APP	09/14/2016	AXJ-114BUSCN2

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PTO/AIA/25 (04-13)
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TERMINAL DISCLAIMER TO OBVIATE A PROVISIONAL DOUBLE PATENTING REJECTION OVER A PENDING "REFERENCE" APPLICATION	Docket Number (Optional) AXJ-114BUSCN2

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

Application No.: 15/148,839-Conf. #3159

Filed: May 6, 2016

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

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

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

Check either box 1 or 2 below, if appropriate.

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

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

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



Signature

02/14/17

Date

Todd Spalding

Typed or printed name

Vice President, Head of Intellectual Property

Title

_____

Telephone Number

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

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

SUPPLEMENTAL SHEET FOR TERMINAL DISCLAIMER TO OBVIATE A PROVISIONAL DOUBLE PATENTING REJECTION OVER A PENDING "REFERENCE" APPLICATION	Docket Number (Optional) AXJ-114BUSCN2

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

15/260,888 (filed September 9, 2016)

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

Corrected Application Data Sheet

Inventor Information

Inventor Number::	1
Given Name::	Leonard
Family Name::	BELL
City of Residence::	Woodbridge
State or Province of Residence::	CT
Country of Residence::	US
Street of mailing address::	59 Tumblebrook Road
City of mailing address::	Woodbridge
State or Province of mailing address::	CT
Country of mailing address::	US
Postal or Zip Code of mailing address::	06525

Inventor Number::	2
Given Name::	Russell
Middle Name::	P.
Family Name::	ROTHER
City of Residence::	Oklahoma City
State or Province of Residence::	OK
Country of Residence::	US
Street of mailing address::	10325 Forest Meadow Drive
City of mailing address::	Oklahoma City
State or Province of mailing address::	OK
Country of mailing address::	US

Postal or Zip Code of mailing address::	73151

Correspondence Information

Correspondence Customer Number::	133485
E-Mail address::	ipboston.docketing@nelsonmullins.com

Application Information

Application Number::	15/148,839
Filing Date::	05/06/16
Title::	TREATMENT OF PAROXYSMAL NOCTURNAL HEMOGLOBINURIA PATIENTS BY AN INHIBITOR OF COMPLEMENT
Attorney Docket Number::	AXJ-114BUSCN2

Domestic Priority Information

Application::	Continuity Type::	Parent Application::	Parent Filing Date::	Prior Appl Status::
This Application	Continuation of	13/426,973	03/22/12	Pending
13/426,973	Continuation of	12/225,040	05/13/09	Pending
12/225,040	National Stage of	PCT/US2007/006606	03/15/07	
~~PCT/US2007/006606~~	~~An application claiming the benefit under 35 USC 119(e)~~	~~60/783070~~	~~03/15/06~~	

Signature:

NOTE: This Application Data Sheet must be signed in accordance with 37 CFR 1.33(b). **However, if this Application Data Sheet is submitted with the INITIAL filing of the application and either box A or B is not checked in subsection 2 of the "Authorization or Opt-Out of Authorization to Permit Access" section, then this form must also be signed in accordance with 37 CFR 1.14(c).**

This Application Data Sheet **must** be signed by a patent practitioner if one or more of the applicants is a **juristic entity** (e.g., corporation or association). If the applicant is two or more joint inventors, this form must be signed by a patent practitioner, **all** joint inventors who are the applicant, or one or more joint inventor-applicants who have been given power of attorney (e.g., see USPTO Form PTO/AIA/81) on behalf of **all** joint inventor-applicants.

See 37 CFR 1.4(d) for the manner of making signatures and certifications.

Signature	/Jill Gorny Sloper, Esq./	Date (YYYY-MM-DD)	2017-02-15
Name	Jill Gorny Sloper, Esq.	Registration Number	60,760

DocCode – SEQ.TXT

SCORE Placeholder Sheet for IFW Content

Application Number: 15148839 Document Date: 02/15/2017

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- Sequence Listing

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Form Revision Date: August 26, 2013

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Dated: February 15, 2017
Electronic Signature for Jill Gorny Sloper, Esq.: /Jill Gorny Sloper, Esq./

Docket No.: AXJ-114BUSCN2
(PATENT)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

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

Application No.: 15/148,839 | Confirmation No.: 3159

Filed: May 6, 2016 | Art Unit: 1644

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

REQUEST FOR CORRECTED FILING RECEIPT

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

Dear Sir:

Applicant hereby requests that a corrected Filing Receipt be issued in the above-identified patent application to reflect an update to the Domestic Priority information.

Please correct the Domestic Priority data as claimed by applicant from:

This application is a CON of 13/426,973 03/22/2012
which is a CON of 12/225,040 05/13/2009 ABN
which is a 371 of PCT/US2007/006606 03/15/2007
which claims benefit of 60/783,070 03/15/2006

to:

This application is a CON of 13/426,973 03/22/2012
which is a CON of 12/225,040 05/13/2009 ABN
which is a 371 of PCT/US2007/006606 03/15/2007
~~**which claims benefit of 60/783,070 03/15/2006**~~

Applicant additionally requests that all pertinent U.S. Patent and Trademark Office records relating to the subject application be changed to reflect this correction.

Applicant believes no fee is due with this statement. However, if a fee is due, please charge our Deposit Account No. 12-0080, under Order No. AXJ-114BUSCN2 from which the undersigned is authorized to draw.

Dated: February 15, 2017

Respectfully submitted,

Electronic signature: /Jill Gorny Sloper, Esq./
Jill Gorny Sloper, Esq.
Registration No.: 60,760
NELSON MULLINS RILEY & SCARBOROUGH LLP
One Post Office Square
Boston, Massachusetts 02109-2127
(617) 217-4630
(617) 217-4699 (Fax)
Attorney/Agent For Applicant

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

Dated: February 15, 2017
Electronic Signature for Jill Gorny Sloper, Esq.: /Jill Gorny Sloper, Esq./

Docket No.: AXJ-114BUSCN2
(PATENT)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

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

Application No.: 15/148,839 Confirmation No.: 3159

Filed: May 6, 2016 Art Unit: 1644

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

Examiner: J. L. Rogers

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

STATEMENT PURSUANT TO 37 CFR 1.821

Dear Sir:

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

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

Applicant believes no fee is due with this statement. However, if a fee is due, please charge our Deposit Account No. 12-0080, under Order No. AXJ-114BUSCN2 from which the undersigned is authorized to draw.

Dated: February 15, 2017

Respectfully submitted,

Electronic signature: /Jill Gorny Sloper, Esq./
Jill Gorny Sloper, Esq.
Registration No.: 60,760
NELSON MULLINS RILEY & SCARBOROUGH LLP
One Post Office Square
Boston, Massachusetts 02109-2127
(617) 217-4630
(617) 217-4699 (Fax)
Attorney/Agent For Applicant

REMARKS

Claim 1 was pending. Claim 1 has been amended and new claims 2-3 have been added. Support for the claim amendments can be found throughout the specification as originally filed and as discussed below (see, *e.g.*, page 21 (line 23) through page 26 (line 27) and page 44 (lines 24-29)).

The claim amendments presented herein should in no way be construed as an acquiescence to any of the Examiner's rejections and have been made solely to expedite prosecution of the application. Applicants reserve the right to pursue claims to any canceled subject matter, or any subject matter which they are entitled to claim, in this or a separate application. *No new matter has been added.*

Information Disclosure Statement

Applicants acknowledge with appreciation the Examiner's indication that the Information Disclosure Statements submitted on May 6, 2016 have been considered. Additionally, Applicants submit herewith a Supplemental Information Disclosure Statement to make of record additional information for the Examiner's consideration.

Priority Claim

Applicants submit herewith a corrected ADS to amend the priority claim, *i.e.*, to remove the priority claim to U.S. Provisional Application Serial No. 60/783,070 (filed 15-Mar-2006). In addition, Applicants have amended the specification to include a "Cross Reference to Related Applications" section.

Replacement Sequence Listing and Amendment to the Specification

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

SEQ ID NO: 4 (Light Chain) MDMRVPAQLLGLLLLWLRGARCDIQMTQSPSSLSASVGDRVTITCGASE NIYGALNWYQQKPGKAPKLLIYGATNLADGVPSRFSGSGSGTDFTLTIS

SLQPEDFATYYCQNVLNTPLTFGQGTKVEIKRTVAAPSVFIFPPSDEQL
KSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYS
LSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC

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

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

Terminal Disclaimer

Applicants submit herewith a terminal disclaimer over U.S. Patent Application No. 15/260,888 and U.S. Patent Application No. 15/284,015.

Rejection Under 35 U.S.C. § 103

Claim 1 is rejected under 35 U.S.C. § 103(a) as being unpatentable over Hillmen *et al.* (*N. Engl. J. Med.* 2004; 350; 552-9), in view of Evans *et al.* (US 6,355,245), Wang (2005/0271660), as is evidenced by the parent specification of US Patent Application No.: 13/426,973.

Applicants respectfully traverse the rejection. As amended, the pending claims are drawn to pharmaceutical compositions comprising eculizumab as defined by its particular heavy and light chain sequences, which were not taught or suggested by the prior art.

Specifically, prior to the March 15, 2007 effective filing date of the present application, the complete structure of eculizumab was not disclosed in the prior art; nor was it available to the public. Hillmen *et al.* fails to teach any part of the sequence of eculizumab. Evans *et al.* and/or Wang, either alone or in combination, fail to cure this deficiency. Importantly, Evans *et al.* fails to teach or in any way suggest the unique, non-naturally occurring, protein-engineered full heavy chain of eculizumab (including the CH1-hinge-CH2-CH3 regions). Moreover, Wang fails to teach any part of the sequence of eculizumab, let alone its unique heavy chain.

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

CONCLUSION

If a telephone conversation with Applicants' attorney would help expedite the prosecution of the above-identified application, the Examiner is urged to call Applicants' attorney at (617) 217-4630. The Director is hereby authorized to charge any deficiency in the fees filed, asserted to be filed or which should have been filed herewith (or with any paper hereafter filed in this application by this firm) to our Deposit Account No. 12-0080, under Order No. AXJ-114BUSCN2.

Dated: February 15, 2017

Respectfully submitted,

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

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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

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Abstract

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

Introduction

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

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

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

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

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

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

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

Methods

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

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

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

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

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

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

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

Results

Hybridomas

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

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*Table I. Summary of Hybridoma Cell Lines**

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

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

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

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

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

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

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

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

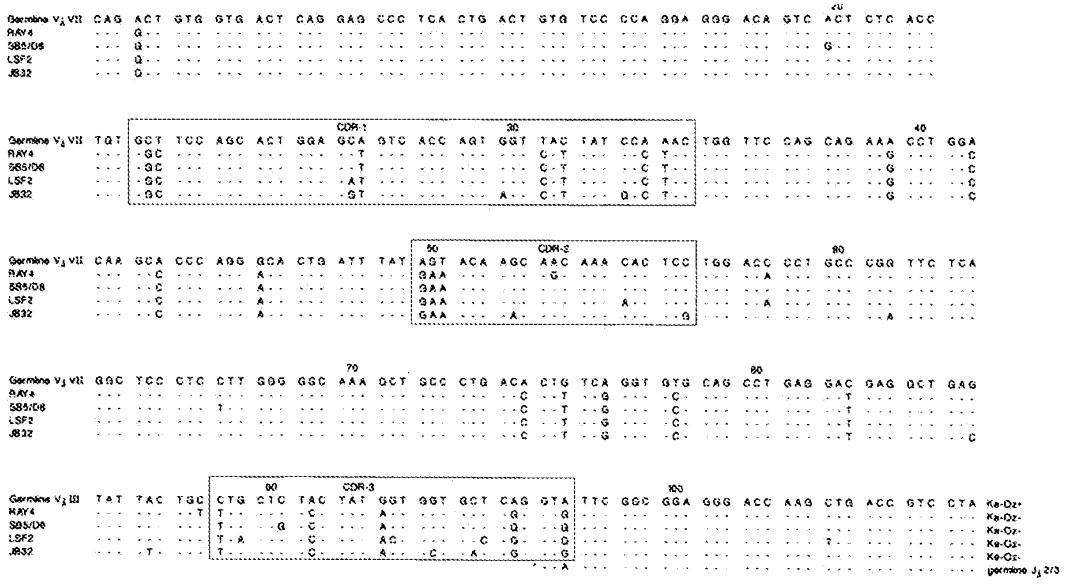


Figure 1. Nucleotide sequences of the V_λ and J_λ genes from four hybridoma cell lines (RAY4, SB5/D6, LSF2, JB32), and from the V_λVII germline gene, 4A (33). Numbering is according to Kabat (23). These sequence data are available from EMBL/GenBank Data Libraries under accession numbers M80917 (RAY4),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

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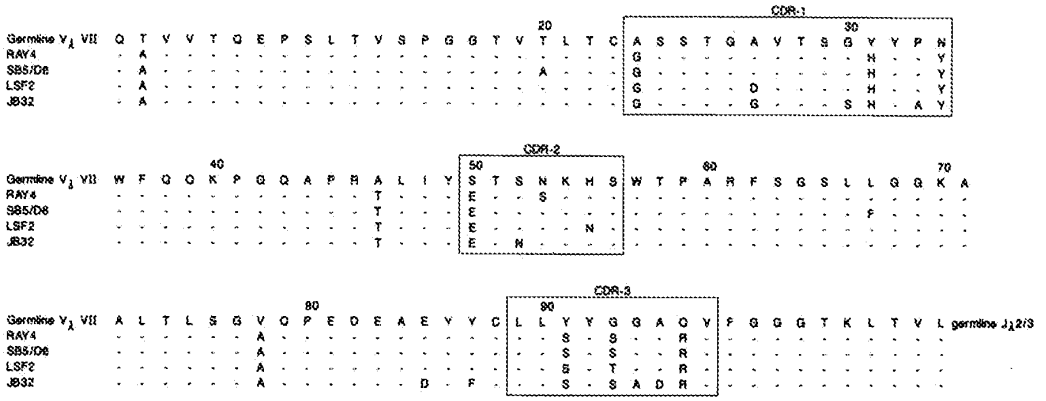


Figure 2. Translated amino acid sequences of V_λ and J_λ from four hybridoma cell lines (RAY4, SB5/D6, LSF2, JB32), and from the V_λVII germline gene, 4A (33). (See Fig. 1.)

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

All four of the V_λVII-encoded antibodies are also encoded by V_HIII segments closely homologous to the germline gene 9.1 (5). Similar V_H segments also encode Ab utilizing other V_λ and V_κ gene segments (Table II) (manuscript in preparation). It is uncertain whether pairing of 9.1-like V_H and V_λVII-encoded heavy and light chains contributes to binding specificity or avidity. JB21 and RC3, also encoded by 9.1-like V_H gene segments, but paired with V_λII- and V_κII-encoded light chains, respectively, do not cross-react with K.100 PS.

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

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

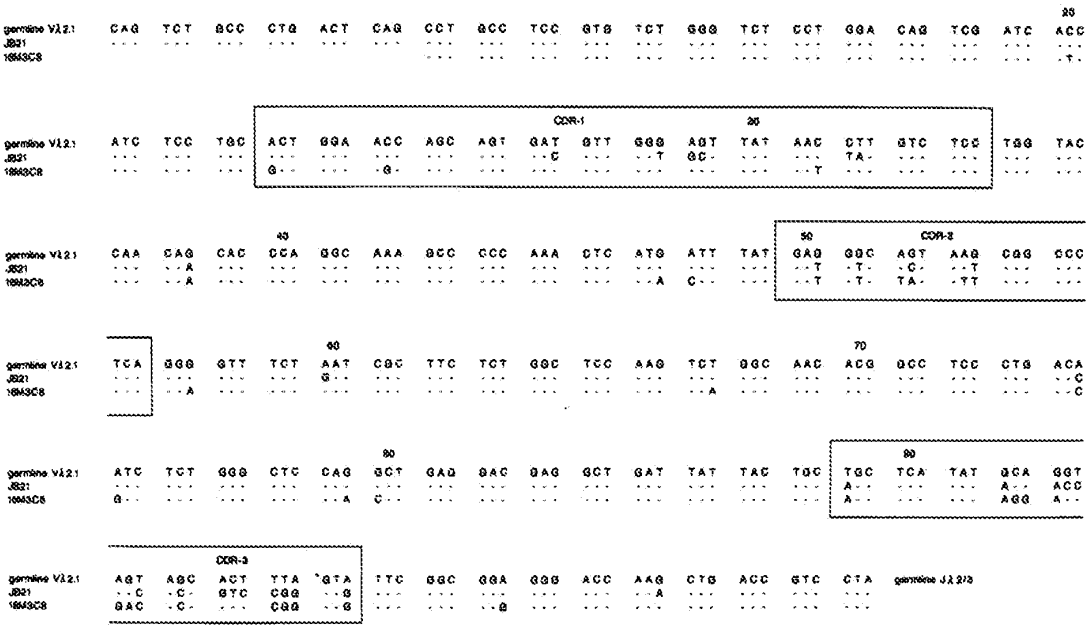


Figure 3. Nucleotide sequences of V_λ and J_λ genes from two hybridoma cell lines (JB21 and 16M3C8). Also shown is a germline gene V2.1 (34), and germline J_λ2/3 gene (23). An asterisk denotes the beginning of the J_λ segment. Numbering is according to Kabat (23). These sequence data are available from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

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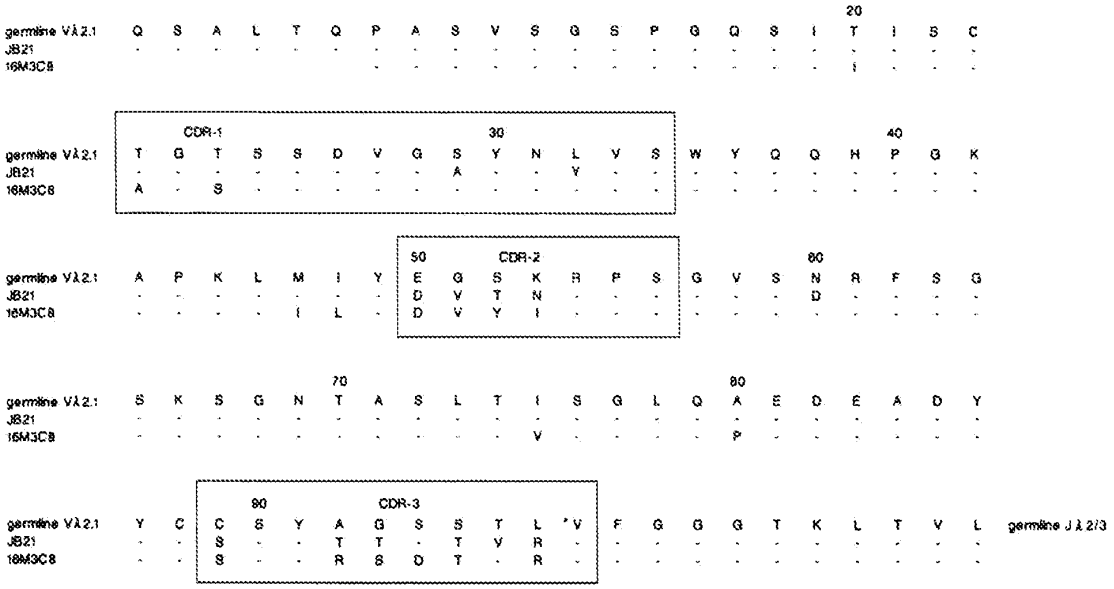


Figure 4. Translated amino acid sequences of V_λ and J_λ genes from two hybridoma cell lines (JB21 and 16M3C8). Shown for comparison is the translated sequence of the V_λ germline gene V_λ2.1, and J_λ2/3 germline gene. An asterisk denotes the beginning of the J_λ segment. (See Fig. 3.)

(36), and uses a J_κ4 segment differing from the germline sequence by a single base (Fig. 6). The ED6.1 sequence is identical to the partial amino acid sequence reported previously for 2 kappa antibodies purified from serum (12).

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

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

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

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

Southern blots/analysis of germline V_λVII genes

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

Discussion

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

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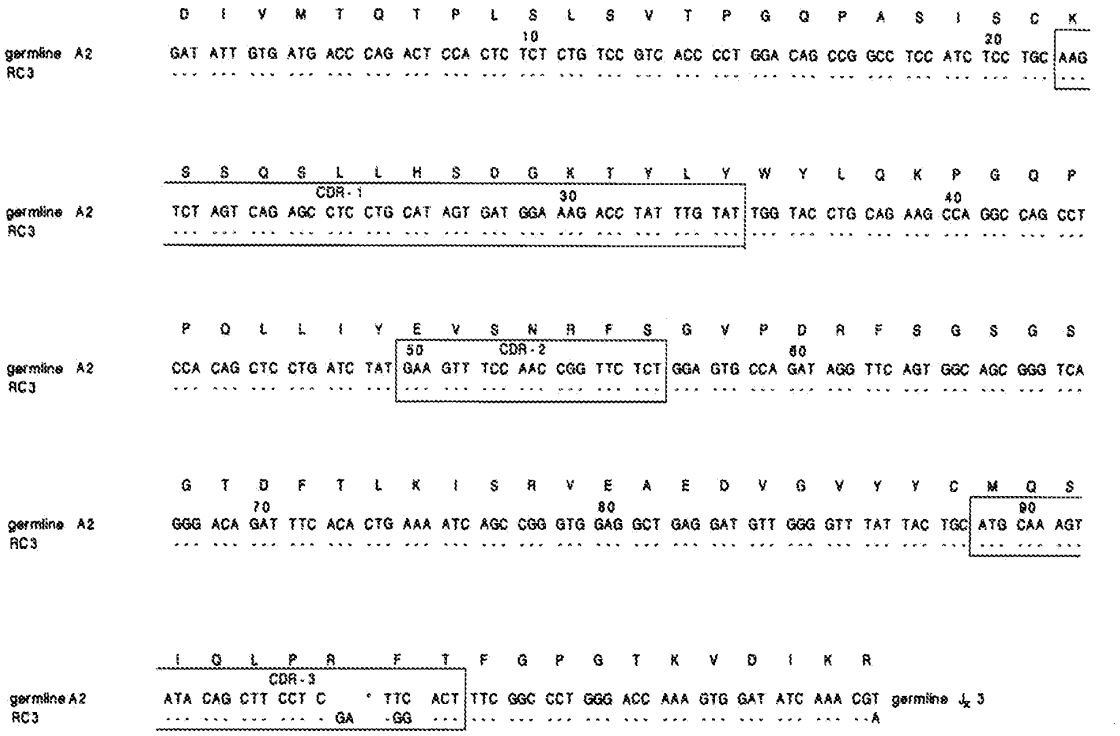


Figure 5. Nucleotide sequences of V_κ and J_κ genes from the hybridoma cell line RC3. Also shown is the translated amino acid sequence of the RC3 V_κ gene. Shown for comparison is the nucleotide sequence of a germline V_κ gene, A2 (13), and germline $J_\kappa 3$ gene. An asterisk denotes the beginning of the J_κ segment. Numbering is according to Kabat (23). This sequence data is available from EMBL/GenBank Data Libraries under accession number M80914 (RC3).

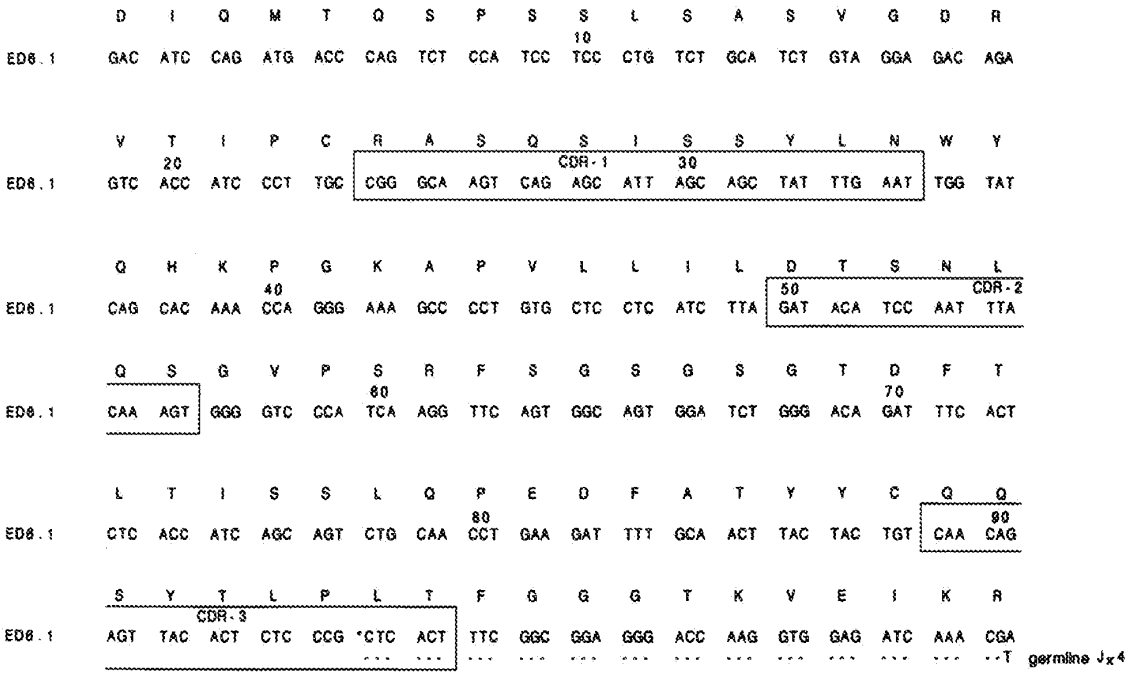


Figure 6. Nucleotide sequence of V_κ and J_κ genes from hybridoma cell line ED6.1. Also shown is the translated amino acid sequence of the ED6.1 V_κ gene. An asterisk denotes the beginning of the J_κ segment. Numbering is according to Kabat (23). This sequence data is available from EMBL/GenBank Data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

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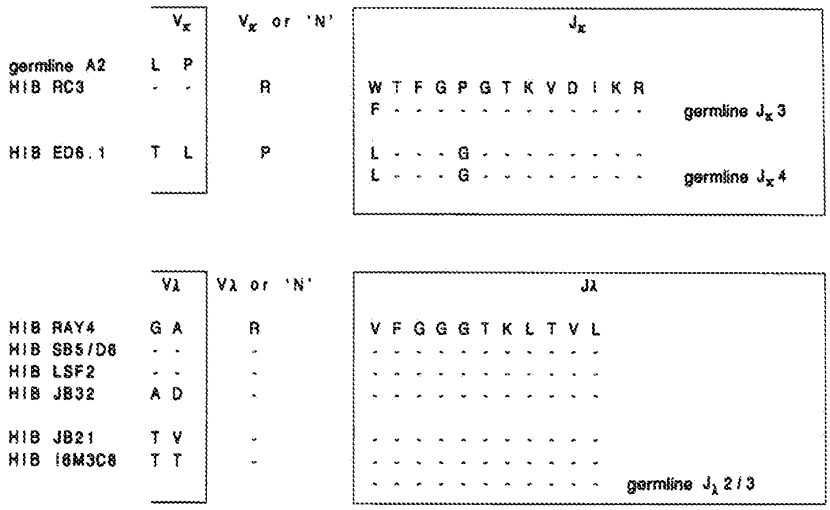


Figure 7. Translated amino acid sequences of VJ joints from seven hybridoma cell lines (RC3, ED6.1, RAY4, SB5/D6, LSF2, JB21, and 16M3C8). Also shown are translated amino acid sequences of the germline V_κ gene A2, and germline $J_\kappa 3$, $J_\kappa 4$, and $J_\lambda 2/3$ genes. (See Figs. 2, 4, and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

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

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

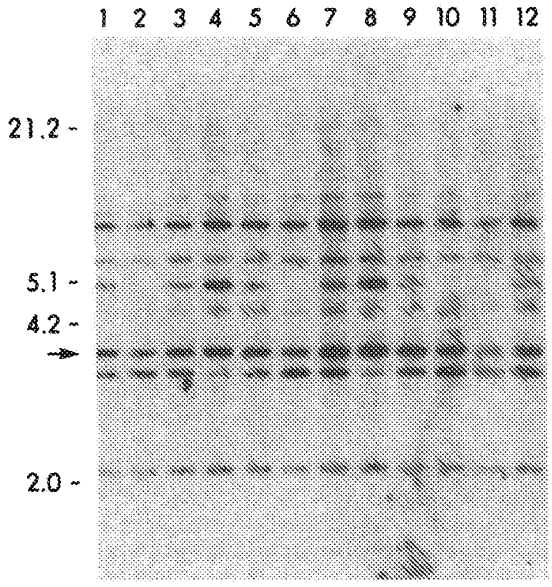


Figure 8. Southern blot analysis for V_λVII family members in BamHI-digested human genomic DNA. Lane *12* contains genomic DNA from the subject from whom hybridoma LSF2 was obtained. Lane *9* contains genomic DNA from a parent of LS. The remaining 10 donors are unrelated. An arrow indicates the 3.7-kb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

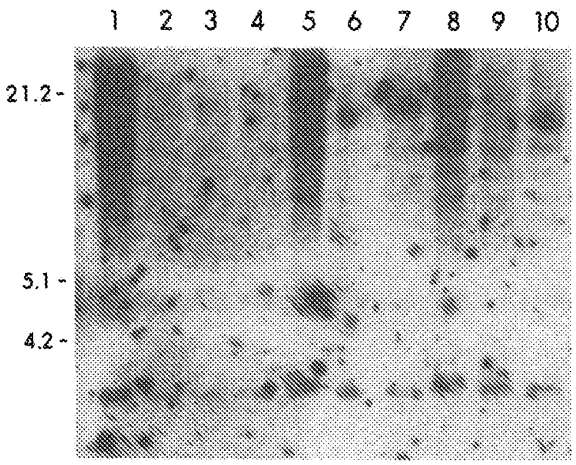


Figure 9. Dried gel hybridization of BamHI-digested human genomic DNA with an oligonucleotide probe corresponding to conserved V_λVII hybridoma CDR-1 sequences. Genomic DNA in lanes *1, 4, 5, 6, 7, 9* and *10* of Fig. 8 corresponds to that in lanes *2, 7, 4, 8, 10, 5* and *9* of Fig. 9, respectively.

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

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

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

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

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

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

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

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

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

Acknowledgments

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AMENDMENTS TO THE CLAIMS

This listing of claims will replace all prior versions, and listings, of claims in the application:

Listing of Claims:

1. **(Currently Amended)** A pharmaceutical composition for use in treating a patient afflicted with paroxysmal nocturnal hemoglobinuria (PNH), wherein the composition is a sterile, preservative free, 300 mg ~~eculizumab~~ single-use dosage form comprising 30 ml of a 10 mg/ml antibody ~~eculizumab/ml sterile, preservative free~~ solution, wherein the antibody comprises a heavy chain consisting of SEQ ID NO: 2 and a light chain consisting of SEQ ID NO: 4.

2. **(New)** A pharmaceutical composition comprising an anti-C5 antibody, wherein the anti-C5 antibody comprises a heavy chain consisting of SEQ ID NO: 2 and a light chain consisting of SEQ ID NO: 4.

3. **(New)** The pharmaceutical composition of claim 2, wherein the pharmaceutical composition is a sterile, preservative free 300 mg single-use dosage form comprising 30 ml of a 10 mg/ml anti-C5 antibody solution.

AMENDMENTS TO THE SPECIFICATION

In the Sequence Listing:

Please replace the Sequence Listing filed on May 6, 2016 with the replacement Sequence Listing submitted herewith.

In the Specification:

Please insert the following paragraphs after the title:

CROSS REFERENCE TO RELATED APPLICATIONS

This application is a continuation of U.S. Patent Application No. 13/426,973, filed March 22, 2012, which is a continuation of U.S. Patent Application No. 12/225,040, filed on May 13, 2009, which is a 35 U.S.C. 371 national stage filing of International Application No. PCT/US2007/006606, filed March 15, 2007. The contents of the aforementioned applications are hereby incorporated by reference in their entireties.

SEQUENCE LISTING

The instant application contains a Sequence Listing which has been submitted electronically in ASCII format and is hereby incorporated by reference in its entirety. Said ASCII copy, created on February 13, 2017, is named AXJ_114BUSCN2_Seq_Listing.txt and is 10,244 bytes in size.

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

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

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

Dated: February 15, 2017
Electronic Signature for Jill Gorny Sloper, Esq.: /Jill Gorny Sloper, Esq./

Docket No.: AXJ-114BUSCN2
(PATENT)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

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

Application No.: 15/148,839

Confirmation No.: 3159

Filed: May 6, 2016

Art Unit: 1644

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

Examiner: J. L. Rogers

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

SUPPLEMENTAL INFORMATION DISCLOSURE STATEMENT (SIDS)

Dear Sir:

In compliance with 37 C.F.R. § 1.56, 1.97 and 1.98, the attention of the Patent and Trademark Office is hereby directed to the documents listed on the attached PTO/SB/08. In accordance with 37 C.F.R. § 1.98(a)(2)(i)-(iv), Applicant submits herewith copies of foreign patents and non-patent literature references, but has not included copies of U.S. patents and U.S. patent applications.

It is respectfully requested that the documents listed on the PTO/SB/08 be expressly considered by the Examiner during the prosecution of this application, and that the documents be made of record therein and appear among the "References Cited" on any patent to issue therefrom.

Applicant calls to the attention of the Examiner the following Applications and provides copies of Office Action cited therein. Applicant also provides a copy of an Office Action from an Application previously made of record:

Applications				
Examiner's Initials	*Serial No.*	*Filing Date*	*First Named Inventor*	*Docket No.*
	15/260,888	09-09-2016	Leonard BELL	AXJ-114BUSCN3
	15/284,015	10-03-2016	Leonard BELL	AXJ-114BUSCN4

Office Actions (copies enclosed)			
Examiner's Initials	Serial No.	Date Mailed from USPTO	Examiner
	15/260,888	12-22-2016	J. Rogers
	15/260,888	10-27-2016	J. Rogers
	15/284,015	11-01-2016	J. Rogers
	13/335,518	08-22-2016	P. Gambel

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

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

Samsung Bioepis Exhibit No. 1002
Page 434

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

This Information Disclosure Statement is filed after the mailing date of a first Office Action on the merits, but before the mailing date of any of a Final Action under 37 C.F.R. § 1.113, a Notice of Allowance under 37 C.F.R. § 1.311 or an action that otherwise closes prosecution in this application (37 C.F.R. § 1.97(c)).

Please charge our Deposit Account No. 12-0080 in the amount of $180.00 covering the fee set forth in 37 C.F.R. § 1.17(p). The Director is hereby authorized to charge any deficiency in the fees filed, asserted to be filed or which should have been filed herewith to our Deposit Account No. 12-0080, under Order No. AXJ-114BUSCN2.

Dated: February 15, 2017

Respectfully submitted,

Electronic signature: /Jill Gorny Sloper, Esq./
Jill Gorny Sloper, Esq.
Registration No.: 60,760
NELSON MULLINS RILEY & SCARBOROUGH LLP
One Post Office Square
Boston, Massachusetts 02109-2127
(617) 217-4630
(617) 217-4699 (Fax)
Attorney/Agent For Applicant

PTO/SB/08a (03-15)
Approved for use through 07/31/2016. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it contains a valid OMB control number.

INFORMATION DISCLOSURE STATEMENT BY APPLICANT
(Not for submission under 37 CFR 1.99)

Application Number	15148839
Filing Date	2016-05-06
First Named Inventor	Leonard BELL
Art Unit	1644
Examiner Name	J. L. Rogers
Attorney Docket Number	AXJ-114BUSCN2

U.S.PATENTS Remove

Examiner Initial*	Cite No	Patent Number	Kind Code[1]	Issue Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear
	1					

If you wish to add additional U.S. Patent citation information please click the Add button. Add

U.S.PATENT APPLICATION PUBLICATIONS Remove

Examiner Initial*	Cite No	Publication Number	Kind Code[1]	Publication Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear
	1	20030049260	A1	2003-03-13	Bell	
	2	20040219147	A1	2004-11-04	Bell	
	3	20040038308	A1	2004-02-26	Rother et al.	
	4	20040253242	A1	2004-12-16	Bowdish et al.	
	5	20050036991	A1	2005-02-17	Fodor	

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
	Application Number	15148839
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	First Named Inventor	Leonard BELL
	Art Unit	1644
	Examiner Name	J. L. Rogers
	Attorney Docket Number	AXJ-114BUSCN2

	6	20050226870	A1	2005-10-13	Wang et al.	
	7	20060057679	A1	2006-03-16	O'Keefe et al.	
	8	20060263349	A1	2006-11-23	McCutcheon et al.	
	9	20160376355	A1	2016-12-29	BELL et al.	
	10	20170015741	A1	2017-01-19	BELL et al.	

If you wish to add additional U.S. Published Application citation information please click the Add button. Add

FOREIGN PATENT DOCUMENTS Remove

Examiner Initial*	Cite No	Foreign Document Number[3]	Country Code[2] i	Kind Code[4]	Publication Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear	T[5]
	1	2007005612	WO	A2	2007-01-11	Medimmune, Inc		
	2	2005110481	WO	A2	2005-11-24	Alexion Pharmaceuticals, Inc		
	3	2007002571	WO	A2	2007-01-04	Alexion Pharmaceuticals, Inc		

If you wish to add additional Foreign Patent Document citation information please click the Add button Add

NON-PATENT LITERATURE DOCUMENTS Remove

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
	Application Number	15148839
	Filing Date	2016-05-06
	First Named Inventor	Leonard BELL
	Art Unit	1644
	Examiner Name	J. L. Rogers
	Attorney Docket Number	AXJ-114BUSCN2

Examiner Initials*	Cite No	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc), date, pages(s), volume-issue number(s), publisher, city and/or country where published.	T[5]
	1	Adis International Limited, "Eculizumab: 5G1.1, h5G1.1, Long-Acting Anti-C5 Monoclonal Antibody 5G1-1, Long-Acting Anti-C5 Monoclonal Antibody 5G1.1," Drugs in Research and Development, vol. 8 (1): 61-68 (2007).	
	2	Rother et al., "Discovery and development of the complement inhibitor eculizumab for the treatment of paroxysmal nocturnal hemoglobinuria," Nature Biotechnology, 25 (11) 1256-1264 (2007)	
	3	Alexion Pharma K.K. "Report on the Deliberation Results" for "Soliris for intravenous infusion 300 mg", Marh 5, 2010, pp. 1-105	
	4	Alexion Pharmaceuticals Inc., "Alexion completes enrollment in Ph II kidney disease trial," Market letter (Feb 25, 2002), 2 pages.	
	5	Alexion Pharmaceuticals Inc., "Alexion Completes Enrollment in Phase II Membranous Nephritis Clinical Trial with 5G1.1; 5G1.1 Receives Orphan Drug Designation in Membranous Nephritis," PR Newswire, February, 20, 2012, 3 pages.	
	6	Alexion Pharmaceuticals Inc., "Alexion issued C5 complement inhibitor patent for inflammatory diseases," ESPICOM Pharmaceutical and Medical Device News (Mar 19, 2002), 1 page.	
	7	Alexion Pharmaceuticals Inc., "Alexion Issued Key C5 Complement Inhibitor Patent for Inflammatory Diseases," PR Newswire(March 15, 2002) 3 pages.	
	8	Alexion Pharmaceuticals Inc., "Alexion Pharmaceuticals Reports Second Quarter and First Half Results," PR Newswire [New York] (March 8, 2001) 8 pages.	
	9	Alexion Pharmaceuticals Inc., "Alexion Pharmaceuticals Reports Second Quarter and First Half Results; - Quarter Highlighted by Successful Revision of Pexelizumab Collaboration With Procter &Gamble Pharmaceuticals and Commencement Of Phase III Pivotal PRIMO-CABG Trial," PR Newswire, March 8, 2002, 6 pages.	
	10	Alexion Pharmaceuticals Inc., "Company reports second quarter, first- half results," Biotech Week (Apr 10, 2002), 2 pages.	

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	Art Unit	1644
	Examiner Name	J. L. Rogers
	Attorney Docket Number	AXJ-114BUSCN2

	11	Alexion Pharmaceuticals Inc., "Eculizumab Alexion clinical data (phase III) (PNH)," R & D Focus Drug News (Feb 6, 2006), 2 pages.	
	12	Alexion Pharmaceuticals Inc., "Eculizumab Alexion clinical data (PNH)," R & D Focus Drug News (Jan 30, 2006), 2 pages.	
	13	Alexion Pharmaceuticals Inc., "Eculizumab Alexion completes enrollment for phase III PNH trial," R & D Focus Drug News, (Apr 25, 2005): 2 pages.	
	14	Alexion Pharmaceuticals Inc., "Eculizumab Alexion completes enrollment," R & D Focus Drug News (Feb 17, 2003), 2 pages.	
	15	Alexion Pharmaceuticals Inc., "Eculizumab Alexion EMEA grants request for accelerated assessment procedure," R & D Focus Drug News (Aug 28, 2006), 2 pages.	
	16	Alexion Pharmaceuticals Inc., "Eculizumab Alexion initiates second phase III study," R & D Focus Drug News, (Jan 17, 2005), 2 pages.	
	17	Alexion Pharmaceuticals Inc., "Eculizumab Alexion plans phase III trials (paroxysmal nocturnal hemoglobinuria)," R & D Focus Drug News (Aug 2, 2004), 2 pages.	
	18	Alexion Pharmaceuticals Inc., "Eculizumab Alexion Priority Review, USA (PNH)," R & D Focus Drug News (Nov 20, 2006), 2 pages.	
	19	Alexion Pharmaceuticals Inc., "Kidney Disease; Enrollment complete for phase II membranous nephritis clinical trial with 5G1.1," Drug Week, page 14 (Apr 12, 2002)	
	20	Alexion Pharmaceuticals Inc., "Kidney Disease; Enrollment complete for phase II membranous nephritis clinical trial with 5G1.1," Immunotherapy Weekly, page 18, (Apr 10, 2002)	
	21	Alexion Pharmaceuticals Inc.,"Eculizumab Alexion phase change III, USA, Europe Canada, Australia (PNH)," R & D Focus Drug News (Nov 15, 2004): 2 pages.	

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	Filing Date	2016-05-06
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	Art Unit	1644
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	Attorney Docket Number	AXJ-114BUSCN2

	22	BC Cancer Agency Cancer Drug Manual, Drug Name Alemtuzumab, June 1, 2013, Pages 11.	
	23	Brekke, O. et al., "Therapeutic Antibodies For Human Diseases at the Dawn of The Twenty-First Century," Nature Reviews, Drug Discovery, vol. 2: 52-62 (2003)	
	24	ESPICOM Pharmaceutical and Medical Device News, "Eculizumab found to be well tolerated and efficacious during 52 weeks of treatment in PNH," (Jan 2, 2007), 2 pages.	
	25	European Decision Revoking The European Patent (Art. 101(2). (3)(b) EPC). 11 pages. dated July 1. 2014.	
	26	European Medicines Agency, EMA/HMPC/16633/2009 section 2, Historical Data on Medicinal Use, 2010, pages 1-40.	
	27	Fung, M. et al., "Inhibition of complement, neutrophil, and platelet activation by an anti-factor D monoclonal antibody in simulated cardiopulmonary bypass circuits," The Journal of Thoracic and Cardiovascular Surgery, vol. 122(1):113-121 (2001)	
	28	Grounds of Appeal filed on November 11,2014 in the related European Opposition, European Patent No. 1720571, pages 1-15.	
	29	Hale, et al., "Blood concentrations of alemtuzumab and antiglobulin responses in patients with chronic lymphocytic leukemia following intravenous or subcutaneous routes of administration," (2004) Blood 224(4), pages 948-955	
	30	Martin, F. et al., "Pathogenic Roles of B Cells in Human Autoimmunity: Insights from the Clinic,"Immunity, vol. 20: 517-527 (2004)	
	31	Mollnes, T. et al., "Strategies of therapeutic complement inhibition," Molecular Immunology, vol. 43: 107-121 (2006)	
	32	Mueller, J., "Humanized Porcine VCAM-Specific Monoclonal Antibodies with Chimeric IgG2/G4 Constant Regions Block Human Leukocyte Binding to Porcine Endothelial Cells," Molecular Immunology, vol. 34(6): 441-452 (1997)	

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	Art Unit	1644
	Examiner Name	J. L. Rogers
	Attorney Docket Number	AXJ-114BUSCN2

	33	Osborne, R., "Alexion Offers Early, Mixedphase III Data for Heart Drug," Bioworld Today, vol. 14, Issue 151 (Aug 6, 2003), 3 pages.	
	34	Osbourn, J. et al., "Current methods for the generation of human antibodies for the treatment of autoimmune diseases," Drug Discovery Today, vol. 8 (18): 845-851 (2003)	
	35	Other News To Note, BIOWORLD Today (Aug 9, 2002): 5 pages.	
	36	Pierangeli,S. et al., "Requirement of activation of complement C3 and C5 for antiphospholipid antibody-mediated thrombophilia," Arthritis & Rheumatology, vol. 52, Issue 7: 2120-2124(2005)	
	37	Ricklin, D. et al., "Complement-targeted therapeutics," Nature Biotechnology, vol. 25(11): 1265-1275 (2007)	

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

EXAMINER SIGNATURE

Examiner Signature		Date Considered	

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

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

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
	Application Number	15148839
	Filing Date	2016-05-06
	First Named Inventor	Leonard BELL
	Art Unit	1644
	Examiner Name	J. L. Rogers
	Attorney Docket Number	AXJ-114BUSCN2

CERTIFICATION STATEMENT

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

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

OR

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

See attached certification statement.

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

☒ A certification statement is not submitted herewith.

SIGNATURE

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

Signature	/Jill Gorny Sloper, Esq./	Date (YYYY-MM-DD)	2017-02-15
Name/Print	Jill Gorny Sloper, Esq.	Registration Number	60,760

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

Privacy Act Statement

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

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

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

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

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

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

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

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

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

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

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

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
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www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
13/335,518	12/22/2011	Leonard Bell	AXJ-114CPCN2RCE	4891

133485 7590 08/22/2016

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

EXAMINER	
GAMBEL, PHILLIP	

ART UNIT	PAPER NUMBER
1644	

NOTIFICATION DATE	DELIVERY MODE
08/22/2016	ELECTRONIC

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

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

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

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

Office Action Summary	Application No. 13/335,518	Applicant(s) BELL ET AL.	
	Examiner PHILLIP GAMBEL	Art Unit 1644	AIA (First Inventor to File) Status No

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

Period for Reply

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

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

Status

1)☒ Responsive to communication(s) filed on *03/12/2015*.

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

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

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

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

Disposition of Claims*

5)☒ Claim(s) *131,133-136,138-141 and 143-146* is/are pending in the application.

5a) Of the above claim(s) *134,135,139,140,144 and 145* is/are withdrawn from consideration.

6)☐ Claim(s) _____ is/are allowed.

7)☒ Claim(s) *131,133,136,138,141, 143, 146* is/are rejected.

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

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

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

Application Papers

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

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

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

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

Priority under 35 U.S.C. § 119

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

Certified copies:

a)☐ All b)☐ Some** c)☐ None of the:

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

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

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

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

Attachment(s)

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

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

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

4) ☐ Other: _____.

DETAILED ACTION

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

2. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office Action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 03/12/2015 has been entered.

Applicant's amendment, filed 03/12/2015, has been entered.

Claims 131, 136 and 141 have been amended.

Claims 152-153 have been added.

Claims 1-130, 132, 137, 142 and 147-153 have been canceled.
Claims 1-130, 132, 137, 142 and 148 have been canceled previously.

Claims 131, 133-136, 138-141 and 143-146 are pending.

As indicated previously, applicant's election of the species (A) (methods of administering anti-C5 antibody, where the claimed do not comprise further administering one or more compounds that increase hematopoiesis in the Response to Restriction Requirement, filed 12/09/2013, has been acknowledged.

Applicant's remarks concerning entitlement of claims to additional species upon allowance of a generic linking claim have been acknowledged.

Claims 131, 133, 136, 138, 141, 143 and 146 are under consideration in the instant application as they read on the elected species.

Claims 134, 135, 139, 140, 144 and 145 have been withdrawn as being drawn to the non-elected species.

3. The text of those sections of Title 35 USC not included in this Office Action can be found in a prior Office Action.

This Office Action will be in response to applicant's arguments and amendments, filed 03/12/2015.

The rejections of record can be found in the previous Office Action, mailed 09/12/2014.

4. Priority.

Applicant's arguments in conjunction with the amended claims, filed 03/12/2015, with respect to priority are acknowledged.

Given the amended claims, filed 03/12/2015, the following is noted.

Newly amended claims 131, 136 and 141 are set forth herein.

131. A method for treating paroxysmal nocturnal hemoglobinuria (PNH) in a patient, the method comprising:
(1) identifying a PNH patient who experiences serum hemolytic activity on a dosing schedule of eculizumab comprising: (i) 600 mg of eculizumab each week for four weeks; (ii) 900 mg of eculizumab on the fifth week; and thereafter, (iii) 900 mg of eculizumab once every two weeks; and
(2) administering 900 mg of eculizumab to the patient once every 12 days to maintain a serum concentration of eculizumab of approximately 35 µg/ml to 50 µg/ml, thereby treating PNH in the patient.

136. A method for treating paroxysmal nocturnal hemoglobinuria (PNH) in a patient, the method comprising:
(1) identifying a PNH patient who experiences serum hemolytic activity on a dosing schedule of eculizumab comprising: (i) 600 mg of eculizumab each week for four weeks; (ii) 900 mg of eculizumab on the fifth week; and thereafter, (iii) 900 mg of eculizumab once every two weeks; and
(2) administering 900 mg of eculizumab to the patient once every 12 days to maintain in the patient a serum complement activity at a level below 20% of the normal serum complement activity, thereby treating PNH in the patient.

141. A method for treating paroxysmal nocturnal hemoglobinuria (PNH) in a patient, the method comprising administering eculizumab to the patient according to the following dosing schedule:
(i) 600 mg of eculizumab each week for four weeks;
(ii) 900 mg of eculizumab on the fifth week; and thereafter,
(iii) 900 mg of eculizumab ~~at least~~ once every 12 days,
wherein the dosing schedule is effective to maintain in the patient a serum complement activity at a level below 20% of the normal serum complement activity, thereby treating PNH in the patient.

Note that not all current claims receive benefit of the previous priority applications.

The recitation of "identifying step" in claims 131 and 136,
"administering once every 12 days to maintain a serum concentration ... / administering once every 12 day to maintain in the patient a serum complement activity …", and
"to maintain a serum concentration of eculizumab of approximately 35 µg/ml to 50 µg/ml"
broadly recited in the newly amended / added claims do not appear to have sufficient written support in the specification as filed.

In addition, the recitation of "wherein the dosing schedule is effective to maintain in the patient a serum complement activity at a level below 20% of the normal serum complement activity, thereby treating PNH in the patient" in claims 141 / 146 is not readily apparent in pages 36-37, overlapping paragraph of the specification (Examples).
The instant application does not particularly identify this particular combination of limitations.

Applicant's remarks, filed 03/12/2015, indicate that the support for the new and amended claims can be found throughout the specification and claims as originally filed.

The written support of the term "identifying" itself is not found in the specification as filed as well as the priority documents.

The written support of the claimed "identifying steps" is not found in the specification as filed as well as the priority documents.

Given the amended claims, it appears that applicant continues to rely upon the Examples to support the current amended claims.

While the term / step of identifying reads on establish or indicating who / someone or what / something is or associated with,

the Example discloses patients who participated in therapy trials to evaluate the effect of anti-C5 antibody on PNH in the absence of clearly disclosing "identifying step(s)" and in the absence of applicant's remarks clearly directing the written support of "identifying" / "identifying steps" in the specification.

Page 36, paragraph 3 of the specification (Examples) discloses the range of "35 µg/ml to *350* µg/ml", not "approximately 35 µg/ml to *50* µg/ml"

in the context of serum hemolytic activity in nine of the elven patients as being completely blocked throughout the 64 week treatment period of trough levels of eculizumab at equilibrium ranging …" rather "to maintain a serum concentration of eculizumab …" as currently claimed.

Pages 36-37, overlapping paragraph of the specification (Examples) disclosing that a reduction of eculizumab above 35 µg//ml and effectively and consistently blocked serum hemolytic activity for the remainder of the extension study for both patients who did not sustain levels of eculizumab necessary to consistently block complement rather than "administering to the patient once every 12 days to maintain a serum complement activity at a level below 20% of the normal serum complement activity …" as currently claimed.

Applicant's reliance on generic disclosure and possibly certain observations in the instant Examples of eleven PNH patients who were transfusion-dependent and hemolytic in therapy trials and who were given a particular therapeutic regimen of eculizumab, including excerpt derived from pages 36-37 of the specification does not provide sufficient written description nor direction and guidance to the "currently claimed limitations".

Note that the explicit recitation of the "limitations" cited above are not readily apparent in the specification as filed.

Note that applicant has amended the claims by relying upon certain observations of the eleven patients either in the treatment period or in an extension study under certain distinct dosing variable and time periods to broadly claim new limitations that departs from the instant disclosure as filed.

The instant disclosure of does not define nor set forth parameters" or provide for the metes and bounds of the "identifying steps".

Obviousness is not the standard for the addition new limitations to the disclosure as filed.
It is noted that entitlement to a filing date does not extend to subject matter which is not disclosed, but would be obvious over what is expressly disclosed. Lockwood v. American Airlines Inc., 41 USPQ2d 1961 (Fed. Cir. 1977).

It is noted that a generic or a sub-generic disclosure cannot support a species unless the species is specifically described. It cannot be said that a subgenus is necessarily described by a genus encompassing it and a species upon which it reads. See In re Smith 173 USPQ 679, 683 (CCPA 1972) and MPEP 2163.05.

The instant claims now recite limitations which were not clearly disclosed in the specification as-filed, and now change the scope of the instant disclosure as-filed. Applicant is claiming a subgenus not supported by the specification as-filed. Such limitations recited in the present claims, which did not appear in the specification, as filed, introduce new concepts and violate the description requirement of the first paragraph of 35 U.S.C. 112.

It is also true that the written description requirement must still be met in some way so as to "describe the claimed invention so that one skilled in the art can recognize what is claimed".

A patent specification should set forth enough detail to allow a person or ordinary skill in the art to understand what is claimed and to recognize that the inventor invented what is claimed.

If applicant desires priority for the above-mentioned limitation / current claims prior to filing date of the instant application (12/22/2011);
applicant is invited to point out and provide documentary support for the priority of the instant claims.

Applicant is reminded that such priority for the instant limitations requires written description and enablement under 35 U.S.C. 112(a) or 35 U.S.C. 112 (pre-AIA), first paragraph.

5. Claims 131, 133, 136 and 146 are rejected under 35 U.S.C. 112(b) or 35 U.S.C. 112 (pre-AIA), second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which the inventor or a joint inventor, or for pre-AIA the applicant regards as the invention.

Claims 131, 133, 136 and 138 are indefinite in the recitation of "the identifying steps…" because these "limitations" are not clearly defined by the claim and the specification does not provide a sufficient standard for ascertaining the requisite degree or endpoints to reasonably apprise one of ordinary skill in the art of the metes and bounds of the invention.

For example, the specification does not set forth nor disclose the term "identifying" / "identifying steps" and does not define the metes and bounds nor the nature of the particular "identifying steps" encompassed by this claimed recitation.

While applicant's remarks, filed 03/12/2015 in response to the previous rejection under 35 U.S.C. 112(b) or 35 U.S.C. 112 (pre-AIA), second paragraph relies upon the current amended claims to address the issue of positive steps by specifying the steps of (1) identifying and (2) administering,
applicant does not provide sufficient written description of the identifying steps in the specification (and priority documents) as filed.

It is noted that this "identifying steps" do not recite any additional active method steps, but simply state a characterization or conclusion of steps (not claimed) or may be performed entirely in the human mind is obviously not tied to any machine and do not transform any article into a different state or thing.
For example, the identifying steps read on mental steps which do not require positive steps.

The instant specification does not provide a sufficient definition nor description of the appropriate steps and readouts to apprise the ordinary artisan of the metes and bounds of the claimed "identifying limitations" indicated herein.

It is not clear as what positive steps, measures / parameters, etc., occur other than mental steps, including oral / written communications such as being informed by another or reading a report.

In the absence of a disclosure / description and/or a clear definition in the specification as filed,
the claimed recitation of the "identifying steps" is indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Applicant is reminded that the amendment must point to a basis in the specification so as not to add any new matter. See MPEP 714.02 and 2163.06.

6. This is a written description rejection, new matter, under 35 U.S.C. 112(a) or 35 U.S.C. 112 (pre-AIA), first paragraph.

Claims 131, 133, 136, 138, 141, 143 and 146 are rejected under 35 U.S.C. 112(a) or 35 U.S.C. 112 (pre-AIA), first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor or a joint inventor, or for pre-AIA the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 131, 136 and 141 are set forth herein.

131. A method for treating paroxysmal nocturnal hemoglobinuria (PNH) in a patient, the method comprising:
(1) identifying a PNH patient who experiences serum hemolytic activity on a dosing schedule of eculizumab comprising: (i) 600 mg of eculizumab each week for four weeks; (ii) 900 mg of eculizumab on the fifth week; and thereafter, (iii) 900 mg of eculizumab once every two weeks; and
(2) administering 900 mg of eculizumab to the patient once every 12 days to maintain a serum concentration of eculizumab of approximately 35 µg/ml to 50 µg/ml, thereby treating PNH in the patient.

136. A method for treating paroxysmal nocturnal hemoglobinuria (PNH) in a patient, the method comprising:
(1) identifying a PNH patient who experiences serum hemolytic activity on a dosing schedule of eculizumab comprising: (i) 600 mg of eculizumab each week for four weeks; (ii) 900 mg of eculizumab on the fifth week; and thereafter, (iii) 900 mg of eculizumab once every two weeks; and
(2) administering 900 mg of eculizumab to the patient once every 12 days to maintain in the patient a serum complement activity at a level below 20% of the normal serum complement activity, thereby treating PNH in the patient.

141. A method for treating paroxysmal nocturnal hemoglobinuria (PNH) in a patient, the method comprising administering eculizumab to the patient according to the following dosing schedule:
(i) 600 mg of eculizumab each week for four weeks;
(ii) 900 mg of eculizumab on the fifth week; and thereafter,
(iii) 900 mg of eculizumab ~~at least~~ once every 12 days,
wherein the dosing schedule is effective to maintain in the patient a serum complement activity at a level below 20% of the normal serum complement activity, thereby treating PNH in the patient.

The recitation of "identifying step" in claims 131 and 136,
"administering once every 12 days to maintain a serum concentration ... / administering once every 12 day to maintain in the patient a serum complement activity …", and
"to maintain a serum concentration of eculizumab of approximately 35 µg/ml to 50 µg/ml"
broadly recited in the newly amended / added claims do not appear to have sufficient written support in the specification as filed.

In addition, the recitation of "wherein the dosing schedule is effective to maintain in the patient a serum complement activity at a level below 20% of the normal serum complement activity, thereby treating PNH in the patient" in claims 141 / 146 is not readily apparent in pages 36-37, overlapping paragraph of the specification (Examples).
The instant application does not particularly identify this particular combination of limitations.

Applicant's remarks, filed 03/12/2015, indicate that the support for the new and amended claims can be found throughout the specification and claims as originally filed.

The written support of the term "identifying" itself is not found in the specification as filed as well as the priority documents.
The written support of the claimed "identifying steps" is not found in the specification as filed as well as the priority documents.

Given the amended claims, it appears that applicant continues to rely upon the Examples to support the current amended claims.

While the term / step of identifying reads on establish or indicating who / someone or what / something is or associated with,

the Example discloses patients who participated in therapy trials to evaluate the effect of anti-C5 antibody on PNH in the absence of clearly disclosing "identifying step(s)" and in the absence of applicant's remarks clearly directing the written support of "identifying" / "identifying steps" in the specification.

Page 36, paragraph 3 of the specification (Examples) discloses the range of "35 µg/ml to *350* µg/ml, not "approximately 35 µg/ml to *50* µg/ml"

in the context of serum hemolytic activity in nine of the elven patients as being completely blocked throughout the 64 week treatment period of trough levels of eculizumab at equilibrium ranging …" rather "to maintain a serum concentration of eculizumab …" as currently claimed.

Pages 36-37, overlapping paragraph of the specification (Examples) disclosing that a reduction of eculizumab above 35 µg//ml and effectively and consistently blocked serum hemolytic activity for the remainder of the extension study for both patients who did not sustain levels of eculizumab necessary to consistently block complement rather than "administering to the patient once every 12 days to maintain a serum complement activity at a level below 20% of the normal serum complement activity …" as currently claimed.

In addition, the recitation of "wherein the dosing schedule is effective to maintain in the patient a serum complement activity at a level below 20% of the normal serum complement activity, thereby treating PNH in the patient" in claims 141 / 146 is not readily apparent in pages 36-37, overlapping paragraph of the specification (Examples).

The instant application does not particularly identify this particular combination of limitations.

Applicant's reliance on generic disclosure and possibly certain observations in the instant Examples of eleven PNH patients who were transfusion-dependent and hemolytic in therapy trials and who were given a particular therapeutic regimen of eculizumab, including excerpt derived from pages 36-37 of the specification does not provide sufficient written description nor direction and guidance to the "currently claimed limitations".

Note that the explicit recitation of the "limitations" cited above are not readily apparent in the specification as filed.

Note that applicant has amended the claims by relying upon certain observations of the eleven patients either in the treatment period or in an extension study under certain distinct dosing variable and time periods to broadly claim new limitations that departs from the instant disclosure as filed.

The instant disclosure of does not define nor set forth parameters" or provide for the metes and bounds of the "identifying steps".

Obviousness is not the standard for the addition new limitations to the disclosure as filed.

It is noted that entitlement to a filing date does not extend to subject matter which is not disclosed, but would be obvious over what is expressly disclosed. Lockwood v. American Airlines Inc., 41 USPQ2d 1961 (Fed. Cir. 1977).

It is noted that a generic or a sub-generic disclosure cannot support a species unless the species is specifically described. It cannot be said that a subgenus is necessarily described by a genus encompassing it and a species upon which it reads. See In re Smith 173 USPQ 679, 683 (CCPA 1972) and MPEP 2163.05.

The instant claims now recite limitations which were not clearly disclosed in the specification as-filed, and now change the scope of the instant disclosure as-filed. Applicant is claiming a subgenus not supported by the specification as-filed. Such limitations recited in the present claims, which did not appear in the specification, as filed, introduce new concepts and violate the description requirement of the first paragraph of 35 U.S.C. 112.

It is also true that the written description requirement must still be met in some way so as to "describe the claimed invention so that one skilled in the art can recognize what is claimed".

A patent specification should set forth enough detail to allow a person or ordinary skill in the art to understand what is claimed and to recognize that the inventor invented what is claimed.

Applicant is reminded that such priority for the instant limitations requires written description and enablement under 35 U.S.C. 112(a) or 35 U.S.C. 112 (pre-AIA), first paragraph.

7. Upon reconsideration of applicant's amended claims and arguments, filed 03/12/2015, the previous rejection rejected under 35 U.S.C. § 102(b) as being anticipated by Hillmen et al. (Blood 102: 1858, 2003) has been withdrawn in view of the recitation of an identifying step and an administering 900 mg eculizumab to the patient every 12 days step has been withdrawn.

8. Upon reconsideration of applicant's amended claims and arguments, filed 03/12/2015, the previous rejection rejected under 35 U.S.C. § 102(b) as being anticipated by Hillmen (44th ASH Annual Meeting Abstract, Blood, Vol. 100, 2002) has been withdrawn in view of the recitation of an identifying step and an administering 900 mg eculizumab to the patient every 12 days step.

9. Upon reconsideration of applicant's amended claims and arguments, filed 03/12/2015, the previous rejection under 35 U.S.C. § 103(a) as being unpatentable over Hillmen et al. (Blood 102: 1858, 2003) (1449) AND/OR Hillmen (44th ASH Annual Meeting Abstract, Blood, Vol. 100, 2002) (1449) in view of Meyers et al. (Int. J. Hematol. 77: 125-132, 2003) (1449) and as evidenced by Garba et al. (Singapore Med. J. 46(11):632-634, 2005) (1449) with respect to normal LDH levels has been withdrawn in view of the recitation of an identifying step and/or an administering 900 mg eculizumab to the patient every 12 days step.

10. New Grounds of Rejection

Claims 131, 133, 136, 138, 141, 143 and 146 are rejected under 35 U.S.C. § 102(b) as being anticipated by Bell et al. US 2005/0191298) (1449) (see entire document).

Given the priority issues set forth above,
this rejection is set forth.

Bell et al. teach the methods of treating PNH with eculizumab, including the dosing regimens recited in the instant claims, including the characterization of the patients and serum complement activity in patents (see entire document, including Abstract, Background, Summary, Detailed Description, particularly paragraphs [0065]-[0067], Examples in paragraphs [0081]-[0096],Claims and Figures).

While Bell et al. teach the same methods as claims,
it is acknowledged that Bell et al. differs from the claims by not reciting the "identifying steps" per se.

However, it is noted that this "identifying steps" do not recite any additional active method steps, but simply state a characterization or conclusion of steps (not claimed) or may be performed entirely in the human mind is obviously not tied to any machine and do not transform any article into a different state or thing.
For example under the broadest reasonable interpretation of the claims,
the identifying steps read on mental steps which do not require positive steps.

Again, the referenced Examples teach the same methods as claimed and that the prior art teachings of the administering step would have been those patients identified / chosen / selected by the physicians in the clinical trials taught by the prior art.

It does not appear that the claim language or limitations result in a manipulative difference in the method steps when compared to the prior art disclosure
In turn, the claimed limitations are explicitly or inherent in the prior art teachings.

11. New Ground of Rejection.

Claims 131, 133, 136, 138, 141, 143 and 146 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Bell et al. US 2005/0191298) (1449) (see entire document).

Given the priority issues set forth above,
this rejection is set forth.

Bell et al. teach the methods of treating PNH with eculizumab, including the dosing regimens recited in the instant claims, including the characterization of the methods (see entire document, including Abstract, Background, Summary, Detailed Description, particularly paragraphs [0065]-[0067], Examples in paragraphs [0081]-[0096],Claims and Figures).

While Bell et al. teach the same methods as claims,
it is acknowledged that Bell et al. differs from the claims by not reciting the "identifying steps" per se.

However, it is noted that this "identifying steps" do not recite any additional active method steps, but simply state a characterization or conclusion of steps (not claimed) or may be performed entirely in the human mind is obviously not tied to any machine and do not transform any article into a different state or thing.
For example under the broadest reasonable interpretation of the claims,
the identifying steps read on mental steps which do not require positive steps.

Again, the referenced Examples teach the same methods as claimed and that the prior art teachings of the administering step would have been those patients identified / chosen / selected by the physicians in the clinical trials taught by the prior art.

It does not appear that the claim language or limitations result in a manipulative difference in the method steps when compared to the prior art disclosure
In turn, the claim limitations are explicitly or inherent / intrinsic in the prior art teachings.

Alternatively, one of ordinary skill in the art at the time the invention was made would have been motivated identify those patients who were treated with the regimen in claims 131(1) and 136(1) as taught in the Examples and then administer 900 mg eculizumab once every 12 days also taught by the Examples to maintain eculizumab concentrations and/or to inhibit serum hemolytic activity in the treatment of PNH (e.g., see Examples, including paragraph [0088].

It does not appear that the claim language or limitations result in an unobvious manipulative difference in the method steps when compared to the prior art disclosure of providing 600 mg weekly for four (4) doses and 900 mg every other week of eculizumab a humanized anti-C5 antibody and maintenance doses in the treatment of patients with PNH at the time the invention was made.

Given the nature of the clinical manifestations of PNH such as hemolysis and anemia, one of ordinary skill in the art at the time the invention was made would have been motivated to identify / select / determine those patients who did not sustain levels of eculizmab necessary to consistenly block complement by administering 900 mg eculizumab once every 12 days also taught by the Examples to maintain eculizumab concentrations and/or to inhibit serum hemolytic activity in the treatment of PNH (e.g., see Examples, including paragraph [0088 select and combine both anti-C5 antibodies and erythropoietin to address and manage the clinical manifestations of PNH over time with an expectation of success.

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

"The test of obviousness is not express suggestion of the claimed invention in any or all of the references but rather what the references taken collectively would suggest to those of ordinary skill in the art presumed to be familiar with them." See In re Rosselet, 146 USPQ 183, 186 (CCPA 1965).

"There is no requirement (under 35 USC 103(a)) that the prior art contain an express suggestion to combine known elements to achieve the claimed invention. Rather, the suggestion to combine may come from the prior art, as filtered through the knowledge of one skilled in the art." Motorola, Inc. v. Interdigital Tech. Corp., 43 USPQ2d 1481, 1489 (Fed. Cir. 1997).

An obviousness determination is not the result of a rigid formula disassociated from the consideration of the facts of a case. Indeed, the common sense of those skilled in the art demonstrates why some combinations would have been obvious where others would not. See KSR Int'l Co. v. Teleflex Inc., 82 USPQ2d 1385 (U.S. 2007).

12. No claim is allowed.

13. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Phillip Gambel whose telephone number is (571) 272-0844. The examiner can normally be reached Monday through Thursday from 7:30 am to 6:00 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Daniel Kolker can be reached on (571) 272-3181.

The fax number for the organization where this application or proceeding is assigned is 571-273-8300.

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

/Phillip Gambel/
Primary Examiner
Technology Center 1600
Art Unit 1644
August 17, 2016

UNITED STATES PATENT AND TRADEMARK OFFICE

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

133485 7590 12/22/2016

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

EXAMINER	
ROGERS, JAMES L	

ART UNIT	PAPER NUMBER
1644	

NOTIFICATION DATE	DELIVERY MODE
12/22/2016	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

ipboston.docketing@nelsonmullins.com
chris.schlauch@nelsonmullins.com
ipqualityassuranceboston@nelsonmullins.com

Office Action Summary	Application No. 15/260,888	Applicant(s) BELL ET AL.	
	Examiner JAMES ROGERS	Art Unit 1644	AIA (First Inventor to File) Status No

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTHS FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *11/4/2016*.

☐ A declaration(s)/affidavit(s) under **37 CFR 1.130(b)** was/were filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ An election was made by the applicant in response to a restriction requirement set forth during the interview on _____; the restriction requirement and election have been incorporated into this action.

4)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims*

5)☒ Claim(s) *1-10* is/are pending in the application.

5a) Of the above claim(s) _____ is/are withdrawn from consideration.

6)☐ Claim(s) _____ is/are allowed.

7)☒ Claim(s) *1-10* is/are rejected.

8)☐ Claim(s) _____ is/are objected to.

9)☐ Claim(s) _____ are subject to restriction and/or election requirement.

* If any claims have been determined allowable, you may be eligible to benefit from the **Patent Prosecution Highway** program at a participating intellectual property office for the corresponding application. For more information, please see http://www.uspto.gov/patents/init_events/pph/index.jsp or send an inquiry to PPHfeedback@uspto.gov.

Application Papers

10)☐ The specification is objected to by the Examiner.

11)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

Certified copies:

a)☐ All b)☐ Some** c)☐ None of the:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

** See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)

2) ☒ Information Disclosure Statement(s) (PTO/SB/08a and/or PTO/SB/08b) Paper No(s)/Mail Date *10/21/2016, 11/4/2016*.

3) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .

4) ☐ Other: _____.

DETAILED ACTION

1. Claims 1-10 pending and under consideration in the instant examination.

2. The present application is being examined under the pre-AIA first to invent provisions.

3. Applicant's IDSs filed on 10/21/2016 and 11/4/2016 are acknowledged and have been considered.

4. Applicant has overcome the ODP rejections which were in the prior OA mailed on 11/4/2016 given applicant's approved TD over US Patent Application 15/148,839 (Note: applicant's has also filed an approved TD over US Patent application 15/284,015).

Claim Rejections - 35 USC § 102

5. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) *the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.*

6. Claims 1-2 and 7-10 are rejected under 35 U.S.C. 102(b) as being anticipated by Hillmen et al. (N Engl J Med 2004; 350: 552-9, IDS Ref. of 10/21/2016), as is evidenced by applicant's specification as filed at p.44 and Thomas et al. (Molecular Immunology, 33(17/18), pp.1389-1401, 1996).

With respect to base claim 1, Hillmen teaches a method for treating a human patient that suffers from paroxysmal nocturnal hemoglobinuria (PNH) by administering to the patient an effective amount of eculizumab (p. 552, "methods") which specifically binds to the terminal complement protein C5, inhibiting its cleavage into C5a and C5b (p. 553, 3rd ¶).

While Hillmen does not specifically recite that the antibody that binds C5 comprises a heavy chain consisting of SEQ ID NO: 2 and a light chain consisting of SEQ ID NO:4, the specification as filed at p. 44 discloses that SEQ ID NO: 2 and SEQ ID NO: 4 constitute the H and L chains for "eculizumab" and Hillmen, as noted supra, teaches administering "eculizumab". Hillmen further teaches that "eculizumab" is a recombinant humanized antibody that binds to C5 (p. 553, 3rd ¶) and cites Thomas which in turn describes in detail humanization of the clone referred to as "5G1.1" arrive at the humanized h5G1.1 which retain both the affinity and blocking functions of the murine 5g1.1 antibody (abstract). Accordingly and in absence of evidence to the contrary, the

currently recited SEQ ID NO: 2 and SEQ ID NO: 4 which constitute the L and H chains of "eculizumab" are considered to be inherent properties of the "eculizumab" anti-C5 humanized monoclonal antibody taught by Hillmen.

Claim 2 is included because Hillmen teaches that the patients received eculizumab by infusion (p. 554 under "Treatment Schedule").

Claim 7 is included because Hillmen teaches that the patients had previously been diagnosed of aplastic anemia (p. 555, 1st ¶).

Claim 8 is included because Hillmen teaches that patients received infusions of eculizumab (600 mg) every week for four weeks, followed one week later by a 900 mg dose and then by a dose of 900 mg every other week through week 12 (p. 552 under "methods" and p. 554 under "treatment schedule").

Claims 9-10 are included because Hillmen teaches that a decrease in lactate dehydrogenase began after a single dose of eculizumab (immediate decrease occurs within 1 week of administration of the antibody) in all patients and remained within or just above the normal range for the duration of the study (sustained decrease in mean levels of LDH) (p. 555, last ¶).

The reference teachings anticipate the claimed invention.

Claim Rejections - 35 USC § 103

7. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained even though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

8. Claims 1-4 and 7-10 rejected under 35 U.S.C. 103(a) as being unpatentable over Hillmen et al. (N Engl J Med 2004; 350: 552-9), in view of Thomas et al. (Molecular Immunology, 33(17/18), pp.1389-1401, 1996) and of Evans et al. (US 6,355,245 B1, issued 3/12/2002).

The prior art teachings of Hillmen are discussed above.

To the extent that applicant intends to argue that Hillmen on its own does not constitute an enabling references because it does not explicitly place the eculizumab antibody in the public domain by not enabling one of ordinary skill in the art to make and use eculizumab comprising SEQ ID NO: 2 and 4 as currently claimed, Hillmen discloses (p. 553, 3rd¶) that eculizumab is a recombinant human antibody that binds to C5, and refers to reference number 15 (Thomas) as disclosing more information about eculizumab. Thomas in turn discloses that eculizumab is the humanized antibody h5G1.1. The '245 patent further discloses and claims the antibody made by hybridoma 5G1.1 (see for example claims 20-21) and thus places the 5G1.1 hybridoma and the antibody produced by it into the public domain.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to follow the teachings of Hillmen, Thomas and the ‘245 patent to arrive at the currently claimed invention. Hillmen and Thomas collectively teach that the 5G1.1 antibody can be used to treat PNH, and the ‘245 patent provides the public with this antibody. Thus one of ordinary skill in the art would have found it obvious to use this publicly available antibody in the methods disclosed by Hillmen.

From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

9. Claims 1-10 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hillmen et al. (N Engl J Med 2004; 350: 552-9), in view of Thomas et al. (Molecular Immunology, 33(17/18), pp.1389-1401, 1996) and of Evans et al. (US 6,355,245 B1, issued 3/12/2002), as applied to claims 1-4 and 7-10 above, and further in view of Wang (US 2005/0271660).

The prior art teachings of Hillmen, Thomas and the ‘245 patent are discussed supra.

The prior art teachings differ from the claimed invention in the recitation that the antibody is administered at a dosage level of between 5-50 mg/kg per patient per

treatment as in claim 3, that the composition is in a single unit dosage form as in claim 4 and that the single unit dosage form is a 300 mg single unit dosage form as in claim 5.

The prior art teachings further differ in the recitation that the pharmaceutical composition comprises a 300 mg single-use formulation of 30 ml of a 10 mg/ml sterile, preservative free solution as in claim 6.

The ‘245 patent further teaches antibody 5G1.1, which is the same as eculizumab (discussion supra), is effective at doses of 2.2, 3, or 5 mg per kg body weight; this corresponds to 154, 210, or 350 mg of antibody for a 70kg adult human (‘245 patent, column 16 lines 10-30). Evans (the ‘245 patent) also teaches that eculizumab is therapeutically effective when as little as 210 mg are present (column 16 lines 10-15). Evans teaches that the antibodies are particularly advantageous in that they are highly active even when administered in low doses (col 8 lines 25-32), providing a reasonable expectation of success in treating PHN with a dose less than what was disclosed by Hillmen. The reference teaches that it is within the skill of an artisan, particularly a physician, to determine the optimal dose (column 18 lines 15-30). Evans teaches formulations of the anti-C5 antibodies may be formulated in a pharmaceutically effective carrier such saline, which is considered to be a "preservative free solution". (col 18 lines 30-45).

Neither Hillmen nor the ‘245 patent (Evans) teaches a 300 mg single unit dosage as recited in the claims.

Nevertheless it would have been obvious to one of ordinary skill in the art to modify the teachings of Hillmen to administer 300 mg single unit dosages. Hillmen teaches that both 600 and 900 mg dosages can be used, and since Evans patent teaches that 210 or 350 mg of antibody would be expected to be therapeutically effective, arriving at the 300 mg dosage would be routine, convenient and obvious. One of ordinary skill in the art would have a reasonable expectation of success, as Evans teaches that the antibody exerts its effect at low doses.

It is further noted, [I]t is not inventive to discover the optimum or workable ranges by routine experimentation.” In re Aller, 220 F.2d 454, 456 (CCPA 1955); see also In re Peterson, 315 F.3d 1325 (Fed. Cir. 2003). “Only if the ‘results of optimizing a variable’ are ‘unexpectedly good’ can a patent be obtained for the claimed critical range.” In re Geisler, 116 F.3d 1465, 1469 (Fed. Cir. 1997) (quoting In re Antonie, 559 F.2d 618, 620 (CCPA 1977)). “[Discovery of an optimum value of a result effective variable in a known process is ordinarily within the skill of the art.” In re Boesch, 617 F.2d 272, 276 (CCPA 1980).

Finally, **Wang** teaches that eculizumab is highly soluble, including at up to 30 mg per ml (paragraph 0171, Figure 10). Wang further teaches that pharmaceutically acceptable carriers include pyrogen-free water may be used in formulation of the antibody (¶71)

(sterile, preservative free solution). Therefore the artisan of ordinary skill would have had a reasonable expectation of success in making a 10 mg / ml solution of the antibody sterile, preservative free solution.

From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

10. No claim is allowed.

11. Any inquiry concerning this communication or earlier communications from the examiner should be directed to James Rogers whose telephone number is (571) 270-5374. The examiner can normally be reached Monday through Friday from 8:00 am to 5:30 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, **Daniel Kolker** can be reached on (571) 272-3181. The fax number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

December 5, 2016 /JAMES ROGERS/
Art Unit 1644

/DANIEL E. KOLKER/

Supervisory Patent Examiner, Art Unit 1644

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15/260,888	09/09/2016	Leonard BELL	AXJ-114BUSCN3	2558

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EXAMINER	
ROGERS, JAMES L	

ART UNIT	PAPER NUMBER
1644	

NOTIFICATION DATE	DELIVERY MODE
10/27/2016	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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Office Action Summary	Application No. 15/260,888	Applicant(s) BELL ET AL.	
	Examiner JAMES ROGERS	Art Unit 1644	AIA (First Inventor to File) Status No

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTHS FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *9/9/2016*.

☐ A declaration(s)/affidavit(s) under **37 CFR 1.130(b)** was/were filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ An election was made by the applicant in response to a restriction requirement set forth during the interview on _____; the restriction requirement and election have been incorporated into this action.

4)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims*

5)☒ Claim(s) *1-10* is/are pending in the application.

5a) Of the above claim(s) _____ is/are withdrawn from consideration.

6)☐ Claim(s) _____ is/are allowed.

7)☒ Claim(s) *1-10* is/are rejected.

8)☐ Claim(s) _____ is/are objected to.

9)☐ Claim(s) _____ are subject to restriction and/or election requirement.

* If any claims have been determined allowable, you may be eligible to benefit from the **Patent Prosecution Highway** program at a participating intellectual property office for the corresponding application. For more information, please see http://www.uspto.gov/patents/init_events/pph/index.jsp or send an inquiry to PPHfeedback@uspto.gov.

Application Papers

10)☐ The specification is objected to by the Examiner.

11)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

Certified copies:

a)☐ All b)☐ Some** c)☐ None of the:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

** See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)

2) ☒ Information Disclosure Statement(s) (PTO/SB/08a and/or PTO/SB/08b) Paper No(s)/Mail Date *10/21/2016*.

3) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .

4) ☐ Other: _____.

DETAILED ACTION

1. Claims 1-10 pending and under consideration in the instant examination.

2. The present application is being examined under the pre-AIA first to invent provisions.

Double Patenting

3. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., In re Berg, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); In re Goodman, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); In re Longi, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); In re Van Ornum, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); In re Vogel, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); In re Thorington, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on nonstatutory double patenting provided the reference application or patent either is shown to be commonly owned with the examined application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement. See MPEP § 717.02 for applications subject to examination under the first inventor to file provisions of the AIA as explained in MPEP § 2159. See MPEP §§ 706.02(l)(1) - 706.02(l)(3) for applications not subject to examination under the first inventor to file provisions of the AIA. A terminal disclaimer must be signed in compliance with 37 CFR 1.321(b).

The USPTO Internet website contains terminal disclaimer forms which may be used. Please visit www.uspto.gov/patent/patents-forms. The filing date of the application in which the form is filed determines what form (e.g., PTO/SB/25, PTO/SB/26, PTO/AIA/25, or PTO/AIA/26) should be used. A web-based eTerminal Disclaimer may be filled out completely online using web-screens. An eTerminal Disclaimer that meets all requirements is auto-processed and approved immediately upon submission. For more information about eTerminal Disclaimers, refer to www.uspto.gov/patents/process/file/efs/guidance/eTD-info-I.jsp.

4. Claims 1-10 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claim 1 of copending Application No. 15/148,839, in view of Hillmen et al. (N Engl J Med 2004; 350: 552-9).

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Although the conflicting claims are not identical, they are not patentably distinct from each other because the '839 application claims a pharmaceutical composition for use in treating a patient afflicted with PNH. The specification of the '516 at ¶158 defines eculizumab as having a heavy chain SEQ ID NO: 2 and light chain SEQ ID NO: 4 which is 100% identical in amino acid sequence to the currently claimed SEQ IDs NO: 2 and 4. (see alignment below).

SEQ ID NO: 2 alignment

```
Qy          1 QVQLVQSGAEVKKPGASVKVSCKASGYIFSNYWIQWVRQAPGQGLEWMGEILPGSGSTEY 60
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db          1 QVQLVQSGAEVKKPGASVKVSCKASGYIFSNYWIQWVRQAPGQGLEWMGEILPGSGSTEY 60

Qy         61 TENFKDRVTMTRDTSTSTVYMELSSLRSEDTAVYYCARYFFGSSPNWYFDVWGQGTLVTV 120
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db         61 TENFKDRVTMTRDTSTSTVYMELSSLRSEDTAVYYCARYFFGSSPNWYFDVWGQGTLVTV 120

Qy        121 SSASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQ 180
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        121 SSASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQ 180

Qy        181 SSGLYSLSSVVTVPSSNFGTQTYTCNVDHKPSNTKVDKTVERKCCVECPPCPAPPVAGPS 240
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        181 SSGLYSLSSVVTVPSSNFGTQTYTCNVDHKPSNTKVDKTVERKCCVECPPCPAPPVAGPS 240

Qy        241 VFLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQFNWYVDGVEVHNAKTKPREEQFNST 300
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        241 VFLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQFNWYVDGVEVHNAKTKPREEQFNST 300

Qy        301 YRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQVYTLPPSQEEMT 360
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        301 YRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQVYTLPPSQEEMT 360

Qy        361 KNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSRLTVDKSRWQE 420
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        361 KNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSRLTVDKSRWQE 420

Qy        421 GNVFSCSVMHEALHNHYTQKSLSLSLGK 448
              ||||||||||||||||||||||||||||
Db        421 GNVFSCSVMHEALHNHYTQKSLSLSLGK 448
```

SEQ ID NO: 4 alignment

```
Qy          1 MDMRVPAQLLGLLLLWLRGARCDIQMTQSPSSLSASVGDRVTITCGASENIYGALNWYQQ 60
```

```
                ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db          1 MDMRVPAQLLGLLLLWLRGARCDIQMTQSPSSLSASVGDRVTITCGASENIYGALNWYQQ 60

Qy         61 KPGKAPKLLIYGATNLADGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCQNVLNTPLTF 120
                ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db         61 KPGKAPKLLIYGATNLADGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCQNVLNTPLTF 120

Qy        121 GQGTKVEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGN 180
                ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        121 GQGTKVEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGN 180

Qy        181 SQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC 236
                |||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        181 SQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC 236
```

While the '839 does not specifically recite that the patient is anemic or that the antibody is administered to the patient at a dosage level of between 5-50 mg per kg per patient per treatment, in a single unit dosage form of the other various dosage schedules currently recited (e.g, 600 m/900/900 mg), Hillman teaches administration of the anti-C5 antibody eculizumab to an anemic patient (p. 555 under "demographic characteristics" at a dosing schedule of 600 mg for four weeks, followed one week later by a 900 mg dose and then by a dose of 900 mg every other week through week 12 (p. 554, under "treatment schedule"). In addition, [I]t is not inventive to discover the optimum or workable ranges by routine experimentation." In re Aller, 220 F.2d 454, 456 (CCPA 1955); see also In re Peterson, 315 F.3d 1325 (Fed. Cir. 2003). "Only if the 'results of optimizing a variable' are 'unexpectedly good' can a patent be obtained for the claimed critical range." In re Geisler, 116 F.3d 1465, 1469 (Fed. Cir. 1997) (quoting In re Antonie, 559 F.2d 618, 620 (CCPA 1977)). "[Discovery of an optimum value of a result effective variable in a known process is ordinarily within the skill of the art." In re Boesch, 617 F.2d 272, 276 (CCPA 1980). Given the teachings of Hillman one of skill in the art would regard administration of the anti-C5 antibody recited in '839 as an optimization variable.

5. Claims 1-10 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 91, 98, 100-106, 110-113, and 115 of copending Application No. 15/148,839.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Although the conflicting claims are not identical, they are not patentably distinct from each other because the '973 application claims a method for treating a patient afflicted with PNH by administration of an anti-C5 antibody in single unit dosage form and at a dosing schedule of 600 for the first 4 weeks, 900 mg for the fifth and 900 mg every 14 days thereafter. The specification of the '839 (¶s 20, 158) defines an anti-C5 antibody as having a heavy chain SEQ ID NO: 2 and light chain SEQ ID NO: 4 which is 100% identical in amino acid sequence to the currently claimed SEQ IDs NO: 2 and 4. (see alignment below).

SEQ ID NO: 2 alignment

```
Qy          1 QVQLVQSGAEVKKPGASVKVSCKASGYIFSNYWIQWVRQAPGQGLEWMGEILPGSGSTEY 60
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db          1 QVQLVQSGAEVKKPGASVKVSCKASGYIFSNYWIQWVRQAPGQGLEWMGEILPGSGSTEY 60

Qy         61 TENFKDRVTMTRDTSTSTVYMELSSLRSEDTAVYYCARYFFGSSPNWYFDVWGQGTLVTV 120
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db         61 TENFKDRVTMTRDTSTSTVYMELSSLRSEDTAVYYCARYFFGSSPNWYFDVWGQGTLVTV 120

Qy        121 SSASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQ 180
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        121 SSASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQ 180

Qy        181 SSGLYSLSSVVTVPSSNFGTQTYTCNVDHKPSNTKVDKTVERKCCVECPPCPAPPVAGPS 240
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        181 SSGLYSLSSVVTVPSSNFGTQTYTCNVDHKPSNTKVDKTVERKCCVECPPCPAPPVAGPS 240

Qy        241 VFLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQFNWYVDGVEVHNAKTKPREEQFNST 300
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        241 VFLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQFNWYVDGVEVHNAKTKPREEQFNST 300

Qy        301 YRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQVYTLPPSQEEMT 360
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        301 YRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQVYTLPPSQEEMT 360

Qy        361 KNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSRLTVDKSRWQE 420
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        361 KNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSRLTVDKSRWQE 420

Qy        421 GNVFSCSVMHEALHNHYTQKSLSLSLGK 448
              ||||||||||||||||||||||||||||
Db        421 GNVFSCSVMHEALHNHYTQKSLSLSLGK 448
```

SEQ ID NO: 4 alignment

```
Qy          1 MDMRVPAQLLGLLLLWLRGARCDIQMTQSPSSLSASVGDRVTITCGASENIYGALNWYQQ 60
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db          1 MDMRVPAQLLGLLLLWLRGARCDIQMTQSPSSLSASVGDRVTITCGASENIYGALNWYQQ 60

Qy         61 KPGKAPKLLIYGATNLADGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCQNVLNTPLTF 120
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db         61 KPGKAPKLLIYGATNLADGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCQNVLNTPLTF 120

Qy        121 GQGTKVEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGN 180
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        121 GQGTKVEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGN 180

Qy        181 SQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC 236
              |||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        181 SQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC 236
```

6. The closest prior art was regarded to be Hillmen et al. (N Engl J Med 2004; 350: 552-9). Hillmen teaches a method for treating a human patient that suffers from paroxysmal nocturnal hemoglobinuria (PNH) by administering to the patient an effective amount of

eculizumab (p. 552, "methods") which specifically binds to the terminal complement protein C5, inhibiting its cleavage into C5a and C5b (p. 553, 3rd ¶). Hillmen teaches that patients received infusions of 600 mg eculizumab weekly for four weeks, followed one week later by a 900 mg dose and then by a dose of 900 mg every other week through week 12 (p. 554 under “treatment schedule”). However, Hillmen does not teach the specific anti-C5 antibody recited by the current application. As evidenced by Report from Alexion Pharma K.K. eculizumab has a H and L chain sequence (p. 3 of the Report) which when compared to the H and L chains of the currently recited anti-C5 antibody are not the same (see sequence alignment below ExPASy (userSeq1 is the imputed sequence of eculizumab and userSeq2 is the amino acid sequence for the H chain of the currently recited claims).

```
98.9% identity in 448 residues overlap; Score: 2364.0; Gap frequency: 0.0%

UserSeq1       1 QVQLVQSGAEVKKPGASVKVSCKASGYIFSNYWIQWVRQAPGQGLEWMGEILPGSGSTEY
UserSeq2       1 QVQLVQSGAEVKKPGASVKVSCKASGYIFSNYWIQWVRQAPGQGLEWMGEILPGSGSTEY
                 ************************************************************

UserSeq1      61 TENFKDRVTMTRDTSTSTVYMELSSLRSEDTAVYYCARYFFGSSPNWYFDVWGQGTLVTV
UserSeq2      61 TENFKDRVTMTRDTSTSTVYMELSSLRSEDTAVYYCARYFFGSSPNWYFDVWGQGTLVTV
                 ************************************************************

UserSeq1     121 SSASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQ
UserSeq2     121 SSASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQ
                 ************************************************************

UserSeq1     181 SSGLYSLSSVVTVPSSNFGTQTYTCNVDHKPSNTKVDKTVERKCCVECPPCPAPPVAGPS
UserSeq2     181 SSGLYSLSSVVTVPSSNFGTQTYTCNVDHKPSNTKVDKTVERKCCVECPPCPAPPVAGPS
                 ************************************************************

UserSeq1     241 VFLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQFNWYVDGVEVHNAKTKPREEQFNST
UserSeq2     241 VFLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQFNWYVDGVEVHANKTKPREEQFNST
                 ********************************************  ************

UserSeq1     301 YRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQVYTLPPSQEEMT
UserSeq2     301 YRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQPEPEQVYTLPPSQEEMT
                 ******************************************   *************

UserSeq1     361 KNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSRLTVDKSRWQE
UserSeq2     361 KNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSRLTVDKSRWQE
                 ************************************************************

UserSeq1     421 GNVFSCSVMHEALHNHYTQKSLSLSLGK
UserSeq2     421 GNVFSCSVMHEALHNHYTQKSLSLSLGK
                 ****************************
```

One of skill in the art would not have been easily guided to using the currently claimed anti-C5 antibody for treating a patient suffering from PNH given the teachings of Hillmen.

7. No claim is allowed.

8. Any inquiry concerning this communication or earlier communications from the examiner should be directed to James Rogers whose telephone number is (571) 270-5374. The examiner can normally be reached Monday through Friday from 8:00 am to 5:30 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, **Daniel Kolker** can be reached on (571) 272-3181. The fax number for the organization where this application or proceeding is assigned is 571-273-8300.

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October 20, 2016

/JAMES ROGERS/

/SHARON WEN/
Primary Examiner, Art Unit 1644

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
15/284,015	10/03/2016	Leonard BELL	AXJ-114BUSCN4	1040

133485 7590 11/01/2016

Nelson Mullins Riley & Scarborough LLP/Alexion
One Post Office Square
30th Floor
Boston, MA 02109-2127

EXAMINER	
ROGERS, JAMES L	

ART UNIT	PAPER NUMBER
1644	

NOTIFICATION DATE	DELIVERY MODE
11/01/2016	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

ipboston.docketing@nelsonmullins.com
chris.schlauch@nelsonmullins.com
ipqualityassuranceboston@nelsonmullins.com

Office Action Summary	Application No. 15/284,015	Applicant(s) BELL ET AL.	
	Examiner JAMES ROGERS	Art Unit 1644	AIA (First Inventor to File) Status No

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTHS FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *10/3/2016*.

☐ A declaration(s)/affidavit(s) under **37 CFR 1.130(b)** was/were filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ An election was made by the applicant in response to a restriction requirement set forth during the interview on _____; the restriction requirement and election have been incorporated into this action.

4)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims*

5)☒ Claim(s) *1* is/are pending in the application.

5a) Of the above claim(s) _____ is/are withdrawn from consideration.

6)☐ Claim(s) _____ is/are allowed.

7)☒ Claim(s) *1* is/are rejected.

8)☐ Claim(s) _____ is/are objected to.

9)☐ Claim(s) _____ are subject to restriction and/or election requirement.

* If any claims have been determined allowable, you may be eligible to benefit from the **Patent Prosecution Highway** program at a participating intellectual property office for the corresponding application. For more information, please see http://www.uspto.gov/patents/init_events/pph/index.jsp or send an inquiry to PPHfeedback@uspto.gov.

Application Papers

10)☐ The specification is objected to by the Examiner.

11)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

Certified copies:

a)☐ All b)☐ Some** c)☐ None of the:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

** See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)

2) ☒ Information Disclosure Statement(s) (PTO/SB/08a and/or PTO/SB/08b) Paper No(s)/Mail Date *10/21/2016*.

3) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .

4) ☐ Other: _____.

DETAILED ACTION

1. Claim 1 is pending and under consideration in the instant examination.

2. The present application is being examined under the pre-AIA first to invent provisions.

3. Applicant's IDS's, filed 10/21/2016, are acknowledged and have been considered.

Double Patenting

4. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., In re Berg, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); In re Goodman, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); In re Longi, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); In re Van Ornum, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); In re Vogel, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); In re Thorington, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on nonstatutory double patenting provided the reference application or patent either is shown to be commonly owned with the examined application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement. See MPEP § 717.02 for applications subject to examination under the first inventor to file provisions of the AIA as explained in MPEP § 2159. See MPEP §§ 706.02(l)(1) - 706.02(l)(3) for applications not subject to examination under the first inventor to file provisions of the AIA. A terminal disclaimer must be signed in compliance with 37 CFR 1.321(b).

The USPTO Internet website contains terminal disclaimer forms which may be used. Please visit www.uspto.gov/patent/patents-forms. The filing date of the application in which the form is filed determines what form (e.g., PTO/SB/25, PTO/SB/26, PTO/AIA/25, or PTO/AIA/26) should be used. A web-based eTerminal Disclaimer may be filled out completely online using web-screens. An eTerminal Disclaimer that meets all requirements is auto-processed and approved immediately upon submission. For more information about eTerminal Disclaimers, refer to www.uspto.gov/patents/process/file/efs/guidance/eTD-info-I.jsp.

5. Claim 1 is provisionally rejected on the ground of nonstatutory obviousness- type double patenting as being unpatentable over claim 1 of copending **Application No. 15/148,839**.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Although the conflicting claims are not identical, they are not patentably distinct from each other because the specification of the '839 at ¶158 defines eculizumab as having a heavy chain SEQ ID NO: 2 and light chain SEQ ID NO: 4 which is 100% identical in amino acid sequence to the currently claimed SEQ IDs NO: 2 and 4. (see alignment below).

SEQ ID NO: 2 alignment

```
Qy          1 QVQLVQSGAEVKKPGASVKVSCKASGYIFSNYWIQWVRQAPGQGLEWMGEILPGSGSTEY 60
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db          1 QVQLVQSGAEVKKPGASVKVSCKASGYIFSNYWIQWVRQAPGQGLEWMGEILPGSGSTEY 60

Qy         61 TENFKDRVTMTRDTSTSTVYMELSSLRSEDTAVYYCARYFFGSSPNWYFDVWGQGTLVTV 120
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db         61 TENFKDRVTMTRDTSTSTVYMELSSLRSEDTAVYYCARYFFGSSPNWYFDVWGQGTLVTV 120

Qy        121 SSASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQ 180
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        121 SSASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQ 180

Qy        181 SSGLYSLSSVVTVPSSNFGTQTYTCNVDHKPSNTKVDKTVERKCCVECPPCPAPPVAGPS 240
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        181 SSGLYSLSSVVTVPSSNFGTQTYTCNVDHKPSNTKVDKTVERKCCVECPPCPAPPVAGPS 240

Qy        241 VFLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQFNWYVDGVEVHNAKTKPREEQFNST 300
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        241 VFLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQFNWYVDGVEVHNAKTKPREEQFNST 300

Qy        301 YRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQVYTLPPSQEEMT 360
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        301 YRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQVYTLPPSQEEMT 360

Qy        361 KNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSRLTVDKSRWQE 420
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        361 KNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSRLTVDKSRWQE 420

Qy        421 GNVFSCSVMHEALHNHYTQKSLSLSLGK 448
              ||||||||||||||||||||||||||||
Db        421 GNVFSCSVMHEALHNHYTQKSLSLSLGK 448
```

SEQ ID NO: 4 alignment

```
Qy          1 MDMRVPAQLLGLLLLWLRGARCDIQMTQSPSSLSASVGDRVTITCGASENIYGALNWYQQ 60
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db          1 MDMRVPAQLLGLLLLWLRGARCDIQMTQSPSSLSASVGDRVTITCGASENIYGALNWYQQ 60
```

```
Qy          61 KPGKAPKLLIYGATNLADGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCQNVLNTPLTF 120
               ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db          61 KPGKAPKLLIYGATNLADGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCQNVLNTPLTF 120

Qy         121 GQGTKVEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGN 180
               ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db         121 GQGTKVEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGN 180

Qy         181 SQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC 236
               |||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db         181 SQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC 236
```

6. The closest prior art was regarded to be Hillmen et al. (N Engl J Med 2004; 350: 552-9). Hillmen teaches a method for treating a human patient that suffers from paroxysmal nocturnal hemoglobinuria (PNH) by administering to the patient an effective amount of eculizumab (p. 552, "methods") which specifically binds to the terminal complement protein C5, inhibiting its cleavage into C5a and C5b (p. 553, 3rd ¶). However, Hillmen does not teach the specific anti-C5 antibody recited by the current application. As evidenced by Report from Alexion Pharma K.K. eculizumab has a H and L chain sequence (p. 3 of the Report) which when compared to the H and L chains of the currently recited anti-C5 antibody are not the same (see sequence alignment below ExPASy (userSeq1 is the imputed sequence of eculizumab and userSeq2 is the amino acid sequence for the H chain of the currently recited claims).

```
98.9% identity in 448 residues overlap; Score: 2364.0; Gap frequency: 0.0%

UserSeq1       1 QVQLVQSGAEVKKPGASVKVSCKASGYIFSNYWIQWVRQAPGQGLEWMGEILPGSGSTEY
UserSeq2       1 QVQLVQSGAEVKKPGASVKVSCKASGYIFSNYWIQWVRQAPGQGLEWMGEILPGSGSTEY
                 ************************************************************

UserSeq1      61 TENFKDRVTMTRDTSTSTVYMELSSLRSEDTAVYYCARYFFGSSPNWYFDVWGQGTLVTV
UserSeq2      61 TENFKDRVTMTRDTSTSTVYMELSSLRSEDTAVYYCARYFFGSSPNWYFDVWGQGTLVTV
                 ************************************************************

UserSeq1     121 SSASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQ
UserSeq2     121 SSASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQ
                 ************************************************************

UserSeq1     181 SSGLYSLSSVVTVPSSNFGTQTYTCNVDHKPSNTKVDKTVERKCCVECPPCPAPPVAGPS
UserSeq2     181 SSGLYSLSSVVTVPSSNFGTQTYTCNVDHKPSNTKVDKTVERKCCVECPPCPAPPVAGPS
                 ************************************************************

UserSeq1     241 VFLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQFNWYVDGVEVHNAKTKPREEQFNST
UserSeq2     241 VFLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQFNWYVDGVEVHANKTKPREEQFNST
                 *********************************************  ************

UserSeq1     301 YRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQVYTLPPSQEEMT
UserSeq2     301 YRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQPEPEQVYTLPPSQEEMT
                 *********************************************   *************

UserSeq1     361 KNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSRLTVDKSRWQE
UserSeq2     361 KNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSRLTVDKSRWQE
                 ************************************************************

UserSeq1     421 GNVFSCSVMHEALHNHYTQKSLSLSLGK
```

```
UserSeq2      421 GNVFSCSVMHEALHNHYTQKSLSLSLGK
                  ****************************
```

One of skill in the art would not have been easily guided to using the currently claimed anti-C5 antibody for treating a patient suffering from PNH given the teachings of Hillmen.

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October 26, 2016

/JAMES ROGERS/
Patent Examiner, AU 1644

/SHARON WEN/
Primary Examiner, Art Unit 1644

Notice of References Cited	Application/Control No. 15/284,015	Applicant(s)/Patent Under Reexamination BELL ET AL.	
	Examiner JAMES ROGERS	Art Unit 1644	Page 1 of 1

U.S. PATENT DOCUMENTS

*		Document Number Country Code-Number-Kind Code	Date MM-YYYY	Name	CPC Classification	US Classification
	A	US-				
	B	US-				
	C	US-				
	D	US-				
	E	US-				
	F	US-				
	G	US-				
	H	US-				
	I	US-				
	J	US-				
	K	US-				
	L	US-				
	M	US-				

FOREIGN PATENT DOCUMENTS

*		Document Number Country Code-Number-Kind Code	Date MM-YYYY	Country	Name	CPC Classification
	N					
	O					
	P					
	Q					
	R					
	S					
	T					

NON-PATENT DOCUMENTS

*		Include as applicable: Author, Title Date, Publisher, Edition or Volume, Pertinent Pages)
	U	Alexion Pharma K.K. "Report on the deliveration results for soliiris for intravenous infusion 300 mg" March 5, 2010, pp. 1-105
	V	
	W	
	X	

*A copy of this reference is not being furnished with this Office action. (See MPEP § 707.05(a).)
Dates in MM-YYYY format are publication dates. Classifications may be US or foreign.

Electronic Acknowledgement Receipt	
EFS ID:	28361701
Application Number:	15148839
International Application Number:	
Confirmation Number:	3159
Title of Invention:	TREATMENT OF PAROXYSMAL NOCTURNAL HEMOGLOBINURIA PATIENTS BY AN INHIBITOR OF COMPLEMENT
First Named Inventor/Applicant Name:	Leonard BELL
Customer Number:	133485
Filer:	Jill R. Gorny Sloper/Anita Costa
Filer Authorized By:	Jill R. Gorny Sloper
Attorney Docket Number:	AXJ-114BUSCN2
Receipt Date:	15-FEB-2017
Filing Date:	06-MAY-2016
Time Stamp:	13:52:05
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	no

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Non Patent Literature	Alexion.pdf	13386358 0ae122e3818b7b8139feb2ea175168f74357aa2f	no	105
Warnings:					

Information:					
2	Foreign Reference	WO2005110481A2.pdf	3921591 2ee498bfad15b6303219e24a66f5e92a577661bf	no	73
Warnings:					
Information:					
3	Foreign Reference	WO2007002571A2.pdf	1588780 5b964e892430f24c0da04c59261a8b5f58718d5f	no	29
Warnings:					
Information:					
4	Foreign Reference	WO2007005612A2.pdf	10286057 42534c997ff3723f1544d2fff9a3582725d49ee7	no	167
Warnings:					
Information:					
5	Non Patent Literature	Adis_International_Limited.pdf	28755 214709e7da5c98817765713ed1a02cc69b477328	no	2
Warnings:					
Information:					
6	Non Patent Literature	Alexion_completes_enrollment_in_Ph_II_kidney_disease_trial.pdf	29992 693f575b2bd0395315cbe9dd1ae0f9924069058e	no	2
Warnings:					
Information:					
7	Non Patent Literature	Alexion_Completes_Enrollment_in_Phase_II_Membranous_02.pdf	38622 258a054bd64de1368286fde21a36fb4e993832fd	no	3
Warnings:					
Information:					
8	Non Patent Literature	Alexion_issued_C5_complement_inhibitor_patent_for_inflammatory_diseases.pdf	22215 b61a48ce2df53309fc1c1f4552b50bbf4e85c82d	no	1
Warnings:					
Information:					

9	Non Patent Literature	Alexion_Issued_Key_C5_Compl ement_Inhibitor_Patent_for_In flammatory_Diseases_02.pdf	35493 1e864dd9d7439d22029401f54c28b562d52 9730a	no	3
Warnings:					
Information:					
10	Non Patent Literature	Alexion_Pharmaceuticals_Repo rts_Second_Quarter_and_First _Half_Results_03.pdf	49539 68a13e5a4b9f36090d97e9524f11a011f522 d98a	no	8
Warnings:					
Information:					
11	Non Patent Literature	Alexion_Pharmaceuticals_Repo rts_Second_Quarter_and_First _Half_Results_- _Quarter_Highlight.pdf	51469 734e29a01d86e56986ee878728a95eb2ece 396e5	no	6
Warnings:					
Information:					
12	Non Patent Literature	Alexion_Pharmaceuticals_Inc_ Company_reports_second_qua rter_first-_half_results.pdf	32779 8297011ea7d8d63a3e7c63baa3ef8e7fdfdd 59ba	no	2
Warnings:					
Information:					
13	Non Patent Literature	eculizumab_Alexion_clinical_d ata_phase_III_PNH.pdf	28006 824d34e4bed4e31451c73442e4f95ce8051 38987	no	2
Warnings:					
Information:					
14	Non Patent Literature	eculizumab_Alexion_clinical_d ata_PNH_R__D_Focus_Drug_N ews_.pdf	28334 bc64556124f25c7738b7de05e7c6d7fb109f 3ad0	no	2
Warnings:					
Information:					
15	Non Patent Literature	eculizumab_Alexion_complete s_enrollment_for_phase_III_PN H_trial.pdf	30519 400a43524514a4b8d782eab2e5278f72acfe d461	no	2
Warnings:					
Information:					

16	Non Patent Literature	eculizumab_Alexion_completes_enrollment_02.pdf	29118 43630129828fb68271fc533c261ba5a927875132	no	2
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Information:					
17	Non Patent Literature	R__D_Focus_Drug_News_Aug_28_2006.pdf	28894 46fe16eba2b4560cbc51c46f8f87e5c3c5cbd4f2	no	2
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18	Non Patent Literature	eculizumab_Alexion_initiates_second_phase_III_study.pdf	31235 7512bd81de01aab49c1c9357b2c22aa02b6a34aa	no	2
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Information:					
19	Non Patent Literature	eculizumab_Alexion_plans_phase_III_trials_paroxysmal_nocturnal_hemoglobinuria.pdf	30749 e4885c3058b052f2a028448f864bce1f5758345a	no	2
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Information:					
20	Non Patent Literature	eculizumab_Alexion_Priority_Review_USA_PNH.pdf	27857 4cf10a374b77c33fd430739a36de9c6ae540d91b	no	2
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Information:					
21	Non Patent Literature	Alexion_Pharmaceuticals_IncKidney_Disease__14.pdf	31235 8ceff4577262b02a0794ed283fce22a1e0f5ecb6	no	2
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Information:					
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Information:					

23	Non Patent Literature	eculizumab_Alexion_phase_change_III_USA_Europe_Canada_Australia_PNH.pdf	32777 82916339def85f3c19629eb208a578973f6725bf	no	2
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24	Non Patent Literature	Brekke.pdf	1280489 f1fc73123aee0451d2d98cd90080d690262b2ca8	no	11
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Information:					
25	Non Patent Literature	ESPICOM_Pharmaceutical_and_Medical_Device_News.pdf	28013 ca9d416b3724c3e3bee5d6ff237dbfd44a7ac7ec	no	2
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Information:					
26	Non Patent Literature	Fung.pdf	224992 a3fa008ad36f05c21be2718c500073d880bc6598	no	10
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Information:					
27	Non Patent Literature	Martin.pdf	587544 a374e9b2f102cd915ea8df9393f6652a603766d8	no	11
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28	Non Patent Literature	MOLLNES.pdf	630714 12982d854797ca3f7e98faaf081c59ef2f63933a	no	15
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29	Non Patent Literature	ALEXION_OFFERS_EARLY_MIXEDPHASE_III_DATA_FOR_HEART_DRUG.pdf	36354 18abf3135d8d4fc7785c526902b613daffada800	no	3
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Information:					

30	Non Patent Literature	Osbourn_03.pdf	1891854 65342efe55c9b71a8f19ebe9c5311fed72ce36d1	no	10
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31	Non Patent Literature	Other_News_To_Note.pdf	42576 1ff8944b729b75b56cee194e64ac04b2a4b0ee0c	no	5
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Information:					
32	Non Patent Literature	Pierangeli.pdf	292873 2030817c44f3a9ae9e447d534e3fecd50a76dec3	no	9
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Information:					
33	Non Patent Literature	Ricklin.pdf	1224810 4720fe3765d191716612b3523455200f3c661257	no	11
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Information:					
34	Foreign Reference	WO2005110481A2_1.pdf	3921591 2ee498bfad15b6303219e24a66f5e92a577661bf	no	73
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35	Non Patent Literature	BC.pdf	2079123 8c5aef68a9f26f11d2b6d17086d9b1dbfc27e85e	no	11
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37	Non Patent Literature	EMA.pdf	6557722 9966034b811d550bb6924821884c14b3d0150fe2	no	40
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Information:					
38	Non Patent Literature	GROUNDS.pdf	2258602 e3f192fe223529f4ca5256587bf7be2eaa301ca3	no	15
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Information:					
39	Non Patent Literature	HALE_Blood_concentrations_of_alemtuzumab_and_anti_globulin_responses.pdf	2509268 ad4f750204b391b1b48a24a201e0c5b2d8d11e9a	no	9
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Information:					
40	Non Patent Literature	Mueller.pdf	2594745 ab69f1134848b937fe1c2db78bde9bc141d6c9c6	no	12
Warnings:					
Information:					
41	Non Patent Literature	Rother_Nature_Biotechnol_25_11_1256-1264_2007.pdf	556896 ed91ebf265527ad69e31468c939bb3adcdfdd87b	no	10
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42	Information Disclosure Statement (IDS) Form (SB08)	IDSTRANS.pdf	32240 8f2a5298412990eb4073b8bde548b66d648047da	no	3
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Information:					
This is not an USPTO supplied IDS fillable form					
43	Information Disclosure Statement (IDS) Form (SB08)	SB08_02.pdf	1038334 5cdcf60cf5958a48fb31bde18574829ad654e798	no	8
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Information:					

44	Other Reference-Patent/App/Search documents	13335518_02.pdf	738468 790e26d2830c10dd705b7e7b256dcb4a36b01ef3	no	13
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Information:					
45	Other Reference-Patent/App/Search documents	15260888_02.pdf	763848 bce63e9cd8523954569f20645d4a28d3d7468966	no	15
Warnings:					
Information:					
46	Other Reference-Patent/App/Search documents	15284015_02.pdf	318097 9362534bcc3abb3169b1834ba2b138e02ffb47a8	no	7
Warnings:					
Information:					
		Total Files Size (in bytes):	60927721		

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111
If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371
If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office
If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

Report on the Deliberation Results

March 5, 2010

Evaluation and Licensing Division, Pharmaceutical and Food Safety Bureau
Ministry of Health, Labour and Welfare

[Brand name]	Soliris for Intravenous Infusion 300 mg
[Non-proprietary name]	Eculizumab (Genetical Recombination) (JAN*)
[Applicant]	Alexion Pharma K.K.
[Date of application]	March 31, 2009

[Results of deliberation]

In the meeting held on February 26, 2010, the First Committee on New Drugs concluded that the product may be approved and that this result should be presented to the Pharmaceutical Affairs Department of the Pharmaceutical Affairs and Food Sanitation Council.

The product is classified as a biological product, the re-examination period is 10 years, and the drug substance and the drug product are both classified as powerful drugs.

[Conditions for approval]

1. Due to limited data from Japanese clinical studies, conduct a post-marketing drug use-results survey over a certain period of time, covering all patients treated with Soliris, in order to obtain the background information of patients treated with Soliris, collect data on the safety and efficacy of Soliris, and take necessary measures to ensure proper use of Soliris.
2. Prior to marketing Soliris, take necessary measures to ensure that Soliris will be administered only under the supervision of a physician at a medical institution, who is familiar with the diagnosis and treatment of paroxysmal nocturnal hemoglobinuria and is also fully capable of managing the risks etc. associated with Soliris, in cooperation with a physician who is familiar with the diagnosis and treatment of meningococcal infection.

**Japanese Accepted Name (modified INN)*

This English version of the Japanese review report is intended to be a reference material to provide convenience for users. In the event of inconsistency between the Japanese original and this English translation, the former shall prevail. The PMDA will not be responsible for any consequence resulting from the use of this English version.

Review Report

February 18, 2010
Pharmaceuticals and Medical Devices Agency

The results of a regulatory review conducted by the Pharmaceuticals and Medical Devices Agency on the following pharmaceutical product submitted for registration are as follows.

[Brand name]	Soliris for Intravenous Infusion 300 mg (Note: The proposed Japanese brand name has been modified.)
[Non-proprietary name]	Eculizumab (Genetical Recombination)
[Name of applicant]	Alexion Pharma K.K.
[Date of application]	March 31, 2009
[Dosage form/Strength]	Concentrated solution for intravenous infusion: Each vial of 30 mL contains 300 mg of Eculizumab (Genetical Recombination).
[Application classification]	Prescription drug (1) Drug with a new active ingredient

[Entity]

Eculizumab is a recombinant humanized monoclonal antibody composed of the variable regions consisting of complementarity-determining regions derived from mouse anti-human complement C5α-chain monoclonal antibody and human framework regions and human IgG constant regions. The L-chain constant region is derived from a human κ-chain. The CH1, hinge and a part of CH2 regions of the H-chain constant regions are derived from human IgG2 (γ2-chain) and the rest of CH2 and CH3 regions are derived from human IgG4 (γ4-chain).
Eculizumab is produced in mouse myeloma cell (NS0).
Eculizumab is a glycoprotein (molecular weight, ca.145,235) composed of 2 H-chain molecules consisting of 448 amino acid residues each and 2 L-chain molecules consisting of 214 amino acid residues each.

This English version of the Japanese review report is intended to be a reference material to provide convenience for users. In the event of inconsistency between the Japanese original and this English translation, the former shall prevail. The PMDA will not be responsible for any consequence resulting from the use of this English version.

Structural formulae:

H-chain

1 QVQLVQSGAE VKKPGASVKV SCKASGYIFS NYWIQWVRQA PGQGLEWMGE

51 ILPGSGSTEY TENFKDRVTM TRDTSTSTVY MELSSLRSED TAVYYCARYF

101 FGSSPNWYFD VWGQGTLVTV SSASTKGPSV FPLAPCSRST SESTAALGCL

151 VKDYFPEPVT VSWNSGALTS GVHTFPAVLQ SSGLYSLSSV VTVPSSNFGT

201 QTYTCNVDHK PSNTKVDKTV ERKCCVECPP CPAPPVAGPS VFLFPPKPKD

251 TLMISRTPEV TCVVVDVSQE DPEVQFNWYV DGVEVHNAKT KPREEQFNST

301 YRVVSVLTVL HQDWLNGKEY KCKVSNKGLP SSIEKTISKA KGQPREPQVY

351 TLPPSQEEMT KNQVSLTCLV KGFYPSDIAV EWESNGQPEN NYKTTPPVLD

401 SDGSFFLYSR LTVDKSRWQE GNVFSCSVMH EALHNHYTQK SLSLSLGK

L-chain

1 DIQMTQSPSS LSASVGDRVT ITCGASENIY GALNWYQQKP GKAPKLLIYG

51 ATNLADGVPS RFSGSGSGTD FTLTISSLQP EDFATYYCQN VLNTPLTFGQ

101 GTKVEIKRTV AAPSVFIFPP SDEQLKSGTA SVVCLLNNFY PREAKVQWKV

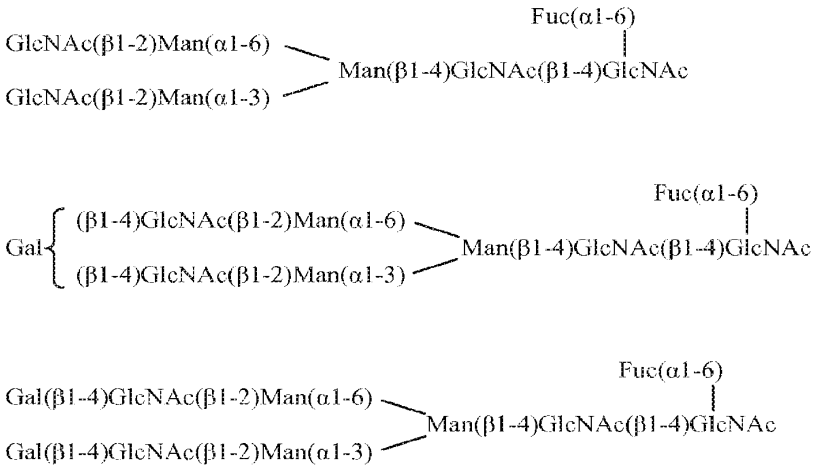
151 DNALQSGNSQ ESVTEQDSKD STYSLSSTLT LSKADYEKHK VYACEVTHQG

201 LSSPVTKSFN RGEC

[The amino acid sequence of Eculizumab (Genetical Recombination)]

pyroglutamic acid at Q1 of the H-chain; glycosylation at N298 of the H-chain; partial processing at K448 of the H-chain; inter-chain disulfide bonds of C136 of the H-chain–C214 of the L-chain, C224 of the H-chain–C224 of the H-chain, C225 of the H-chain–C225 of the H-chain, C228 of the H-chain–C228 of the H-chain, and C231 of the H-chain–C231 of the H-chain (intra-chain disulfide bonds are represented by solid lines); murine complementarity-determining regions (CDRs): N31 to Q35 of the H-chain, E50 to D66 of the H-chain, Y99 to V111 of the H-chain, G24 to N34 of the L-chain, G50 to D56 of the L-chain, and Q89 to T97 of the L-chain

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[Predicted main carbohydrate structures of Eculizumab (Genetical Recombination)]

[Items warranting special mention]	Orphan drug ("Orphan Drug Designation" [PFSB/ELD Notification No. 1222007 dated December 22, 2008])
[Reviewing office]	Office of New Drug I

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Review Results

February 18, 2010

[Brand name]	Soliris for Intravenous Infusion 300mg (Note: The proposed Japanese brand name has been modified.)
[Non-proprietary name]	Eculizumab (Genetical Recombination)
[Name of applicant]	Alexion Pharma K.K.
[Date of application]	March 31, 2009

[Results of review]

Based on the submitted data, the efficacy of the product in patients with paroxysmal nocturnal hemoglobinuria has been demonstrated. On the other hand, regarding safety, as the use of eculizumab may increase the risk of developing a meningococcal infection and a serious hemolytic crisis may occur after eculizumab discontinuation, it is necessary to inform physicians and patients of these risks and take adequate safety measures. The safety of the product is acceptable in view of its observed benefits, provided that the product is used under a proper safety control system.

As a result of its regulatory review, the Pharmaceuticals and Medical Devices Agency has concluded that the product may be approved for the indication and dosage and administration as shown below, with the following conditions.

[Indication]

Reduction of hemolysis in patients with paroxysmal nocturnal hemoglobinuria

[Dosage and administration]

The usual adult dosage is 600 mg as Eculizumab (Genetical Recombination) given as an intravenous infusion weekly for a total of 4 doses, followed 1 week later (4 weeks after the first dose) by 900 mg given every 2 weeks thereafter.

[Conditions for approval]

1. Due to limited data from Japanese clinical studies, conduct a post-marketing drug use-results survey over a certain period of time, covering all patients treated with Soliris, in order to obtain the background information of patients treated with Soliris, collect data on the safety and efficacy of Soliris, and take necessary measures to ensure proper use of Soliris.
2. Prior to marketing Soliris, take necessary measures to ensure that Soliris will be administered only under the supervision of a physician at a medical institution, who is familiar with the diagnosis and treatment of paroxysmal nocturnal hemoglobinuria and is also fully capable of managing the risks etc. associated with Soliris, in cooperation with a physician who is familiar with the diagnosis and treatment of meningococcal infection.

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Review Report (1)

December 16, 2009

I. Product Submitted for Registration

[Brand name]	Soliris for Intravenous Infusion 300 mg
[Non-proprietary name]	Eculizumab (Genetical Recombination)
[Name of applicant]	Alexion Pharma K.K.
[Date of application]	March 31, 2009
[Dosage form/Strength]	Concentrated solution for intravenous infusion: Each vial of 30 mL contains 300 mg of Eculizumab (Genetical Recombination).
[Proposed indication]	Paroxysmal nocturnal hemoglobinuria (PNH)
[Proposed dosage and administration]	Soliris should be administered by intravenous infusion at a dose of 600 mg every 7 days for the first 4 weeks followed by 900 mg for the fifth dose 7 days later and then 900 mg every 14 days thereafter.

II. Summary of the Submitted Data and Outline of Review by the Pharmaceuticals and Medical Devices Agency

A summary of the submitted data and an outline of the review by the Pharmaceuticals and Medical Devices Agency (PMDA) are as shown below.

1. Origin or history of discovery and usage conditions in foreign countries etc.

Paroxysmal nocturnal hemoglobinuria (PNH) is an acquired genetic disorder due to a somatic mutation of the phosphatidylinositol glycan-A (PIG-A) gene on chromosome X, which is necessary for the biosynthesis of glycosylphosphatidylinositol (GPI) anchors. The mutation leads to a deficiency of the GPI-anchored terminal complement inhibitor CD59 on the surface of clonal populations of hematopoietic stem cells. CD59 inhibits C9 binding to complement C5 and blocks the formation of the terminal complement complex C5b-9 on the red blood cell (RBC) surface. Deposition of cytolytic C5b-9 on the surface of CD59-deficient PNH RBCs results in intravascular hemolysis. PNH is characterized by recurrent episodes of hemolysis and chronic hemolysis, and intravascular hemolysis leads to hemoglobinuria and fatigue and poor physical functioning associated with anemia. It is thought that intravascular hemolysis releases excessive amount of hemoglobin (Hb), which induces the activation of platelets and blood coagulation cascade, causing thrombosis. Meanwhile, free Hb deposition in the kidney may lead to kidney diseases such as nephritis and renal tubule abnormalities.

According to the results of a 1998 survey conducted by a major research institution, the estimated

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number of PNH patients in Japan is approximately 430 (Health Science Research Grants, Research Project on Intractable Diseases, Research Committee for determining the epidemiology of diseases not covered by Research Project on Treatment of Intractable Diseases, 1999 Research Results, 2000). A comparative survey between Japan and the US revealed that in Japan, the median survival time after diagnosis is 25.0 years and the main causes of death are thrombosis, haemorrhage, infections, and renal failure (*Medicine*. 2004;83:193-207.).

There are only palliative therapies for PNH that aim to relieve symptoms temporarily. Blood transfusions are used for temporarily improving the symptoms associated with anemia, short-term steroid therapy is used for acute hemolysis, and anticoagulant therapy is used to prevent and treat thrombosis. Although allogeneic hematopoietic stem cell transplantation is available as a curative option, as PNH is a slowly progressive disease, it is indicated for severe patients only, taking account of the risks associated with transplantation.

Eculizumab (Genetical Recombination) (eculizumab) is a humanized monoclonal antibody that binds with high affinity to human complement C5. Eculizumab is expected to reduce intravascular hemolysis mediated by C5b-9 by inhibiting C5 activity and the development of eculizumab for PNH patients was initiated.

Eculizumab received approval in the US in March 2007. As of October 2009, eculizumab has been approved for the indication of PNH in 33 countries including the US and Europe.

Eculizumab was designated as an orphan drug for the intended indication of "paroxysmal nocturnal hemoglobinuria" as of December 22, 2008.

2. Data relating to quality

2.A Summary of the submitted data

Eculizumab is a glycoprotein (approximately 145,235 Da) composed of two 448 amino acid heavy chains ($C_{2205}H_{3378}N_{576}O_{683}S_{19}$, approximately 49,493 Da) and two 214 amino acid light chains ($C_{1016}H_{1583}N_{271}O_{334}S_6$, approximately 23,130 Da) produced in a murine myeloma cell line (NS0 cell line). The molecule contains 14 disulfide bonds and there is one *N*-linked glycosylation site on the C_H2 region of the heavy chain.

Eculizumab is a humanized anti-human C5 monoclonal antibody composed of the variable regions consisting of complementarity determining regions (CDRs) derived from mouse anti-human C5α chain monoclonal antibody (m5G1.1 mAb) and human framework regions, and human IgG constant regions. The C_H1, hinge and a part of C_H2 regions of the heavy chain constant regions are derived from human IgG_2 (γ2-chain) and the rest of C_H2 and C_H3 regions are derived from human IgG_4 (γ4-chain). The light

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chain constant region is derived from a human κ-chain.

2.A.(1) Drug substance

2.A.(1).1) Manufacturing process

(a) Assembly of the expression construct and cell banking

To generate and select m5G1.1 mAb, hybridomas were generated from mice immunized with human complement component C5 and the antibodies produced by these hybridomas were evaluated for their ability to block complement-mediated hemolysis and C5a generation. The m5G1.1 mAb gene was cloned from cDNA prepared from the hybridoma. The CDRs of the genes for human heavy chain variable and C_H1 regions (hereinafter referred to as "Fd fragment") and for a human light chain were replaced by the CDRs from the genes for the variable heavy and light chains of the m5G1.1 mAb, respectively. Thus, an intermediate vector containing the gene encoding a heavy chain Fd fragment ("[redacted]") and an intermediate vector containing the gene encoding a light chain ("[redacted]") were constructed. Then, the DNA segment encoding the heavy chain formed by joining the DNA fragment encoding the heavy chain Fd fragment excised from [redacted] with a DNA fragment encoding the hinge, C_H2, and C_H3 regions, and the DNA segment encoding the light chain excised from [redacted] were inserted to construct a double-gene vector ([redacted]). The DNA segments encoding the heavy and light chains excised from the vector were inserted into a vector containing the glutamine synthetase gene, which functions as a selection marker, to generate the expression plasmid [redacted].

[redacted] was introduced by electroporation into a NS0 cell line. The cell clones selected in serum-supplemented medium containing [redacted] were adapted to serum-free medium, and pre-seed stock [redacted] of the seed cell line [redacted] was prepared. This [redacted] was cultured in the medium for preparing cell banks ([redacted]) to prepare a master cell bank (MCB) [redacted]M and a working cell bank (WCB) was prepared from [redacted]M.

(b) Characterization and control of cell banks

The results of tests for identity and purity of the MCB, WCB, and cells at the limit of *in vitro* cell age used for production (CAL) are shown in Table 1. The results of genetic stability studies on the MCB, WCB, end of production cells (EOP), and CAL are shown in Table 2.

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Table 1. Results of tests for identity and purity of cell banks and CAL

Test			Results		
			MCB	WCB	CAL
			[redacted]M	[redacted]W	[redacted] (Process [redacted])
Cell viability			Constant		NT
Isoenzyme analysis			Of mouse origin		
Mycoplasma testing (culture method, indicator cell culture method)			Negative		
Sterility test (bacteria/fungi)			No evidence of microbial growth 14 days later		NT
Tests for adventitious viruses	*In vitro* assay for adventitious viruses		Negative (Balb-C, HeLa, MRC-5, NS0, RK-13, Vero)	Negative (MRC-5, NS0, Vero)	Negative (MRC-5, NIH/3T3, Vero)
	In vitro bovine virus assay		Negative (BT, MA104)	Negative (BT, Vero)	NT
	In vivo assay to reveal latent viruses (inoculation into suckling and adult mice and guinea pigs, and in embryonated eggs)		Negative	NT	Negative
	Mouse antibody production test*		Negative	NT	Negative
	Quantitative PCR		Negative (bovine polyoma virus, bovine and porcine circovirus, MVM)	NT	Negative (MVM)
Tests for retroviruses	Transmission electron microscopy	Examination of cell sections	A-type and C-type retrovirus-like particles were observed.	NT	A-type and C-type retrovirus-like particles were observed.
		Negative staining	NT	NT	Retrovirus-like particle count < 1.4×10^5/mL
	Mink S^+L^- focus assay		Direct assay: 27 ffu/mL Extended assay: fusion foci	NT	Negative
	In vitro XC plaque assay		Negative	NT	Negative
	In vitro assay for infectious X MuLV		Negative	NT	Negative
	Reverse transcriptase activity (Mg^{2+} and Mn^{2+} dependent)		Negative	NT	Negative
	Cocultivation (MRC-5, LEX98)		Negative	NT	Negative

NT: No Tested

Balb-C: BALB/c mouse embryo cell line, BT: bovine nasal turbinate cell line, HeLa: human cervical carcinoma cell line, MA104: fetal rhesus monkey kidney cell line, MRC-5: human diploid lung cell line, MVM: minute virus of mice, NIH/3T3: mouse fibroblast cell line, RK-13: rabbit kidney cell line, Vero: African green monkey kidney cell line, X MuLV: xenotropic murine leukemia virus

*Lymphocytic Choriomeningitis Virus, Mouse Hepatitis Virus, Pneumonia Virus of Mice, Minute Virus of Mice, Sendai Virus, Ectromelia Virus, Mouse Rotavirus, Reovirus Type 3, Mouse Encephalomyelitis Virus, Mouse Adenovirus, Polyoma Virus, Hantaan Virus, Mouse Thymic Virus, Mouse Salivary Gland Virus, K Virus, Lactic Dehydrogenase Virus

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Table 2. Results of genetic stability studies on cell banks, EOP, and CAL

Test item (Test method)		Results				
		MCB	WCB	EOP		CAL
		[redacted]M	[redacted]W	[redacted] (Process [redacted])	[redacted] (Process [redacted])	[redacted] (Process [redacted])
Site of integration of expression plasmid (Southern blotting)		Expected bands were detected.	Identical banding pattern with MCB			
Copy number/cell (Southern blotting)	Heavy chain	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Light chain	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Heavy and light chain mRNA (Northern blotting)		Expected bands were detected.	NT			Identical banding pattern with MCB
cDNA sequence		Identical to the nucleic acid sequence determined for the expression construct	NT			Identical to the nucleic acid sequence determined for the expression construct

NT: No Tested

The MCB and WCB are preserved at -100°C at [redacted] sites and it has been confirmed that they are stable for [redacted] years. Whether the shelf life may be extended will be determined by assessing cell viability and cellular proliferative capacity every [redacted] years.

An additional WCB will be prepared in accordance with the current cell banking procedures based on the number of ampoules left and a newly prepared WCB will be qualified (identity [cell viability, isoenzyme analysis], purity [sterility test, mycoplasma testing, *in vitro* assay for adventitious viruses (MRC-5, NIH/3T3, Vero)]).

There is no plan for generating a new MCB.

(c) Manufacturing process

The manufacturing process and controls for the drug substance are as shown below.

Manufacturing process		Control item
Step 1	Cell thawing and inoculum preparation Cell thawing: [redacted] ampoule from WCB Medium: [redacted]	At thawing: cell [redacted]
Seed culture 1	Equipment: [redacted]mL, [redacted]mL, [redacted]mL flask ([redacted]rpm)	
Seed culture 2-5	Equipment: [redacted]mL, [redacted] mL roller bottle ([redacted]rpm)	
Seed culture 6	Equipment: [redacted]mL spinner flask ([redacted]rpm)	After Step 1 culture: [redacted] cell [redacted], cell [redacted], cell [redacted], bioburden
Step 2a	Expansion of the culture Equipment: [redacted]L bioreactor Medium: [redacted]	At Step 2a inoculation: pH, bioburden, [redacted]
Step 2b	Expansion of the culture Equipment: [redacted]L bioreactor Medium: [redacted]	During Step 2b culture: pH, bioburden, [redacted] After Step 2b culture: cell [redacted]
Step 2c	Production culture Equipment: [redacted]L bioreactor Medium: [redacted]	During Step 2c culture: pH, bioburden, [redacted] [redacted]: mycoplasma testing, test for absence of MVM[a] (quantitative PCR), *in vitro* assay for adventitious viruses (MRC-5, NIH/3T3, Vero)
Step 3	Harvest and concentration Equipment: centrifuge, depth filter ([redacted] [redacted] [redacted] [redacted]μm), [redacted]L container, ultrafiltration membrane ([redacted]kDa)	When the volume of harvest supernatant reaches [redacted] L: bioburden After concentration: bioburden

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Step 4	Buffer exchange Equipment: depth filter ([redacted] µm), hydrophilic membrane filter ([redacted] µm)	After filtration: bioburden After storage: bioburden
Step 5	Affinity chromatography Equipment: [redacted] protein A [redacted] column	At the time of loading: pH, bioburden After the first cycle: [redacted]
Step 6	Virus inactivation Equipment: storage container Conditions: pH[redacted], [redacted] minutes	During treatment: pH After treatment: Step [redacted], pH, bioburden, endotoxin Before storage: bioburden, endotoxin
Step 7	Concentration/buffer exchange Equipment: ultrafiltration membrane ([redacted] kDa)	Before concentration: pH, electrical conductivity After dialysis: pH, electrical conductivity Before concentration adjustment: protein concentration After concentration adjustment: bioburden, endotoxin Before storage: protein concentration, pH, electrical conductivity
Step 8	[redacted]ion exchange chromatography (non-adsorbed) Equipment: [redacted] column Recovery: non-adsorbed fraction	At the time of loading: pH, electrical conductivity, bioburden, endotoxin Non-adsorbed fraction: [redacted], pH, electrical conductivity, bioburden, endotoxin
Step 9	Virus removal Equipment: [redacted] ([redacted]nm) Pressure: [redacted]psig ([redacted]bar)	After filtration: filter integrity test, bioburden, endotoxin
Step 10	[redacted]ion exchange chromatography (bind and elute) Equipment: [redacted] column Recovery: eluate fraction	Eluate before loading: pH, electrical conductivity, endotoxin At the time of loading: bioburden, endotoxin Eluate: bioburden, endotoxin, pooling criteria (monomer content)
Step 11	Preparation of drug substance (concentration/buffer exchange, addition of polysorbate 80) Equipment: ultrafiltration membrane ([redacted] kDa)	Before concentration: pH, electrical conductivity After concentration: protein concentration Before permeation: pH, electrical conductivity After permeation: protein concentration, bioburden Before concentration adjustment: protein concentration After addition of polysorbate 80: protein concentration
Step 12a	Final sterile filtration and filling Equipment: [redacted]L LDPE[c] bag with hydrophilic membrane filter ([redacted] µm)	After filtration: filter integrity test, bioburden
Step 12b	Storage Condition: 2°C-8°C	

[redacted]: Steps [redacted]

a) MVM (minute virus of mice)

b) [redacted]

c) Very low density polyethylene

Process validation of the commercial-scale manufacturing process for the drug substance was carried out and analyses have been performed for the following parameters in addition to the above control items.

Cell growth profile (cell number, viability, population doubling rate, [redacted], [redacted], etc.) and product yield and its quality attributes ([redacted] SDS-PAGE [CBB staining], isoelectric focusing [IEF]) for the fermentation process and the processing time and the percent yield and yield of product for the harvesting step have been determined.

For the purification process, the percent yield of product at each step and monomer content at each chromatographic step and virus removal step have been determined and reducing/non-reducing

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SDS-PAGE and IEF have been carried out at each chromatographic step. Removal of process-related impurities and product-related impurities has been evaluated and host cell protein (HCP), host cell DNA, bovine serum albumin (BSA), antifoaming agents [redacted] and [redacted], and cholesterol are reduced by affinity chromatography, aggregates (dimers), HCP, host cell DNA, BSA, and protein A are reduced by [redacted] ion exchange chromatography (non-adsorbed), and aggregates are reduced by [redacted] ion exchange chromatography (bind and elute) and it has been confirmed that impurities can be controlled at a certain level or lower. Furthermore, re-filtration using a virus removal membrane or a membrane filter for the final sterile filtration has been evaluated at scales of 1/[redacted] or 1/[redacted], respectively, and re-filtration can be carried out up to [redacted] times each, respectively, for each drug substance lot and if re-filtration is actually carried out, its impact on product quality and the integrity of the membrane filter are to be determined. The re-use of each column has also been evaluated and it has been confirmed that at a commercial scale, [redacted] ([redacted] [redacted]) protein A [redacted] column, [redacted] column (non-adsorbed), and [redacted] column (bind and elute) maintain consistent purification performance for up to [redacted], [redacted], and [redacted] re-uses, respectively. The re-use of an ultrafiltration membrane has also been evaluated and it was confirmed that the membrane can be used consistently for up to [redacted] re-uses at a scale of 1/[redacted] of Step 7, which was selected as the worst case scenario, and up to [redacted] re-uses of ultrafiltration membranes for Steps 7 and 11 are allowed. The storage conditions for intermediates obtained at different steps have been established based on the results of stability studies and sterility test, as shown in Table 3.

Table 3. Storage conditions for intermediates obtained at different steps

Intermediate	Container	Maximum allowable holding time	
		[redacted]°C	[redacted]°C
Filtrate after the end of Step 4	Stainless container	[redacted] days	[redacted] hours[a]
Treated solution after the end of Step 6 Filtrate after the end of Step 7	LDPE bag (after sterile filtration)	[redacted] days	[redacted] days
Non-adsorbed fraction from column after the end of Step 8	Stainless container	[redacted] hours	[redacted] hours
	LDPE bag (after sterile filtration)	[redacted] days	[redacted] days
Filtrate after the end of Step 9	Stainless container	[redacted] hours	[redacted] hours
	LDPE bag (after sterile filtration)	[redacted] days	[redacted] days
Loading solution for column in Step 10	Stainless container	-	[redacted] hours
Column eluate after the end of Step 10	Stainless container LDPE bag (after sterile filtration)	[redacted] hours	[redacted] hours
Drug substance solution after the end of Step 11	Stainless container	[redacted] hours	[redacted] hours

[a] Storage temperature is 25°C.

(d) Adventitious agents safety evaluation

i) Non-viral adventitious agents

The raw materials of animal origin used in the drug substance manufacturing process are New Zealand-sourced fetal bovine serum as a medium component in the preparation of the MCB and the preservation of the current WCB and US-sourced BSA and ovine cholesterol sourced from Australia or New Zealand as media components for cell banking and cell culture. These raw materials are derived from healthy animals and the absence of infectious contaminants has been confirmed by the supplier and manufacturer. Moreover, BSA that does not conform to the Standards for Biological Ingredients has been confirmed to meet a threshold to provide safety assurance in accordance with "Handling of Risk

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Assessment etc. in Partial Change Applications for Drugs, Medical Devices, etc., Using Bovine Derived Raw Materials etc." (PFSB/ELD Notification No. 0801001 dated August 1, 2003). A partial change application for switching to BSA sourced from another country will be filed by the 4th quarter of 2011.

ii) Adventitious viruses etc.

Tests of purity were performed on the MCB, WCB, and CAL, and the absence of contamination by mycoplasma, bacteria, infectious retroviruses, and adventitious viruses have been confirmed. Mycoplasma testing, test for the absence of MVM, and *in vitro* assay for adventitious viruses are performed at the unprocessed bulk level in the fermentation process, endotoxin and bioburden are assessed at each purification step, and furthermore, sterility test is performed at the formulation step. Therefore, the manufacturing process of the drug substance is controlled against adventitious agents. The capacity of each purification step to clear viruses is shown in Table 4.

Table 4. Results of viral clearance studies

Purification process	Virus reduction factor (Log_{10})				
	X MuLV	HSV	BAV	POL	MVM
Affinity chromatography	[redacted] a), b)	[redacted] b), c)	[redacted] c), d)	[redacted] c)	[redacted]
Virus inactivation (pH[redacted], [redacted] minutes)	[redacted] c)	[redacted] c)	[redacted]	[redacted]	[redacted]
[redacted]ion exchange chromatography (non-adsorbed)	[redacted] c), d)	[redacted] c), d)	[redacted]	[redacted]	[redacted]
Virus removal (pore size [redacted] nm)	[redacted] c)	[redacted] 1 c)	[redacted] c)	[redacted]	[redacted] c)
Overall reduction factor	**≥ 16.98** e)	**≥ 16.33** e)	**≥ 7.66** e)	**3.91**	**4.59**

NR: No Reduction, NT: No Tested
BAV (bovine adeno virus), HSV (herpes simplex virus), MVM (minute virus of mice), POL (poliovirus), X MuLV (xenotropic murine leukemia virus)

a) Quantitative PCR
b) As inactivation of eluted viruses by elution buffer (pH[redacted]) has not been confirmed, the reduction factor is not included in an overall reduction factor.
c) 50% tissue culture infectious dose: $TCID_{50}$
d) Virus reduction factor for used resin
e) The sum of the individual factors

(e) Manufacturing process development (Comparability)

The drug substance manufacturing process has undergone four changes during product development (Processes A-D; Process E is the commercial process). Of the main clinical studies in PNH patients, a foreign phase III clinical study (C04-001 [TRIUMPH]), a foreign phase III clinical study (C04-002 [SHEPHERD]), and their extension study (E05-001) used clinical trial material produced by Process D or E and a Japanese clinical study (C07-001) and its extension study (E07-001) used clinical trial material produced by Process E.

The seed cell line for the preparation of the MCB was changed from [redacted] to [redacted] that was of the same origin and had higher expression, which was used in Processes B to E. The fermentation process was scaled up from [redacted] L at the early stage of development to [redacted] L or [redacted] L in Process B, [redacted] L in Processes C and D, and [redacted] L in Process E. In the purification process, protein A derived from *Staphylococcus aureus* to be used in the affinity chromatographic step was changed to [redacted] protein A (genetical recombination) produced without using raw materials of biological origin and pH[redacted] treatment time in the virus inactivation step was changed from [redacted] to [redacted] minutes to [redacted] to [redacted] minutes,

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which were employed in Processes C to E. In order to consistently reduce an increase in aggregates as observed in 1 drug substance lot produced by Process C, [redacted] ion exchange chromatographic step was included in Process D. That step was further changed to [redacted] ion exchange chromatographic step in Process E in order to optimize the process. The pore size of a membrane filter for the virus removal step was changed from [redacted] nm to [redacted] nm, which was employed in Process E.

The comparability of the drug substances before and after manufacturing process changes has been demonstrated by comparing the results of specification tests and characterization studies between post-change drug substance and pre-change reference material.

2.A.(1).2) Structure/Composition

The following characterization studies were performed.

(a) Primary structure

i) Amino acid composition

After hydrolysis, each amino acid was quantified. As a result, the determined amino acid composition agreed with the theoretical values deduced from the cDNA sequence.

ii) N-terminal and C-terminal amino acid sequences

・No heterogeneity of the heavy- and light-chain N-terminal amino acid sequences was detected by Edman degradation. The heavy chain N-terminus was modified with pyroglutamic acid.

・Although no heterogeneity of the light-chain C-terminal amino acid residues was detected by nano-electrospray ionization-tandem mass spectrometry, the C-terminal Gly^{487} or Lys^{488} residue of the heavy chain was detected at a level of [redacted]% or [redacted]%, respectively.

iii) Peptide map

・The protein was reduced, alkylated and digested with trypsin and the obtained peptides were analyzed using reverse-phase chromatography-electrospray ionization-mass spectrometry (RP HPLC-ESI-MS). The results were consistent with the amino acid sequence deduced from cDNA.

・A glycosylation site was identified at Asn298 of the heavy chain CH2 region. No aglycosylation of tryptic peptide T21 (amino acid residues 294-302 of the heavy chain) was detected.

・The deamidation rate was about [redacted]% for T22 (amino acid residues 303-318 of the heavy chain) and [redacted]% for T32 (amino acid residues 372-393 of the heavy chain).

iv) Carbohydrate structure

・Monosaccharide compositional analysis was performed and four monosaccharides (fucose, mannose, galactose [Gal], and *N*-acetylglucosamine [GlcNAc]; about [redacted], [redacted], [redacted], and [redacted] nmol/mg, respectively) were identified and *N*-acetylgalactosamine was not detected, which indicated that eculizumab has no *O*-linked glycosylation. Sialic acid analysis was performed. As a result, the content of

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N-glycolylneuraminic acid (Neu5Gc) was about [redacted] mmol/mol and *N*-acetylneuraminic acid was detected in trace amount, but was below the lower limit of quantification (≤ [redacted] mmol/mol). Carbohydrate constitutes about [redacted]% of the mass of eculizumab.

· Matrix-assisted laser desorption/ionization time-of-flight mass spectrometry (MALDI-TOF-MS) or anion exchange chromatography of fluorescently labeled *N*-linked glycans was performed. As a result, fucosylated biantennary *N*-linked glycans with zero, one, or two non-reducing terminal Gal residue(s) (G0F, G1F, G2F; [redacted]%-[redacted]% in total) were mainly detected and glycans lacking the terminal GlcNAc (G0F-GN) and high mannose-type glycans (Man5) were slightly detected. Furthermore, αGal (Galα1-3Gal) glycans were detected at levels of [redacted]% to [redacted]% (size profile of glycans). Neutral and sialylated oligosaccharides were detected at levels of [redacted]% to [redacted]% and [redacted]% to [redacted]%, respectively (glycan charge profile).

(b) Physicochemical properties

i) Molecular weight

MALDI-TOF-MS and ESI-TOF-MS indicated that the molecular weight of the molecule is in agreement with the theoretical molecular mass of 147,870 Da.

ii) Electrophoretic patterns

· IEF showed [redacted] major bands and [redacted] to [redacted] minor bands within a pI range of [redacted] to [redacted].

· SDS-PAGE (CBB staining) yielded two major bands (heavy and light chains) and [redacted] minor bands whose intensities were below the lower limit of quantification (staining intensity, [redacted]%) (antibodies lacking [redacted] light chain, antibodies lacking [redacted] light chain and [redacted] heavy chain [[redacted] form]) under reducing conditions and one major band (monomer, ≥ [redacted]%), [redacted] minor bands (antibodies lacking [redacted] light chain, antibodies lacking [redacted] light chains, ≤ [redacted]% and ≤ [redacted]%, respectively), and [redacted] bands whose intensities were below the lower limit of quantification ([redacted] form, [redacted] different light chain fragments) under non-reducing conditions.

iii) Liquid chromatographic patterns

· Size exclusion chromatography (GE HPLC) yielded a main peak (monomer, ≥ [redacted]%) and a minor high molecular weight peak presumed to represent aggregates (≤ [redacted]%). The molecular weights of monomer and aggregates as determined by LC-ESI-TOF-MS matched the theoretical molecular masses of eculizumab and the dimer, respectively. The potency of aggregates (C5 binding assay) was about [redacted]%. Aggregates produced percent hemolysis of [redacted]% at [redacted] μg/mL and [redacted]% at [redacted] μg/mL, which were lower than monomer ([redacted]% and [redacted]%, respectively).

· Weak acid cation exchange column chromatography yielded one main peak and broad peaks unresolved from the main peak ([redacted] acidic peaks and [redacted] basic peaks).

· Reverse-phase chromatography yielded a single main peak and when the protein was reduced and alkylated, [redacted] main peaks (heavy and light chains) and [redacted] minor peaks were observed.

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· Hydrophobic interaction chromatography yielded a single main peak.

iv) Higher order structure

· The concentration of free sulfhydryl groups in eculizumab as determined by Ellman's assay was below the lower limit of quantification (10 μM).

· Analysis of non-reduced, alkylated tryptic peptides by RP HPLC-ESI-MS confirmed that 28 (14 pairs) out of a total of 36 Cys residues form disulfide bonds within the heavy chain, within the light chain, and between the heavy and light chains (Cys^{22} of the heavy chain-Cys^{96} of the heavy chain, Cys^{136} of the heavy chain-Cys^{214} of the light chain, Cys^{149} of the heavy chain-Cys^{205} of the heavy chain, Cys^{262} of the heavy chain-Cys^{322} of the heavy chain, Cys^{368} of the heavy chain-Cys^{426} of the heavy chain, Cys^{23} of the light chain-Cys^{88} of the light chain, Cys^{134} of the light chain-Cys^{194} of the light chain).

·Near-ultraviolet and far-ultraviolet circular dichroism (CD) yielded the spectra that are characteristic of an antibody. The wavelength of maximum absorption was [redacted] nm and the wavelength of minimum absorption was [redacted] nm. The percentage of β-sheet structure was about [redacted]%.

(c) Biological properties

· The binding affinity of eculizumab for human C5 (dissociation constant), association rate constant, and dissociation rate constant, as determined by surface plasmon resonance, were approximately [redacted] pM, approximately [redacted]$\times 10^{5}$ $M^{-1}s^{-1}$, and approximately [redacted]$\times 10^{-5}$ s^{-1}, respectively, at [redacted]°C and were approximately [redacted] pM, approximately [redacted]$\times 10^{6}$ $M^{-1}s^{-1}$, and approximately [redacted]$\times 10^{-4}$ s^{-1}, respectively, at [redacted]°C.

· The functional complement inhibition activity of eculizumab in human serum was assessed using a hemolytic assay measuring the hemoglobin release from chicken red blood cells. Eculizumab produced percent hemolysis of > [redacted]% at [redacted] μg/mL, but < [redacted]% at [redacted] μg/mL, and almost completely inhibited hemolysis at [redacted] μg/mL.

· Since eculizumab has an IgG_2-IgG_4 heavy chain backbone, eculizumab is not considered to exhibit complement-dependent cytotoxicity activity or antibody-dependent cell-mediated cytotoxicity (ADCC) activity.

· [redacted] mAb epitope mapping ([redacted] and [redacted] using [redacted] or [redacted], and [redacted]) and [redacted] various domains [redacted] and its [redacted]) indicated that [redacted]-terminal [redacted] domain of the human C5α chain is recognized as an epitope.

2.A.(1).3) Product-related substances

Heavy chain N-terminal pyroglutamate, loss of C-terminal lysine residue of the heavy chain, deamidation, oligosaccharide variants, and charge variants have been detected.

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2.A.(1).4) Impurities

(a) Process-related impurities

It has been confirmed that the media components used in the cell culture process, i.e. [redacted], [redacted], and cholesterol are removed to below the lower limit of quantification ([redacted] ppm, [redacted] μg/mL, and [redacted] ng/mL, respectively) by the affinity chromatographic step. Protein A, BSA, HCP, and host cell DNA are reduced in the purification process (< [redacted] ng/mg, < [redacted] ng/mg, < [redacted] ng/mg, and < [redacted] pg/mg, respectively) and listed as impurities in the drug substance specification.

(b) Product-related impurities

Antibody fragments have consistently been detected as minor bands on reducing/non-reducing SDS-PAGE (CBB staining) [see "2.A.(1).2) Structure/Composition (b) Physicochemical properties ii) Electrophoretic patterns"]. The impurities that increase during the shelf-life of the drug substance or the drug product are aggregates identified on reducing/non-reducing SDS-PAGE (CBB staining) and GE HPLC and acidic variants identified by IEF.

2.A.(1).5) Drug substance specification

The proposed specifications for the drug substance are description (appearance), identification (peptide map, size profile of glycans, IEF), osmolality, pH, purity (protein A, BSA, HCP, host cell DNA), polysorbate 80, test for total viable count, bacterial endotoxins, reducing/non-reducing SDS-PAGE (CBB staining), GE HPLC, hemolytic assay, C5 binding assay, and protein concentration.

2.A.(1).6) Stability of drug substance

Using commercial scale lots of the drug substance stored in [redacted] mL LDPE bags, long-term testing (2°C-8°C, 24 months, 3 lots) and accelerated testing ([redacted]°C-[redacted]°C, [redacted] months, 3 lots; [redacted]°C-[redacted]°C, [redacted] months, 1 lot) were conducted and the following stability information was evaluated: description (appearance), peptide map, IEF, osmolarity, pH, reducing/non-reducing SDS-PAGE (CBB staining), GE HPLC, sterility test, bacterial endotoxins, hemolytic assay, C5 binding assay, and protein concentration. At the long-term storage condition, although an increase of aggregates associated with a [redacted]% to [redacted]% decrease of monomers were detected by GE HPLC, there were no marked changes in other attributes tested up to 24 months. At the accelerated condition, the percentage of acidic bands on IEF increased from [redacted]% to [redacted]% at the initial timepoint to [redacted]% to [redacted]%, an increase of aggregates associated with a [redacted]% to [redacted]% decrease of monomers were detected by GE HPLC, and reducing SDS-PAGE (CBB staining) showed about [redacted]% decreases in the heavy and light chains. Since the formulation of the drug product is the same as that of the drug substance, stress testing was performed on the drug product.

Based on the above, a shelf life of 18 months has been proposed for the drug substance when stored in [redacted] L LDPE bags at 2°C to 8°C, protected from light.

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2.A.(2) Drug product

2.A.(2).1) Formulation development

The drug product is an injectable solution and each glass vial contains 300 mg of Eculizumab (Genetical Recombination), the active ingredient, in 30 mL of product solution and the other ingredients are 263.1 mg sodium chloride as an isotonizing agent, 13.8 mg sodium dihydrogenphosphate monohydrate and 53.4 mg disodium hydrogenphosphate heptahydrate as buffering agents, 6.6 mg polysorbate 80 as a stabilizer, and the appropriate amount of water for injection as a solvent. The vial contains an overfill of 1.7 mL.

2.A.(2).2) Drug product manufacturing process

The formulated drug substance is mixed (mixing process), sterile filtered using a hydrophilic membrane filter ([redacted] μm), filled into colorless glass vials, stoppered with siliconized butyl rubber stoppers, and sealed with aluminum seals with polypropylene flip-off caps (sterile filtration/filling/closing process) and packaged (packaging process) and primarily stored at 2°C to 8°C (storage process). The vials are allowed to adjust to room temperature, labelled, and secondary packaged and then stored at 2°C to 8°C (packaging/storage process). The sterile filtration/filling/closing, storage, and packaging/storage processes have been defined as critical process steps. As in-process control tests, test for total viable count during the mixing process, filter integrity test and sterility test during the sterile filtration process, fill weight testing during the filling process, visual inspection during the packaging process, and visual inspection during the packaging/storage process are performed. IEF and hemolytic assay are performed at release. [redacted] to [redacted] at [redacted] ([redacted]) or [redacted] ([redacted]) and [redacted].

During the drug product development, the volume was changed from [redacted] mL to [redacted] mL and [redacted] mL, and then to 30 mL, but the formulation did not change.

2.A.(2).3) Drug product specification

The proposed specifications for the drug product are description (appearance), identification (peptide map), osmolarity, pH, reducing/non-reducing SDS-PAGE (CBB staining), GE HPLC, bacterial endotoxins, sterility test, extractable volume, insoluble particulate matter, foreign insoluble matter, C5 binding assay, and protein concentration.

2.A.(2).4) Stability of drug product

Stability studies of the drug product are summarized in Table 5.

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Table 5. Summary of stability studies of drug product

Stability testing	Test attributes	Test results	
		[redacted]	[redacted]
Long-term testing 2°C-8°C 36 months Protected from light Upright and inverted positions	description (appearance), pH, osmolarity, peptide map, IEF, reducing/non-reducing SDS-PAGE (CBB staining), GE HPLC, sterility test, bacterial endotoxins, insoluble particulate matter, C5 binding assay, protein concentration	3 lots The percentage of acidic bands on IEF increased from [redacted]% at the initial time point to [redacted]% and an increase of aggregates associated with a [redacted]% decrease of monomers were detected by GE HPLC, but there were no marked changes in other attributes tested up to 36 months.	3 lots Stable up to 3 months. Testing will continue up to 36 months.
Accelerated testing 1 20°C-25°C 12 months Protected from light Inverted position	description (appearance), pH, osmolarity, peptide map, IEF, reducing/non-reducing SDS-PAGE (CBB staining), GE HPLC, C5 binding assay, bacterial endotoxins, protein concentration	3 lots As the percentage of the major band on IEF decreased from [redacted]% at the initial time point to [redacted]%, a new band was detected. An increase of aggregates associated with a [redacted]% decrease of monomers were detected by GE HPLC. A new band with a slight increase of aggregates were detected by non-reducing SDS-PAGE. Increases of low and high molecular weight bands with about [redacted]% decreases of heavy and light chains were detected by reducing SDS-PAGE.	—
Accelerated testing 2 23°C-27°C 12 months Protected from light Inverted position	description (appearance), pH, osmolarity, IEF, reducing/non-reducing SDS-PAGE (CBB staining), GE HPLC, hemolytic assay,[1] C5 binding assay, bacterial endotoxins, protein concentration	1 lot Stable up to [redacted] months. Testing will continue up to [redacted] months.	3 lots A slightly broader range of pIs was detected by IEF at [redacted] months, but there were no changes in other attributes tested. Testing will continue up to [redacted] months.
Stress testing[2] (a) Forced degradation low pH, high pH, oxidation, deamidation, storage at high temperature (b) Extreme temperature ・High temperature ([redacted] hours): [redacted]°C-[redacted]°C, [redacted]°C-[redacted]°C ・Low temperature ([redacted] days): [redacted]°C-[redacted]°C (c) [redacted] temperature cycles [redacted]°C-[redacted]°C ([redacted] days) followed by [redacted]°C-[redacted]°C ([redacted] days) [redacted]°C-[redacted]°C ([redacted] days) followed by [redacted]°C-[redacted]°C ([redacted] days) ・[redacted]°C-[redacted]°C ([redacted] days) followed by [redacted]°C-[redacted]°C ([redacted] hours) (d) Photostability Light exposure condition ([redacted] million lx·h, [redacted] W·h/m²) Ambient temperature (e) Vibration 2°C-8°C	(a)-(e): description (appearance), reducing/non-reducing SDS-PAGE (CBB staining), IEF, GE HPLC (d) (light-protected samples only): pH, osmolarity, insoluble particulate matter (a) and (d) (light-protected samples only) peptide map, hemolytic assay (a), (c)-(e): C5 binding assay (c)-(e): protein concentration	(a) pH[redacted]: Degradation occurred. pH[redacted]: Stable for [redacted] days. Oxidation: Degradation occurred. Deamidation: Degradation occurred. 40°C: Stable for [redacted] hours. (b) Comparable to controls. (c) Comparable to controls. (d) Following light exposure, a decrease of monomers was detected by GE HPLC, a decrease of monomers was detected by non-reducing SDS-PAGE, and a decrease of the major band and a new minor band were detected by IEF. Comparable to controls when protected from light. (e) Comparable to controls.	—

[1] Not performed for DSM.
[2] Upright position for (b) and inverted position for others.

In addition to the above studies, a preliminary study to explore the storage conditions for reference materials was conducted. As a result, a decrease of monomers was detected by GE HPLC when stored frozen ([redacted]°C, [redacted]°C) vs. refrigerated (2°C-8°C). Therefore, taking account of the impact of prolonged freezing on drug product quality, a shelf-life of 30 months has been proposed for the drug product when stored at 2°C to 8°C, protected from light.

The drug product was diluted with each intravenous solution (Isotonic Sodium Chloride Solution, JP;

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Glucose Injection, JP [5%]; or Ringer's Solution, JP) to the final concentration of 5 mg/mL. The stability of the diluted solutions when stored at 2°C to 8°C or 20°C to 25°C for up to 72 hours was assessed. As a result, there were no marked changes in description (appearance), IEF, reducing/non-reducing SDS-PAGE (CBB staining), GE HPLC, hemolytic assay, or C5 binding assay in each solution.

2.A.(3) Reference materials

The current reference materials, [redacted] and [redacted] are drug substances produced in accordance with the drug substance manufacturing process (Process E) (Lot numbers, [redacted] and [redacted]) and stored at 2°C to 8°C. Reference materials should meet the drug substance specification and should be tested for quality attributes (IEF, reducing/non-reducing SDS-PAGE [CBB staining], GE HPLC, hemolytic assay, C5 binding assay, protein concentration) and characterized (monosaccharide compositional analysis, sialic acid analysis, glycan charge profile, molecular weight [MALDI-TOF-MS, ESI-MS], N-terminal amino acid sequencing, CD).

The tentative shelf-life of the reference materials is [redacted] years and the stability of the reference materials during storage will be assessed by evaluating the quality attributes every [redacted] years and whether the shelf life may be extended will be determined.

A new reference material will be prepared in accordance with the current drug substance manufacturing process based on the shelf-life and the amount left and a newly prepared reference material will be tested for quality attributes and characterized.

2.B Outline of the review by PMDA

2.B.(1) Evaluation of disulfide bond heterogeneity

Though eculizumab has an IgG_2-IgG_4 heavy chain backbone and different patterns of disulfide bonds between Cys residues are expected compared with other IgG subclasses, inter-heavy chain disulfide bonds involving 8 residues in the hinge regions of the two heavy chains (Cys^{224}-Cys^{224}, Cys^{225}-Cys^{225}, Cys^{228}-Cys^{228}, Cys^{231}-Cys^{231}) have not been detected. Thus, PMDA asked the applicant if the patterns of disulfide bonds in eculizumab have been fully analyzed and if their consistency is controlled.

The applicant conducted an additional study, identified peptides containing 9 different hinge regions by ESI-Q-TOF-MS, and presented the structures of 3 different disulfide bond variants deduced from the detected peptides. The applicant responded that although these variants are considered to be consistently present, it is technically difficult to control the variants quantitatively.

Although it is understood that quantitative control is difficult, PMDA is asking the applicant to show their view on the need to control the heterogeneity of these variants, taking account of the possible

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effects of these variants on the safety and efficacy of eculizumab.

2.B.(2) Control of immunogenic glycans

Since eculizumab contains fucosylated biantennary *N*-linked oligosaccharides bearing immunogenic Neu5Gc or αGal (including Galα1-3Gal), PMDA asked the applicant to explain the influences of glycan structure and its heterogeneity on the safety of eculizumab. In terms of ensuring safety, PMDA is also asking the applicant to explain the need to include the Neu5Gc content in the specification and provide a justification for the specification limit for the αGal content.

2.B.(3) C5 binding assay

PMDA asked the applicant to explain the reasons for changing the C5 binding assay method and for variability in assay values despite the principle of the assay being the precise ELISA (enzyme-linked immunosorbent assay) method and provide a justification for the specification limits.

The applicant responded as follows:

Although biotinylated protein L was used for the detection of eculizumab bound to C5 protein in the old assay, as the production of the detection reagents including this reagent and the detector was discontinued, a new assay has been employed, which uses HRP (horseradish peroxidase)-labeled mouse anti-human IgG_4 antibody for detection. Although the values obtained with the new assay are about [redacted]% lower than those obtained with the old assay, the robustness of the new assay has been demonstrated through a validation study. The values obtained with the new assay for the internal standard, the clinical formulation, and the proposed commercial formulation were within a range of 800,000 to 1,200,000 BU/mg, as with the old assay. The change to the new assay was approved by EMEA in April 2009 and FDA in June 2009.

PMDA is asking the applicant to provide a justification for the specification limits, taking account of the values obtained with the new assay for the clinical formulation and the proposed commercial formulation that have been used in patients.

2.B.(4) Drug product specification

2.B.(4).1) Inclusion of foreign insoluble matter test

PMDA asked the applicant to consider including Foreign Insoluble Matter Test for Injections, JP in the drug product specification.

The applicant responded that although foreign insoluble matters have never been detected so far, Foreign Insoluble Matter Test will be included in the specification.

PMDA accepted the response.

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2.A.(4).2) Inclusion of IEF and hemolytic assay

PMDA is asking the applicant to explain the reason for not including IEF and hemolytic assay in the specification in Japan despite IEF and hemolytic assay being included in the drug product specification in the US and Europe and the basis for considering that the quality of the drug product can be assured by the results of these tests performed at the time of its release.

3. Non-clinical data

3.(i) Summary of pharmacology studies

3.(i).A Summary of the submitted data

3.(i).A.(1) Primary pharmacodynamics

There are three pathways of complement activation and C3a and C3b are formed from C3 in all three pathways. C3b cleaves C5 into C5a and C5b. C5a has anaphylatoxin activity and leukocyte chemotactic activity and induces mast cell degranulation, vascular hyperpermeability, and smooth muscle contraction etc. C5b interacts with C6 to C9, allowing for the formation of the complex C5b-9 and C5b-9 causes cell lysis. As eculizumab is an anti-C5 antibody, the potency of each anti-C5 antibody was assessed by measuring hemolytic activity* and C5a generation.

3.(i).A.(1).1) Generation of eculizumab (4.2.1.1.1-4.2.1.1.3, Studies GTR49, GTR56, and GTR52)

Murine anti-human C5 (hC5) mAbs were screened and m5G1.1 mAb as an inhibitor of both hemolytic activity (complete inhibition at [redacted] μg/mL) and C5a generation (complete inhibition at [redacted] μg/mL) was selected. The K_D of m5G1.1 mAb for hC5 was 29.5 pmol/L.

In order to reduce immunogenicity in humans, the CDRs of m5G1.1 mAb were inserted into a human antibody (h5G1.1) and using the Fab region of the generated antibody (h5G1.1 Fab (CDR)), the capacity to compete with m5G1.1 mAb for binding to hC5 was compared. As a result, the Fab region of m5G1.1 mAb and h5G1.1 Fab (CDR) exhibited similar capacities to compete with m5G1.1 mAb for binding to hC5 at [redacted] ng/mL to [redacted] μg/mL. Thus, the applicant explained that humanization of the framework regions had no effect on the hC5 binding capacity of the antibody.

For further humanization, an antibody containing the variable regions of h5G1.1 Fab (CDR), human κ light-chain constant regions, and hybrid human IgG_2-IgG_4 heavy-chain constant regions, which have been reported to be unable to activate complement or bind to the Fc-γ receptor of effector cells (h5G1.1 G2/G4 mAb: eculizumab), was generated.

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* Chicken erythrocytes sensitized with anti-chicken erythrocyte antibody were added to human serum for hemolysis.

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3.(i).A.(1).2) C5 inhibition activity of eculizumab (4.2.1.1.4 and 4.2.1.1.6, Studies GTR84 and BP 26FR)

Eculizumab, h5G1.1 G4 mAb[†], and m5G1.1 mAb inhibited human serum-mediated hemolysis of chicken erythrocytes sensitized with anti-chicken erythrocyte antibody (almost complete inhibition at 100 μg/mL, [redacted] μg/mL, and [redacted] μg/mL, respectively) and the applicant explained that the difference in the heavy-chain constant regions were shown not to affect C5 inhibition activity.

In another study, eculizumab almost completely blocked human serum-mediated hemolysis of chicken erythrocytes sensitized with anti-chicken erythrocyte antibody at 25 μg/mL, but did not inhibit hemolysis in rhesus monkey, baboon, chimpanzee, cynomolgus monkey, pig, rabbit, rat, or guinea pig sera even at 100 μg/mL.

3.(i).A.(1).3) Affinity of eculizumab for hC5 (4.2.1.1.5, Study GTR109)

The K_D of eculizumab for hC5 (mean ± standard deviation [SD]) was 46 ± 1.6 pmol/L (25°C) or 120 ± 5.5 pmol/L (37°C).

3.(i).A.(1).4) Epitope mapping of hC5 (4.2.1.1.7, Study GTR55)

Epitope mapping of hC5 using m5G1.1 mAb was performed, which indicated that the antibody recognizes the amino acid sequences at positions 822 to 826 (DVFLE), 879 to 883 (KSSKC), and 930 to 933 (VPEG) as an epitope cluster.

3.(i).A.(2) Secondary pharmacodynamics

3.(i).A.(2).1) Cross-reactivity with human tissues (4.2.1.2.1, Study PAI-IM1184)

The potential cross-reactivity of eculizumab (5 and 30 μg/mL) with cryosections of normal human tissues was evaluated by immunostaining. As a result, eculizumab staining was observed in smooth and striated muscle in various tissues, myoepithelium, myofibroblasts, renal tubular epithelium, reticulum cells, and platelets etc. The applicant discussed that eculizumab is not considered to have cross-reacted with human tissues because (a) C5 expression in vascular smooth muscle cells and heart muscle have been demonstrated (*Microbiol Immunol.* 1999;43:585-593, *Circ Res.* 1998;83:860-869.), (b) C5 is a secreted protein and is not expressed on cell surface (*Annu Rev Immunol.* 1995;13:277-305.), and (c) the staining likely represents staining of intracellular C5 as acetone fixation and cryotomy of the tissue/cell samples expose intracellular sites.

3.(i).A.(3) Safety pharmacology

Since eculizumab has high selectivity for hC5 and is species-specific, no safety pharmacology studies have been conducted.

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† An antibody containing the variable regions of h5G1.1 Fab (CDR), human κ light-chain constant regions and human IgG4 heavy-chain constant regions

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3.(i).B Outline of the review by PMDA

3.(i).B.(1) Efficacy of eculizumab in PNH

PNH arises from the deficiency of the GPI-anchored terminal complement inhibitor CD59 on hematopoietic stem cells. Since CD59 inhibits C9 binding to complement C5 and blocks the formation of the terminal complement complex C5b-9 on the RBC surface, the deficiency of CD59 on PNH RBCs leads to deposition of cytolytic C5b-9 on the surface, which results in hemolysis.

Eculizumab binds to hC5, preventing the formation of C5b-9 by inhibiting the cleavage of C5 and is expected to reduce C5b-9-mediated hemolysis.

Although non-clinical pharmacology studies submitted in the application have not demonstrated hemolytic inhibitory activity *in vivo*, as there is no animal model of PNH and eculizumab was created as an antibody against hC5 and did not inhibit hemolysis in non-human sera, suggesting that eculizumab does not inhibit C5 in sera of other species, the lack of a non-clinical *in vivo* study to demonstrate efficacy of eculizumab was unavoidable. On the other hand, since *in vitro* studies using eculizumab showed that eculizumab binds to hC5 and inhibits human serum-mediated hemolysis, it can be inferred that eculizumab reduces hemolysis by inhibiting the cleavage of C5 and preventing the formation of C5b-9.

However, many of *in vitro* studies were performed once. Data from repeated studies were needed for explanation in order to check the reproducibility of studies.

3.(i).B.(2) Cross-reactivity of eculizumab

PMDA's view on the applicant's discussion that eculizumab does not cross-react with various human tissues is as follows:

It has been reported that C5 is a secreted protein and is not expressed on cell surface and it has also been explained that secreted proteins were fully removed. Thus, an inference that the observed staining was due to the binding of eculizumab to intracellular C5 is understandable. However, since the cross-reactivity study of eculizumab with human tissues was conducted by the methods that expose intracellular sites, it is difficult to determine whether eculizumab staining of tissues represents eculizumab binding to cell surface or intracellular sites of tissues. If eculizumab cross-reacts with the cell surface of tissues, there should be potentially some effects on biological functions. However, except for headache, there were no particular adverse events reported at a higher incidence by the eculizumab group than by the placebo group in a clinical study (C04-001 [TRIUMPH]). The applicant discussed the mechanism of eculizumab-induced headache as follows: hemolysis inhibition by eculizumab leads to reduced free Hb, which scavenges nitric oxide (NO), and increased free NO dilates blood vessels, causing headache. However, as the mechanism is undefined, the possible involvement of the cross-reactivity of eculizumab can not be excluded.

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PMDA asked the applicant about findings on the cross-reactivity of eculizumab with complements other than C5 or cytokines. The applicant responded that no cross-reactivity study of eculizumab with complements other than C5 or cytokines had been conducted.

PMDA considers as follows:
If eculizumab cross-reacts with complements other than C5 or cytokines, the immune function will be affected. However, as no marked increase in the incidence of infection-related adverse events was observed in the clinical study (C04-001 [TRIUMPH]), the possibility that the cross-reactivity of eculizumab with complements other than C5 or cytokines leads to clinically immediately relevant events has not been suggested so far.

3.(i).B.(3) Safety pharmacology

Since no safety pharmacology studies of eculizumab have been performed, PMDA asked the applicant to explain the effects of eculizumab on the central nervous, cardiovascular, and respiratory systems based on the results from toxicity and clinical studies, etc.

The applicant explained as follows:
In a 26-week intravenous injection toxicity study in mice of a murine anti-C5 antibody, BB5.1 mAb, there were no effects on the central nervous, cardiovascular, or respiratory systems at the doses inhibiting hemolytic activity [see "3.(iii).A.(2) Repeat-dose toxicity"]. In clinical studies, except for headache, there were few adverse events involving central nervous, cardiovascular, or respiratory system, etc. Therefore, it is considered that eculizumab has no significant effects on the central nervous, cardiovascular, or respiratory systems.

PMDA considers as follows:
Since eculizumab was developed as an antibody against hC5 and there is no cross-reactivity of eculizumab with C5 from other species and eculizumab is a humanized antibody except for the CDRs, it is understood that safety pharmacology evaluation is difficult. On the other hand, there were no treatment-related effects on the central nervous, cardiovascular, or respiratory systems at the doses inhibiting hemolytic activity in the 26-week repeat-dose toxicity study in mice of a murine anti-C5 antibody, BB5.1 mAb. Thus, non-clinical data indicate that there are no effects of C5 inhibition on the central nervous, cardiovascular, and respiratory systems.

See "4.(iii).B.(5) Safety" for the safety of eculizumab in clinical studies.

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3.(ii) Summary of pharmacokinetic studies

3.(ii).A Summary of the submitted data

Since eculizumab binds specifically to hC5, a C5-deficient mouse model reconstituted with hC5, and an IgG_4 isotype of eculizumab (h5G1.1 G4 mAb), which is identical in amino acid sequence to eculizumab except that it contains the human IgG_4 heavy-chain constant region, instead of eculizumab, were used to determine the serum concentrations of the antibody over time and assess hemolytic activity.[‡]

The hC5 and h5G1.1 G4 mAb levels were determined by ELISA assay.

3.(ii).A.(1) Absorption

3.(ii).A.(1).1) Single-dose studies (4.2.2.2.1, Studies GTR-0104.00 and GTR-0104.01)

Male mice were intravenously or subcutaneously injected a single dose of h5G1.1 G4 mAb at 5, 17, 50, 100, or 150 µg, or 190 µg of 2A2 HuG4[§] as a negative control antibody, or vehicle (0.2 mL phosphate-buffered saline) and hemolytic activity inhibition was assessed for up to 48 hours after injection. Hemolytic activity inhibition was detected from 2 minutes until 48 hours following the intravenous administration of 50 to 150 µg of h5G1.1 G4 mAb and hemolytic activity inhibition was detected, but delayed by 24 hours following the subcutaneous injection of 50 µg.

Female mice were intravenously or subcutaneously injected a single dose of 50 µg of h5G1.1 G4 mAb or 60 µg of 2A2 HuG4 and serum h5G1.1 G4 mAb and 2A2 HuG4 concentrations over time were determined. Serum h5G1.1 G4 mAb concentrations over time following the single intravenous or subcutaneous administration of 50 µg of h5G1.1 G4 mAb are shown in Figure 1.

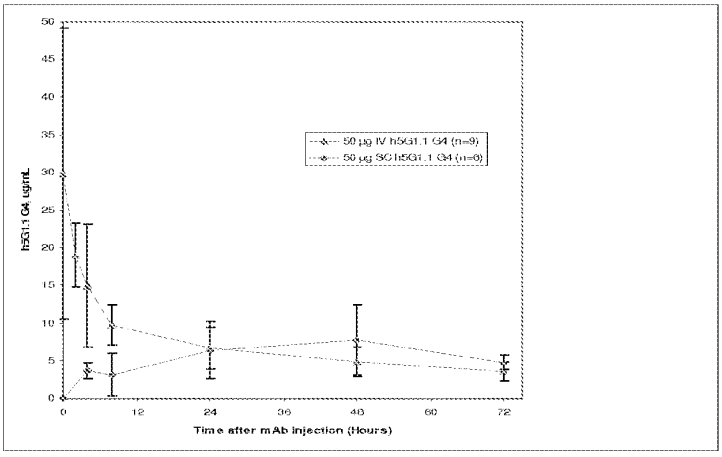


Figure 1. Serum h5G1.1 G4 mAb concentrations over time following single administration of h5G1.1 G4 mAb

‡ Chicken erythrocytes sensitized with anti-chicken erythrocyte antibody were added to mouse serum for hemolysis.

§ An unrelated antibody with a human IgG_4 heavy-chain constant region

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3.(ii).A.(2) Distribution, metabolism, excretion, and pharmacokinetic drug interactions

As eculizumab and h5G1.1 G4 mAb bind to a soluble protein, hC5, which is secreted into the blood and do not bind to murine C5, a distribution (organ/tissue distribution, protein binding, placental transfer, etc.), metabolism, excretion, or pharmacokinetic drug interaction study has not been performed.

The applicant discussed as follows:

Generally, placental transfer of maternal IgG antibodies to the fetus is known and antibodies are excreted in milk. Thus, eculizumab is also expected to cross the placenta and be excreted in milk.

3.(ii).B Outline of the review by PMDA

3.(ii).B.(1) Non-clinical pharmacokinetic studies

PMDA considers as follows:

Since eculizumab, developed as an antibody against hC5, does not demonstrate cross-reactivity with C5 from other species and is a humanized antibody except for the CDRs, the lack of non-clinical pharmacokinetic assessment of eculizumab was unavoidable. The h5G1.1 G4 mAb concentrations over time determined in mice are just reference information because a C5-deficient mouse model reconstituted with hC5 was used and the heavy-chain constant region structure of h5G1.1 G4 mAb, which was used instead of eculizumab, is different from that of eculizumab, and it is difficult to predict the pharmacokinetics of eculizumab in humans.

3.(iii) Summary of toxicology studies

3.(iii).A Summary of the submitted data

Since eculizumab binds specifically to hC5 and did not inhibit hemolysis in sera from the non-human animals studied [see "3.(i).A.(1).2) C5 inhibition activity of eculizumab"], a non-clinical toxicity study of eculizumab has not been performed. However, using a surrogate murine anti-murine C5 monoclonal antibody, BB5.1 mAb, 26-week repeat-dose and reproductive and developmental toxicity studies in mice were conducted to evaluate the long-term treatment effects of C5 inhibition on tissue toxicity and reproductive function. BB5.1 mAb is a full-length monoclonal antibody of IgG_1 isotype and its amino acid sequence is different from that of eculizumab, but publications (*J Clin Invest.* 2005;115:1590-1600, etc.) have reported that BB5.1 mAb binds specifically to murine C5 and blocks C5b-9 activity and C5a activity *in vitro* and *in vivo*.

For serum BB5.1 mAb concentrations, percent hemolysis at each timepoint was measured using a serum complement hemolytic activity assay system [see "3.(i).A.(1).2) C5 inhibition activity of eculizumab"] and a lower percent hemolysis compared with the control group was a qualitative indicator of systemic exposure.

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3.(iii).A.(1) Single-dose toxicity

No single-dose studies have been conducted.

3.(iii).A.(2) Repeat-dose toxicity (4.2.3.2-1 and 4.2.3.2-2, Studies 6709-108 and 6709-109)

Female mice were intravenously administered vehicle (20 mM Tris-buffered saline three times weekly) or 30 mg/kg of BB5.1 mAb once, twice, or three times weekly (30, 60, or 90 mg/kg/week) for 4 weeks. No toxic signs were observed. The percent hemolysis was 92% to 94% in the control group, 3% to 34% in the once weekly (30 mg/kg/week) group, 1% to 13% in the twice weekly (60 mg/kg/week) group, and 0% to 15% in the three times weekly (90 mg/kg/week) group. Since hemolytic activity was similar for mice treated with BB5.1 mAb twice weekly (60 mg/kg/week) and three times weekly (90 mg/kg/week), it was concluded that the highest dose of BB5.1 mAb in future toxicology studies is 60 mg/kg/week.

Female or male mice were intravenously administered vehicle (20 mM Tris-buffered saline twice weekly) or 30 mg/kg of BB5.1 mAb once or twice weekly (30 or 60 mg/kg/week) for 26 weeks (a 4-week recovery period was scheduled for mice in the control and 60 mg/kg/week groups). Five mice (3 males and 2 females) in the 60 mg/kg/week group died and the cause of deaths was unknown. Even in the control group, 4 deaths (3 males and 1 female) occurred. As there were no toxicologically significant changes, the no observed adverse effect level (NOAEL) was determined to be 60 mg/kg/week.

The mean percent hemolysis was 68.3% to 86.6% in the control group (including prior to initiation of treatment and after a 4-week recovery), 13.3% to 18.8% in the 30 mg/kg/week group (during treatment), and 3.9% to 21.0% in the 60 mg/kg/week group (during treatment). The mean percent hemolysis was 41.7% in females and 67.5% in males (after a 4-week recovery) and there was no particular gender-related difference.

3.(iii).A.(3) Genotoxicity and carcinogenicity

Eculizumab is specific to hC5 and does not have cell proliferative activity or growth factor-like activity and it was considered that genotoxic substances are unlikely to arise from the manufacturing process of eculizumab. Thus, no genotoxicity or carcinogenicity studies have been conducted.

3.(iii).A.(4) Reproductive and developmental toxicity

Although the placental transfer of eculizumab or BB5.1 mAb has not been studied, as BB5.1 mAb is an IgG_1 antibody, it is inferred that it may cross the placenta.

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3.(iii).A.(4).1) Study of fertility and early embryonic development to implantation (4.2.3.5.1.1, Study 6709-104)

Mice were intravenously administered vehicle (20 mM Tris-buffered saline twice weekly) or 30 mg/kg of BB5.1 mAb once or twice weekly (30 or 60 mg/kg/week). Male mice were dosed from 4 weeks prior to mating until 1 or 2 days prior to necropsy and female mice were dosed from 2 weeks prior to mating, throughout the mating period, and until gestation day 7. Although dose-related, reduced body weight gain, reduced food consumption, and decreased prostate gland weight were observed in males, there were no abnormalities in copulation index, sperm motility, or epididymal sperm count, etc. There were no abnormalities in clinical signs or reproductive performance in females. The NOAELs for parental general toxicity, parental reproductive toxicity, and embryo-fetal viability were all determined to be 60 mg/kg/week.

The percent hemolysis (mean ± SD) was 90.2 ± 11.9% (at Week 4) and 100.0 ± 0.0% (at Week 10) in males and 98.4 ± 3.0% (on gestation day 12) in females in the control group, 24.6 ± 16.5% (at Week 4) and 27.2 ± 14.6% (at Week 10) in males and 50.6 ± 46.0% (on gestation day 12) in females in the 30 mg/kg/week group, and 7.0 ± 6.2% (at Week 4) and 16.2 ± 10.1% (at Week 10) in males and 50.6 ± 29.5% (on gestation day 12) in females in the 60 mg/kg/week group.

3.(iii).A.(4).2) Embryofetal development study (4.2.3.5.2.1, Study 6709-105)

Pregnant mice were intravenously administered vehicle (20 mM Tris-buffered saline twice weekly) or 30 mg/kg of BB5.1 mAb once or twice weekly (30 or 60 mg/kg/week) from gestation day 6 to gestation day 15. There were no abnormal findings in dams. In fetuses, one case of malrotated hindlimbs and one case of cleft palate were observed at 30 mg/kg/week, but not at 60 mg/kg/week and therefore, these findings were considered unrelated to BB5.1 mAb. At 60 mg/kg/week, one case of umbilical hernia and two cases (from two different litters) of unilateral retinal dysplasia (folded retina: a severe fold or multiple folds of the retina) were observed and these findings were considered related to BB5.1 mAb.

Evaluations for the umbilical hernia and folded retinas observed in mouse fetuses were performed by an external consultant. According to a report by Research Triangle Institute international, a laboratory and research organization (RTI project No. 08412.007), these findings did not occur. There is a case in which fetal retinal folds were shown to be artifacts produced by the process of tissue preparation (*Toxicol Appl Pharmacol.* 1976;35:347-354.) and although congenital retinal dysplasia should be usually bilateral, the retinal dysplasia was unilateral in this study and there were no other intraocular abnormalities or haemorrhage, etc. Therefore, the applicant explained that the folded retinas may have been artifacts. The development of umbilical hernia was assessed as unknown relationship to BB5.1 mAb.

The NOAEL was determined to be 60 mg/kg/week for maternal general and reproductive toxicity and

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the NOAEL for fetal developmental toxicity was determined to be 30 mg/kg/week as umbilical hernia was noted at 60 mg/kg/week.

The percent hemolysis (mean ± SD) (on gestation day 18) was 78.0 ± 43.8% in the control group, 52.6 ± 49.0% in the 30 mg/kg/week group, and 62.4 ± 37.8% in the 60 mg/kg/week group.

3.(iii).A.(4).3) Study for effects on pre- and postnatal development, including maternal function (4.2.3.5.3.1, Study 6709-107)

Pregnant mice were intravenously administered vehicle (20 mM Tris-buffered saline twice weekly) or 30 mg/kg of BB5.1 mAb once or twice weekly (30 or 60 mg/kg/week) from gestation day 6 to lactation day 18. There were no abnormal findings in maternal animals or pups and the NOAELs for maternal general toxicity and reproductive performance and for F_1 pups were both determined to be 60 mg/kg/week.

The percent hemolysis (mean ± SD) (on lactation day 14) was 95.6 ± 7.0% in the control group, 80.6 ± 20.5% in the 30 mg/kg/week group, and 83.6 ± 16.6% in the 60 mg/kg/week group.

Pregnant and lactating mice in the above 1) to 3) reproductive and developmental toxicity studies exhibited higher percent hemolysis (50.6%-80.6% at 30 mg/kg/week and 50.6%-83.6% at 60 mg/kg/week [mean]) than the non-pregnant female mice in the 26-week repeat-dose toxicity study (13.3%-14.5% at 30 mg/kg/week and 3.9%-4.6% at 60 mg/kg/week). The applicant inferred that pregnancy and lactation may have affected the amount of complement or the complement inhibitory function of the antibody, but the cause is unknown.

3.(iii).A.(5) Local tolerance

No local tolerance studies have been performed with eculizumab or other anti-C5 antibodies. However, BB5.1 mAb or vehicle-related local irritation at the injection site was not observed in repeat-dose or reproductive and developmental toxicity studies.

3.(iii).B Outline of the review by PMDA

3.(iii).B.(1) Retinal dysplasia

PMDA's view on the retinal dysplasia observed in an embryofetal development study is as follows:

The conducting laboratory concluded that the folded retinas were due to a teratogenic effect of BB5.1 mAb, whereas the applicant explained that the folded retinas were not related to BB5.1 mAb, based on the inference mainly from the background data for the cases of folded retina and the case of artifacts. However, histopathological findings of the retinas, hemolytic inhibition in the dams of normal fetuses vs. the dams of the fetuses with folded retinas, or receptor distribution in ocular tissue, etc. have not been examined based on the data from this study. Therefore, the applicant's explanation that the folded

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retinas were not related to BB5.1 mAb is not based on solid evidence and like umbilical hernia, whether the folded retinas were related to BB5.1 mAb or not is unknown.

Umbilical hernia and folded retinas were observed in the high dose group (60 mg/kg/week) only and the incidence of umbilical hernia was 0.4% (1 of 230 offspring) and the incidence of folded retina was 1.7% (2 of 114 offspring). In addition, the two cases of folded retina were unilateral and there were no abnormalities in clinical observations or necropsy findings of offspring born to mothers exposed to BB5.1 mAb (388 offspring) in a study for effects on pre- and postnatal development, including maternal function (6709-107). Furthermore, no effects on the eyes of the offspring of women who were treated with eculizumab during pregnancy have been reported in clinical studies or foreign post-marketing surveillance [see "4.(iii).B.(8).2) Use during pregnancy or lactation"]. Taking account of the above, although it is necessary to provide information on these findings, there is little need for further investigation.

3.(iii).B.(2) Toxicity studies using an anti-C5 antibody other than eculizumab

PMDA's view on the use of an anti-C5 antibody other than eculizumab in toxicity studies submitted in the application is as follows:

Although the amino acid sequence of either the variable or constant region of BB5.1 mAb, an anti-C5 antibody used in place of eculizumab, is not similar to that of eculizumab, it has been reported that BB5.1 mAb binds specifically to murine C5 and inhibits hemolytic activity in mice (*J Clin Invest.* 2005; 115:1590-1600, etc.). Toxicity studies with BB5.1 mAb evaluated chronic effects and reproductive and developmental effects at doses that demonstrated the reduction of the mean percent hemolysis by C5 inhibition, which showed no toxicity findings. Therefore, C5 inhibition is unlikely to result in chronic toxicity or reproductive and developmental toxicity. As no toxicity studies with eculizumab have been conducted, the effects of eculizumab other than those of C5 inhibition are unknown.

However, since eculizumab does not cross-react with C5 from other species, toxicological evaluation based on studies with eculizumab is difficult. Therefore, toxicological evaluation is inevitably based on studies with BB5.1 mAb.

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4. Clinical data

4.(i) Summary of biopharmaceutic studies and associated analytical methods

The to-be-marketed formulation was used in all clinical studies submitted as evaluation data in the application.

Concentrations of eculizumab, soluble C5b-9 (sC5b-9) and human anti-human antibodies (HAHA) in human serum were measured using an ELISA method and an electro-chemiluminescent immunoassay.

No data from biopharmaceutic studies have been submitted.

4.(ii) Summary of clinical pharmacology studies

4.(ii).A Summary of the submitted data

4.(ii).A.(1) Studies using human biomaterials

No data from studies using human biomaterials have been submitted.

4.(ii).A.(2) Japanese phase II clinical study (5.3.4.2.6 and 5.3.5.2.6, Study C07-001 [[redacted] 20[redacted] to [redacted] 20[redacted]])

See "4.(iii).A.(1) Japanese phase II clinical study (C07-001)" for a brief description of the study.

Pharmacokinetic analysis showed that the trough serum concentrations of eculizumab (mean ± standard error [SE]) at Week 2 and Week 12 were 90.5 ± 6.25 μg/mL and 116.5 ± 10.93 μg/mL, respectively. The pharmacokinetic parameters estimated by a population pharmacokinetic (PPK) analysis with a 1-compartmental model are shown in Table 6.

Table 6. Estimated pharmacokinetic parameters using a 1-compartmental model

CL (L/h)	V_d (L)	K_{el} (1/h)	$t_{1/2}$ (h)
0.0173 ± 0.00633	6.09 ± 1.417	0.00288 ± 0.000928	265.6 ± 83.9

Mean ± SD, n = 26

Pharmacodynamic analysis showed that the proportion of patients with hemolytic activity values ≤ 20%** was 62.1% (18 of 29 patients) at Week 1 and reached 93.1% (27 of 29 patients) at Week 8 and at Week 12. The pharmacodynamic parameters for hemolytic activity estimated using the cumulative Weibull function are shown in Table 7.

Table 7. Estimated pharmacodynamic parameters using the cumulative Weibull function

E_0 (%)	E_{diff} (%)	C_{diff} (μg/mL)	sf
100.2 ± 34.54	96.7 ± 33.34	36.5 ± 18.05	2.61

Mean ± SD, n = 27

E_0: hemolytic activity at baseline, E_{diff}: theoretical maximal inhibitory effect,
C_{diff}: eculizumab concentration required to produce 1/e (36.8%) effect, sf: slope of PK/PD relationship

** At least 100 serum samples from healthy adults were assayed for hemolytic activity and a cutoff value of 20% ("mean minus 3SD") was chosen based on the idea that hemolytic activity of ≤ 20% represents complete blockade of terminal complement activity in serum.

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4.(ii).A.(3) Foreign phase I clinical study (5.3.5.2.1, Study C02-001 [May 2002 to January 2003]; *N Engl J Med.* 2004;350:552-558.)

See "4.(iii).A.(3) Foreign phase I clinical study (C02-001)" for a brief description of the study.

Pharmacokinetic analysis showed that the trough serum concentrations of eculizumab (mean ± SD) at Week 10 and Week 12 were 108.1 ± 55.33 μg/mL and 70.2 ± 20.13 μg/mL, respectively, and the peak serum concentrations of eculizumab at Week 4 and Week 10 were 259.12 ± 51.47 μg/mL and 201.09 ± 96.28 μg/mL, respectively, and the applicant explained that serum concentrations did not reach a steady-state by Week 12.

Pharmacodynamic analysis showed that ≤ 20% hemolytic activity was maintained from Week 3 to Week 12 in 90.9% of patients (10 of 11 patients).

4.(ii).A.(4) Foreign phase I clinical study (5.3.5.2.2, Study E02-001 [August 2002 to December 2003]; *Blood.* 2005;106:2559-2565.)

See "4.(iii).A.(4) Foreign phase I clinical study (E02-001)" for a brief description of the study.

Pharmacokinetic analysis showed that the trough serum concentrations of eculizumab (mean ± SD) at baseline (after 12 weeks of treatment), Week 28 (after 40 weeks of treatment), and Week 52 (after 64 weeks of treatment) were 81.8 ± 48.54 μg/mL, 166.9 ± 102.1 μg/mL, and 112.4 ± 46.88 μg/mL, respectively.

Pharmacodynamic analysis showed that the level of hemolytic activity was ≤ 20% at all timepoints in all patients up to Week 52.

4.(ii).A.(5) Foreign phase II clinical studies (5.3.5.2.3, Studies X03-001 and X03-001A [August 2003 to December 2005]; *Haematologica.* 2005;90:ECR40.)

See "4.(iii).A.(5) Foreign phase II clinical studies (X03-001 and X03-001A)" for a brief description of the studies.

Pharmacokinetic analysis showed that the trough serum concentrations of eculizumab (mean ± SD) at baseline (after 64 weeks of treatment) and Week 50 (after 114 weeks of treatment) were 106.8 ± 47.62 μg/mL and 80.5 ± 37.26 μg/mL, respectively.

Pharmacodynamic analysis showed that although the level of hemolytic activity exceeded 20% in one patient each at Weeks 4, 42, and 50, the level of hemolytic activity was ≤ 20% at all timepoints in the remaining patients.

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4.(ii).A.(6) Foreign phase III clinical study (5.3.5.1.1, Study C04-001 [TRIUMPH] [August 2004 to December 2005]; *Br J Haematol.* 2008;142:263-272, *N Engl J Med.* 2006;355:1233-1243.)

See "4.(iii).A.(6) Foreign phase III clinical study (C04-001)" for a brief description of the study.

Pharmacokinetic analysis showed that the trough serum concentrations of eculizumab (mean ± SE) in the eculizumab and placebo groups were 113.5 ± 8.70 μg/mL and 10.1 ± 0.08 μg/mL, respectively, at Week 4 and 101.8 ± 10.8 μg/mL and 10.1 ± 0.09 μg/mL, respectively, at Week 26.

Pharmacodynamic analysis showed that the proportions of patients with hemolytic activity values ≤ 20% at Week 4 and Week 26 were 100.0% (42 of 42 patients) and 97.6% (41 of 42 patients), respectively.

4.(ii).A.(7) Foreign phase III clinical study (5.3.4.2.5 and 5.3.5.2.4, Study C04-002 [SHEPHERD] [December 2004 to October 2006]; *Blood.* 2008;111: 1840-1847, *Br J Haematol.* 2008;142:263-272.)

See "4.(iii).A.(7) Foreign phase III clinical study (C04-002)" for a brief description of the study.

Pharmacokinetic analysis showed that the trough serum concentrations of eculizumab (mean ± SE) at Week 4 and Week 52 were 104.5 ± 5.08 μg/mL and 110.3 ± 8.92 μg/mL, respectively. The pharmacokinetic parameters estimated by a PPK analysis with a 1-compartmental model are shown in Table 8.

Table 8. Estimated pharmacokinetic parameters using a 1-compartmental model

CL (mL/h/kg)	V_d (mL/kg)	K_{el} (1/h)	$t_{1/2}$ (h)
0.3349 ± 0.13401	113.93 ± 28.719	0.003077 ± 0.0013682	261.07 ± 90.795

Mean ± SD, n = 97

Pharmacodynamic analysis showed that the proportions of patients with hemolytic activity values ≤ 20% at Week 4 and Week 52 were 95.8% (91 of 95 patients) and 84.9% (79 of 93 patients), respectively. The pharmacodynamic parameters for hemolytic activity estimated using an E_{max} model with Hill coefficient are shown in Table 9. The applicant discussed that the very large Hill coefficient indicated that eculizumab inhibits C5 at low concentrations.

Table 9. Estimated pharmacodynamic parameters using an E_{max} model with Hill coefficient

E_0 (%)	E_{max} (%)	EC_{50} (μg/mL)	Hill coefficient
90.14 ± 4.418	88.14 ± 4.583	31.509 ± 7.8152	7.2521 ± 2.82334

Mean ± SD, n = 97

E_0: hemolytic activity at baseline, E_{max}: theoretical maximal inhibitory effect

EC_{50}: eculizumab concentration required to produce 50% of E_{max}

4.(ii).A.(8) Foreign phase III clinical study (5.3.4.2.4 and 5.3.5.2.5, Study E05-001 [May 2005 to March 2006 (Interim report)])

See "4.(iii).A.(8) Foreign phase III clinical study (E05-001)" for a brief description of the study.

The pharmacokinetic parameters estimated by a PPK analysis with a 1-compartmental model are shown

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in Table 10.

Table 10. Estimated pharmacokinetic parameters using a 1-compartmental model

CL (mL/h/kg)	V_d (mL/kg)	K_{el} (1/h)	$t_{1/2}$ (h)
0.329 (39.0%)	113.0 (23.7%)	0.0030 (41.4%)	263 (34.2%)

Mean (CV%), n = 141

The pharmacodynamic parameters for hemolytic activity estimated using the cumulative Weibull function are shown in Table 11.

Table 11. Estimated pharmacodynamic parameters using the cumulative Weibull function

E_0 (%)	E_{diff} (%)	C_{deff} (μg/mL)	sf
93.8 (9.35%)	91.0 (9.56%)	30.6 (27.2%)	2.61 (43.5%)

Mean (CV%), n = 141

E_0: hemolytic activity at baseline, E_{diff}: theoretical maximal inhibitory effect

C_{deff}: eculizumab concentration required to produce 1/e (36.8%) effect, sf: slope of PK/PD relationship

4.(ii).B Outline of the review by PMDA

4.(ii).B.(1) Relationship between serum eculizumab concentration and hemolytic activity

The applicant explained that eculizumab is effective at serum concentrations of ≥ 35 μg/mL and described its rationale as follows:

Eculizumab concentrations below 35 μg/mL tended to result in an increased level of hemolytic activity in a clinical study in patients with idiopathic membranous glomerulopathy (C99-004) and it was shown that ≥ 35 μg/mL of eculizumab blocked C5 (as assessed by measuring hemolytic activity) in ≥ 90% of blood samples obtained from all clinical studies conducted before Study C99-004 (Investigator's Brochure, Eculizumab. Version 11, 28 July 2005 [Alexion Pharmaceuticals Inc. In-house material]).

On the other hand, the serum concentrations of C5 in 7 normal volunteers were 99 to 134 μg/mL and the serum concentrations of C5 in 21 patients with diseases associated with C3 or C5 abnormalities were 86 to 122 μg/mL (*J Clin Invest.* 1977;59:704-715.). Eculizumab binds to C5, blocks its cleavage into C5a and C5b, and inhibits terminal complement activity. Theoretically, one molecule of eculizumab binds to two molecules of C5. Taking account of these findings, as 35 μg/mL of eculizumab (about 236 nM; molecular weight, about 148 kDa) is considered to bind to 95 μg/mL of C5 (about 500 nM; molecular weight, about 196 kDa) in human serum, a serum eculizumab concentration of "35 μg/mL" has been chosen as a threshold for efficacy.

The relationship between serum concentration and hemolytic activity in clinical studies in PNH patients (C02-001, TRIUMPH, SHEPHERD, C07-001) also showed that serum trough concentrations of ≥ 35 μg/mL are sufficient to maintain a hemolytic activity of ≤ 20% in the majority of patients (see Figure 2).

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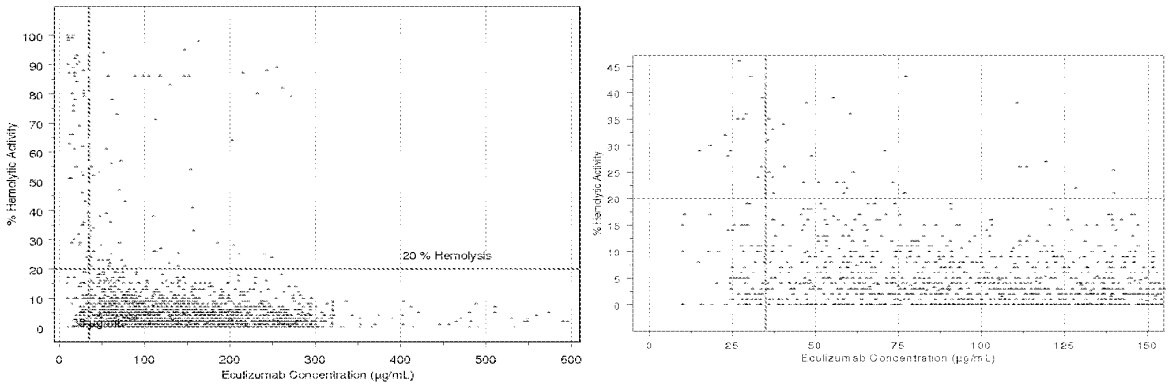


Figure 2. Relationship between serum eculizumab concentration and hemolytic activity in PNH patients (Left figure, All plots; Right figure, Magnification of the plots)

PMDA considers as follows:

With respect to the relationship between eculizumab serum concentration and hemolytic activity, as shown in Figure 2, the level of hemolytic activity was < 20% at serum concentrations of ≥ 35 μg/mL in the majority of samples (89.8% [1886 of 2101 samples]) while the level of hemolytic activity was ≥ 20% even at serum concentrations of ≥ 35 μg/mL in some patients (4.1% [87 of 2101 samples]). Therefore, serum concentrations of eculizumab ≥ "35 μg/mL" do not necessarily sufficiently inhibit hemolysis in all patients. However, taking account of the results from the TRIUMPH study, the efficacy of eculizumab can be expected at the proposed dosage regimen [see "4.(iii).B.(4) Efficacy" and "4.(iii).B.(7) Dosage and administration"].

4.(ii).B.(2) Pharmacokinetics/pharmacodynamics in Japan and overseas

The applicant explained about differences in the pharmacokinetics and pharmacodynamics (hemolytic activity) of eculizumab between Japan and overseas as follows:

Although the CL and Vc estimated from a PPK analysis in Japanese PNH patients are as shown in Table 6, when adjusted for body weight (mean ± SD), the CL was 0.282 ± 0.0870 mL/h/kg and the Vc was 101.9 ± 27.51 mL/kg, which were similar to the CL and Vc estimated from a PPK analysis in foreign PNH patients (see Table 8 and Table 10).

Observed serum concentrations of eculizumab over time in a Japanese clinical study (C07-001) and foreign clinical studies (C02-001, TRIUMPH, SHEPHERD) are as shown in Figure 3 and there were no particularly major differences.

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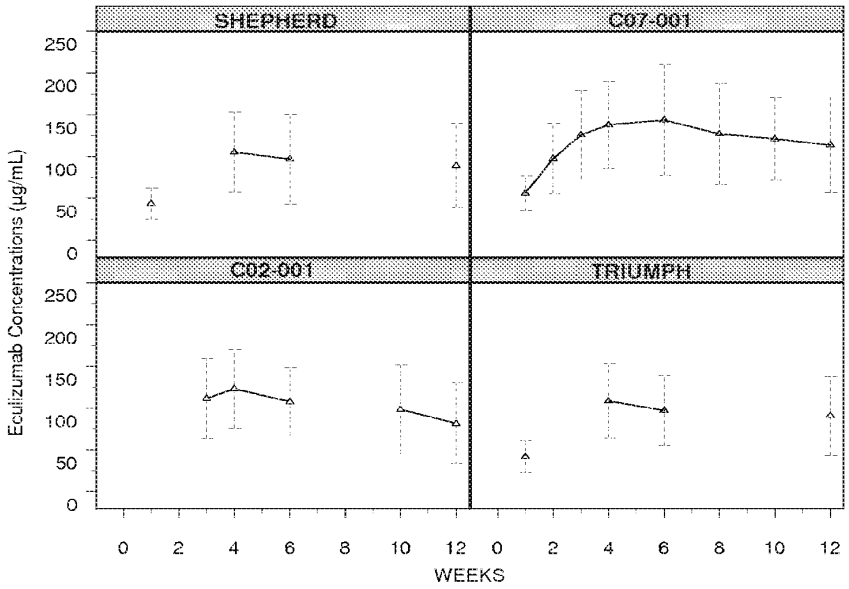


Figure 3. Serum eculizumab concentrations over time in clinical studies (C02-001, TRIUMPH, SHEPHERD, C07-001)

Furthermore, as to the pharmacodynamics of eculizumab, though figures showing the measured hemolytic activity over time in the Japanese clinical study (C07-001) and foreign clinical studies (TRIUMPH, SHEPHERD) are currently being prepared, the eculizumab pharmacodynamic parameters for hemolytic activity estimated using the cumulative Weibull function were similar between Japan and overseas (see Table 7 and Table 11).

The data from all Japanese and foreign studies in PNH patients (C02-001, TRIUMPH, SHEPHERD, E05-001, C07-001; a total of 177 patients) were pooled and the PK/PD relationship of eculizumab was investigated. As a result, although the statistically significant covariates were an effect of body weight on CL and Vc and an effect of gender on CL, there were no particular differences in the pharmacodynamic effect (hemolytic activity) except for Week 1. The CL of eculizumab (C02-001, TRIUMPH, SHEPHERD, and C07-001 were pooled; mean ± SD) was 0.0268 ± 0.0115 L/h in male patients and 0.0182 ± 0.0071 L/h in female patients and there were no major differences.

Based on the above, although the pharmacokinetics of eculizumab in Japanese and foreign PNH patients may be slightly different due to the effect of body weight, the pharmacodynamic effect is similar and there are no particular differences in the safety profile of eculizumab between Japan and overseas. Therefore, no dose adjustment should be required for Japanese PNH patients.

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PMDA considers as follows:
Concerning the pharmacokinetics and pharmacodynamics of eculizumab in Japan and overseas, the observed pharmacokinetic data were compared, PPK analysis was performed and the pharmacodynamic parameters were estimated using the cumulative Weibull function. As a result, since blood trough concentrations over time were slightly higher in Japanese PNH patients with lower body weight compared with foreign PNH patients, body weight may affect eculizumab blood concentrations over time. However, though the results of the pharmacodynamic hemolytic assay from Japanese and foreign clinical studies are currently being requested, there were no particular differences in the pharmacodynamic parameters (hemolytic activity) estimated using the cumulative Weibull function between Japan and overseas and there was also little difference in the CL value estimated from a PPK analysis between Japan and overseas. Therefore, differences in the pharmacokinetics of eculizumab due to the effect of body weight are unlikely to significantly affect inhibition of hemolysis by eculizumab.

The above analysis indicated the possibility that body weight affects the pharmacokinetics of eculizumab and safety data from Japanese and foreign clinical studies (TRIUMPH, SHEPHERD, C07-001) showed higher incidences of nasopharyngitis, headache, and eczema, etc. in Japanese PNH patients than in foreign PNH patients [see "4.(iii).B.(5) Safety"]. As Japanese patients tend to have lower body weight than foreign patients, PMDA is currently asking the applicant about the effects of body weight on the safety and efficacy of eculizumab.

4.(ii).B.(3) HAHA induction and its impact on the pharmacokinetics of eculizumab
Based on the results from Japanese and foreign clinical studies of eculizumab, the applicant explained the impact of HAHA induction on the pharmacokinetics of eculizumab as follows:
A total of 940 patients including non-PNH patients were treated with eculizumab in Japanese and foreign clinical studies. There was no apparent impact of HAHA induction on the pharmacokinetic parameters of eculizumab.

Among PNH clinical studies, there were no patients with a positive HAHA response in Studies C02-001, E02-001, and X03-001. Although 1 patient in the placebo group and 1 patient in the eculizumab group had a positive HAHA response in the TRIUMPH study and 2 patients had a positive HAHA response in the SHEPHARD study, there was no apparent impact on the pharmacokinetics of eculizumab. In Study C07-001, there were 3 patients with positive HAHA response before eculizumab treatment, but none after eculizumab treatment. No analysis has been performed for Study E05-001.

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PMDA considers as follows:

An assay method to detect HAHA used in studies other than the Japanese clinical study (C07-001) was the method before improvement. Even in the Japanese clinical study (C07-001), a positive HAHA response was detected before eculizumab treatment and the assay may need further improvement. Furthermore, the number of patients who developed HAHA in clinical studies was limited. Therefore, the impact of HAHA induction on the pharmacokinetics of eculizumab is undefined at present. It is desirable to further increase the assay sensitivity to HAHA and establish an assay for the measurement of neutralizing HAHA to eculizumab. After the market launch, if adverse events of infusion reaction etc. which are considered associated with HAHA induction are reported or there is loss of efficacy etc., the HAHA assay should be performed as appropriate and information on HAHA should be collected and provided to the medical practice [see "4.(iii).B.(5).7) Immunogenicity and human anti-human antibodies (HAHA)"].

4.(iii) Summary of clinical efficacy and safety

4.(iii).A Summary of the submitted data

A total of 8 clinical studies presented in the following Table 12 were submitted as evaluation data.

Table 12. Listing of PNH clinical studies submitted

	Study Number	Phase	Primary objective of study	Design	N	Duration of treatment	Primary efficacy endpoint
Japan	C07-001	II	Efficacy, safety, pharmacokinetics, and pharmacodynamics	Open-label, uncontrolled study	29	12 weeks	Change of LDH
	E07-001 (Interim report)	II	Efficacy, safety, pharmacokinetics, and pharmacodynamics	Open-label, uncontrolled study (C07-001 extension)	27	26 weeks	–
Overseas	C02-001	I	Efficacy, safety, pharmacokinetics, and pharmacodynamics	Open-label, uncontrolled study	11	12 weeks	–
	E02-001	I	Safety	Open-label, uncontrolled study (C02-001 extension)	11	52 weeks	–
	X03-001/ X03-001A	II	Safety	Open-label, uncontrolled study (E02-001 extension)	11/10	A total of 104 weeks	–
	C04-001 (TRIUMPH)	III	Efficacy and safety	Placebo-controlled, double-blind, comparative study	43 (eculizumab group) 44 (placebo group)	26 weeks	Hb stabilization, PRBC units transfused
	C04-002 (SHEPHERD)	III	Efficacy and safety	Open-label, uncontrolled study	97	52 weeks	LDH AUC
	E05-001 (Interim report)	III	Safety	Open-label, uncontrolled study (X03-001, C04-001, and C04-002 extension)	187	Up to 2 years	–

LDH: lactate dehydrogenase, PRBC: packed red blood cell

4.(iii).A.(1) Japanese phase II clinical study (5.3.5.2.6, Study C07-001 [20 to 20])

A multicenter, open-label, uncontrolled study was conducted at 9 centers in Japan to evaluate the efficacy, safety, pharmacokinetics, and pharmacodynamics of eculizumab in PNH patients aged ≥ 12 years having a GPI-deficient RBC clone (PNH type III) ≥ 10% (Target sample size of 25).

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Eculizumab was to be administered by intravenous infusion over 25 to 45 minutes at a dose of 600 mg weekly for a total of 4 doses followed 1 week later by 900 mg every 2 weeks for a total of 5 doses (the duration of treatment was 12 weeks). Patients were to receive a meningococcal vaccine (serogroups "A, C, Y, and W135") at least 2 weeks prior to treatment with eculizumab.

All of 29 treated patients were included in the per protocol set (PPS) and in the efficacy, safety, pharmacokinetic, and pharmacodynamic analyses. Two patients were discontinued from the study after 10 weeks of treatment due to lack of efficacy.

The primary efficacy endpoint was the change of lactate dehydrogenase (LDH) from baseline[††] to Week 12. There was a significant reduction in LDH from baseline (median [min., max.], 1814.0 units/L (U/L) [627.8 U/L, 3642.5 U/L]) to Week 12[‡‡] (244.0 U/L [187.0 U/L, 2715.0 U/L]) ($P < 0.0001$, Wilcoxon signed-rank test).

Regarding safety, the incidence of adverse events was 96.6% (28 of 29 patients) and the incidence of adverse events for which a causal relationship to study drug could not be denied (adverse drug reactions) was 93.1% (27 of 29 patients). Adverse events occurring in at least 10.0% of patients were headache (51.7% [15 of 29 patients]), nasopharyngitis (41.4% [12 of 29 patients]), nausea (20.7% [6 of 29 patients]), diarrhoea (13.8% [4 of 29 patients]), vomiting (10.3% [3 of 29 patients]), pyrexia (10.3% [3 of 29 patients]), and eczema (10.3% [3 of 29 patients]) and adverse drug reactions occurring in at least 10.0% of patients were headache (51.7% [15 of 29 patients]), nasopharyngitis (37.9% [11 of 29 patients]), nausea (20.7% [6 of 29 patients]), vomiting (10.3% [3 of 29 patients]), pyrexia (10.3% [3 of 29 patients]), and eczema (10.3% [3 of 29 patients]).

No deaths occurred. Serious adverse events of "pyrexia and CRP increased" were reported by 1 patient and their causal relationship to study drug could not be denied.

4.(iii).A.(2) Japanese phase II clinical study (5.3.5.2.7, Study E07-001 [[redacted] 20[redacted] to [redacted] 20[redacted] (Interim report)])

A multicenter, open-label, uncontrolled study was conducted at 9 centers in Japan to evaluate the safety, efficacy, pharmacokinetics, and pharmacodynamics of eculizumab in PNH patients who completed Study C07-001 (Target number of patients of 27).

Eculizumab was to be administered by intravenous infusion over 25 to 45 minutes at a dose of 900 mg every 2 weeks for 52 weeks (The interim report contains data up to Week 26).

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†† Mean LDH over the 4 weeks prior to start of treatment

‡‡ Missing data were imputed using last observation carried forward (LOCF).

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All of 27 treated patients were included in the PPS and in the efficacy, safety, pharmacokinetic, and pharmacodynamic analyses. One patient was discontinued from the study at Week 18 due to patient request.

Regarding safety, the incidence of adverse events was 100.0% (27 of 27 patients) and the incidence of adverse drug reactions was 92.6% (25 of 27 patients). Adverse events occurring in at least 10.0% of patients were nasopharyngitis (51.9% [14 of 27 patients]), headache (18.5% [5 of 27 patients]), blood ALP increased (18.5% [5 of 27 patients]), and anaemia (11.1% [3 of 27 patients]) and adverse drug reactions occurring in at least 10.0% of patients were nasopharyngitis (51.9% [14 of 27 patients]), headache (18.5% [5 of 27 patients]), and blood ALP increased (18.5% [5 of 27 patients]).

No deaths occurred. Serious adverse events reported were "sepsis, cellulitis, skin disorder, and acute renal failure" in 1 patient, "anaemia" in 1 patient, "pyrexia and herpes simplex infection" in 1 patient, and "bronchitis" in 1 patient and a causal relationship to study drug could not be denied for all events except for anaemia.

Efficacy, pharmacokinetic, and pharmacodynamic evaluations are not planned for the interim report and the final report will be complete in June 2011.

4.(iii).A.(3) Foreign phase I clinical study (5.3.5.2.1, Study C02-001 [May 2002 to January 2003]; *N Engl J Med.* 2004;350:552-558.)

A multicenter, open-label, uncontrolled study was conducted at 2 centers overseas to evaluate the safety, tolerability, pharmacokinetics, and pharmacodynamics of eculizumab in PNH patients who were at least 18 years of age and had a GPI-deficient RBC clone (PNH type III) ≥ 10% (Target number of patients of 10).

Eculizumab was to be administered by intravenous infusion over at least 30 minutes at a dose of 600 mg weekly for a total of 4 doses followed 1 week later by 900 mg every 2 weeks for a total of 4 doses (the duration of treatment was 10 weeks). Patients received a meningococcal vaccine (serogroups "A and C") at least 2 weeks prior to treatment with eculizumab.

All of 11 treated patients were included in the PPS and in the safety, pharmacokinetic, and pharmacodynamic analyses. None of the patients was discontinued from the study.

Regarding safety,[§§] the incidence of adverse events was 100.0% (11 of 11 patients). Adverse events occurring in at least 2 patients were headache and upper respiratory tract infection (3 patients each) and

[§§] The causal relationship of an adverse event to study drug was assessed on a 3-point scale (unlikely, possible, probable).

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dizziness, nasal congestion, chest pain, influenza-like symptoms, chills, insomnia, arthralgia, and nausea (2 patients each).

No deaths occurred. Serious adverse events reported were "chest infection" in 1 patient and "nausea, vomiting, headache, dizziness, and shivering" in 1 patient.

4.(iii).A.(4) Foreign phase I clinical study (5.3.5.2.2, Study E02-001 [August 2002 to December 2003]; *Blood*. 2007;110:4123-4128, *Blood*. 2005;106:2559-2565.)

A multicenter, open-label, uncontrolled study was conducted at 2 centers overseas to evaluate the safety and tolerability of eculizumab in PNH patients who completed Study C02-001 (Target number of patients of 11).

Eculizumab was to be administered by intravenous infusion over at least 30 minutes at a dose of 900 mg every 2 weeks for 52 weeks.

All of 11 treated patients were included in the safety analysis population. None of the patients was discontinued from the study.

Regarding safety,[***] the incidence of adverse events was 100.0% (11 of 11 patients). Adverse events occurring in at least 2 patients are presented in Table 13.

Table 13. Adverse events occurring in at least 2 patients

Adverse event	Incidence	N	Adverse event	Incidence	N	Adverse event	Incidence	N
Overall	100.0%	11	Abdominal pain	18.2%	2	Myalgia	18.2%	2
Throat sore	36.4%	4	Constipation	18.2%	2	Nasal congestion	18.2%	2
Influenza-like symptoms	36.4%	4	Diarrhoea	18.2%	2	Loose stools	18.2%	2
Upper respiratory tract infection	27.3%	3	Feeling cold	18.2%	2	Throat pain	18.2%	2
Nausea	27.3%	3	Herpes simplex	18.2%	2	Throat tightness	18.2%	2
Contusion	27.3%	3	Inflicted injury	18.2%	2	Fatigue	18.2%	2
Cough	27.3%	3	Lethargy	18.2%	2	Vomiting	18.2%	2
Pain	27.3%	3	Lower respiratory tract infection	18.2%	2			

n = 11

No deaths occurred. Serious adverse events of "extravascular haemolysis, viral syndrome, and neutropenia" were reported by 1 patient.

4.(iii).A.(5) Foreign phase II clinical studies (5.3.5.2.3, Studies X03-001 and X03-001A [August 2003 to December 2005]; *Haematologica*. 2005;90:ECR40.)

Study X03-001 was a multicenter, open-label, uncontrolled study conducted at 2 centers overseas to evaluate the safety and tolerability of eculizumab in PNH patients who completed Study E02-001. PNH

[***] The causal relationship of an adverse event to study drug was assessed on a 3-point scale (unlikely, possible, probable).

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patients who completed Study X03-001 were to participate in Study X03-001A.

Eculizumab was to be administered by intravenous infusion over at least 30 minutes at a dose of 900 mg every 2 weeks for a total of 104 weeks (52 weeks for Study X03-001; 52 weeks for Study X03-001A). Patients received a meningococcal vaccine (serogroups "C" or "A, C, Y, and W135").

A total of 11 treated patients in Study X03-001 and a total of 10 treated patients in Study X03-001A were included in the safety analysis. One patient was discontinued from Study X03-001 at about Week 38 due to patient request. None of the patients was discontinued from Study X03-001A.

Regarding safety,[†††] the incidence of adverse events was 100.0% (11 of 11 patients) in Study X03-001 and the incidence of adverse events was 90.0% (9 of 10 patients) and the incidence of adverse drug reactions was 20.0% (2 of 10 patients) in Study X03-001A. Adverse events occurring in at least 2 patients in Study X03-001 are presented in Table 14.

Table 14. Adverse events occurring in at least 2 patients in Study X03-001

Adverse event	Incidence	N	Adverse event	Incidence	N	Adverse event	Incidence	N
Overall	100.0%	11	Headache	27.3%	3	Viral infection	18.2%	2
Fatigue	45.5%	5	Dyspnoea	27.3%	3	Contusion	18.2%	2
Lower respiratory tract infection	36.4%	4	Nasal congestion	27.3%	3	Arthralgia	18.2%	2
Pain in extremity	36.4%	4	Abdominal pain	18.2%	2	Dizziness	18.2%	2
Pharyngolaryngeal pain	36.4%	4	Nausea	18.2%	2	Insomnia	18.2%	2
Abdominal discomfort	27.3%	3	Lethargy	18.2%	2	Epistaxis	18.2%	2
Diarrhoea	27.3%	3	Cystitis	18.2%	2	Rhinitis	18.2%	2
Influenza	27.3%	3	Upper respiratory tract infection	18.2%	2	Hypertension	18.2%	2
Nasopharyngitis	27.3%	3						

n = 11

Adverse events occurring in at least 2 patients in Study X03-001A were pharyngolaryngeal pain (40.0% [4 of 10 patients]), nasopharyngitis (30.0% [3 of 10 patients]), pyrexia (20.0% [2 of 10 patients]), lower respiratory tract infection (20.0% [2 of 10 patients]), and viral infection (20.0% [2 of 10 patients]) and there were no adverse drug reactions reported by ≥ 2 patients.

No deaths occurred. Serious adverse events reported were "abscess limb and infected left thumb" in 1 patient in Study X03-001 and "pyrexia" in 1 patient, "viral infection," in 1 patient, and "urinary tract infection" in 1 patient in Study X03-001A and a causal relationship to study drug was denied only for "viral infection" observed in Study X03-001A.

[†††] While the causal relationship of an adverse event to study drug was assessed on a 3-point scale (unlikely, possible, probable) in Study X03-001, the causal relationship of an adverse event to study drug was assessed on a 4-point scale (unrelated, possible, probable, definite) in Study X03-001A.

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4.(iii).A.(6) Foreign phase III clinical study (5.3.5.1.1, Study C04-001 [TRIUMPH] [August 2004 to December 2005]; *Br J Haematol.* 2008;142:263-272, *N Engl J Med.* 2006;355:1233-1243.)

A multicenter, randomized, placebo-controlled, double-blind, comparative study was conducted at 34 centers overseas to evaluate the efficacy and safety of eculizumab in PNH patients who were at least 18 years of age and had a GPI-deficient RBC clone (PNH type III) ≥ 10% (Target number of patients of 75).

Eculizumab or placebo was to be administered by intravenous infusion over 25 to 45 minutes at a dose of 600 mg weekly for a total of 4 doses, followed by 900 mg 1 week later, and then 900 mg every 2 weeks for a total of 26 weeks. Patients received a meningococcal vaccine (serogroups "C," "A and C" or "A, C, Y, and W135") at least 2 weeks prior to treatment with eculizumab or placebo.

All of 87 treated patients (44 patients in the placebo group, 43 patients in the eculizumab group) were included in the intent to treat population and in the efficacy and safety analyses. Two patients in the eculizumab group were discontinued from the study due to an adverse event or patient request and 10 patients in the placebo group were discontinued from the study due to lack of efficacy.

The co-primary efficacy endpoints were Hb stabilization[‡‡‡] and the number of packed red blood cell (PRBC) units transfused. Hb stabilization was achieved in 0.0% of the placebo group (0 of 44 patients) compared with 48.8% of the eculizumab group (21 of 43 patients) and there was a significant difference between the groups ($P < 0.001$, Fisher's exact test). Ten units [2 units, 21 units] (median [min., max.]) of PRBCs were administered in the placebo group compared with 0 units [0 unit, 16 units] in the eculizumab group and there was a significant difference between the groups ($P < 0.001$, Wilcoxon's rank sum test).

Regarding safety, adverse events occurred in 90.9% of the placebo group (40 of 44 patients) and 100.0% of the eculizumab group (43 of 43 patients). Adverse drug reactions occurred in 25.0% of the placebo group (11 of 44 patients) and 55.8% of the eculizumab group (24 of 43 patients). Adverse events occurring in at least 10.0% of patients in either group are presented in Table 15. Adverse drug reactions occurring in at least 10.0% of patients in either group were headache only and the incidence of headache as an adverse drug reaction was 4.5% (2 of 44 patients) in the placebo group and 32.6% (14 of 43 patients) in the eculizumab group.

‡‡‡ Each patient underwent an initial observation period to identify the Hb concentration that necessitated RBC transfusion (the set-point). To achieve Hb stabilization, a patient had to maintain an Hb concentration above the Hb set-point and avoid any RBC transfusion for the entire treatment period.

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Table 15. Adverse events occurring in at least 10.0% of patients in either group

Adverse event	Placebo (N = 44)		Eculizumab (N = 43)	
	Incidence	N	Incidence	N
Overall	90.9%	40	100.0%	43
Headache	27.3%	12	44.2%	19
Nasopharyngitis	18.2%	8	23.3%	10
Back pain	9.1%	4	18.6%	8
Nausea	11.4%	5	16.3%	7
Upper respiratory tract infection	22.7%	10	14.0%	6
Cough	9.1%	4	11.6%	5
Fatigue	2.3%	1	11.6%	5
Diarrhoea	11.4%	5	9.3%	4
Arthralgia	11.4%	5	7.0%	3
Abdominal pain	11.4%	5	4.7%	2
Dizziness	11.4%	5	4.7%	2
Vomiting	11.4%	5	4.7%	2
Viral infection	11.4%	5	2.3%	1

No deaths occurred. Serious adverse events occurred in 20.5% of the placebo group (9 of 44 patients) and 9.3% of the eculizumab group (4 of 43 patients), which included "exacerbation of PNH" (3 patients) and "urinary tract infection and central line infection," "exacerbation of PNH, anaemia, and pyrexia," "neutropenia," "neutropenia, cellulitis, and folliculitis," "haemolysis and upper respiratory tract infection," and "viral infection" (1 patient each) in the placebo group and "exacerbation of PNH," "renal colic," "prolapsed lumbosacral disc," and "α-Streptococcal bacteraemia" (1 patient each) in the eculizumab group and a causal relationship to study drug could not be denied only for pyrexia in the placebo group.

4.(iii).A.(7) Foreign phase III clinical study (5.3.5.2.4, Study C04-002 [SHEPHERD] [December 2004 to October 2006]; *Blood*. 2008;111:1840-1847, *Br J Haematol*. 2008;142:263-272.)

A multicenter, open-label, uncontrolled study was conducted at 33 centers overseas to evaluate the safety and efficacy of eculizumab in PNH patients who were at least 18 years of age and had a GPI-deficient RBC clone (PNH type III) ≥ 10% (Target number of patients of 85).

Eculizumab was to be administered by intravenous infusion over 25 to 45 minutes at a dose of 600 mg weekly for a total of 4 doses, followed by 900 mg 1 week later, and then 900 mg every 2 weeks for a total of 52 weeks. Patients received a meningococcal vaccine (serogroups "C," "A and C," or "A, C, Y, and W135") at least 2 weeks prior to treatment with eculizumab.

All of 97 treated patients were included in the PPS and in the efficacy and safety analyses. One patient was discontinued from the study because the patient died due to an adverse event (brain herniation) at Week 4.

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The primary efficacy endpoint was LDH area under the curve (AUC) from baseline to Week 52 (LDH AUC) and the change in the LDH AUC[§§§] (median [min., max.]) was -632263.5 U/L × day [-1788823.5 U/L × day, -74498.0 U/L × day], which was significantly different from zero ($P < 0.001$, Wilcoxon signed rank test).

Regarding safety, the incidence of adverse events was 97.9% (95 of 97 patients) and the incidence of adverse drug reactions was 64.9% (63 of 97 patients). Adverse events occurring in at least 10.0% of patients are presented in Table 16. Adverse drug reactions occurring in at least 10.0% of patients were headache only (42.3% [41 of 97 patients]).

Table 16. Adverse events occurring in at least 10.0% of patients

Adverse event	Incidence	N	Adverse event	Incidence	N	Adverse event	Incidence	N
Overall	97.9%	95	Pyrexia	19.6%	19	Arthralgia	12.4%	12
Headache	52.6%	51	Back pain	15.5%	15	Abdominal pain	11.3%	11
Nasopharyngitis	32.0%	31	Dizziness	14.4%	14	Myalgia	10.3%	10
Upper respiratory tract infection	29.9%	29	Urinary tract infection	13.4%	13	Vomiting	10.3%	10
Nausea	20.6%	20	Diarrhoea	12.4%	12			

n = 97

One patient with "brain herniation" died, but its causal relationship to study drug was denied. The incidence of serious adverse events was 19.6% (19 of 97 patients) and serious adverse events occurring in at least 2 patients were anaemia (4 patients), pyrexia (3 patients), haemolysis (2 patients), and headache (2 patients). Among the observed serious adverse events, a causal relationship to study drug could not be denied for pyrexia (2 patients) and abdominal distension, renal impairment, headache, anxiety, cholangitis, and viral infection (1 patient each).

4.(iii).A.(8) Foreign phase III clinical study (5.3.5.2.5, Study E05-001 [May 2005 to March 2006 (Interim report)]; *Blood*. 2007;110:4123-4128.)

An open-label, uncontrolled study was conducted at 33 centers overseas to evaluate the safety of eculizumab in PNH patients who completed the TRIUMPH study, the SHEPHERD study, or Study X03-001A[****] (Target number of patients was not specified [up to 170 patients]).

Patients who completed the SHEPHERD study or Study X03-001 were to receive 900 mg of eculizumab every 2 weeks via 25 to 45 minute intravenous infusion. On the other hand, study drug was to be administered by intravenous infusion over 25 to 45 minutes to patients who completed the TRIUMPH study as follows: placebo-treated patients were to receive 600 mg of blinded eculizumab weekly for a total of 4 doses followed 1 week later by 900 mg of open-label eculizumab every 2 weeks; and eculizumab-treated patients were to receive 900 mg of blinded eculizumab in Week 1 and Week 3 and blinded placebo in Week 2 and Week 4 followed 1 week later by 900 mg of open-label eculizumab

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§§§ The LDH AUC from baseline to 52 weeks calculated by the trapezoidal rule minus the baseline LDH AUC calculated by assuming no change in LDH from baseline through 52 weeks

**** TRIUMPH patients who had discontinued receiving study drug before Week 26 were also eligible, if their data up to Week 26 had been evaluated for efficacy and safety.

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every 2 weeks. The duration of treatment was up to 2 years. Patients received a meningococcal vaccine (serogroups "A and C" or "A, C, Y, and W135") as appropriate.

All of 96 treated patients were included in the PPS and in the safety analysis (at the time of interim analysis in March 2006, the mean duration of treatment was 5.7 ± 1.9 months). None of the patients was discontinued from the study.

Regarding safety, the incidence of adverse events was 89.6% (86 of 96 patients) and the incidence of adverse drug reactions was 38.5% (37 of 96 patients). Adverse events occurring in at least 10.0% of patients are presented in Table 17. Adverse drug reactions occurring in at least 10.0% of patients were headache only (14.5% [14 of 96 patients]).

Table 17. Adverse events occurring in at least 10.0% of patients

Adverse event	Incidence	N	Adverse event	Incidence	N	Adverse event	Incidence	N
Overall	89.6%	86	Upper respiratory tract infection	15.6%	15	Cough	10.4%	10
Headache	30.2%	29	Diarrhoea	12.5%	12	Nausea	10.4%	10
Nasopharyngitis	30.2%	29	Arthralgia	10.4%	10			

No deaths occurred. The incidence of serious adverse events was 9.4% (9 of 96 patients) and serious adverse events occurring in at least 2 patients were cellulitis (2 patients), infection (2 patients), and viral infection (2 patients). Among the observed serious adverse events, a causal relationship to study drug could not be denied for cellulitis, infection, viral infection, haemophilus infection, septic shock, and headache (1 patient each).

The final report will be submitted in the [redacted] quarter of 20[redacted].

4.(iii).B Outline of the review by PMDA

PMDA's review focused on the following points.

4.(iii).B.(1) Clinical positioning of eculizumab in PNH treatment

The applicant explained the pathology and treatment of PNH and the clinical positioning of eculizumab as follows:

It has been reported that in PNH patients, hemolysis results in symptoms of anaemia requiring blood transfusions, fatigue, hemoglobinuria, and recurrent abdominal pain, etc. and furthermore, serious events associated with pulmonary hypertension, renal failure, and thromboembolism (TE) occur (*Blood.* 2007;110:4123-4128, *JAMA.* 2005;293:1653-1662, *Blood.* 1981;57:83-89.). Patients with aplastic anemia (AA) or myelodysplastic syndromes (MDS) may go on to develop PNH and PNH patients often have AA or MDS as well.

Currently, the following therapies are used for PNH patients with clinically relevant hemolysis to relieve clinical symptoms considered associated with chronic intravascular hemolysis (anaemia, fatigue,

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abdominal pain, TE, renal failure, pulmonary hypertension, etc.): (1) iron preparation/folic acid, (2) erythropoietin, (3) blood transfusion, (4) haptoglobin preparation, (5) corticosteroids, (6) anabolic steroids, (7) anticoagulants, (8) allogeneic hematopoietic stem cell transplantation, etc. However, the therapies (1) to (7) do not inhibit hemolysis itself. Allogeneic hematopoietic stem cell transplantation is the curative therapy for PNH, but is indicated for PNH patients with severe bone marrow failure only. Reports on the outcome of allogeneic hematopoietic stem cell transplants for PNH are shown in Table 18.

Table 18. The outcome of allogeneic hematopoietic stem cell transplants for PNH

Publication	No. of patients	Age (Median)	Mortality
Br J Haematol. 1999;104:392-396.	57	28	44% after 2 years[b]
Biol Blood Marrow Transplant. 2003;9:689-697.	7	34	43% at about 2-year follow-up
Blood. 2005;106:3699-3709.[a]	121	30	44% after 10 years
Thomas' Hematopoietic Cell transplantation. 3rd ed.; 2007:1002-1006.	23	29	39% (the duration of follow-up is unknown)

a) The supplemental document link at the top of the online article, at the Blood website
b) Outcome of 48 recipients of HLA-identical sibling bone marrow transplants

Since PNH patients with AA or MDS also have bone marrow failure, basically, AA or MDS is also treated simultaneously (immunosuppressants, blood transfusion, allogeneic hematopoietic stem cell transplantation, etc.).

On the other hand, since the main clinical studies of eculizumab (TRIUMPH, SHEPHERD, C07-001) have demonstrated that eculizumab reduces hemolysis, eculizumab is positioned as a first-choice drug for PNH patients. As allogeneic hematopoietic stem cell transplantation is associated with high rates of transplant-related complications and mortality, eculizumab should be considered first for PNH patients with severe bone marrow failure as well.

PMDA considers as follows:

There is no effective existing therapy for the hemolysis of PNH at present. Since the TRIUMPH study demonstrated that eculizumab stabilized Hb levels and reduced transfusion requirements by reducing hemolysis [see "4.(iii).B.(4) Efficacy"], if appropriate patients are selected, eculizumab will become an effective therapy for the hemolysis of PNH. Although allogeneic hematopoietic stem cell transplantation can be a curative therapy for PNH, not every patient can find a suitable donor and the rates of transplant-related complications and mortality are high. Thus, the decision of whether or not to perform allogeneic hematopoietic stem cell transplantation should be carefully considered, taking account of the bone marrow function and age of the patient, etc. It is understood that eculizumab may be used first also for candidates for allogeneic hematopoietic stem cell transplantation.

Meanwhile, eculizumab is not a curative therapy for PNH and continued treatment is needed to inhibit hemolysis. By protecting PNH type III RBCs against hemolysis, the percentage of PNH type III RBCs in blood increases in patients being treated with eculizumab and serious hemolysis may be induced if

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eculizumab is discontinued [see "4.(iii).B.(5).8) Safety after eculizumab discontinuation"]. The effects of hemolysis inhibition by eculizumab on the development of TE and survival prognosis are unclear and moreover, eculizumab may increase the risk of infections with *Neisseria meningitidis* etc. [see "4.(iii).B.(5).4) Meningococcal infections" and "4.(iii).B.(5).5) Other infections"]. Therefore, prior to the initiation of eculizumab treatment, patients should be fully assessed for the severity of hemolysis or anaemia and complications etc. and then, eculizumab should be used only when the clinical benefits of eculizumab can be reasonably expected to outweigh the possible risks [see "4.(iii).B.(6) Indication" for the intended population].

4.(iii).B.(2) Differences in PNH between Japan and overseas

The results of a comparison of the epidemiology of PNH between Japan and the US based on the publication (*Medicine*. 2004;83:193-207.) are shown in Table 19.

Table 19. Comparison of the epidemiology of PNH between Japan and the US

		Japan	US
Gender difference in prevalence (Male/Female)		1.3	0.8
Age of onset (Median [min., max.])		45 years [10 years, 86 years]	30 years [4 years, 80 years]
Survival time after diagnosis (Median)		25.0 years	23.3 years
Preceding AA or MDS (%)	AA	37.8%	29.0%
	MDS	4.8%	5.1%
Initial symptoms (%)	Hemoglobinuria	33.5%	50.0%
	Anaemia	94.3%	88.1%
	Leukopenia/Neutropenia	7.23%	45.5%
	Thrombocytopenia	63.2%	52.3%
	Infection	3.4%	13.6%
	TE	6.2%	19.3%
Laboratory findings (Mean ± SE)	Hb level	8.2 ± 0.2 g/dL	9.7 ± 0.2 g/dL
	Reticulocyte count	78.3 ± 6.2×10^9/L	195.3 ± 13.1×10^9/L
	White blood cell count	3475.3 ± 137.5×10^6/L	4947 ± 198.6×10^6/L
	Neutrophil count	1781.6 ± 132.5×10^6/L	3005.1 ± 156.4×10^6/L
	Platelet count	96.0 ± 5.8×10^9/L	140.1 ± 8.6×10^9/L
	LDH level	1572.3 ± 91.7 U/L	2337.2 ± 405.6 U/L
Complication (%)	TE	4.3%	31.8%
	Severe infection	9.1%	18.2%
	Hematopoietic failure	36.4%	33.0%
	MDS	3.8%	3.4%
	Leukemia	2.9%	0.6%
	Renal failure	10.5%	9.1%
Cause of death (%)	TE	7.9%	42.1%
	Severe infection	36.8%	36.8%
	Renal failure	18.4%	7.9%
	Haemorrhage	23.7%	10.5%
	MDS/Leukemia	15.8%	7.9%
	Cancer	5.3%	5.3%
	Unknown	0.0%	5.3%
Treatment (%)	No treatment	28.2%	5.7%
	Blood transfusion	40.2%	61.9%
	Anabolic steroids	39.7%	36.9%
	Steroids	46.9%	82.4%
	ATG/ALG	2.9%	15.3%
	Cyclosporine	8.1%	9.7%
	Erythropoietin	3.3%	6.8%
	G-CSF	7.7%	1.7%
	Anticoagulants	4.3%	26.7%
	Allogeneic hematopoietic stem cell transplantation	1.9%	8.0%

ATG: antithymocyte globulin, ALG: antilymphocyte globulin, G-CSF: granulocyte-colony stimulating factor

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It has been reported that there were marked differences in the prevalences of TE and severe infection as complications between Japan and the US and the causes of death were also different, i.e. the percentages of patients who died from TE, renal failure, or haemorrhage etc. were different.

PMDA considers that as the results of this epidemiological study have indicated differences in complications and causes of death etc. between Japan and overseas, these differences should be noted when evaluating foreign clinical study data [see "4.(iii).B.(4) Efficacy" and "4.(iii).B.(5) Safety"].

4.(iii).B.(3) Data subject to evaluation

PMDA planned its review for eculizumab as follows:

For the clinical data submitted in the application, a confirmatory study in Japanese PNH patients has not been conducted. The estimated number of PNH patients in Japan is approximately 430 (Health Science Research Grants, Research Project on Intractable Diseases, Research Committee for determining the epidemiology of diseases not covered by Research Project on Treatment of Intractable Diseases, 1999 Research Results, 2000) and it is understood that it is difficult to conduct a confirmatory, double-blind comparative study in Japan alone. PNH is an acquired genetic disorder characterized by intravascular hemolysis due to a deficiency of the GPI-anchored terminal complement inhibitor CD59 and eculizumab is an anti-C5 antibody and reduces hemolysis by inhibiting C5 and blocking the formation of the terminal complement complex C5b-9. It is inferred from the pathology of the disease and the mechanism of action that eculizumab is insensitive to ethnic factors and is expected to have similar effects also in Japanese PNH patients.

Therefore, PMDA decided to position the TRIUMPH study, which is a foreign randomized, placebo-controlled, double-blind, comparative study, as the pivotal study and use the SHEPHERD study, which is an open-label, uncontrolled, phase III study enrolling a broader range of PNH patients than in the TRIUMPH study and Study C07-001, which is a Japanese open-label, uncontrolled, phase II study, as supporting efficacy and safety data, for evaluations. However, when evaluating the efficacy and safety of eculizumab in Japanese patients by comparing the results from the Japanese clinical study (C07-001) with the results from the foreign clinical studies (TRIUMPH and SHEPHERD), epidemiological differences in PNH [see "4.(iii).B.(2) Differences in PNH between Japan and overseas"] and differences in patient background etc. among the studies need to be fully taken into consideration and the following reviews were conducted [see "4.(iii).B.(4) Efficacy" and "4.(iii).B.(5) Safety"].

4.(iii).B.(4) Efficacy

As a result of the following reviews, PMDA considers that although the effects of eculizumab on the development of TE, which is a cause of death and is regarded as a serious problem in PNH patients, and survival prognosis etc. are undefined, as eculizumab has been shown to reduce hemolysis, if appropriate

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patients are selected, the clinical benefits of inhibition of decrease in Hb levels and reductions in transfusion requirements resulting from hemolysis inhibition by eculizumab can be expected. A final conclusion on the efficacy of eculizumab will be made, taking account of comments from the Expert Discussion.

4.(iii).B.(4).1) Efficacy endpoints

As the primary endpoints for the main clinical studies, "Hb stabilization" and "the number of PRBC units transfused" for the TRIUMPH study, "LDH AUC" from baseline to Week 52 for the SHEPHERD study, and "change of LDH" from baseline to Week 12 for Study C07-001 were chosen.

PMDA asked the applicant to provide a rationale for the primary endpoint for each study and explain the relationship between LDH, which was used as a primary endpoint measure for the SHEPHERD study and Study C07-001, and hemolysis inhibition, taking also into account that LDH can be a non-specific marker.

The applicant responded as follows:

Hemolysis is the underlying cause of clinical symptoms of PNH and it was decided to choose an objective measure of eculizumab-induced reduction of hemolysis as the primary endpoint. Achievement of "Hb stabilization" was defined as maintenance of an Hb concentration above the Hb set-point and avoidance of any RBC transfusion for the entire treatment period (each patient underwent an initial observation period to identify the Hb concentration that necessitated RBC transfusion [the set-point]). This is considered a measure of stable anemia. "The number of PRBC units transfused" is considered a measure that can assess the need for blood transfusion objectively to some extent, because patients received transfusion if Hb was ≤ 9.0 g/dL with clinical symptoms or if Hb was ≤ 7.0 g/dL without clinical symptoms in the TRIUMPH study.

On the other hand, LDH can be used as a marker for intravascular hemolysis because LDH is released into the bloodstream during the hemolysis of erythrocytes and LDH is considered a measure that can assess the reduction of hemolysis by eculizumab. Although LDH may be elevated due to other tissue damage or bone marrow failure associated with MDS etc., whether or not an elevated LDH is associated with hemolysis can be determined by checking for increased free Hb, decreased haptoglobin, and decreased PNH RBCs. In clinical studies, since treatment with eculizumab resulted in lowering of LDH levels with decreased free Hb, increased haptoglobin, and increased PNH RBCs, LDH isozyme analysis was not performed, but it was thought that hemolysis inhibition was related to lowering of LDH levels.

PMDA's view on the primary endpoints for the main clinical studies is as follows:

For PNH patients presenting with progressive anemia due to chronic intravascular hemolysis, hemolysis inhibition resulting in Hb stabilization and reduced transfusion requirements has clinical significance.

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Therefore, choosing "Hb stabilization" and "the number of PRBC units transfused" as the primary endpoints for the TRIUMPH study was appropriate for demonstrating the clinical significance of eculizumab.

On the other hand, although PMDA understands that the applicant used "LDH AUC" and "change of LDH" chosen as the primary endpoints for the SHEPHERD study and Study C07-001, respectively, as a measure of LDH reduction due to hemolysis inhibition, because LDH levels are known to change also in various diseases, isozyme analysis should have been performed. However, elevated LDH levels in PNH patients are considered due mainly to hemolysis and in light of the relationship to changes in free Hb, haptoglobin, and PNH RBCs etc., elevated LDH levels observed in clinical studies are considered due mainly to hemolysis. Thus, taking account of the mechanism of action of eculizumab, LDH can be used as a measure that indirectly assess hemolysis inhibition. Meanwhile, since clinically significant LDH AUC and LDH changes were not defined prior to their use as the endpoints, a problem still remains as to using these as a measure of treatment effect. The efficacy data from the SHEPHERD study and Study C07-001 demonstrated reduction of hemolysis by eculizumab rather than the favourable treatment effect of eculizumab in enrolled patients with PNH.

4.(iii).B.(4).2) Efficacy evaluation in the TRIUMPH study

For the co-primary endpoints in the TRIUMPH study, the Hb stabilization rate was 0.0% (0 of 44 patients) in the placebo group and 48.8% (21 of 43 patients) in the eculizumab group ($P < 0.001$, Fisher's exact test) and the number of PRBC units transfused (median [min., max.]) was 10 units [2 units, 21 units] in the placebo group and 0 units [0 units, 16 units] in the eculizumab group ($P < 0.001$, Wilcoxon's rank sum test). There were significant differences between the groups for both endpoints. Hb was maintained at levels that did not necessitate blood transfusion and transfusion requirements were reduced in more patients in the eculizumab group than in the placebo group among the PNH patients enrolled into the TRIUMPH study. Therefore, PMDA concluded that the clinical significance of hemolysis inhibition by eculizumab was demonstrated. However, as only 48.8% (21 of 43 patients) of patients achieved Hb stabilization, PMDA considered that there is a possibility that adequate treatment effect was not achieved in the study population as a whole.

4.(iii).B.(4).3) Comparison of the eligibility criteria among the main clinical studies

PMDA asked the applicant to compare the eligibility criteria among the TRIUMPH study, SHEPHERD study, and Study C07-001 and explain the reasons for differences in the criteria.

The applicant responded as follows:

The main common eligibility criteria among the 3 studies are shown in Table 20, the main different eligibility criteria are shown in Table 21, and the demographics and baseline characteristics of enrolled patients are shown in Table 22.

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Table 20. Main common eligibility criteria among the TRIUMPH study, SHEPHERD study, and Study C07-001

Inclusion criteria	PNH type III RBCs ≥ 10%, LDH ≥ 1.5 times the upper limit of laboratory reference range[a)]
Exclusion criterion	Neutrophil count < 500/μL

a) 103 to 223 U/L in the TRIUMPH and SHEPHERD studies; 120 to 240 U/L in Study C07-001

Table 21. Main different eligibility criteria among the TRIUMPH study, SHEPHERD study, and Study C07-001

	TRIUMPH	SHEPHERD	C07-001
Age	≥ 18 years	≥ 18 years	≥ 12 years
Transfusion	≥ 4 transfusions in the past 12 months for anemia or anemia-related symptoms	≥ 1 transfusion in the past 2 years for anemia or anemia-related symptoms or personal beliefs that precluded transfusions	≥ 1 transfusion in the past 2 years for anemia or anemia-related symptoms or personal beliefs that precluded transfusions
Platelet count	≥ 100 000/μL	≥ 30 000/μL	≥ 30 000/μL
Hb level	Pre-transfusion Hb ≤ 10.5 g/dL over the past 12 months	Not specified	Not specified

Table 22. Demographics and baseline characteristics of patients in the TRIUMPH study, SHEPHERD study, and Study C07-001

		Overseas			Japan
		TRIUMPH		SHEPHERD	C07-001
		Placebo	Eculizumab	N = 97	N = 29
		N = 44	N = 43		
Age (Mean ± SD)		38.45 ± 13.43 years	42.26 ± 15.45 years	41.11 ± 14.40 years	47.40 ± 12.39 years
Body weight (Mean ± SD)		72.8 ± 14.04 kg	74.94 ± 11.69 kg	73.72 ± 14.29 kg	61.48 ± 11.32 kg
LDH (Mean ± SD)		2258.0 ± 1027.1 U/L	2199.7 ± 1033.8 U/L	2199.8 ± 1034.4 U/L	1845.1 ± 621.14 U/L
Hb level (Mean ± SD)		9.63 ± 1.20 g/dL	10.01 ± 1.20 g/dL	9.19 ± 1.57 g/dL	7.90 ± 1.67 g/dL
PNH RBCs (Mean ± SD)		1.26 ± 0.69 × 10^{12}/L	1.12 ± 0.49 × 10^{12}/L	1.32 ± 0.75×10^{12}/L	1.26 ± 0.74 × 10^{12}/L
Percentage of PNH type III RBC clone (Mean ± SD)		35.14 ± 18.17%	27.98 ± 13.26%	38.72 ± 21.34%	43.89 ± 24.01%
Platelet count (Mean ± SD)		157.07 ± 76.67 × 10^9/L	188.84 ± 83.33 × 10^9/L	141.36 ± 78.54 × 10^9/L	146.2 ± 12.21 × 10^9/L
PNH duration (Mean ± SD)		10.7 ± 8.75 years	7.19 ± 7.21 years	7.41 ± 6.82 years	10.40 ± 6.14 years
History of AA or MDS (%)	AA	27.3% (N = 12)	14.0% (N = 6)	30.9% (N = 30)	37.9% (N = 11)
	MDS	0.0% (N = 0)	4.7% (N = 2)	1.0% (N = 1)	6.9% (N = 2)
No. of transfusions in the past 12 months (Mean ± SE)		9.0 ± 0.62	8.5 ± 0.61	5.9 ± 0.60	8.6 ± 1.50
No. of PRBC units transfused in the past 12 months (Mean ± SE)		19.8 ± 1.40 units	19.2 ± 1.28 units	12.2 ± 1.26 units	18.0 ± 3.02 units

It is difficult to directly compare the amount of PRBC transfused between Japan and overseas because the volume of 1 unit of PRBC is different between Japan and overseas and the volume of 1 unit of PRBC used at each trial site was not documented in clinical studies.

PMDA considers as follows:

The eligibility criteria for the SHEPHERD study and Study C07-001 were almost the same except for age. On the other hand, the eligibility criteria as to transfusion requirements prior to study entry, platelet count, and Hb level were different between these 2 studies and the TRIUMPH study. While only patients whose bone marrow was relatively spared and who were highly transfusion-dependent were eligible for the TRIUMPH study, patients with decreased bone marrow function and patients who required relatively fewer transfusions were also eligible for the SHEPHERD study and Study C07-001.

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With regard to the demographics and baseline characteristics of patients enrolled into these clinical studies, it is difficult to directly compare the amount of PRBC transfused because the specification for PRBC is different between Japan and overseas and the volume of 1 unit of PRBC used at each trial site was not documented, but patients in the SHEPHERD study and Study C07-001 tended to have lower platelet counts compared with patients in the TRIUMPH study. Patients in the C07-001 study tended to be older and have lower body weight, longer PNH duration, and lower LDH and Hb levels than patients in the TRIUMPH and SHEPHERD studies.

As described above, because differences in the demographics and baseline characteristics of patients among the studies were found, PMDA decided that subgroup analyses of the main clinical studies should be performed to identify the background factors affecting the efficacy of eculizumab [see "4.(iii).B.(4).5) Background factors affecting the efficacy of eculizumab"].

4.(iii).B.(4).4) Comparison of efficacy in the main clinical studies

PMDA asked the applicant to compare and present the results of the efficacy endpoints (Hb stabilization, the number of PRBC units transfused, LDH levels over time, change of LDH, LDH AUC) in the TRIUMPH study, SHEPHERD study, and Study C07-001.

The applicant explained as follows:

The number of PRBC units transfused, LDH levels over time, change of LDH, and LDH AUC up to Week 26 are presented in Table 23. "Hb stabilization" rates could not be calculated for the SHEPHERD study and Study C07-001 because the Hb concentration that necessitated transfusion during the observation phase (the set-point) had not been measured.

PMDA's view on comparison of efficacy in the studies is as follows:

Since "Hb stabilization" rates could not be calculated for the SHEPHERD study or Study C07-001, comparison with that in the TRIUMPH study is impossible. As previously noted, it is also difficult to simply compare "the number of PRBC units transfused" because the specification for PRBC is different between Japan and overseas and the volume of 1 unit of PRBC used at each trial site was not documented. Namely, the efficacy of eculizumab in the SHEPHERD study and Study C07-001 could not be compared with that in the TRIUMPH study in terms of improvement of anemia as indicated by "Hb stabilization" or transfusion requirements as indicated by "the number of PRBC units transfused." However, the SHEPHERD study and Study C07-001 also demonstrated a reduction in LDH from baseline, which is an indirect indicator of reduction in hemolysis, and a reduction in the number of PRBC units transfused from baseline.

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Table 23. Comparison of efficacy in the main clinical studies (TRIUMPH, SHEPHERD, C07-001)

		Overseas			Japan
		TRIUMPH		SHEPHERD	C07-001
		Placebo	Eculizumab		
		N = 44	N = 43	N = 97	N = 29
PRBC units transfused	12 weeks prior to start of treatment	4.5 [2.0, 15.0]	6.0 [2.0, 9.0]	2.0 [0.0, 12.0]	2.0 [0.0, 22.0]
	12 weeks after start of treatment	4.0 [0.0, 12.0]	0.0 [0.0, 8.0]	0.0 [0.0, 14.0]	0.0 [0.0, 14.0]
	26 weeks after start of treatment	10.0 [2.0, 21.0]	0.0 [0.0, 16.0]	0.0 [0.0, 26.0]	–
LDH	Baseline (U/L)	2234.5 [a), c)] [636.0, 5530.0]	2032.0 [a)] [499.0, 5962.0]	2051.0 [a)] [537.0, 5245.0]	1814.0 [b)] [627.8, 3642.5]
	Week 1 (U/L)	2089.0 [c)] [915.0, 4753.0]	621.0 [249.0, 2453.0]	580.0 [e)] [158.0, 3166.0]	542.0 [308.0, 2230.0]
	Week 12 (U/L)	2204.0 [d)] [550.0, 4682.0]	254.0 [d)] [136.0, 6067.0]	277.0 [f)] [120.0, 4147.0]	244.0 [187.0, 2715.0]
	Week 26 (U/L)	2166.5 [1183.0, 5643.0]	239.0 [d)] [142.0, 7692.0]	270.0 [g)] [98.0, 2944.0]	–
	Change at Week 12 (U/L)	145.0 [-1578.0, 3751.0]	-1739.0 [-4138.0, 105.0]	-1758.0 [f)] [-5008.0, 975.0]	-1327 [-3166.0, 436.3]
	Change at Week 26 (U/L)	57.0 [c)] [-1426.0, 1859.0]	-1840.0 [d)] [-4065.0, -300.0]	-1795.0 [g)] [-4678.0, 931.0]	–
	LDH AUC up to Week 12 (U/L·day)	4894.8 [-164 666.5, 138 509.0]	-142 387.0 [-333 776.5, -21 437.5]	-131 723.0 [-392 532.0, -20 126.0]	-107 613.6 [-238 162.8, 10 628.1]
	LDH AUC up to Week 26 (U/L·day)	–	-313 853.0 [-733 639.0, -50 767.5]	-301 837.0 [-881 797, -39 392.5]	–

Median [Min., Max.], –: Not calculable

a) Baseline LDH (Missing data were imputed from the last visit)

b) Baseline LDH was defined as mean LDH over the 4 weeks prior to start of treatment

c) N = 43

d) N = 41

e) N = 94

f) N = 95

g) N = 96

4.(iii).B.(4).5) Background factors affecting the efficacy of eculizumab

PMDA asked the applicant to explain the influences of patient background factors on the efficacy of eculizumab.

The applicant explained as follows:

Subgroup analyses by baseline levels of transfusion requirements and Hb, which are considered an indicator of hemolysis characteristic of PNH, and baseline level of platelet count, which is considered an indicator of bone marrow function, were performed to examine the influences of these patient background factors on the efficacy endpoints (Hb stabilization, the number of PRBC units transfused). The influences of age, PNH duration, and body weight, which tended to be different between Japanese and foreign clinical studies, were examined. Furthermore, in order to assess the effects of bone marrow function and the severity of PNH, the percentage of PNH type III RBCs and concurrent AA or MDS were examined.

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(a) Transfusion requirements

As shown in Table 24, regardless of transfusion requirements in the prior 12 months, the Hb stabilization rate was higher and the number of PRBC units transfused was fewer in the eculizumab group than in the placebo group in the TRIUMPH study.

In the TRIUMPH study, SHEPHERD study, and Study C07-001, when patients were stratified by transfusion requirement in the prior 12 months, there was no consistent trend in the number of PRBC units transfused by transfusion requirement in the prior 12 months.

Table 24. Influence of baseline transfusion requirements on efficacy

					Transfusion requirements in the prior 12 months (Unit)			Overall
					4-14	15-25	≥ 26	
Hb stabilization[a]	Up to Week 12	TRIUMPH	Placebo	N = 44	6.7% (1/15)	5.6% (1/18)	0.0% (0/11)	4.5% (2/44)
			Eculizumab	N = 43	100.0% (15/15)	41.2% (7/17)	63.6% (7/11)	67.4% (29/43)
	Up to Week 26	TRIUMPH	Placebo	N = 44	0.0% (0/15)	0.0% (0/18)	0.0% (0/11)	0.0% (0/44)
			Eculizumab	N = 43	80.0% (12/15)	29.4% (5/17)	36.4% (4/11)	48.8% (21/43)
PRBC units transfused[b]	Up to Week 12	TRIUMPH	Placebo	N = 44	2.0 [0.0, 6.0] (N = 15)	4.0 [0.0, 9.0] (N = 18)	8.0 [3.0, 12.0] (N = 11)	4.0 [0.0, 12.0] (N = 44)
			Eculizumab	N = 43	0.0 [0.0, 0.0] (N = 15)	0.0 [0.0, 6.0] (N = 17)	0.0 [0.0, 9.0] (N = 11)	0.0 [0.0, 9.0] (N = 43)
		SHEPHERD		N = 97	0.0 [0.0, 8.0] (N = 62)	0.5 [0.0, 8.0] (N = 12)	2.0 [0.0, 14.0] (N = 23)	0.0 [0.0, 14.0] (N = 97)
		C07-001		N = 29	0.5 [0.0, 3.0] (N = 15)	1.0 [0.0, 12.0] (N = 4)	0.5 [0.0, 13.0] (N = 10)	0.64 [0.0, 13.0] (N = 29)
	Up to Week 26	TRIUMPH	Placebo	N = 44	6.0 [2.0, 12.0] (N = 15)	10.0 [2.0, 12.0] (N = 18)	18.0 [10.0, 20.0] (N = 11)	10.0 [2.0, 21.0] (N = 44)
			Eculizumab	N = 43	0.0 [0.0, 4.0] (N = 15)	2.0 [0.0, 15.0] (N = 17)	3.0 [0.0, 16.0] (N = 11)	0.0 [0.0, 16.0] (N = 43)
		SHEPHERD		N = 97	0.0 [0.0, 16.0] (N = 62)	0.0 [0.0, 15.0] (N = 12)	3.0 [0.0, 26.0] (N = 23)	0.0 [0.0, 26.0] (N = 97)

[a] Hb stabilization rate (N)
[b] Median [Min., Max.] (N)

(b) Hb levels

As shown in Table 25, regardless of Hb levels prior to study entry, the Hb stabilization rate was higher and the number of PRBC units transfused was fewer in the eculizumab group than in the placebo group in the TRIUMPH study.

In the TRIUMPH study, SHEPHERD study, and Study C07-001, when patients were stratified by baseline Hb level, there was no consistent trend in the number of PRBC units transfused by baseline Hb level.

(c) Platelet count

As shown in Table 26, regardless of platelet counts prior to study entry, the number of PRBC units transfused was fewer in the eculizumab group than in the placebo group in the TRIUMPH study. On the other hand, although there was no difference in the Hb stabilization rate between placebo- and

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eculizumab-treated patients among the subgroup of patients with a baseline platelet count ≥ 50000/μL and < 100000/μL at Week 26, the Hb stabilization rate was higher in eculizumab-treated patients than in placebo-treated patients among the subgroups of patients with a baseline platelet count ≥ 100000/μL.

In the three studies, when patients were stratified by baseline platelet count, there was no consistent trend in the number of PRBC units transfused by baseline platelet count.

Table 25. Influence of baseline Hb levels on efficacy

					Hb levels prior to study entry (g/dL)				Overall
					< 7.0	≥ 7.0 to < 9.0	≥ 9.0 to < 11.0	≥ 11.0	
Hb stabilization[a]	Up to Week 12	TRIUMPH	Placebo	N = 44	-- (N = 0)	0.0% (0/13)	4.3% (1/23)	14.3% (1/7)	4.7% (2/43)
			Eculizumab	N = 43	100.0% (1/1)	50.0% (3/6)	66.7% (20/30)	83.3% (5/6)	67.4% (29/43)
	Up to Week 26	TRIUMPH	Placebo	N = 44	-- (N = 0)	0.0% (0/13)	0.0% (0/23)	0.0% (0/7)	0.0% (0/43)
			Eculizumab	N = 43	100.0% (1/1)	33.3% (2/6)	43.3% (13/30)	83.3% (5/6)	48.8% (21/43)
PRBC units transfused[b]	Up to Week 12	TRIUMPH	Placebo	N = 44	-- (N = 0)	7.0 [3.0, 12.0] (N = 13)	4.0 [0.0, 9.0] (N = 23)	2.0 [0.0, 8.0] (N = 7)	4.0 [0.0, 12.0] (N = 43)
			Eculizumab	N = 43	0.0 [0.0, 0.0] (N = 1)	1.5 [0.0, 9.0] (N = 6)	0.0 [0.0, 8.0] (N = 30)	0.0 [0.0, 0.0] (N = 6)	0.0 [0.0, 9.0] (N = 43)
		SHEPHERD		N = 97	2.0 [0.0, 14.0] (N = 10)	0.0 [0.0, 9.0] (N = 33)	0.0 [0.0, 10.0] (N = 42)	0.0 [0.0, 8.0] (N = 12)	0.0 [0.0, 14.0] (N = 97)
		C07-001		N = 29	0.0 [0.0, 13.0] (N = 8)	0.0 [0.0, 12.0] (N = 15)	0.0 [0.0, 0.0] (N = 5)	0.0 [0.0, 0.0] (N = 1)	0.0 [0.0, 13.0] (N = 29)
	Up to Week 26	TRIUMPH	Placebo	N = 44	-- (N = 0)	16.0 [5.0, 21.0] (N = 13)	8.0 [2.0, 20.0] (N = 23)	8.0 [6.0, 20.0] (N = 7)	10.0 [2.0, 21.0] (N = 44)
			Eculizumab	N = 43	0.0 [0.0, 0.0] (N = 1)	4.0 [0.0, 12.0] (N = 6)	1.0 [0.0, 16.0] (N = 30)	0.0 [0.0, 2.0] (N = 6)	0.0 [0.0, 16.0] (N = 43)
		SHEPHERD		N = 97	2.5 [0.0, 26.0] (N = 10)	2.0 [0.0, 19.0] (N = 33)	0.0 [0.0, 3.0] (N = 42)	0.0 [0.0, 15.0] (N = 12)	0.0 [0.0, 26.0] (N = 97)

[a] Hb stabilization rate (N)
[b] Median [Min., Max.] (N)

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Table 26. Influence of baseline platelet counts on efficacy

					Platelet counts prior to study entry (/μL)					Overall
					< 30 000	≥ 30 000 to < 50 000	≥ 50 000 to < 100 000	≥ 100 000 to < 150 000	≥ 150 000	
Hb stabilization[a]	Up to Week 12	TRIUMPH	Placebo	N = 44	– (N = 0)	– (N = 0)	0.0% (0/7)	0.0% (0/16)	10.5% (2/19)	4.8% (2/42)
			Eculizumab	N = 43	– (N = 0)	– (N = 0)	75.0% (3/4)	46.2% (6/13)	76.9% (20/26)	67.4% (29/43)
	Up to Week 26	TRIUMPH	Placebo	N = 44	– (N = 0)	– (N = 0)	0.0% (0/7)	0.0% (0/16)	0.0% (0/19)	0.0% (0/42)
			Eculizumab	N = 43	– (N = 0)	– (N = 0)	0.0% (0/4)	38.5% (5/13)	61.5% (16/26)	48.8% (21/43)
PRBC units transfused[b]	Up to Week 12	TRIUMPH	Placebo	N = 44	– (N = 0)	– (N = 0)	6.0 [2.0, 8.0] (N = 7)	4.5 [2.0, 12.0] (N = 16)	3.0 [0.0, 8.0] (N = 19)	4.0 [0.0, 12.0] (N = 42)
			Eculizumab	N = 43	– (N = 0)	– (N = 0)	0.0 [0.0, 6.0] (N = 4)	2.0 [0.0, 8.0] (N = 13)	0.0 [0.0, 6.0] (N = 26)	0.0 [0.0, 9.0] (N = 43)
		SHEPHERD		N = 97	4.5 [0.0, 9.0] (N = 2)	0.0 [0.0, 6.0] (N = 6)	2.0 [0.0, 14.0] (N = 27)	0.0 [0.0, 8.0] (N = 19)	0.0 [0.0, 8.0] (N = 43)	0.0 [0.0, 14.0] (N = 97)
		C07-001		N = 29	7.5 [2.0, 13.0] (N = 2)	0.0 [0.0, 0.0] (N = 1)	5.0 [0.0, 12.0] (N = 4)	0.0 [0.0, 0.0] (N = 8)	0.0 [0.0, 3.0] (N = 14)	0.0 [0.0, 13.0] (N = 29)
	Up to Week 26	TRIUMPH	Placebo	N = 44	– (N = 0)	– (N = 0)	15.0 [6.0, 20.0] (N = 7)	11.5 [5.0, 21.0] (N = 16)	8.0 [2.0, 18.0] (N = 19)	10.0 [2.0, 21.0] (N = 42)
			Eculizumab	N = 43	– (N = 0)	– (N = 0)	4.5 [2.0, 15.0] (N = 4)	6.0 [0.0, 16.0] (N = 13)	0.0 [0.0, 12.0] (N = 26)	0.0 [0.0, 16.0] (N = 43)
		SHEPHERD		N = 97	9.5 [0.0, 19.0] (N = 2)	3.5 [0.0, 14.0] (N = 6)	2.0 [0.0, 26.0] (N = 27)	0.0 [0.0, 15.0] (N = 19)	0.0 [0.0, 16.0] (N = 43)	0.0 [0.0, 26.0] (N = 97)

[a] Hb stabilization rate (N)
[b] Median [Min., Max.] (N)

(d) Age and body weight

With respect to age, younger patients tended to achieve Hb stabilization and require fewer PRBC units. PMDA is currently asking the applicant about the results on the influence of body weight.

(e) Percentage of PNH type III RBCs, PNH duration, and concurrent AA or MDS

There was no consistent trend for the influence of the percentage of PNH type III RBCs, PNH duration, or concurrent AA or MDS.

PMDA's view on the association between the patient background factors and efficacy is as follows: Regardless of the patient background factors, the number of PRBC units transfused was fewer in the eculizumab group than in the placebo group in the TRIUMPH study. The Hb stabilization rate tended to decrease with higher transfusion requirement in the 1 year prior to study treatment (Table 24), which indicated the possibility that adequate effect can not be achieved in patients with higher transfusion requirements.

Patients with low baseline Hb or platelet count tended to be unlikely to achieve Hb stabilization and

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transfusion avoidance (Table 25 and Table 26). There has so far been no information that there are differences in efficacy between PNH patients with and without AA or MDS.

Based on the above, although it was suggested that patients with higher baseline transfusion requirements and patients with low baseline Hb or platelet count tended to be unlikely to achieve Hb stabilization, it does not mean that treatment effect was not achieved, taking into account that the number of PRBC units transfused tended to decrease. Therefore, it is necessary to administer eculizumab to appropriate patients, taking account of clinical treatment effect and safety [see "4.(iii).B.(5) Safety"] needed for each patient, referring to the main study data.

Especially, in a patient population not included in the TRIUMPH study, reduction in hemolysis has been demonstrated, but treatment effect, e.g. Hb stabilization, has not been studied. Thus, information should continue to be collected via post-marketing surveillance etc. and should be provided to the clinical practice as appropriate.

PMDA is currently asking the applicant about the results on the influence of body weight.

4.(iii).B.(4).6) Long-term efficacy of eculizumab

LDH levels over time in the SHEPHERD study with a treatment duration of 52 weeks are shown in Table 27.

Table 27. LDH levels over time in the SHEPHERD study

Week	Week 0 (Baseline)	Week 1	Week 2	Week 4	Week 8	Week 12	Week 26	Week 52
N	97	94	97	96	95	95	96	94
LDH (U/L)	2051.0 [537.0, 5245.0]	580.0 [158.0, 3166.0]	351.0 [149.0, 1933.0]	262.5 [93.0, 1208.0]	284.0 [118.0, 3381.0]	277.0 [120.0, 4147.0]	270.0 [98.0, 2944.0]	269.0 [106.0, 2117.0]

Median [Min., Max.]

As shown in Table 27, lowering of LDH levels was sustained in the SHEPHERD study. Thus, PMDA considered that treatment with eculizumab results in sustained decrease in hemolysis.

PMDA is currently asking the applicant about LDH levels over time and transfusion requirements over time based on pooled analyses of the submitted foreign clinical studies (TRIUMPH, SHEPHERD, C02-001, E02-001, X03-001, X03-001A, E05-001).

4.(iii).B.(4).7) Lack of efficacy of eculizumab

Since treatment discontinuation due to lack of efficacy occurred in Study C07-001 only (2 patients) among the main clinical studies (TRIUMPH, SHEPHERD, C07-001), PMDA asked the applicant to explain its cause.

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The applicant responded as follows:
In Study C07-001, 2 patients did not show a pharmacodynamic response as measured by LDH levels. In an *in vitro* assay using serum samples from these 2 patients, serum complement activity was not inhibited by eculizumab, but hemolytic activity was inhibited by an anti-C5 antibody that is slightly different in structure from eculizumab (ALXN-Ab). Therefore, there is a possibility that eculizumab did not bind to C5 due to a functional variation in C5, but the cause is undefined and a detailed investigation of C5 in serum from these patients will be conducted.

PMDA considers as follows:
As lack of efficacy was observed in the Japanese clinical study only, the possibility that there are differences in efficacy between Japan and overseas also can not be ruled out, but the cause is undefined and it is necessary to continue to collect information on ineffective cases via post-marketing surveillance etc. and provide the information to the clinical practice as appropriate. Except for these 2 patients, as shown in Tables 23 and 27, LDH levels were reduced by Week 1. Therefore, if LDH levels are not reduced by Week 1, whether or not to continue treatment should be considered.

As lack of efficacy has been reported from foreign post-marketing surveillance (Table 32), PMDA is currently asking the applicant about the details.

4.(iii).B.(4).8) Efficacy against TE

TE is one of the leading causes of death in PNH and thrombus formation is considered attributed to platelet activation induced by increased free Hb concentration due to intravascular hemolysis. According to a foreign single-center, retrospective study with a 6-year [0.2 years, 38 years] (median [min., max.]) follow-up of 163 PNH patients, there were 19 TE events in 511.5 patient-years in 67 patients without history of TE and not taking warfarin; and the incidence of TE in PNH was estimated to be 3.7 per 100 patient-years (*Blood.* 2003;102:3587-3591.). On the other hand, the incidence of TE in the general population was 5.04 per 10000 person-years (*Eur J Vasc Endovasc Surg.* 2003;25:1-5.). A higher incidence of TE in PNH patients has been suggested.

With regard to the effect of eculizumab on TE, 1 TE event occurred in the placebo group and 0 TE event occurred in the eculizumab group in the TRIUMPH study. The incidence of TE was 2.34 per 100 patient-years prior to the start of treatment (calculated from previous TE events in the past) and 4.38 per 100 patient-years after the start of treatment in the placebo group, compared with 5.18 per 100 patient-years prior to the start of treatment and 0.00 per 100 patient-years after the start of treatment in the eculizumab group. Based on the pooled data from eculizumab-treated patients in foreign clinical studies (TRIUMPH, SHEPHERD, C02-001, E02-001, X03-001, E05-001), the incidence of TE was 7.37 per 100 patient-years before the start of eculizumab treatment compared with 1.07 per 100 patient-years after eculizumab treatment.

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On the other hand, in the Japanese study C07-001, 5 of 29 patients had previously experienced 5 TE events and the incidence of TE was 1.66 per 100 patient-years before the start of treatment, but TE did not occur in the 3-month study period.

PMDA considers as follows:
The above results were not based on studies intended to investigate the incidence of TE and the detailed background information on concurrent use of anticoagulants, etc. is unknown and the possible influences of other factors also can not be excluded. However, foreign clinical studies have suggested that treatment with eculizumab may reduce the incidence of TE. The prevention of TE in PNH patients has a significant impact on survival prognosis. On the other hand, as it has been reported that the mortality from TE as well as the incidence of TE are lower in Japanese PNH patients than in foreign PNH patients [*Medicine*. 2004;83:193-207, see "4.(iii).B.(2) Differences in PNH between Japan and overseas"], the clinical benefits obtained from the prevention of TE may be different between Japanese PNH patients and PNH patients in the US/Europe. Therefore, the information on the development of TE, concurrent use of anticoagulants and other TE risk factors, etc. should be collected via post-marketing surveillance, differences between Japan and overseas should also be investigated, and then the information should be provided to the medical practice as appropriate.

4.(iii).B.(4).9) Efficacy during an acute hemolytic crisis
Since PNH patients are known to develop an acute hemolytic crisis associated with infections or trauma, PMDA asked the applicant to explain if there is clinical experience with eculizumab during an acute hemolytic crisis and whether or not to use eculizumab during an acute hemolytic crisis.

The applicant responded as follows:
Although there were no patients who started treatment with eculizumab after the onset of an acute hemolytic crisis associated with infections or trauma in clinical studies in PNH patients, the case of a PNH patient who developed an acute hemolytic crisis after delivery and started treatment with eculizumab has been reported from the foreign marketing experience. The patient received dialysis due to acute renal failure following the acute hemolytic crisis, but LDH levels returned to normal following treatment with eculizumab and the renal function was normalized; and dialysis was discontinued. Then, the patient was discharged and received treatment with eculizumab on an outpatient basis and was lost to follow-up thereafter.

On the other hand, the cases of hemolysis associated with infections or trauma during treatment with eculizumab (breakthrough hemolysis) were investigated. In the TRIUMPH and SHEPHERD studies, a total of 2 PNH patients experienced severe hemolysis associated with trauma during treatment with eculizumab, but continued treatment. Therefore, even if a patient develops an acute hemolytic crisis during treatment with eculizumab, treatment may be continued carefully at the discretion of the

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physician.

PMDA considers as follows:
Theoretically, eculizumab is expected to be effective during an acute hemolytic crisis, as with in the setting of chronic hemolysis, but there is very limited clinical experience and the efficacy and safety information is insufficient. Thus, it is difficult to recommend the use of eculizumab for treating acute hemolytic crises. However, if patients treated with eculizumab during an acute hemolytic crisis are identified after the market launch, it is important to collect information and provide information on actions to be taken in the event of an acute hemolytic crisis to the clinical practice as appropriate.

4.(iii).B.(5) Safety
As a result of the following safety reviews on comparison of the eculizumab and placebo groups in the TRIUMPH study and on long-term safety of eculizumab etc., PMDA confirmed based on the clinical study data that special attention should be paid to the possible occurrence of headache. Furthermore, as it is inferred that patients treated with eculizumab are at an increased risk for infections with encapsulated bacteria including *Neisseria meningitidis*, PMDA reviewed the issue of the risk of meningococcal infection, including its incidence in the foreign marketing experience [see "4.(iii).B.(5).4) Meningococcal infections"]. Especially, as measures against *Neisseria meningitidis* are an important issue for the safety of eculizumab, eculizumab should be used after carefully balancing the clinical benefits and the risks. The package insert should contain stringent warnings and precautions and a fully prepared safety control system is needed.

A final conclusion on the safety of eculizumab will be made, taking account of comments from the Expert Discussion.

4.(iii).B.(5).1) Safety in the eculizumab group in the TRIUMPH study
In the TRIUMPH study, adverse events reported at a ≥ 5.0% higher incidence in the eculizumab group than in the placebo group were headache, nasopharyngitis, back pain, and fatigue (Table 15). There were no particular differences in serious adverse events.

The applicant discussed that inhibition of intravascular hemolysis by eculizumab leads to reduced free Hb, which scavenges nitric oxide (NO) and increased free NO dilates blood vessels, causing headache. PMDA is currently asking the applicant to discuss nasopharyngitis, back pain, and fatigue.

PMDA considers as follows:
No serious adverse events unique to the eculizumab group were reported and although the incidences of adverse events of headache, nasopharyngitis, back pain, and fatigue tended to be higher in the eculizumab group compared with the placebo group, headache occurred as a severe event in 1 patient

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each in the placebo and eculizumab groups and there were no other severe events. Thus, although attention should be paid to the possible occurrence of headache, the results of the placebo-controlled TRIUMPH study indicate that adverse events associated with eculizumab are tolerable.

4.(iii).B.(5).2) Long-term safety of eculizumab and the influences of patient background factors on safety

Adverse events occurring in ≥ 10.0% of patients in either group up to Week 12 in the TRIUMPH study, SHEPHERD study, and Study C07-001 are shown in Table 28. Adverse events occurring in ≥ 10.0% of patients in either group during the entire treatment period in pooled foreign clinical studies (TRIUMPH, SHEPHERD, C02-001, E02-001, X03-001, E05-001) are shown in Table 29. Serious adverse events occurring in at least 2 patients up to Week 12 were anemia (3.1% [3 of 97 patients]) in the SHEPHERD study only. Serious adverse events occurring in at least 2 patients during the entire treatment period in pooled foreign clinical studies (TRIUMPH, SHEPHERD, C02-001, E02-001, X03-001, E05-001) are shown in Table 30. Of the serious adverse events listed in Table 30, those for which a causal relationship to study drug could not be denied were pyrexia (2.6% [5 of 195 patients]), headache (1.5% [3 of 195 patients]), viral infection (1.0% [2 of 195 patients]), and septic shock (1.0% [2 of 195 patients]).

Table 28. Adverse events occurring in ≥ 10.0% of patients in either group up to Week 12

	TRIUMPH				SHEPHERD		C07-001	
	Placebo (N = 44)		Eculizumab (N = 43)		Eculizumab (N = 97)		Eculizumab (N = 29)	
	Incidence	N	Incidence	N	Incidence	N	Incidence	N
Overall	84.1%	37	93.0%	40	85.6%	83	96.6%	28
Headache	20.5%	9	39.5%	17	45.4%	44	51.7%	15
Nasopharyngitis	11.4%	5	18.6%	8	11.3%	11	41.4%	12
Nausea	6.8%	3	14.0%	6	11.3%	11	20.7%	6
Diarrhoea	6.8%	3	4.7%	2	6.2%	6	13.8%	4
Vomiting	6.8%	3	4.7%	2	7.2%	7	10.3%	3
Pyrexia	4.5%	2	2.3%	1	5.2%	5	10.3%	3
Eczema	0.0%	0	0.0%	0	0.0%	0	10.3%	3
Dizziness	11.4%	5	2.3%	1	6.2%	6	3.4%	1

Table 29. Adverse events occurring in ≥ 10.0% of patients in either group during the entire treatment period in foreign clinical studies (Pooled analysis)

	Placebo (N = 44)		Eculizumab (N = 195)			Placebo (N = 44)		Eculizumab (N = 195)	
	Incidence	N	Incidence	N		Incidence	N	Incidence	N
Overall	90.9%	40	99.0%	193	Dizziness	11.4%	5	15.4%	30
Headache	27.3%	12	51.3%	100	Pharyngolaryngeal pain	9.1%	4	14.4%	28
Nasopharyngitis	18.2%	8	42.1%	82	Pain in extremity	2.3%	1	14.4%	28
Upper respiratory tract infection	22.7%	10	30.8%	60	Abdominal pain	11.4%	5	12.8%	25
Nausea	11.4%	5	25.1%	49	Insomnia	6.8%	3	11.8%	23
Diarrhoea	11.4%	5	22.1%	43	Constipation	4.5%	2	11.8%	23
Back pain	9.1%	4	20.0%	39	Viral infection	11.4%	5	11.3%	22
Pyrexia	4.5%	2	16.9%	33	Urinary tract infection	9.1%	4	11.3%	22
Vomiting	11.4%	5	16.4%	32	Contusion	6.8%	3	11.3%	22
Arthralgia	9.1%	4	15.9%	31	Influenza like illness	2.3%	1	11.3%	22
Cough	9.1%	4	15.9%	31	Myalgia	2.3%	1	10.8%	21

Foreign studies: TRIUMPH, SHEPHERD, C02-001, E02-001, X03-001, and E05-001

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Table 30. Serious adverse events occurring in at least 2 patients in either group during the entire treatment period in foreign clinical studies (Pooled analysis)

	Placebo (N = 44)		Eculizumab (N = 195)			Placebo (N = 44)		Eculizumab (N = 195)	
	Incidence	N	Incidence	N		Incidence	N	Incidence	N
Overall	20.5%	9	25.6%	50	Thrombocytopenia	0.0%	0	1.0%	2
Pyrexia	2.3%	1	3.6%	7	Abdominal pain	0.0%	0	1.0%	2
Viral infection	2.3%	1	2.6%	5	Cholelithiasis	0.0%	0	1.0%	2
Anaemia	2.3%	1	2.1%	4	Viral gastroenteritis	0.0%	0	1.0%	2
Headache	0.0%	0	2.1%	4	Septic shock	0.0%	0	1.0%	2
Intervertebral disc protrusion	0.0%	0	1.5%	3	Convulsion	0.0%	0	1.0%	2
PNH	6.8%	3	1.0%	2	Nephrolithiasis	0.0%	0	1.0%	2
Cellulitis	2.3%	1	1.0%	2	Acute renal failure	0.0%	0	1.0%	2
Haemolytic anaemia	0.0%	0	1.0%	2	Neutropenia	4.5%	2	0.5%	1

Foreign studies: TRIUMPH, SHEPHERD, C02-001, E02-001, X03-001, and E05-001

Since eculizumab is an anti-C5 antibody and was considered to possibly affect the immune function, the incidence of malignant tumors was investigated.

According to foreign post-marketing surveillance (March 16, 2007 to April 1, 2009), 19 cases of neoplasms benign, malignant and unspecified (incl cysts and polyps) (acute myeloid leukaemia [3], MDS [3], skin cancer [2], acute leukaemia [1], basal cell carcinoma [1], brain neoplasm [1], endometrial cancer stage I [1], hepatic neoplasm malignant [1], leukaemia [1], lung adenocarcinoma [1], lymphoma [1], pseudolymphoma [1], renal cancer [1], uterine leiomyoma [1]) were reported, but their relationship to eculizumab is undefined at present.

On the other hand, PMDA asked the applicant to explain differences in safety profile according to patient background, based on the results from the TRIUMPH study, SHEPHERD study, and Study C07-001.

The applicant responded as follows:
Although the incidences of adverse events of nasopharyngitis, headache, and eczema etc. tended to be higher in Study C07-001 than in foreign studies, these differences are considered of no clinical significance because the diagnostic criteria are different between Japan and overseas.

The influences of body weight, age, the percentage of PNH type III RBCs, and reticulocyte count at baseline as the background factors were examined. As a result, there was no clinically significant consistent trend in the incidence of adverse events.

On the other hand, with respect to gender, the incidences of adverse events of headache, nausea, back pain, and abdominal pain tended to be higher in female patients than in male patients, but its cause is unknown. Although the incidence of headache tended to be higher in patients with fewer PRBC units transfused over the 1 year prior to the start of treatment, patients with lower baseline Hb, patients with

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lower baseline platelet counts, and patients with AA or MDS, the results were inconsistent across the studies.

PMDA's view on adverse events associated with eculizumab is as follows:
The safety data up to Week 12 from the Japanese and foreign clinical studies in PNH patients showed that the incidence of headache was higher in the eculizumab group than in the placebo group and most of the events occurred by Week 5 (the incidence of headache in eculizumab-treated patients in the main clinical studies [TRIUMPH, SHEPHERD, C07-001] was 34.7% [68 of 169 patients] up to Week 5 and 7.7% [13 of 169 subjects] in Weeks 6-12). The events of headache were mostly mild or moderate in severity, but during the entire treatment period including the period beyond 12 weeks (C02-001, E02-001, X03-001, TRIUMPH, SHEPHERD, E05-001, C07-001), severe headache occurred at an incidence of 4.9% (11 of 224 patients) and serious headache occurred at an incidence of 1.8% (4 of 224 patients). Thus, attention should be paid to the possible occurrence of headache, especially during the early phase of treatment.

Other than headache, only pyrexia occurred at an incidence of ≥ 10.0% and was reported as a severe adverse event in at least 2 patients during the entire treatment period including the period beyond 12 weeks and serious pyrexia also occurred at an incidence of 3.6% (8 of 224 patients). Thus, like headache, pyrexia deserves attention. There were no other particular adverse events that deserve clinical attention. There have so far been no events that increased in incidence or severity with prolonged treatment with eculizumab. However, since there is limited clinical experience with long-term treatment with eculizumab and eculizumab possibly affects the immune function, it is important to collect information on events occurring during long-term treatment, such as influences of eculizumab on occurrence of malignant tumors and leukemia, after the market launch and provide the information to the clinical practice as appropriate.

On the other hand, as it is difficult to compare in details the safety of eculizumab, including the influences of patient background factors, between Japan and overseas due to the limited number of patients in clinical studies, the possibility of differences in safety profile between Japan and overseas can not be ruled out, but the submitted study data do not suggest the presence of differences that would significantly affect the tolerability of eculizumab.

Although no background factor that limits the use of eculizumab or requires careful administration has been identified, it is necessary to continue to collect information and provide the information as appropriate.

The safety data (adverse events and serious adverse events) from pooled Japanese (C07-001, E07-001) and foreign (TRIUMPH, SHEPHERD, C02-001, E02-001, X03-001, X03-001A, E05-001) clinical

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studies are currently being requested.

4.(iii).B.(5).3) Foreign post-marketing data

Adverse events and serious adverse events reported in clinical studies in PNH patients (C07-001, E07-001, TRIUMPH, SHEPHERD, C02-001, E02-001, X03-001, X03-001A, E05-001) were compared with those reported from foreign post-marketing surveillance (from March 17, 2007 to April 1, 2009). The cumulative number of patients exposed to eculizumab was 281.03 patient-years in the PNH clinical studies and 1249 patient-years in the foreign post-marketing surveillance. Adverse events occurring at an incidence of ≥ 5.0 per 100 patient-years in either the clinical studies or foreign post-marketing surveillance are shown in Table 31 and serious adverse events occurring at an incidence of ≥ 1.0 per 100 patient-years in either the clinical studies or foreign post-marketing surveillance are shown in Table 32. No new safety issues were identified.

Table 31. Adverse events occurring at an incidence of ≥ 5.0 per 100 patient-years in either clinical studies or foreign post-marketing surveillance

Adverse event	Clinical studies		Foreign post-marketing surveillance		Adverse event	Clinical studies		Foreign post-marketing surveillance	
	Events per 100 patient-years	No. of events	Events per 100 patient-years	No. of events		Events per 100 patient-years	No. of events	Events per 100 patient-years	No. of events
Headache	40.0	115	19.5	244	Constipation	8.0	23	0.2	3
Nasopharyngitis	32.7	94	4.5	56	Urinary tract infection	7.6	22	1.7	21
Upper respiratory tract infection	20.8	60	0.7	9	Myalgia	7.6	22	1.0	13
Nausea	19.1	55	5.8	73	Flu-like symptoms	7.6	22	0.6	8
Diarrhoea	16.3	47	2.7	34	Contusion	7.6	22	0.6	8
Back pain	13.6	39	4.8	60	Viral infection	7.6	22	0.5	6
Pyrexia	12.5	36	6.2	77	Fatigue	7.3	21	6.6	83
Vomiting	12.2	35	3.0	37	Epistaxis	6.6	19	0.7	9
Arthralgia	11.1	32	2.6	32	Abdominal pain upper	5.6	16	1.2	15
Cough	11.1	32	1.4	18	Herpes labialis	5.6	16	0.4	5
Dizziness	10.8	31	2.6	33	Itching	5.2	15	1.2	15
Pain in extremity	10.1	29	1.8	23	Influenza	5.2	15	1.0	12
Pharyngolaryngeal pain	9.7	28	0.0	0	Hb decreased	0.0	0	9.7	121
Abdominal pain	8.7	25	3.4	42					

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Table 32. Serious adverse events occurring at an incidence of ≥ 1.0 per 100 patient-years in either clinical studies or foreign post-marketing surveillance

Serious adverse event	Clinical studies		Foreign post-marketing surveillance		Serious adverse event	Clinical studies		Foreign post-marketing surveillance	
	Events per 100 patient-years	No. of events	Events per 100 patient-years	No. of events		Events per 100 patient-years	No. of events	Events per 100 patient-years	No. of events
Pyrexia	2.8	8	4.0	50	Pneumonia	0.3	1	1.0	13
Viral infection	1.7	5	0.4	5	Pain	0.3	1	1.0	12
Headache	1.4	4	3.0	38	Hb decreased	0.0	0	4.6	57
Anaemia	1.4	4	2.2	28	Fatigue	0.0	0	2.2	27
Abdominal pain	0.7	2	1.7	21	Blood LDH increased	0.0	0	1.4	17
Dyspnoea	0.3	1	1.8	22	Asthenia	0.0	0	1.3	16
Back pain	0.3	1	1.5	19	Death	0.0	0	1.2	15
Sepsis	0.3	1	1.1	14	Lack of efficacy	0.0	0	1.1	14
Urinary tract infection	0.3	1	1.1	14	Platelet count decreased	0.0	0	1.1	14

Although PMDA is currently asking the applicant for its view on the safety of eculizumab based on the data from the post-marketing surveillance, PMDA found no particular events that were reported at a markedly higher incidence in the foreign post-marketing surveillance than in the clinical studies. However, since cases of lack of efficacy have been reported overseas, the details of these cases are currently being requested.

4.(iii).B.(5).4) Meningococcal infections

(a) The risk of developing a meningococcal infection in patients treated with eculizumab

Eculizumab blocks the formation of the terminal complement complex (C5b-9). As *Neisseria meningitidis* having a polysaccharide capsule is lysed by the terminal complement complex (C5b-9), as with patients with a genetic disease, late complement component deficiency (LCCD), patients treated with eculizumab are considered susceptible to infections with *Neisseria meningitidis*. Although the risk of developing a meningococcal infection in LCCD patients differs depending on which terminal complement component (C5b-9) is deficient, it has been reported that the risk of meningococcal disease among LCCD individuals is 1400- to 10000-fold greater than that in normal individuals (*Clin Microbiol.* 1991;Rev 4:359-395, *J Pediatr.* 1989;114:260-264.). Thus, patients treated with eculizumab are also expected to have a similar level of risk.

On the other hand, the clinical development of eculizumab for non-PNH patients was initiated in 19[redacted] and a total of 716 patients unvaccinated against *Neisseria meningitidis* received eculizumab. In Study E99-044 in patients with idiopathic membranous glomerulonephritis, 1 patient developed meningitis caused by *Neisseria meningitidis* infection. Considering the potential risk of infection based on the mechanism of action of eculizumab, Alexion (the US) decided to require patients to be immunized with

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a meningococcal vaccine prior to receiving eculizumab in subsequent clinical studies. The package inserts for eculizumab in the US/Europe state as follows: "Immunize patients with a meningococcal vaccine at least 2 weeks prior to administering the first dose of eculizumab and then revaccinate patients periodically." and "Eculizumab is contraindicated in patients who are not currently vaccinated with a meningococcal vaccine." However, a reduction in the risk of developing a meningococcal infection in eculizumab-treated patients immunized with a meningococcal vaccine has not been confirmed.

PMDA confirmed the following points:

· Based on its mechanism of action, eculizumab is expected to increase the risk of developing a meningococcal infection.

· The reason for requiring patients to be immunized with a meningococcal vaccine in clinical studies

· In the US/Europe where eculizumab has already been approved, the package insert requires meningococcal vaccination prior to administering eculizumab.

On the other hand, taking into account that a vaccine against *Neisseria meningitidis* is unapproved in Japan, etc., the applicant explained safety measures against meningococcal infections associated with the use of eculizumab in Japan as follows: meningococcal vaccination will not be required; the measures to reduce the risks associated with meningococcal infections, which are being implemented in foreign countries, will be employed; and a system for detecting meningococcal infections early and taking appropriate and prompt actions will be established.

Taking meningococcal infections and its safety measures seriously for the safety of eculizumab, PMDA reviewed the epidemiology of meningococcal infections, the status of meningococcal infections among patients treated with eculizumab, the effectiveness of meningococcal vaccines, and measures against meningococcal infections, as shown in (b) to (e).

(b) Epidemiology of meningococcal infections

i) Overview of meningococcal infections

The applicant explained the risk factors, clinical findings, and treatments of meningococcal infections as follows:

LCCD is known as a definitive risk factor for meningococcal infections and other risk factors include the carriage of *Neisseria meningitidis*, children at ≤ 4 years of age, and people in communal living settings at high risk of contagion.

Clinical findings of meningococcal infection include pyrexia, headache, photophobia, nuchal rigidity, mental status changes, convulsion, nausea, vomiting, and purpura/petechiae and usually, these symptoms occur acutely. Purpura/petechiae deserves attention because systemic manifestations of meningitis associated with high fatality rates, e.g. fulminant meningococcal sepsis accompanied by

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hypotension, shock, and multi-organ failure, occur.

Regarding treatments, although a definitive diagnosis of meningococcal infection is made with blood/cerebrospinal fluid culture, as meningococcal infection can progress rapidly, it is important to start administering a third-generation cephem antibiotic soon after the onset of symptoms ahead of test results, if meningococcal infection is suspected. Although *Neisseria meningitidis* is generally highly susceptible to antibiotics, the fatality rate for meningococcal meningitis is as high as 10% (*IASR.* 2005;26:33-34.), and if patients respond to treatment, 10% to 15% of survivors will be left with serious sequelae.

With regard to the outcomes of meningococcal infections according to serogroup, it has been reported that the fatality rate by serogroup was 7.3% (3 of 41 patients) for serogroup B, 10.5% (2 of 19 patients) for serogroup C, and 0.0% (0 of 6 patients) for serogroup W135 in Israel (*Infection.* 1999;27:261-264.) and 11% for serogroup B, 12% for serogroup C, 17% for serogroup Y, and 8% for serogroup W135 in Sweden (*Scand J Infect Dis.* 2008;40:734-744.). No trend towards marked differences in the fatality rate according to serogroup was observed and adequate attention should be paid to all serogroups.

The extent of the risk of infection with *Neisseria meningitidis* and the incidence and prognosis of meningococcal infection, etc., in patients treated with eculizumab are undefined.

ii) Differences in meningococcal infections between Japan and overseas

The applicant explained differences in the meningococcal carriage rate, the incidence of meningococcal disease, and meningococcal serogroups, etc. between Japan and overseas as follows:

The meningococcal carriage rate among healthy adults has been estimated to be 0.64% in Japan, which has been reported to be lower than those in foreign countries (16.7% in the UK, 9.6% in Norway, 16% in Israel) (*J Med Microbiol.* 2004;53:657-662, *Lancet.* 2002;359:1829-1831, *Epidemiol Infect.* 1999; 122:51-57, *J Clin Microbiol.* 1994; 32: 323-330.).

In Japan, more than 4000 cases of meningococcal infections were reported in around 1945, which was reduced to less than 100 cases per year after 1969 and then to less than 10 cases per year in 1990s. After the enforcement of the Infectious Diseases Control Law in 1999, 8 to 22 cases of meningococcal infections occurred annually. According to a survey conducted from April 1999 to December 2004, there were 82 cases of meningococcal infections, including 8 fatal cases (*IASR.* 2005;26:33-34.), indicating that the fatality rate is about 10%. On the other hand, according to an US epidemiological surveillance, the annual incidence decreased from 1.3/100,000 population in 1989 to 0.9/100,000 population in 1991 and increased from 0.8/100,000 population in 1992 to 1.0/100,000 population in 1996 and then the annual incidence was 0.8/100,000 population in 1997 and 0.9/100,000 population in 1998 (*J Infect Dis.* 1999;180:1894-1901.), and it has been suggested that the case-fatality rate is

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approximately 10% (*Emerg Infect Dis.* 2003;9:355-361.).

With respect to meningococcal serogroups, the serogroups of isolates for 182 cases collected between 1974 and 2003 in Japan were reported to be B (56.5%), Y (21.4%), W135 (0.5%), and unknown (21.4%) (*IASR.* 2005;26:36-37.) and the serogroups of isolates for 82 cases collected between April 1999 and December 2004 were reported to be B (26.8%), Y (18.3%), A (3.7%), C (1.2%), and unknown (50.0%) (*IASR* 26: 33-34, 2005). The serogroups of isolates for 807 cases collected between 1992 and 1996 in the US were C (35%), B (32%), and Y (26%) and the proportion of meningococcal cases due to serogroup Y tended to increase from 10.6% in 1992 to 32.6% in 1996 (*J Infect Dis.* 1999;180: 1894-1901.).

As shown in the above, the carriage rate, incidence, and serogroups differed from region to region and from period to period.

The information on the carriage of *Neisseria meningitidis* was not collected in clinical studies of eculizumab in PNH patients. Also in the foreign marketing experience, patients have not been tested for meningococcal carriage prior to receiving eculizumab and the information on the carriage of *Neisseria meningitidis* is not available.

There is no report suggesting that the carriage of *Neisseria meningitidis* in PNH patients is different from that in the general population.

Based on i) and ii), PMDA considers as follows:
Although it is understood that based on the presented reports, the meningococcal carriage rate is lower and the incidence of meningococcal disease is expected to be lower in the general population of Japan compared with foreign countries, as *Neisseria meningitidis* is transmitted easily by droplets from the upper respiratory tract of carriers, the risk of developing a meningococcal infection in patients treated with eculizumab is an important issue also in Japan where the carriage rate is low. Since the clinical course of meningococcal infection is generally rapid with a high fatality rate of around 10% and the rate of sequelae is also high, adequate caution and measures against meningococcal infections are needed.

(c) The occurrence and course of meningococcal infections in clinical studies and foreign marketing experience

The applicant explained the occurrence of meningococcal infections in clinical studies and marketing experience of eculizumab as follows:
Among a total of 911 patients treated with eculizumab in clinical studies up to [redacted], 3 patients developed a meningococcal infection. The cumulative number of patients exposed to eculizumab from the market launch to [redacted] overseas was estimated to be 1030 patient-years and 6 cases of

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meningococcal infections were reported (Periodic safety update report from [redacted], 20[redacted] to [redacted], 20[redacted]). Meningococcal infections reported in patients treated with eculizumab are outlined in Table 33.

PMDA considers as follows:
Among the patients who developed a meningococcal infection, all patients except for 1 patient with idiopathic membranous glomerulonephritis had been vaccinated with meningococcal vaccine. The timing of vaccination was unknown for the 2 cases in clinical studies. Among the 6 cases reported from the marketing experience, 4 cases were caused by serogroup B, which was not covered by the vaccine, and the remaining 2 cases were caused by serogroup Y or C in spite of vaccination with a tetravalent (serogroups A, C, Y, and W135) vaccine, indicating that vaccination can not completely protect against the development of meningococcal infection. However, in the cases of a 2[redacted]-year-old woman in the US with serogroup Y meningococcal disease and a 3[redacted]-year-old man in the UK with serogroup C meningococcal disease, the disease developed shortly (i.e. 1 month) after revaccination 3 years after the first vaccination and 27 months after vaccination, respectively. Therefore, it can not clearly be concluded that vaccination is ineffective.

The protective efficacy of vaccine against meningococcal infections in patients treated with eculizumab is not adequately proven because comparison with unvaccinated patients has not been made. In the clinical studies and foreign marketing experience, patients who developed a meningococcal infection in spite of vaccination with meningococcal vaccine were reported and it was confirmed that even vaccinated patients can develop a meningococcal infection. Although most of the patients with meningococcal infection recovered following antibiotic treatment, there were patients who died or were left with sequelae and it was confirmed that the development of meningococcal infection can lead to a serious outcome.

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Table 33. Patients of meningococcal infections reported in clinical studies and marketing experience

	Patient background (primary disease, country, sex, age)	Vaccine serogroups	Serogroup of infecting meningococcus	Time to onset		Event	Initial treatment (Antibiotics)	Outcome	Eculizumab was continued or not / Revaccination
				after vaccination	after eculizumab initiation				
Clinical studies	Idiopathic membranous glomerulonephritis US Female 2[redacted] years	Unvaccinated	A	----	----	Meningitis	Ceftriaxone Vancomycin Ampicillin	Recovered (with sequelae)	Unknown Unknown
	PNH US Male 2[redacted] years	A, C, Y, W135	B	Unknown	11 months	Sepsis	Ceftriaxone Vancomycin	Recovered	Unknown Unknown
	PNH Spain Female 5[redacted] years	A, C	B or Y or W135	Unknown	13 months	Sepsis	Ceftriaxone	Recovered	Unknown Unknown
Marketing experience	PNH US Female 4[redacted] years	A, C, Y, W135	B	6 months	4 months	Meningitis	Ceftriaxone	Recovered	Continued Unknown
	PNH Ireland Male 2[redacted] years	C	B	6 months	5 months	Sepsis	Cefotaxime Benzylpenicillin Gentamicin Metronidazole	Death	-- --
	PNH US Female 2[redacted] years	A, C, Y, W135	Y	3 years after the first vaccination, 1 month after revaccination	2 months	Sepsis	Ceftriaxone	Recovered	Continued Unknown
	PNH UK Male 2[redacted] years	A, C, Y, W135	B	3 months	2 months	Infection	Ceftazidime	Recovered	Continued Unknown
	PNH Denmark Male 2[redacted] years	C	B	12 months	9 months (36 days after eculizumab discontinuation)	Sepsis	Ceftazidime	Recovered	Discontinued Unknown
	PNH UK Male 3[redacted] years	A, C, Y, W135	C	27 months after the first vaccination	21 months	Sepsis	Ceftriaxone	Recovered	Continued Revaccinated

(d) Effectiveness of meningococcal vaccines

The protective efficacy of tetravalent meningococcal vaccines, which are currently used overseas, as described in the product package inserts, are summarized in Table 34.

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Table 34. Efficacy rates of tetravalent meningococcal vaccines approved overseas

Brand name	Age	Efficacy rate as measured by serum bactericidal activity			
		A	C	Y	W-135
Menactra	2-3 years	57%	62%	84%	53%
	4-10 years	69%	81%	98%	69%
	11-18 years	100%	99%	98%	99%
	18-55 years	100%	99%	91%	97%
Menomune ACYW135	2-12 years	72%	58%	90%	82%
Menomune ACYW135	2-3 years	55%	30%	57%	26%
	4-10 years	48%	38%	84%	68%
	11-18 years	100%	99%	100%	99%
	18-55 years	99%	98%	97%	99%
Mencevax ACWY	2-5 years	90.9%	78.6%	100%	92.9%
	≥ 6 years	100%	99%	100%	100%

On the other hand, the applicant explained the status of development of vaccines other than the tetravalent meningococcal vaccines approved overseas as follows:

Concerning the status of development of a serogroup B meningococcal vaccine, two products, [redacted] ([redacted]) and [redacted] ([redacted]) are marketed in certain regions only (Cuba, Brazil, Chile, Argentina, New Zealand, etc.) to control and prevent strain-specific infections and a phase III clinical trial of [redacted] is currently ongoing overseas, but the details are unknown.

PMDA considers as follows:

According to a survey of 45 Russian patients with LCCD who experienced recurrent meningococcal infections followed for 3 to 8 years, 31 of the 45 patients were immunized with a tetravalent (serogroups A, C, Y, and W135) meningococcal vaccine and the survival rate was improved in vaccinees compared with non-vaccinees (*Vaccine*. 2003;21:4437-4447.). Thus, the efficacy of vaccination can be expected also in patients treated with eculizumab in whom the formation of C5b-9 is blocked, like LCCD patients. On the other hand, as described in "(b) Epidemiology of meningococcal infections ii) Differences in meningococcal infections between Japan and overseas," it is considered that serogroup B disease is most common in Japan (serogroup B accounted for 56.5% of isolates for 182 cases collected between 1974 and 2003; serogroup B accounted for 26.8% of isolates for 82 cases collected between April 1999 and December 2004; and serogroup B accounted for 32% of isolates for 807 cases collected between 1992 and 1996 in the US) and adverse events of Guillain-Barré syndrome etc., among recipients of a tetravalent meningococcal vaccine commonly used overseas have been reported (*MMWR Morb Mortal Wkly Rep*. 2006;55:1120-1124.). Therefore, the clinical benefits of vaccinating PNH patients in Japan need investigation.

(e) Measures against meningococcal infections in Japan

PMDA considers as follows:

Although meningococcal infections are manageable with appropriate and prompt diagnosis and treatment, as the disease can become serious/fatal, its diagnosis and treatment should begin as soon as

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possible. Therefore, prior to the use of eculizumab, adequate information must be provided to hematologists who are likely prescribers of eculizumab and patients must be educated.

PMDA asked the applicant to explain the planned measures to reduce the risks associated with meningococcal infections.

The applicant responded as follows:
In foreign countries, meningococcal vaccination as a measure to minimize the risk of developing a meningococcal infection, early detection of a suspected case of the disease, and early treatment are emphasized and healthcare professionals and patients have been educated with information materials. Patients are required to carry a Patient Safety Card and show this card to any doctor at each visit.

After the market launch in Japan, as PNH is a rare disease, eculizumab is expected to be used at medical institutions that are equivalent in size to clinical trial institutes and such medical institutions are considered to be prepared for the diagnosis and treatment of PNH and meningococcal infections. However, if eculizumab is used at a medical institution that is not sufficiently prepared to treat meningococcal infections, the medical institution should seek cooperation in advance from its neighboring medical institution that is fully prepared for the treatment of meningococcal infections. The applicant will develop materials covering the information on meningococcal infections as well as PNH for physicians and for patients and establish a system for measures against meningococcal infections in PNH patients.

In order to call attention to meningococcal infections, the applicant will state in the warnings section of the package insert that "patients should be fully informed of meningococcal infections," state in the contraindications section of the package insert that "eculizumab is contraindicated in patients with symptoms of meningococcal infection," and list "patients with a history of meningococcal infection" in the careful administration section of Precautions of the package insert.

PMDA's view on the measures against the risk of meningococcal infections is as follows:
Since the initial symptoms of meningococcal infection are largely non-specific and the disease can progress rapidly, become serious and lead to sequelae or death, adequate measures against meningococcal infections should be taken. Based on its mechanism of action, eculizumab is expected to increase the risk of infections with *Neisseria meningitidis*, patients were required to be vaccinated with meningococcal vaccine also in Study C07-001, and patients are required to be immunized with a meningococcal vaccine prior to receiving eculizumab overseas. Thus, in order to reduce the risk of meningococcal infections, meningococcal vaccination can be used as a promising measure against meningococcal infections also in Japan. However, there is currently no approved meningococcal vaccine whose efficacy and safety have been demonstrated in Japanese subjects and since i) the major

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tetravalent vaccines (serogroups A, C, Y, and W135), which are currently used overseas, are expected to have limited efficacy against serogroup B disease, which has been relatively commonly reported in Japan, ii) a reduction in the risk of developing a meningococcal infection in patients treated with eculizumab has not been confirmed for any vaccine including the serogroup B vaccines which are used in certain regions, and iii) in clinical studies in PNH patients and foreign post-marketing surveillance, in spite of vaccination, meningococcal infections including those caused by the serogroups covered by the vaccine occurred, etc., even vaccinated patients can develop a meningococcal infection.

Based on the above, although vaccination can also become a measure to minimize the risks associated with meningococcal infections, considering that even vaccination can not completely protect against the disease, other feasible measures in Japan should be taken first, regardless of meningococcal vaccination status. In order to reduce the risks associated with meningococcal infections, adequate measures against meningococcal infections should be built, adequate information on the risks and benefits of eculizumab should be provided to healthcare professionals and patients, and eculizumab should be initiated after both the healthcare professional and patient understand the risks and benefits of eculizumab. It is necessary to continue to review the need for meningococcal vaccination while collecting information actively in Japan and overseas.

4.(iii).B.(5).5) Other infections

The incidences of infections up to Week 12 in the TRIUMPH study, SHEPHERD study, and Study C07-001 and during the entire study period in studies in PNH patients (C07-001, E07-001, TRIUMPH, SHEPHERD, C02-001, E02-001, X03-001, X03-001A, E05-001) are shown in Table 35.

Table 35. Incidences of infections in Japanese and foreign clinical studies

	Up to Week 12								Entire study period					
	TRIUMPH				SHEPHERD		C07-001		TRIUMPH		Foreign clinical studies		Japanese clinical studies	
	Placebo (N = 44)		Eculizumab (N = 43)		Eculizumab (N = 97)		Eculizumab (N = 29)		Placebo (N = 44)		Eculizumab (N = 195)		Eculizumab (N = 29)	
	Incidence	N	Incidence	N	Incidence	N	Incidence	N	Incidence	N	Incidence	N	Incidence	N
Infection	68.2%	30	55.8%	24	45.4%	44	62.1%	18	77.3%	34	92.8%	181	75.9%	22
Serious infection	6.8%	3	0.0%	0	1.0%	1	3.4%	1	11.4%	5	13.8%	27	10.3%	3

TRIUMPH study (study duration, 26 weeks)
Japanese clinical studies (study duration, up to 38 weeks): C07-001, E07-001 (Interim report)
Foreign clinical studies (study duration, up to 206 weeks): TRIUMPH, SHEPHERD, C02-001, E02-001, X03-001, X03-001A, and E05-001 (Interim report)

PMDA confirmed that there were no major differences in the incidence of infections between the placebo and eculizumab groups and between Japan and overseas (up to Week 12).

PMDA asked the applicant to explain about any infection that deserves special attention other than that with *Neisseria meningitidis*.

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The applicant responded as follows:
Since eculizumab is a specific anti-C5 antibody and blocks the formation of the terminal complement complex C5b-9 without inhibiting the formation of an early complement component, C3b, which is essential for microbial opsonization and immune complex clearance, eculizumab is not considered to increase the risk of other common infections except for those caused by encapsulated bacteria (especially, *Neisseria meningitidis*) that are cleared by terminal complement components. This has been suggested also by clinical studies in PNH patients in which the overall incidence and severity of infections were similar between the eculizumab and placebo groups.

On the other hand, when opinions on the effect of eculizumab on the risk of infections other than those caused by *Neisseria meningitidis* were sought from an infection specialist and the investigators, they responded that the risk of infections with encapsulated bacteria, e.g. *Streptococcus pneumoniae* or *Haemophilus influenzae*, associated with eculizumab can not be denied. The frequency of occurrence of infections with encapsulated bacteria in patients with complement deficiencies differs depending on which complement is deficient and it has been reported that in patients with C5-9 deficiencies, the frequency of occurrence of *Neisseria sp.* infection was 57% (151 patients), the frequency of occurrence of *Streptococcus pneumoniae* infection was 0.8% (2 patients), and the frequency of occurrence of *Haemophilus influenzae* infection was 0% (0 patients) (*Clin Microbiol.* 1991;Rev 4:359-395.).

Even taking account of the above points, based on its mechanism of action, eculizumab may increase the risk of infections with encapsulated bacteria, e.g. *Streptococcus pneumoniae* or *Haemophilus influenzae*. Therefore, the applicant will develop materials calling attention to infections for patients and for healthcare professionals and list "patients with systemic infections" in the careful administration section of Precautions of the package insert.

PMDA considers as follows:
Although the submitted clinical study data showed no clear trend towards an increased risk of infections associated with eculizumab, the limited number of patients were studied and since eculizumab blocks the formation of the terminal complement complex acting on capsular polysaccharides, there may be a theoretical increased risk of infections with not only *Neisseria meningitidis*, but also *Streptococcus pneumoniae* and *Haemophilus influenzae*. In patients with C5b-9 deficiency, the incidence of *Streptococcus pneumoniae* or *Haemophilus influenzae* infection tended to be lower than the incidence of *Neisseria* infection, but it is difficult to completely deny an increased risk of infections with these bacteria.

Based on the above, there is no problem with listing "patients with infections" in the careful administration section of Precautions of the package insert. It is also necessary to develop materials for patients and for healthcare professionals to call attention to infections as a whole. In addition, it is

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necessary to collect information on the incidence, severity, and outcome of infections via post-marketing surveillance etc. and provide the information appropriately to healthcare professionals and patients if a new finding becomes available.

4.(iii).B.(5).6) Infusion reactions

Since eculizumab is an antibody preparation, administration of eculizumab may result in infusion reactions. PMDA asked the applicant to explain how to prevent/manage infusion reactions.

The applicant responded as follows:

In clinical studies, a specific guidance on how to manage infusion reactions was not provided and infusion reactions were prevented and managed at the discretion of the physician. Mild to moderate infusion reactions were reported by 1 patient in the TRIUMPH study and 3 patients in the SHEPHERD study, which resolved following interruption of eculizumab or symptomatic treatment and then the patients were able to continue treatment with eculizumab with preventive measures taken before the administration of eculizumab.

It is recommended to slow the infusion rate (up to 5 mg/min for 600 mg doses, up to 7.5 mg/min for 900 mg doses) and administer an histamine H_1 antagonist, an histamine H_2 antagonist, or a steroid, etc. At the medical institution, patients should be monitored for at least 1 hour following the completion of the infusion or patients with an infusion reaction or a history of an infusion reaction should be monitored for at least 2 hours following the completion of the infusion to ensure safety.

PMDA considers as follows:

The information on the recommended practices for the prevention and management of infusion reactions should be provided appropriately. After the market launch, the information on the development of infusion reactions, its relationship with the infusion rate, and how infusion reactions were managed and prevented should be collected and the information should be provided to the medical practice as appropriate.

4.(iii).B.(5).7) Immunogenicity and human anti-human antibodies (HAHA)

The applicant explained the immunogenicity and HAHA induction following treatment with eculizumab as follows:

The rates of the induction of HAHA in foreign clinical studies of eculizumab in PNH and non-PNH subjects are shown in Table 36. HAHA was not detected in a Japanese clinical study C07-001 and analysis has not been performed in Study E07-001 (Interim report). The presence of neutralizing antibodies has not been determined because its assay is under development.

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Table 36. HAHA response following treatment with eculizumab

	PNH clinical studies				Non-PNH clinical studies[a)]				All studies			
	Placebo		Eculizumab		Placebo		Eculizumab		Placebo		Eculizumab	
No. of patients with HAHA measurement	N = 44		N = 151		N = 206		N = 677		N = 250		N = 828	
	Incidence	N	Incidence	N	Incidence	N	Incidence	N	Incidence	N	Incidence	N
Positive HAHA response	2.3%	1	1.3%	2	5.3%	11	3.8%	26	4.8%	12	3.4%	28
Positive IgM response	–	–	0.7%	1	2.4%	5	1.0%	7	2.0%	5	1.0%	8
Positive IgG response	2.3%	1	1.3%	2	3.4%	7	3.0%	20	3.2%	8	2.0%	21
Positive IgG and IgM response	--	--	--	--	0.5%	1	0.1%	1	0.4%	1	0.1%	1

a) Clinical studies in patients with rheumatoid arthritis, idiopathic membranous glomerulonephritis, dermatomyositis, or psoriasis

Regarding safety in patients with a positive HAHA response, 1 patient each in the TRIUMPH and SHEPHERD studies developed HAHA within 26 weeks of treatment and the 1 patient in the TRIUMPH study had coagulopathy, headache, and haematoma and the 1 patient in the SHEPHERD study had pyrexia and nasopharyngitis. One patient in the placebo group in the TRIUMPH study also had a positive HAHA response, which was considered due to measurement errors or contaminants. The assay method for the measurement of HAHA has been improved and the sensitivity of the assay method used in the Japanese clinical study is higher than that used in the foreign clinical studies. As the assay reagent used in Study C07-001 will become unavailable at the end of 2010, a new assay method will be employed in January 2010.

PMDA considers as follows:

At present, the relationship between positive HAHA response and the occurrence of adverse events is unknown. After the market launch, if adverse events of infusion reactions etc. possibly related to HAHA induction occur or there is loss of efficacy of eculizumab etc., HAHA should be measured as appropriate and the information on HAHA should be collected and provided to the medical practice as appropriate.

4.(iii).B.(5).8) Safety after eculizumab discontinuation

By protecting PNH type III RBCs against intravascular hemolysis, the percentage of PNH type III RBCs increases in patients being treated with eculizumab (Based on the pooled data from the TRIUMPH and SHEPHERD studies, the percentage of PNH type III RBCs [median] was 31.7% at baseline, 46.5% at Week 8, and 51.5% at Week 26) and a serious hemolytic crisis may be induced if eculizumab is discontinued. PMDA asked the applicant to explain the clinical courses of patients who were discontinued from treatment with eculizumab and necessary measures after discontinuation.

The applicant responded as follows:

In Japanese and foreign clinical studies in PNH patients, a total of 13 patients were discontinued from eculizumab treatment due to lack of efficacy or adverse events etc. In the foreign marketing experience, 67 cases of treatment discontinuation were reported and the information after treatment discontinuation was obtained for 51 of the 67 cases. When "serious hemolysis" after treatment discontinuation is defined as a rise in LDH above the baseline level at the onset of the event and either (a) a ≥ 25%

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reduction in PNH type III RBCs within 1 week of the onset of the event, (b) Hb < 5.0 g/dL or a > 4.0 g/dL reduction in Hb within 1 week of the onset of the event, (c) the occurrence of angina pectoris or TE, (d) mental status changes, or (e) a 50% increase in serum creatinine, serious hemolysis meeting this definition has not been reported among the patients who were discontinued from eculizumab treatment in the clinical studies and marketing experience.

However, as the risk of serious hemolysis can not be denied theoretically, after the market launch, patients will be monitored for at least 8 weeks after eculizumab discontinuation to detect serious hemolysis. If serious hemolysis occurs after eculizumab discontinuation, PRBC transfusion, readministration of eculizumab, and exchange transfusion etc. should be considered.

PMDA considers as follows:
Although there has so far been no patients who developed serious hemolysis meeting the applicant's definition after eculizumab discontinuation, as the risk of a serious hemolytic crisis exists theoretically, the information on the risks associated with eculizumab discontinuation and the need for monitoring patients after eculizumab discontinuation should be provided to the medical practice appropriately. Since appropriate management after eculizumab discontinuation has not been established, it is unavoidable that the patients are treated at the physician's discretion according to individual patients' symptoms. After the market launch, the information on the clinical course and management of patients after eculizumab discontinuation should be collected and the information on the risks associated with discontinuation and management should be provided to the medical practice as appropriate.

4.(iii).B.(6) Indication
The proposed indication was "paroxysmal nocturnal hemoglobinuria (PNH)."

PMDA's view on the indication for eculizumab is as follows:
The TRIUMPH study demonstrated the superiority of eculizumab over placebo for "Hb stabilization" and "the number of PRBC units transfused" and the SHEPHERD study and Study C07-001 showed reductions in LDH from baseline. The results of these studies and subgroup analyses indicate that eculizumab reduces hemolysis in PNH patients while Hb stabilization and a reduction in the number of PRBC units transfused, which are considered clinical indicators of treatment effect, have been demonstrated in the TRIUMPH study only. Therefore, although the submitted data have shown reduction in hemolysis in PNH patients, treatment effect associated with reduction in hemolysis has been demonstrated only in the TRIUMPH study population, i.e. patients who are relatively more dependent on transfusions and whose bone marrow is relatively spared.

The effects of eculizumab on the incidence of TE, which is regarded as a clinically serious problem in PNH patients, and survival prognosis have been undefined also in the TRIUMPH study and whether

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reduction in hemolysis and improvement of anemia by eculizumab are related to the ultimate improvement in survival prognosis is unknown.

On the other hand, regarding safety, although there has been no serious problem in clinical studies, as the potential risks of eculizumab, an increased risk of infections with encapsulated bacteria, e.g. *Neisseria meningitidis*, *Streptococcus pneumoniae*, and *Haemophilus influenzae* and the risk of a serious hemolytic crisis after treatment discontinuation have been identified.

Therefore, eculizumab should be used in appropriate patients, fully examining treatment effects and potential risks, taking into account that eculizumab is palliative and improvement in survival prognosis has not been demonstrated at present.

Based on the above, the appropriate indication statement should be "reduction of hemolysis in patients with paroxysmal nocturnal hemoglobinuria" etc. and it should be stated that eculizumab is indicated for transfusion-dependent patients with a PNH type III RBC clone ≥ 10%, i.e. the patient population included in the clinical studies. The package insert should state that Hb stabilization and reductions in transfusion requirements have been demonstrated in the TRIUMPH study population and advise that eculizumab should be used only if the clinical benefits are considered to outweigh the potential risks.

Moreover, the following information should also be provided appropriately: the eligibility criteria for the TRIUMPH study; and the efficacy of eculizumab during an acute hemolytic crisis has not been demonstrated.

Since foreign extension studies suggest that eculizumab may reduce the incidence of TE, it is desirable to continue to collect information and investigate the incidence of TE, taking account of differences in PNH conditions between Japan and overseas.

The way of providing information on the intended population for eculizumab, e.g. the indication and precautions for indication of the package insert, will be finalized, taking account of comments from the Expert Discussion.

4.(iii).B.(7) Dosage and administration

The applicant explained the rationale for the dosage regimen used in clinical studies in PNH patients and how dosage and administration was established as follows:

In a study of eculizumab in patients with rheumatoid arthritis conducted in the early phase of development, although weekly administration of 8 mg/kg completely inhibited C5 activity in the sera from all patients, when the patients were switched to once every 2 weeks administration, C5 concentrations recovered in several patients. Then, considering that 35 μg/mL of eculizumab can

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theoretically bind to all C5 in human serum and based on the results from clinical studies in patients with rheumatoid arthritis or idiopathic membranous glomerulonephritis etc., a serum eculizumab concentration of 35 μg/mL was chosen as a threshold for efficacy [see "4.(ii).B.(1). Relationship between serum eculizumab concentration and hemolytic activity"].

Since a simulation showed that the trough concentrations corresponding to the 8 mg/kg dose can be maintained at a fixed dose of 600 mg, Study C02-001 in PNH patients used fixed doses of eculizumab and a dosage regimen of 600 mg weekly for 4 doses followed by 900 mg every 2 weeks for the purpose of maintaining serum eculizumab concentrations sufficient to completely inhibit C5 activity during the study period. In order to determine the dosage regimen that maintains serum trough concentrations of ≥ 35 μg/mL based on the results from Study C02-001, a simulation was performed using model parameters obtained from 11 PNH patients to assess dosage regimens. Finally, the relationships between serum eculizumab concentration and hemolytic activity in the TRIUMPH study, SHEPHERD study, and Study C07-001 were assessed and dosage and administration for eculizumab was established.

PMDA's view on dosage and administration for eculizumab is as follows:
Although how dosage and administration was established is understood, even serum concentrations of eculizumab above 35 μg/mL do not sufficiently inhibit hemolysis in some patients [see "4.(ii).B..(1) Relationship between serum eculizumab concentration and hemolytic activity"] and as other dosage regimens have not been investigated in PNH patients, there is no sufficient information to determine whether the proposed dosage regimen has been optimized and the appropriateness of dosage and administration is questionable. However, since the pivotal clinical study of eculizumab in PNH patients, the TRIUMPH study, has confirmed the efficacy of eculizumab [see "4.(iii).B.(4) Efficacy"], Study C07-001 has suggested reduction in hemolysis at the same dosage regimen also in Japanese patients, and the safety profile of eculizumab is also tolerable, it is unavoidable to select the dosage regimen used in the TRIUMPH study and Study C07-001 etc.

Dosage and administration for eculizumab will be finalized, taking account of comments from the Expert Discussion.

4.(iii).B.(8) Use in children, pregnant women, and nursing mothers

4.(iii).B.(8).1) Pediatric use

The applicant explained the pediatric use of eculizumab as follows:
Although pediatric patients aged ≥ 12 years were eligible for a Japanese clinical study (C07-001), no patients aged ≥ 12 and < 18 years were enrolled into the study.

In the foreign marketing experience, 34 children were treated with eculizumab (as of August 24, 2009), including 17 PNH patients, 14 patients with atypical hemolytic uremic syndrome, 1 patient with bone

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marrow transplant rejection, 1 renal transplant recipient, and 1 patient with membranoproliferative glomerulonephritis II. Adverse events reported by at least 2 patients were headache only (2 patients) and there were no major differences in the safety profile between pediatric and adult patients.

Meanwhile, for the development of eculizumab for pediatric use, a clinical study to evaluate the pharmacokinetics, pharmacodynamics, and safety of eculizumab in about 6 to 8 pediatric and adolescent patients with PNH (2-17 years) is scheduled to be initiated in the US and Europe in 2009 (Study M07-005), but there is no plan to enroll Japanese patients. Clinical studies in adolescent patients with atypical hemolytic uremic syndrome are ongoing in the US and Europe. A study in pediatric patients with atypical hemolytic uremic syndrome is also under planning and the participation of Japanese patients is under consideration.

PMDA concluded as follows:
There is very limited clinical experience with eculizumab in pediatric patients at present. Although the majority of patients are adults based on the age of onset of PNH, as there are also pediatric patients, it is preferable to develop eculizumab for Japanese pediatric patients as well.

PMDA is currently asking the applicant about the seriousness of adverse events and their causal relationship to eculizumab in the foreign post-marketing surveillance and any plan of a clinical study in Japanese pediatric patients with PNH.

4.(iii).B.(8).2) Use during pregnancy or lactation
PMDA asked the applicant to explain the use of eculizumab during pregnancy in clinical studies and foreign post-marketing surveillance.

The applicant responded as follows:
Reported pregnancies from patients on eculizumab during clinical studies and post-marketing surveillance (up to August 15, 2009) are as shown in Table 37.

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Table 37. Reported pregnancies during clinical studies and post-marketing surveillance

		Actions taken and Outcome
Clinical studies	E02-004 (Rheumatoid arthritis)	The patient discontinued eculizumab treatment and elected to terminate her pregnancy.
	SHEPHERD	The patient discontinued eculizumab treatment and elected to terminate her pregnancy.
	TRIUMPH	The patient discontinued eculizumab treatment and delivered a healthy baby by cesarean section at 39 weeks of gestation.
	E05-001	The patient discontinued eculizumab treatment and delivered a healthy baby by cesarean section at 38 weeks of gestation.
	E05-001	The patient discontinued eculizumab treatment and had a normal delivery with a healthy baby at 39 weeks of gestation.
	C02-001 and E05-001	The patient continued eculizumab treatment and delivered a healthy baby at 38 weeks of gestation (probably, a normal delivery)
Post-marketing surveillance		The patient discontinued eculizumab treatment, but recommenced due to hemolysis during pregnancy and delivered healthy babies by cesarean section (twins). (The patient developed a post-partum hemorrhage due to persistent retained products of conception.)
		The patient continued eculizumab treatment and had a spontaneous abortion at 8-9 weeks of gestation.
		The patient discontinued eculizumab treatment, but recommenced at 30 weeks of gestation and delivered healthy babies by cesarean section at 36 weeks of gestation (twins).
		The patient discontinued eculizumab treatment and elected to terminate her pregnancy due to severe AA, severe thrombocytopenia, and severe neutropenia associated with Escherichia sepsis. (Autopsy revealed no fetal abnormalities and the patient underwent allogeneic bone marrow transplantation 27 days after termination of pregnancy.)
		The patient continued eculizumab treatment and had a normal delivery with a healthy baby.
		The patient continued eculizumab treatment and had a preterm cesarean delivery at 27 weeks of gestation.
		Whether eculizumab treatment was continued or not is unknown. Due to intestinal ischaemia followed by knee pain, pneumonia, septic shock, and respiratory failure, the patient underwent a cesarean section at 27 weeks of gestation, but her baby died.
		The patient continued eculizumab treatment and was in her first month of gestation as of March 2009.
		The patient discontinued eculizumab treatment and was in the first trimester as of March 2009.
		The patient discontinued eculizumab treatment, but will recommence in the third trimester. The patient was in her 7th week of gestation as of March 2009.
		The patient continued eculizumab treatment and had a spontaneous abortion.
		Whether eculizumab treatment was continued or not is unknown. The patient had a therapeutic abortion.
		The patient continued eculizumab treatment and was in her 8th to 10th week of gestation as of April 2009.
		The patient continued eculizumab treatment and had a preterm cesarean delivery at 27 weeks of gestation.

It has been reported that PNH patients who received eculizumab and low-molecular-weight heparin during the third trimester and the perinatal period and after delivery had no adverse events from Week 30 of gestation to 3 months post-partum (*Leuk Res*. 2009;33:e4-e5.).

Although it is unknown whether eculizumab is excreted into human milk, as IgG is considered to be excreted in human milk, the possibility that eculizumab is excreted into human milk can not be ruled out and in accordance with the package insert in Europe, it will be stated in the package insert that "breast-feeding should be discontinued during treatment and up to 5 months after treatment."

PMDA considers as follows:

There is very limited clinical experience with eculizumab in pregnant women. Based on the currently available information, fetal effects are unknown.

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It is necessary to call attention to potential excretion in milk. Meanwhile, although the maximum $t_{1/2}$ (estimated by an analysis with a 1-compartmental model) in the TRIUMPH study, SHEPHERD study, Study E05-001, and Study C07-001 (566.9 hours [23.6 days]) indicates that eculizumab is almost completely eliminated from blood at 5 months after treatment, there is no definitive basis for 5 months of discontinuation of breast-feeding. Therefore, it is unnecessary to specify the period of discontinuation in the package insert.

Eculizumab is intended for chronic use and may be used in pregnant women or nursing mothers after the market launch. Thus, it should be advised that the information is limited as described above and eculizumab may be excreted into milk and it is necessary to collect information on the effects of eculizumab on pregnant women and fetuses and nursing mothers and babies and appropriately provide the information to the medical practice as needed.

4.(iii).B.(9) Post-marketing surveillance etc.

The applicant presented an outline of post-marketing surveillance (draft) as shown in Table 38.

Table 38. Outline of post-marketing surveillance plan (draft)

Objectives	Detection of unknown and serious adverse drug reactions Long-term safety and efficacy Effects of eculizumab on the course of PNH (the course and prognosis etc. of the disease)
Survey period	8 years (≥ 3 years as a survey of long-term use)
Planned number of cases	All treated patients
Target patient population	PNH patients
Major items to be investigated	・ Patient background (medical history [TE, others], underlying disease [AA, MDS, others], PNH duration, complications [major vascular events, hepatic impairment/renal impairment, others]) ・ The status of administration of eculizumab (including the reason for discontinuation) ・ Concomitant medications (steroids, immunosuppressants, anticoagulants, others) ・ Adverse events ・ Efficacy (change of LDH, improvement in QOL [fatigue, abdominal pain, dyspnoea, dysphagia], change in Hb, the number of PRBC units transfused) ・ Clinical course up to 8 weeks after treatment discontinuation (the development of a hemolytic crisis, etc.) ・ Significant events including malignant tumors (meningococcal infection, infections leading to serious outcomes such as hospitalization and death, death, serious hemolysis after discontinuation, pregnancy, TE, malignant tumors) [Priority item] ・ Development of infections

As an epidemiological study, the PNH registry is run by Alexion, the US, which will be incorporated into post-marketing surveillance after necessary modifications.

PMDA considers as follows:

Besides the above, the information regarding the following (a) to (c) should also be collected and monitoring after treatment discontinuation and the development of TE should be treated as priority items. As eculizumab is an orphan drug and there is very limited clinical experience with eculizumab in Japan, as a condition for approval, the applicant is required to conduct a post-marketing survey covering all treated patients. Post-marketing commitments will be finalized, taking account of comments from the Expert Discussion.

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An overview of the global PNH registry is currently being requested.

(a) PNH type III RBC clone over time
(b) Information on HAHA
(c) Safety of eculizumab in children and pregnant women/nursing mothers

III. Results of Compliance Assessment Concerning the Data Submitted in the New Drug Application and Conclusion by PMDA

1. PMDA's conclusion on the results of document-based GLP/GCP inspections and data integrity assessment

A document-based compliance inspection and data integrity assessment was conducted in accordance with the provisions of the Pharmaceutical Affairs Act for the data submitted in the new drug application. As a result, there were no particular problems. Thus, PMDA concluded that there should be no problem with conducting a regulatory review based on the submitted application documents.

2. PMDA's conclusion on the results of GCP on-site inspection

GCP on-site inspection was conducted in accordance with the provisions of the Pharmaceutical Affairs Act for the data submitted in the new drug application (Study C07-001, 5.3.5.2-6 and Study E07-001, 5.3.5.2-7). As a result, failure to operate the IRB in accordance with the SOP (in response to the reports of adverse drug reactions etc. notified by the sponsor, the appropriateness of continuing the clinical trial and amendments to the written information were reviewed through expedited review procedures) and protocol deviations (a chest X-ray had not been performed in some subjects) were found at some clinical trial sites. Furthermore, there were imperfections in the sponsor's monitoring report on the operation of the IRB regarding the above-mentioned reports of adverse drug reactions etc., but PMDA concluded that there should be no problem with conducting a regulatory review based on the submitted application dossier.

IV. Overall Evaluation

Based on the submitted data, the efficacy of eculizumab in patients with PNH has been demonstrated and its safety is acceptable in view of its observed benefits. Since eculizumab is an anti-C5 antibody and offers a new treatment for patients with PNH, it has clinical significance. PMDA considers that the points listed below need to be further reviewed.

Eculizumab may be approved if it can be concluded based on comments from the Expert Discussion that there are no particular problems.

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- Data subject to evaluation
- Efficacy
- Safety
- Measures against meningococcal infections
- Indication
- Dosage and administration
- Post-marketing commitments

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Review Report (2)

February 18, 2010

I. Product Submitted for Registration

[Brand name]	Soliris for Intravenous Infusion 300 mg (Note: The proposed Japanese brand name has been modified.)
[Non-proprietary name]	Eculizumab (Genetical Recombination)
[Name of applicant]	Alexion Pharma K.K.
[Date of application]	March 31, 2009

II. Content of the Review

The Expert Discussion and subsequent review by the Pharmaceuticals and Medical Devices Agency (PMDA) are outlined below.

The expert advisors for the Expert Discussion were nominated based on their declarations etc. concerning the product submitted for registration, in accordance with the provisions of the "Rules for Convening Expert Discussions etc. by Pharmaceuticals and Medical Devices Agency" (PMDA Administrative Rule No. 8/2008 dated December 25, 2008).

(1) Quality

As a result of the following reviews including the questions asked to the applicant, PMDA concluded that the quality of the drug product to be marketed is adequately controlled.

(1).1) Evaluation of disulfide bond heterogeneity

Although it is understood that it is difficult to control disulfide bond variants quantitatively, PMDA asked the applicant to explain the need to control the heterogeneity of these variants, taking account of the possible effects of these variants on the safety and efficacy of eculizumab.

The applicant responded as follows:

Since disulfide bond variants are considered to be present also in the previous lots, based on the previous clinical studies and foreign clinical experience, disulfide bond variants are unlikely to affect the safety and efficacy of eculizumab. However, as the possibility that differences in disulfide bond heterogeneity affect the safety and efficacy of eculizumab can not be ruled out, a quantitative assay for determining the relative abundance of disulfide bond variants will be developed and the acceptance criteria will be established.

PMDA accepted the applicant's response that although no specification for disulfide bond variants is set

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at present, an assay will be developed to control disulfide bond variants, taking account of previous clinical experience and the clinical need for eculizumab.

(1).2) Control of immunogenic glycans

Since eculizumab contains fucosylated biantennary *N*-linked oligosaccharides bearing immunogenic Neu5Gc or αGal (including Galα1-3Gal), PMDA asked the applicant to explain the influences of glycan structure and its heterogeneity on the safety of eculizumab and the need to include the Neu5Gc content in the specification and provide a justification for the specification limit for the αGal content.

The applicant responded as follows:

Glycans in the Fc region are considered to be inside eculizumab and not to be recognized by molecules in the body. No adverse events of anaphylactic shock etc. following the administration of eculizumab have been reported so far. The number of patients who developed HAHA was limited (see Review Report (1) "4.(iii).B.(5).7) Immunogenicity and human anti-human antibodies (HAHA)"). Therefore, these glycans are unlikely to affect the immunogenicity of eculizumab.

The glycan structure of eculizumab and its heterogeneity can be controlled by the drug substance specifications for glycan profile and the upper limit for the αGal content and there is no plan to include the Neu5Gc content in the specification at present. However, if adverse events considered associated with glycans are reported in the safety information in future, the acceptance criteria for glycans will be reviewed. The current specification limit for the αGal content was established based on the results of lot analyses (10 drug substance lots produced by July 2005) that were available at the time of setting the specification in the US/Europe (July 2008). Whether the specification limit should be reviewed will be determined, based on the analytical results on recently manufactured lots.

PMDA concluded that although the immunogenicity of Neu5Gc and Galα1-3Gal has not completely been defined at present, based on previous clinical experience, glycan structure is unlikely to affect the safety of eculizumab as long as glycosylation is controlled by the current specifications, and accepted the response. However, depending on future safety information, it is necessary to consider reviewing the acceptance criteria for glycans, etc.

(1).3) C5 binding assay

PMDA asked the applicant to provide a justification for the specification limits, taking account of the potencies of the clinical formulation and the proposed commercial formulation analyzed by the new assay employed in [redacted] 20[redacted] and clinical experience.

The applicant responded as follows:

The potencies of [redacted] lots of the proposed commercial formulation analyzed by the new assay were

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871,237 to 1,149,500 BU/mg, which were within the current specification limits (700,000-1,300,000 BU/mg) and no new adverse events associated with a switch to the proposed commercial formulation analyzed by the new assay have been reported so far. Therefore, the performance of the new assay is considered to be comparable to that of the old assay and the same specification limits can be used. As analytical results are limited at present, whether the specification limits should be reviewed will be determined, based on future manufacturing experience.

PMDA accepted the response.

(1).4) Drug product specification

The applicant explained as follows:

Though IEF and hemolytic assay are included in the drug product specification in the US and Europe, IEF and hemolytic assay are not included in the drug product specification in Japan because it is difficult to perform these tests in Japan for the following reasons:

- Skills and experience are required for performing the tests.
- It is difficult to maintain the precision and reproducibility of the tests with limited drug product lots imported to Japan and perform the tests consistently.
- It is uncertain if the reagents used in hemolytic assay (chicken erythrocytes, etc.) can be procured in Japan.

The quality of the drug product to be marketed in Japan can be assured by the results of IEF and hemolytic assay performed at the time of its release. The drug product after release testing is stored and shipped under adequate control and shipping validation and quality assessments of the drug product before and after shipment have demonstrated that the quality of the drug product is unaffected.

PMDA requested the applicant to take the following actions:

If IEF and hemolytic assay can not be included in the drug product specification in Japan, these tests that are performed overseas should be performed as in-process controls in the drug product manufacturing process, for the time being. Since IEF can separate differently charged species, it is preferable to include IEF in the specification. Thus, a system under which IEF can be performed should be established promptly and IEF should be included in the drug product specification. According to the results of validation of hemolytic assay presented in the application dossier, the assay results tend to be inherently variable. From this and other reasons, it is understood that it is technically difficult to perform hemolytic assay in Japan. However, since hemolytic assay can assess the ability and capacity of eculizumab to achieve a biological effect (a pharmacodynamic effect), including hemolytic assay in the drug product specification in Japan in future should be considered.

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The applicant responded as follows:
For the time being, the both tests will be performed as in-process controls. A system under which IEF can be performed in Japan will be established promptly after approval and IEF will be included in the drug product specification. Furthermore, the possibility of performing hemolytic assay in Japan will continue to be reviewed.

PMDA accepted the response.

(1).5) Conformity of raw materials of animal origin to the Standard for Biological Ingredients
US-sourced BSA that does not conform to the Standard for Biological Ingredients is used as a medium component in the preparation and preservation of the MCB and WCB and for cell culture. PMDA asked the applicant to explain the risk assessment of BSA, the benefit of eculizumab, and the timing of switching. The Standard for Biological Ingredients does not apply to US-sourced BSA that is used in the preparation and preservation of the MCB and WCB in accordance with "Partial Revision of the Standard for Biological Ingredients" (PFSB Notification No. 0705001 dated July 5, 2004).

The applicant responded as follows:
With respect to the risk of transmissible spongiform encephalopathy (TSE) infection associated with the use of this raw material, "geographical risk and risk of the specific parts used for raw materials of drugs etc." and "risks associated with treatment in the product manufacturing process and product usage" ("Handling of Risk Assessment etc. in Partial Change Applications for Drugs, Medical Devices, etc., Using Bovine Derived Raw Materials etc." [PFSB/ELD Notification No. 0801001 and PFSB/SD Notification No. 0801001 dated August 1, 2003]) were assessed. As a result, the total risk assessment score was "less than -3," which met a threshold to provide a certain safety assurance and the risk of TSE infection associated with the use of eculizumab is very low. At present, there is no effective existing therapy for the hemolysis of PNH and the medical benefit of eculizumab is high. Switching to New Zealand-sourced BSA is currently under consideration and a partial change application for switching to BSA sourced from another country will be filed by the 4th quarter of 2011.

PMDA considers as follows:
Although the risk of TSE infection associated with the use of eculizumab can not be excluded, the result of risk assessment indicates that its risk is very low. There is no effective therapy for the hemolysis of PNH at present and as eculizumab stabilized Hb levels and reduced transfusion requirements by reducing hemolysis in the TRIUMPH study, eculizumab is expected to become an effective therapy for the hemolysis of PNH (However, it is necessary to select patients carefully in view of safety concerns [e.g. theoretical increase in the risk of infection with *Neisseria meningitidis* etc.]). Therefore, the medical usefulness of eculizumab should outweigh the risks associated with the use of this raw material.

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Based on the above, as this case falls under 4-1-(5) of the Standard for Biological Ingredients, there is no need to withhold the approval of eculizumab until the raw material is switched to that sourced from countries where no bovine spongiform encephalopathy (BSE) has been reported. However, it should be stated in the package insert that the risk of TSE infection can not be excluded and patients should be fully explained about this risk prior to the use of eculizumab.

The above conclusion is based on the premise that the product will be manufactured using the raw material that conforms to the Standard for Biological Ingredients as soon as it becomes possible.

(2) Results from clinical pharmacology studies

PMDA reviewed the applicant's response to the question as follows and considered that there are no major differences in the effect of eculizumab between Japan and overseas.

(2).1) Hemolytic activity over time in clinical studies

The measured hemolytic activity over time in the C02-001, TRIUMPH, SHEPHERD, and C07-001 studies are shown in Figure 4. There were no major differences in the results.

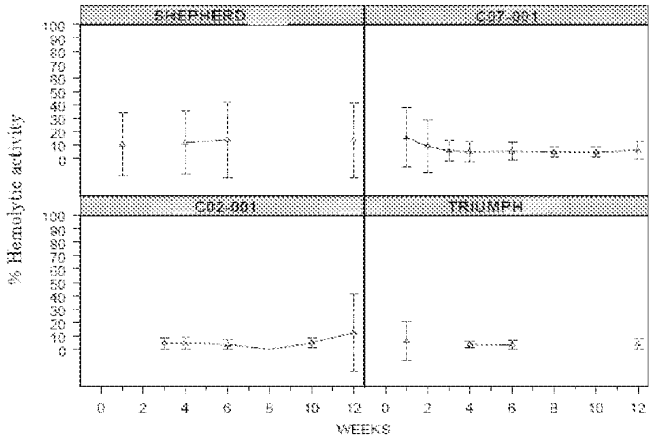


Figure 4. Hemolytic activity over time in clinical studies (C02-001, TRIUMPH, SHEPHERD, C07-001)

(3) Data subject to evaluation

For the review of the application, PMDA decided to position the foreign TRIUMPH study as the pivotal study and use the foreign SHEPHERD study and the Japanese C07-001 study as supporting efficacy and safety data, taking fully into consideration epidemiological differences in PNH between Japan and overseas and differences in patient background etc. among the studies, for evaluations, for the following reasons: since PNH is a rare disease, it is difficult to conduct a confirmatory clinical study in Japan alone; and since PNH is an acquired genetic disorder and eculizumab is an anti-C5 antibody, it is

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inferred from the pathology of the disease and the mechanism of action that eculizumab is insensitive to ethnic factors.

The expert advisors made the following comment and supported the PMDA's decision:

- While TE is a clinical problem for PNH patients in the US and Europe, fewer patients develop TE and hematopoietic failure and renal impairment are more likely to become problems in Japan, etc., indicating differences in the clinical symptoms and causes of death of PNH between Japan and overseas. Therefore, what clinical significance is ultimately expected of hemolysis inhibition by eculizumab may be different between Japan and the US/Europe. However, as long as the efficacy of eculizumab is evaluated based on hemolysis inhibition, it is inferred that eculizumab is insensitive to ethnic factors.

(4) Efficacy

The following conclusions by PMDA were supported by the expert advisors:

Choosing "Hb stabilization" and "the number of PRBC units transfused" as the primary efficacy endpoints for the TRIUMPH study was appropriate for demonstrating the clinical significance of eculizumab as PNH patients primarily present with progressive anemia due to chronic intravascular hemolysis. Although the effects of eculizumab on the development of TE and survival prognosis etc. are undefined at present, as eculizumab was shown to be effective in maintaining Hb at levels that did not necessitate transfusions and reducing transfusion requirements in the TRIUMPH study, the clinical significance of hemolysis inhibition by eculizumab was demonstrated. The SHEPHERD study and Study C07-001 demonstrated reduction in hemolysis as indicated by changes of LDH, but have not assessed treatment effect, e.g. Hb stabilization.

PMDA reviewed the applicant's responses to the questions about efficacy as follows and considered that the efficacy of eculizumab can be expected.

(4).1) Influence of body weight

The applicant responded that there was no particular trend for the influence of body weight on the efficacy and safety of eculizumab in the TRIUMPH study, SHEPHERD study, and Study C07-001 and PMDA accepted the response.

(4).2) Long-term efficacy

LDH levels over time and transfusion requirements over time based on pooled analyses of the submitted foreign clinical studies (TRIUMPH, SHEPHERD, C02-001, E02-001, X03-001, X03-001A, E05-001) are shown in Tables 39 and 40, respectively. PMDA considered that it was suggested that continued treatment with eculizumab resulted in sustained decrease in hemolysis up to 24 months after start of treatment.

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Table 39. LDH levels over time in foreign clinical studies[a)]

	Baseline	3 months	6 months	9 months	12 months	15 months	18 months	24 months
N	151	150	147	107	102	11	11	11
LDH (U/L)	2238.0 [511.8, 8600.0]	364.8 [126.7, 2594.0]	290.7 [111.7, 5117.0]	299.7 [109.3, 1192.3]	285.4 [103.0, 821.0]	528.5 [155.5, 755.0]	500.5 [157.5, 683.0]	532.0 [141.0, 740.0]

Median [Min., Max.]
a) TRIUMPH, SHEPHERD, C02-001, E02-001, X03-001, X03-001A, E05-001

Table 40. Transfusion requirements over time in foreign clinical studies[a)]

	Baseline[b)]	0-3 months	3-6 months	6-9 months	9-12 months	12-15 months	15-18 months	21-24 months
N	151	150	147	107	102	11	11	11
No. of units transfused	3.3 [0.0, 16.5]	0.0 [0.0, 16.0]	0.0 [0.0, 14.0]	0.0 [0.0, 12.0]	0.0 [0.0, 16.0]	2.0 [0.0, 6.0]	0.0 [0.0, 3.0]	0.0 [0.0, 5.0]

Median [Min., Max.]
a) TRIUMPH, SHEPHERD, C02-001, E02-001, X03-001, X03-001A, E05-001
b) The number of units transfused in the past 1 year divided by 4

(4).3) Lack of efficacy

PMDA asked the applicant about the details of 14 cases of lack of efficacy reported from foreign post-marketing surveillance (Table 32).

The applicant explained as follows:

Among the 14 patients diagnosed with lack of efficacy, 4 patients continued treatment, 8 patients discontinued treatment, and 2 patients had unknown status regarding treatment continuation. The reasons for classifying patients as lack of efficacy included complications (worsening of AA or MDS, etc.), inadequate doses, a hemolytic crisis associated with a reduced dose of steroids, no reduction in transfusion requirements, and death due to sepsis. Changes in LDH levels were reported in 6 of the 14 patients and treatment with eculizumab resulted in reductions in LDH levels in all 6 patients.

PMDA considered as follows:

Concerning the information on the patients reported as lack of efficacy via foreign post-marketing surveillance, there were patients classified as lack of efficacy in the judgment of the attending physician despite the fact that LDH levels were reduced following treatment with eculizumab. In the Japanese clinical study (C07-001), 2 patients were classified as lack of efficacy as LDH levels were not reduced. Based on these findings, it is necessary to continue to collect information on patients classified as lack of efficacy also after the market launch and investigate the reasons for classifying patients as lack of efficacy and the causes for lack of efficacy.

(5) Safety

(5).1) Overall safety of eculizumab

PMDA concluded as follows:

The incidences of adverse events of headache, nasopharyngitis, back pain, and fatigue tended to be higher in the eculizumab group than in the placebo group in the TRIUMPH study[††††] and attention

[††††] In response to the request from PMDA, the applicant discussed that the causes for higher incidences of nasopharyngitis, back pain, and fatigue in the eculizumab group than in the placebo group in the TRIUMPH study are unknown.

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should be paid to the possible occurrence of headache, especially during the early phase of treatment. There were no serious adverse events unique to the eculizumab group or no adverse events unique to long-term treatment. Thus, adverse events associated with eculizumab are tolerable.

On the other hand, based on its mechanism of action, eculizumab may increase the risk of infections with encapsulated bacteria (especially, *Neisseria meningitidis*) that are cleared by terminal complement components and attention should be paid to infections, especially meningococcal infection [see "(5).2) Meningococcal infections"]. Furthermore, since there is a concern about the development of a serious hemolytic crisis after eculizumab discontinuation due to the accumulation of PNH type III RBCs in patients being treated with eculizumab, the information on the risks associated with discontinuation of eculizumab and the need for monitoring patients after eculizumab discontinuation should be provided appropriately to the medical practice.

The above conclusions by PMDA were largely supported by the expert advisors, but the following comments were raised from some expert advisors.

- Although the incidence of headache was higher in the eculizumab group, as headache occurs also as an initial symptom of meningococcal infection, it may become necessary to differentiate the causes of headache. How headache is managed overseas should be checked, an appropriate approach to headache should be considered, and information should be provided to the medical practice.
- Theoretically, the risk of infections with not only *Neisseria meningitidis*, but also other encapsulated bacteria, e.g. *Streptococcus pneumoniae* and *Haemophilus influenzae*, may be increased. The status of vaccination against *Streptococcus pneumoniae* and *Haemophilus influenzae* in foreign countries where eculizumab has been approved should be checked and then the incidence of infections among eculizumab-treated patients in Japanese and foreign marketing experience should continue to be investigated and necessary actions should be taken.
- Theoretically, the risk of a serious, acute hemolytic crisis is increased after eculizumab discontinuation and adequate caution should be provided. For the cases of treatment discontinuation, the information after discontinuation should be collected.

PMDA asked the applicant to explain how to differentiate a headache associated with eculizumab from a headache caused by *Neisseria meningitidis*.

The applicant explained as follows:
It is difficult to specifically differentiate a headache associated with eculizumab from a headache caused by meningococcal infection if there are no other symptoms. Meanwhile, differentiation is considered possible in most cases based on (a) the presence or absence of other symptoms of meningococcal infection (pyrexia, nausea/vomiting, neck or back stiffness, rash, mental confusion, severe myalgia

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accompanied by flu-like symptoms, photophobia) or (b) antipyretic analgesics are ineffective against a headache caused by meningococcal infection. Performing head tapping test, jolt accentuation test, vascular compression test, nerve compression test, muscle compression test, and tension sign tests etc. as appropriate and determining the presence or absence of symptoms of meningeal irritation due to bacterial meningitis should also be considered in order to diagnose the cause of headache.

However, basically, at the discretion of specialists, tests for infections (blood culture and lumbar puncture etc.) will be performed and antibiotics will be administered.

PMDA asked the applicant to explain the status of vaccination against *Streptococcus pneumoniae* and *Haemophilus influenzae* in foreign countries where eculizumab has been approved.

The applicant explained as follows:
The status of vaccination in a Japanese clinical study (C07-001) and foreign clinical studies (TRIUMPH, SHEPHERD) is shown in Table 41.

According to the foreign post-marketing data as of January 31, 2010 (1700 case reports), about 1% of patients were vaccinated against *Streptococcus pneumoniae* or *Haemophilus influenzae*, or both.

Table 41. Status of vaccination against *Streptococcus pneumoniae* and *Haemophilus influenzae* in Japanese and foreign clinical studies (TRIUMPH, SHEPHERD, C07-001)

Clinical study		No. of patients	No. of vaccinated patients	
			Streptococcus pneumoniae	*Haemophilus influenzae*
TRIUMPH	Eculizumab	43	0	2
	Placebo	44	0	2
SHEPHERD		97	2	22
C07-001		29	0	0

PMDA considers as follows:
Headache is an adverse event with a high incidence as the incidence of headache in patients treated with eculizumab was 51.3% (100 of 195 patients) in foreign clinical studies (TRIUMPH, SHEPHERD, C02-001, E02-001, X03-001, X03-001A, E05-001) and 58.6% (17 of 29 patients) in the Japanese clinical study (C07-001). Differentiating a headache as an adverse drug reaction from a headache caused by meningococcal infection is important and patients must understand that they should contact their doctors immediately if headache occurs during treatment with eculizumab. Adequate information on differentiation of headaches should be provided to patients and healthcare professionals.

Taking account of the overseas situation, there seems no need to mandate vaccination against *Streptococcus pneumoniae* and *Haemophilus influenzae* at present. However, as treatment with eculizumab may theoretically increase the risk of infections with *Streptococcus pneumoniae* and *Haemophilus influenzae*, physicians should be alerted to these infections and vaccination against *Streptococcus pneumoniae* and *Haemophilus influenzae* should be considered as appropriate, at the

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discretion of the physician.

Based on the above discussion, PMDA instructed the applicant to appropriately provide information and issue an alert, based on the comments from the expert advisors, via the package insert and information leaflet. The applicant responded appropriately and PMDA accepted it.

(5).2) Meningococcal infections

PMDA concluded as follows:

Based on its pharmacological action, eculizumab may increase the risk of developing a meningococcal infection. As part of measures against meningococcal infections, patients are required to be immunized with a meningococcal vaccine prior to the use of eculizumab in the US/Europe (eculizumab is contraindicated in unvaccinated patients) and patients were required to be immunized with a meningococcal vaccine also in the TRIUMPH study, SHEPHERD study, and a Japanese clinical study (C07-001). Meningococcal vaccination can be used as a promising safety measure also in Japan. However, there is currently no approved meningococcal vaccine whose efficacy and safety have been demonstrated in Japanese subjects and the major tetravalent vaccines (serogroups A, C, Y, and W135), which are currently used overseas, are expected to have limited efficacy against serogroup B disease, which has been relatively commonly reported in Japan, etc. Thus, it is necessary to continue to review the need for meningococcal vaccination while collecting information actively from Japan and overseas. In order to reduce the risks associated with meningococcal infections, adequate measures against meningococcal infections, e.g. early detection and early initiation of treatment with antibiotics, should be taken. Adequate information on the risks and benefits of eculizumab should be provided to healthcare professionals and patients and eculizumab should be initiated after both the healthcare professional and patient understand the risks and benefits of eculizumab.

The expert advisors made the following comments on the above conclusions by PMDA:

- PNH patients with decreased white blood cells due to AA or MDS are susceptible to infections and especially among Japanese PNH patients, the proportion of patients with AA or MDS is relatively high. Therefore, if they develop a meningococcal infection, the disease is likely to become serious.
- Even if the major tetravalent meningococcal vaccines, which are currently used overseas, have limited efficacy in Japan, these vaccines can be expected to be effective in some patients. Therefore, at least, an environment where meningococcal vaccination is available upon request should be created.
- The regulatory authorities should guide the industry to proceed with the development of meningococcal vaccine in Japan.
- Since meningococcal infections will be manageable in most cases with early detection and appropriate early treatment, adequate information on infections, e.g. treatment with antibiotics,

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should be provided and cooperation with a medical institution prepared to treat infections is needed.

- Prior to the use of eculizumab, adequate information on the risk of meningococcal infections should be provided to healthcare professionals. Patients should also be fully informed of the risk and their consent should be obtained before the initiation of treatment.

Taking account of the comments from the expert advisors, PMDA asked for the applicant's view on the provision of information on meningococcal infections and meningococcal vaccination after marketing approval of eculizumab.

The applicant explained meningococcal vaccination prior to the use of eculizumab as follows:
(a) In cooperation with a foreign vaccine manufacturer ([redacted]), a clinical trial of a tetravalent meningococcal vaccine (serogroups, A, C, Y, and W135) (brand name, [redacted]) intended for the prevention of meningococcal infections in PNH patients will be initiated as soon as possible in Japan.
(b) The following procedures will be followed until meningococcal vaccine receives marketing approval in Japan.

i) The physician identifies a PNH patient considered to require treatment with eculizumab and provides the patient with the information on the risk of developing a meningococcal infection associated with eculizumab, the prevention and treatment methods of meningococcal infections, and its efficacy and safety.
ii) Ask the patient if he/she wishes to receive meningococcal vaccine.
iii) If the patient wishes to receive meningococcal vaccine, ask the patient if he/she wishes to participate in a clinical trial of meningococcal vaccine. If the patient wishes not to participate in the clinical trial of meningococcal vaccine or the medical institution treating the patient does not participate in the clinical trial of meningococcal vaccine, provide the information on the private import method or the health facilities providing meningococcal immunization services for overseas travelers, etc.‡‡‡‡ to the medical institution to explain to the patient.
iv) Deliver eculizumab after confirming that the patient has received meningococcal vaccine.
v) If the patient wishes not to receive meningococcal vaccine, receive a written pledge from the patient stating that the patient fully understands the risk of meningococcal infections and starts treatment with eculizumab, before delivery of eculizumab.

PMDA considers as follows:
In light of the current situation where there is no approved meningococcal vaccine in Japan, it is unavoidable at present to follow the procedures proposed by the applicant.

Since even meningococcal vaccination can not completely protect against meningococcal infections, as

‡‡‡‡ In cooperation with the Japanese Society of Travel and Health.

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feasible measures to reduce the risks associated with meningococcal infections in Japan, measures against meningococcal infections, e.g. cooperation with a medical institution prepared to treat infections, early detection, and early initiation of treatment with antibiotics, should be built, adequate information on the risks and benefits of eculizumab should be provided to healthcare professionals and patients, and eculizumab should be initiated after both the healthcare professional and patient understand the risks and benefits of eculizumab.

The applicant responded that they will address accordingly and PMDA accepted it.

PMDA instructed the applicant to prepare the details of information leaflets before the market launch and the applicant responded that they will do so.

(5).3) Results of foreign post-marketing surveillance

In response to the request from PMDA, the applicant explained differences in observed adverse events between clinical studies and post-marketing surveillance as follows:

Hb decreased was observed in the foreign post-marketing surveillance only. This is possibly because PNH-related laboratory findings may have been regarded as adverse events in the post-marketing surveillance but were not reported as adverse events in the clinical studies. Thus, the differences in observed serious adverse events are considered to have no clinically relevant significance.

PMDA considers as follows:

Although no particular events were reported at a markedly higher incidence in the foreign post-marketing surveillance than in the clinical studies, it is necessary to continue to collect information on the cases of lack of efficacy, e.g. Hb decreased, via post-marketing surveillance etc. and provide the information to the clinical practice as appropriate.

(5).4) Adverse events in pooled Japanese and foreign clinical studies

In response to the request from PMDA, the applicant presented adverse events occurring in ≥ 10.0% of patients in either group during the entire treatment period in all clinical studies as shown in Table 42 and serious adverse events occurring in at least 2 patients in either group during the entire treatment period as shown in Table 43.

PMDA confirmed the following:

Even when adverse events occurring up to Week 12 in the TRIUMPH study, SHEPHERD study, and Study C07-001 and foreign clinical studies (TRIUMPH, SHEPHERD, C02-001, E02-001, X03-001, E05-001) were pooled with other clinical studies, there were no significant major differences compared with Tables 29 and 30 and no problematic adverse events or serious adverse events were reported in Japan compared with overseas.

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Table 42. Adverse events occurring in ≥ 10.0% of patients in either group during the entire treatment period in clinical studies (Pooled analysis)

	Foreign clinical studies				Japanese clinical studies				Foreign clinical studies				Japanese clinical studies	
	Placebo (N = 44)		Eculizumab (N = 195)		Eculizumab (N = 29)				Placebo (N = 44)		Eculizumab (N = 195)		Eculizumab (N = 29)	
	Incidence	N	Incidence	N	Incidence	N			Incidence	N	Incidence	N	Incidence	N
Overall	90.9%	40	99.0%	193	100.0%	29	Arthralgia		9.1%	4	15.9%	31	3.4%	1
Headache	27.3%	12	51.3%	100	58.6%	17	Cough		9.1%	4	15.9%	31	3.4%	1
Nasopharyngitis	18.2%	8	42.1%	82	58.6%	17	Dizziness		11.4%	5	15.4%	30	3.4%	1
Nausea	11.4%	5	25.1%	49	20.7%	6	Pain in extremity		2.3%	1	14.4%	28	3.4%	1
Diarrhoea	11.4%	5	22.1%	43	17.2%	5	Influenza like illness		2.3%	1	11.3%	22	3.4%	1
Pyrexia	4.5%	2	16.9%	33	13.8%	4	Myalgia		2.3%	1	10.8%	21	3.4%	1
Anaemia	2.3%	1	3.6%	7	13.8%	4	Pharyngolaryngeal pain		9.1%	4	14.4%	28	0.0%	0
Conjunctival haemorrhage	0.0%	0	1.0%	2	13.8%	4	Abdominal pain		11.4%	5	12.8%	25	0.0%	0
Oedema	0.0%	0	0.0%	0	13.8%	4	Insomnia		6.8%	3	11.8%	23	0.0%	0
Upper respiratory inflammation	0.0%	0	0.0%	0	13.8%	4	Constipation		4.5%	2	11.8%	23	0.0%	0
Vomiting	11.4%	5	16.4%	32	10.3%	3	Viral infection		11.4%	5	11.3%	22	0.0%	0
Upper respiratory tract infection	22.7%	10	30.8%	60	6.9%	2	Urinary tract infection		9.1%	4	11.3%	22	0.0%	0
Back pain	9.1%	4	20.0%	39	3.4%	1	Contusion		6.8%	3	11.3%	22	0.0%	0

Japanese clinical studies (study duration, up to 38 weeks): C07-001 and E07-001 (Interim report)
Foreign clinical studies (study duration, up to 206 weeks): TRIUMPH, SHEPHERD, C02-001, E02-001, X03-001, X03-001A, and E05-001 (Interim report)

Table 43. Serious adverse events occurring in at least 2 patients in either group during the entire treatment period in clinical studies (Pooled analysis)

	Foreign clinical studies				Japanese clinical studies				Foreign clinical studies				Japanese clinical studies	
	Placebo (N = 44)		Eculizumab (N = 195)		Eculizumab (N = 29)				Placebo (N = 44)		Eculizumab (N = 195)		Eculizumab (N = 29)	
	Incidence	N	Incidence	N	Incidence	N			Incidence	N	Incidence	N	Incidence	N
Overall	20.5%	9	25.6%	50	13.8%	4	Headache		0.0%	0	2.1%	4	0.0%	0
Abdominal pain	0.0%	0	1.0%	2	0.0%	0	Convulsion		0.0%	0	1.0%	2	0.0%	0
Pyrexia	2.3%	1	3.6%	7	3.4%	1	Acute renal failure		0.0%	0	1.0%	2	3.4%	1
Cholelithiasis	0.0%	0	1.0%	2	0.0%	0	Nephrolithiasis		0.0%	0	1.0%	2	0.0%	0
Cellulitis	2.3%	1	1.0%	2	3.4%	1	PNH		6.8%	3	1.0%	2	0.0%	0
Viral infection	2.3%	1	2.6%	5	0.0%	0	Anaemia		2.3%	1	2.1%	4	3.4%	1
Viral gastroenteritis	0.0%	0	1.0%	2	0.0%	0	Haemolytic anaemia		0.0%	0	1.0%	2	0.0%	0
Septic shock	0.0%	0	1.0%	2	0.0%	0	Thrombocytopenia		0.0%	0	1.0%	2	0.0%	0
Intervertebral disc protrusion	0.0%	0	1.5%	3	0.0%	0	Neutropenia		4.5%	2	0.5%	1	0.0%	0

Japanese clinical studies (study duration, up to 38 weeks): C07-001 and E07-001 (Interim report)
Foreign clinical studies (study duration, up to 206 weeks): TRIUMPH, SHEPHERD, C02-001, E02-001, X03-001, X03-001A, and E05-001 (Interim report)

(6) Indication

PMDA concluded as follows:

Eculizumab is palliative and is not a curative therapy for PNH. Improvement in survival prognosis has not been demonstrated at present. Eculizumab may increase the risk of developing an infection with encapsulated bacteria, e.g. *Neisseria meningitidis*. Once treatment is initiated, continued treatment is needed. Taking account of these points, eculizumab should be used only in appropriate patients, fully examining treatment effects and potential risks. Therefore, the package insert should state that Hb stabilization and reductions in transfusion requirements have been demonstrated only in the TRIUMPH study population and advise that eculizumab should be used only if the clinical benefits are considered to outweigh the potential risks. It is also necessary to state that the efficacy of eculizumab during an acute hemolytic crisis has not been demonstrated.

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The expert advisors made the following comments and supported the above conclusions by PMDA.

- PNH is considered associated with a relatively good survival prognosis, in view of the age of onset and survival time after diagnosis (Table 19). As the effects of eculizumab on the development of TE and survival prognosis are undefined, the significance of administering eculizumab to less transfusion-dependent patients is not high and it should be advised that eculizumab should be used in patients who are expected to require regular transfusions.
- Eculizumab reduces hemolysis, but may increase the risk of a serious hemolytic crisis due to the accumulation of PNH type III RBCs.
- Prior to the use of eculizumab, risk-benefit assessment is needed on an individual basis and it is difficult to define the intended population, but appropriate patients may be selected based on the patient populations enrolled in clinical studies.
- Given the risks associated with eculizumab, adequate information should be provided to ensure that eculizumab will not be initiated easily in patients in less need of treatment with eculizumab.
- In clinical practice, it is envisaged that treatment initiation will be considered if a patient is hospitalized due to an acute hemolytic crisis, etc. Thus, it should be stated that the efficacy of eculizumab in such cases is unknown.

Based on the above comments from the expert advisors, PMDA instructed the applicant to modify the proposed indication and precautions of indication statements of the package insert. The applicant responded that the statements will be modified as follows and PMDA accepted it.

[Indication]

Reduction of hemolysis in patients with paroxysmal nocturnal hemoglobinuria

[Precautions for indication]

- Treatment with Soliris should be initiated in patients with a diagnosis of paroxysmal nocturnal hemoglobinuria established by flow cytometry etc.
- Treatment with Soliris should be initiated in patients considered to require RBC transfusions due to hemolysis and expected to require regular transfusions.
- Prevention of thromboembolism, improvement in renal function, or survival benefit of Soliris has not been demonstrated.
- The efficacy of Soliris during an acute hemolytic crisis has not been demonstrated.
- Due to the following potential risks, after fully understanding the efficacy and safety of Soliris, whether or not to use Soliris should be determined carefully and treatment with Soliris should be initiated in appropriate patients (see "Clinical Studies").
  - An increased risk of infections with *Neisseria meningitidis* etc. (Soliris inhibits complement C5 and may increase a patient's susceptibility to infections with encapsulated bacteria, e.g. *Neisseria meningitidis*.)

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- Development of a serious hemolytic crisis after Soliris discontinuation (As PNH RBCs increase in patients being treated with Soliris, serious intravascular hemolysis may be induced if Soliris is discontinued.)

(7) Dosage and administration

PMDA concluded as follows:

Although the rationale for the proposed dosage and administration is not necessarily sufficient, the TRIUMPH study has confirmed the efficacy of eculizumab, Study C07-001 in Japanese PNH patients also has suggested reduction in hemolysis, and based on the submitted clinical study data, eculizumab increases the risk of developing a meningococcal infection, but otherwise the safety profile of eculizumab is tolerable. Therefore, eculizumab has certain usefulness at the dosage regimen used in clinical studies in PNH patients. It should be stated in the precautions for dosage and administration section of the package insert that as a hemolytic crisis due to decreased blood concentrations may occur, the labeled dosage and administration instructions should be complied with and that if LDH levels are not reduced for a certain period of time, whether or not to continue treatment should be determined.

The above conclusions by PMDA were supported by the expert advisors and PMDA instructed the applicant to modify the dosage and administration and precautions for dosage and administration statements of the package insert.

The applicant explained that although LDH levels were reduced by Week 1 in the majority of patients, as it took about 2 weeks for LDH levels to be reduced in some patients, whether or not to continue treatment with eculizumab should be determined at around Week 2. The applicant then modified the dosage and administration and precautions for dosage and administration statements as follows and PMDA accepted it.

[Dosage and administration]

The usual adult dosage is 600 mg as Eculizumab (Genetical Recombination) given as an intravenous infusion weekly for a total of 4 doses, followed 1 week later (4 weeks after the first dose) by 900 mg given every 2 weeks thereafter.

[Precautions for dosage and administration]

- Diluted Soliris should be administered by intravenous infusion over 25 to 45 minutes via a dedicated infusion line.
- Comply with the recommended dosing intervals as an acute hemolytic crisis due to decreased blood concentrations of Soliris may occur.
- If serum lactate dehydrogenase (LDH) activity is not reduced by Week 2, whether or not to continue treatment with Soliris should be determined.

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(8) Pediatric indication

In response to the questions on a pediatric indication, the applicant explained as follows:

Among 34 pediatric patients treated with eculizumab in the foreign marketing experience (as of August 24, 2009), 6 patients experienced serious adverse events ("central line infection" in 1 patient, "anaemia and *Pseudomonas aeruginosa* infection" in 1 patient, "tooth infection" in 1 patient, "thrombosis, abdominal pain, and constipation" in 1 patient, "bronchospasm" in 1 patient, "respiratory failure, cerebral aspergillosis, and enterococcal sepsis" in 1 patient). A causal relationship to eculizumab could not be denied for "anaemia and *Pseudomonas aeruginosa* infection" and no causality assessment was reported for "tooth infection," "thrombosis, abdominal pain, and constipation," and "bronchospasm."

Although there is no plan to develop eculizumab for Japanese pediatric patients with PNH at present, the development of eculizumab for pediatric use will be considered based on the planned foreign clinical study and the uses of eculizumab in Japan.

PMDA concluded as follows:

As it is known that children also develop PNH, a pediatric indication should also be considered. Due to very limited information on the efficacy and safety of eculizumab in children at present, for the time being, the phrase "adult dosage" should be included in the dosage and administration statement and it should be stated in the precautions section that "the efficacy and safety of eculizumab in children has not been established."

The following comment on the above conclusions by PMDA was raised from the expert advisors: as the risk of infections is different between adults and children, special caution is required when using eculizumab in children. The conclusions by PMDA were supported by the expert advisors.

If a pediatric patient treated with eculizumab is reported from a post-marketing surveillance study covering all treated patients, the case should be reviewed and it will be necessary to provide information and take safety measures as appropriate [see "(9) Post-marketing surveillance etc."].

(9) Post-marketing surveillance etc.

In response to the request from PMDA, the applicant explained an overview of the PNH registry, a foreign epidemiological study, as follows:

The objectives of the study are to capture the clinical courses of patients with PNH and to raise awareness of PNH among healthcare professionals and patients. In the study, patient demographics, the drugs used, disease progression, and clinical outcomes have been surveyed based on the data collected during patient visits.

The applicant explained that based on this PNH registry, a post-marketing survey (survey period, 8

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years; a survey covering all treated patients) as shown in Table 38 will be conducted in Japan.

PMDA concluded that in addition to the items presented by the applicant, (a) PNH type III RBC clone over time (collect the information if analyzed), (b) the information on HAHA (antibody titers, neutralizing antibodies, etc.), and (c) the information on the use of eculizumab in children and pregnant women/nursing mothers should be collected. This conclusion was supported by the expert advisors. The expert advisors commented that the following items should also be included: (d) the reason for definitive diagnosis of PNH, (e) concurrent AA or MDS, (f) the information on the cases of lack of efficacy, (g) the information on the use of eculizumab during an acute hemolytic crisis, (h) the information on meningococcal infections (meningococcal carriage [if tested], a history of meningococcal infection, meningococcal vaccination status [vaccination date, vaccine type, etc.]), (i) detailed information on the development of infections including meningococcal infection, (j) the development of TE during treatment period, and (k) the reason for eculizumab discontinuation and the severity of hemolysis after discontinuation.

PMDA instructed the applicant to submit a draft outline of a post-marketing surveillance plan incorporating the above points and the applicant submitted an outline of a post-marketing surveillance plan (draft) as summarized in Table 44 and PMDA accepted it.

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Table 44. Outline of post-marketing surveillance plan (draft)

Objectives	· Detection of unknown and serious adverse drug reactions · Long-term safety and efficacy · Effects of eculizumab on the course of PNH (progression, course, and prognosis etc. of the disease)
Survey period	Re-examination period
Planned number of patients	All patients treated with eculizumab
Target patient population	Patients diagnosed with PNH
Major items to be investigated	(a) Patient background analysis: Indication for use: reduction of hemolysis in patients with paroxysmal nocturnal hemoglobinuria · The reason for definitive diagnosis of PNH (the basis of the diagnosis) Priority items (Patient background for safety) · Meningococcal carriage (if tested) Risk analysis of healthy carriers and noncarriers, Effects of eculizumab · History of meningococcal infection Risk analysis of patients with or without a history of meningococcal infection, Effects of eculizumab · Meningococcal vaccination (vaccination date, vaccine type) Risk analysis by vaccination status, vaccine type, and time after vaccination, Effects of eculizumab (b) Priority items (Safety) · Development of infections during treatment period (especially, *Neisseria meningitidis*, *Streptococcus pneumoniae*, *Haemophilus influenzae*) Risk analysis of the development of infections, Effects of eculizumab · Development of thromboembolism during treatment period Risk analysis of the development of thromboembolism, Effectiveness of eculizumab · Presence or absence of concomitant medications for the prevention of thromboembolism Risk analysis of the development of thromboembolism, Effectiveness of concomitant medications · Development and severity of hemolysis after eculizumab discontinuation, the reason for discontinuation Safety analysis after the withdrawal of eculizumab · Development of headache symptoms (including associated symptoms), course, outcome, cause (meningococcal infection, other infections, infusion reactions to eculizumab, etc.), treatment instituted (c) Other items Information required for safety factor analysis will be focused, but efficacy items will also be investigated. · Concomitant medications: Effects of corticosteroids, immunosuppressants, erythropoietin, and anticoagulants on the safety and efficacy of eculizumab · Other medical history etc. (already cured/remitted before the initiation of treatment): Effects of eculizumab on the development (recurrence) of major vascular events and other diseases · Underlying disease (concurrent disease) etc.: Effects of AA, MDS, or other myeloid disorders on the safety and efficacy of eculizumab · PNH duration etc., Time after PNH diagnosis: Effects of time elapsed after definitive diagnosis on the effectiveness of eculizumab · Complications (comorbidities/symptoms) etc.: Effects of major vascular events, hepatic impairment/renal impairment, or the symptoms of other complications/comorbidities etc. on the safety and efficacy of eculizumab · Change in LDH from baseline over time · Improvement in QOL (fatigue, abdominal pain, dyspnoea, dysphagia) · Change in Hb from baseline over time · Change in the number of PRBC units transfused from baseline over time · Change from baseline in PNH type III or II RBCs (if analyzed) · Change from baseline in the percentage of PNH type I, II, or III RBCs as measured by flow cytometry (if analyzed) · Cases of lack of efficacy (Identify its cause) · Efficacy of eculizumab during an acute hemolytic crisis · Information on HAHA (antibody titers, neutralizing antibodies, etc.) (if assay is requested by the medical institution)

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III. Overall Evaluation

As a result of the above review, PMDA concludes that eculizumab may be approved after modifying the indication and dosage and administration statements as shown below, with the following conditions. As eculizumab is an orphan drug, the re-examination period is 10 years, the drug substance and the drug product are both classified as powerful drugs, and the product is classified as a biological product.

[Indication]

Reduction of hemolysis in patients with paroxysmal nocturnal hemoglobinuria

[Dosage and administration]

The usual adult dosage is 600 mg as Eculizumab (Genetical Recombination) given as an intravenous infusion weekly for a total of 4 doses, followed 1 week later (4 weeks after the first dose) by 900 mg given every 2 weeks thereafter.

[Conditions for approval]

1. Due to limited data from Japanese clinical studies, conduct a post-marketing drug use-results survey over a certain period of time, covering all patients treated with Soliris, in order to obtain the background information of patients treated with Soliris, collect data on the safety and efficacy of Soliris, and take necessary measures to ensure proper use of Soliris.
2. Prior to marketing Soliris, take necessary measures to ensure that Soliris will be administered only under the supervision of a physician at a medical institution, who is familiar with the diagnosis and treatment of paroxysmal nocturnal hemoglobinuria and is also fully capable of managing the risks etc. associated with Soliris in cooperation with a physician who is familiar with the diagnosis and treatment of meningococcal infection.

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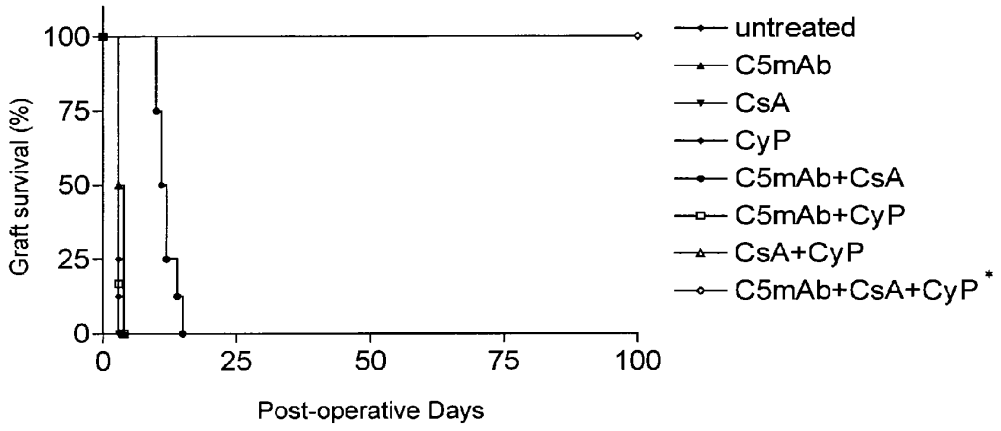
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(54) Title: PROLONGATION OF SURVIVAL OF AN ALLOGRAFT BY INHIBITING COMPLEMENT ACTIVITY



(57) Abstract: Methods of prolonging survival of allotransplanted cells, tissues or organs are presented. These methods are directed to administering to the allotransplant recipient an inhibitor of complement activity together with one or more immunosuppressants. The inhibitor of complement activity is administered chronically. These methods have been determined to aid in preventing chronic rejection of allografts. These methods can additionally be used in cases in which the recipient has been presensitized to the allograft or in which there is an ABO mismatch between the allograft and the recipient.

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PROLONGATION OF SURVIVAL OF AN ALLOGRAFT BY INHIBITING COMPLEMENT ACTIVITY

RELATED APPLICATIONS

This application claims the benefit of and priority to U.S. Provisional Patent Application No. 60/571,444, filed May 14, 2004, the disclosure of which is incorporated herein by reference in its entirety.

TECHNICAL FIELD

The present disclosure relates to methods for prolonging survival of an allograft in a mammal. In particular, the present disclosure relates to prolonging survival of an allograft by administering an inhibitor of complement or terminal complement formation, especially an inhibitor of complement C5 cleavage, in addition to one or more drugs that are immunosuppressant.

BACKGROUND

Organ transplantation is the preferred treatment for most patients with chronic organ failure. Although transplantation of kidney, liver, lung, and heart offers an excellent opportunity for rehabilitation as recipients return to a more normal lifestyle, it is limited by the medical/surgical suitability of potential recipients, an increasing shortage of donors, and premature failure of transplanted organ function.

Transplantation of cells, tissues and organs has become very common and is often a life-saving procedure. Organ transplantation is the preferred treatment for most patients with chronic organ failure. Despite great improvement in treatments to inhibit rejection, rejection continues to be the single largest impediment to successful organ transplantation. Rejection includes not only acute rejection but also chronic rejection. One-year survival rates for transplanted kidneys average 88.3% with kidneys from deceased donors and 94.4% with kidneys received from living donors. The corresponding five year survival rates for the transplanted kidneys are 63.3% and 76.5% (OPTN/SRTR Annual Report, 2002). For livers the one year survival rates are 80.2% and 76.5% for livers from deceased and living donors, respectively. The corresponding five year liver graft survival rates are 63.5% and 73.0% (OPTN/SRTR Annual Report, 2002). The use of immunosuppressant drugs, especially cyclosporin A and more recently tacrolimus, has dramatically improved the success rate of organ transplantation especially by preventing acute rejection. But as the numbers above

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show, there is still a need to improve the success rates, both short-term and especially long-term. As seen from the above numbers for kidney and liver transplants, the five year failure rates for these transplanted organs are on the order of 25-35%. In the year 2001 alone there were more than 23,000 patients who received an organ transplant of which approximately 19,000 were kidney or liver (OPTN/SRTR Annual Report, 2002). For this one year of transplants alone, with present techniques it can be expected that approximately 5,000-6,000 of these transplanted kidneys and livers will fail within 5 years. These numbers do not even include other transplanted organs or transplanted tissues or cells such as bone marrow.

There are multiple types of transplants. These are described in Abbas et al., 2000. A graft transplanted from one individual to the same individual is called an autologous graft or autograft. A graft transplanted between two genetically identical or syngeneic individual is called a syngeneic graft. A graft transplanted between two genetically different individuals of the same species is called an allogeneic graft or allograft. A graft transplanted between individuals of different species is called a xenogeneic graft or xenograft. The molecules that are recognized as foreign on allografts are called alloantigens and those on xenografts are called xenoantigens. The lymphocytes or antibodies that react with alloantigens or xenoantigens are described as being alloreactive or xenoreactive, respectively.

Currently more than 40,000 kidney, heart, lung, liver and pancreas transplants are performed in the United States each year (Abbas et al., 2000). Other possible transplants include, but are not limited to, vascular tissue, eye, cornea, lens, skin, bone marrow, muscle, connective tissue, gastrointestinal tissue, nervous tissue, bone, stem cells, islets, cartilage, hepatocytes, and hematopoietic cells. Unfortunately, there are many more candidates for a transplant than there are donors. To overcome this shortage, a major effort is being made to learn how to use xenografts. While progress is being made in this field, the fact is that at present most transplants are allografts. An allogeneic transplant, while presently being more likely to be successful than a xenogeneic transplant, must surmount numerous obstacles to be successful. There are several types of immunological attacks made by the recipient against the donor organ which can lead to rejection of the allograft. These include hyperacute rejection, acute vascular rejection (including accelerated humoral rejection and de novo acute humoral rejection), and chronic rejection. Rejection is normally a result of T-cell mediated or humoral antibody attack, but may include additional secondary factors such as the effects of complement and cytokines.

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An ever growing gap between the number of patients requiring organ transplantation and the number of donor organs available has become a major problem throughout the world. Park et al., 2003. Individuals who have developed anti-HLA antibodies are said to be immunized or sensitized. Gloor, 2005. HLA sensitization is the major barrier to optimal utilization of organs from living donors in clinical transplantation (Warren et al., 2004) due to the development of severe antibody-mediated rejection (ABMR). For example, more than 50% of all individuals awaiting kidney transplantation are presensitized patients (Glotz et al., 2002) who have elevated levels of broadly reactive alloantibodies, resulting from multiple transfusions, prior failed allografts, or pregnancy (Kupiec-Weglinski, 1996). The role of ABMR is currently one of the most dynamic areas of study in transplantation, due to recognition that this type of rejection can lead to either acute or chronic loss of allograft function. Mehra et al., 2003. Numerous cases of ABMR, including hyperacute rejection (HAR) or accelerated humoral rejection (ACHR), have been reported that are characterized by acute allograft injury that is resistant to potent anti-T cell therapy, the detection of circulating donor specific antibodies, and the deposition of complement components in the graft. ABMR with elevated circulating alloantibodies and complement activation that occurs in 20-30% of acute rejection cases has a poorer prognosis than cellular rejection. Mauiyyedi et al., 2002.

Highly presensitized patients, who exhibit high levels of alloantibodies, usually suffer an immediate and aggressive HAR. In clinical practice, with great efforts and significant advances in technology, HAR is avoided by obtaining a pretransplant lymphocytotoxic cross-match to identify sensitized patients with antibodies specific for donor HLA antigens. However, circulating antibodies against donor HLA or other non-MHC endothelial antigens may also be responsible for a delayed form of acute humoral rejection, which is associated with an increased incidence of graft loss. Collins et al., 1999. Therefore, development of a novel presensitized animal model to mimic ABMR in clinical settings would be beneficial to studies on the mechanism, and to the much needed progress in the management of allograft rejection in presensitized hosts.

Some highly presensitized patients can benefit from intervention programs such as immunoadsorption (Palmer et al.,1989; Ross et al., 1993; Kriaa et al., 1995), plasmapheresis and intravenous immunoglobulin (Sonnenday et al., 2002; Rocha et al., 2003), that have been designed and implemented to temporarily eliminate anti-donor antibodies. However, in addition to their benefits, the aforementioned therapies carry with them numerous drawbacks

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as some individuals are less susceptible to their effects (Kriaa et al., 1995; Hakim et al., 1990; Glotz et al., 1993; Tyan et al., 1994); they are extremely expensive, time-consuming, and risky (Salama et al., 2001). Moreover, the transient and variable effect of these protocols has limited their impact. Glotz et al., 2002; Kupin et al., 1991; Schweitzer et al., 2000. Therefore, developing novel strategies to reduce the risk and cost in prevention of ABMR would be beneficial to presensitized recipients receiving an allograft.

SUMMARY

Accordingly, methods of prolonging survival of transplanted cells, tissues or organs are provided. In particular, methods of prolonging survival of allotransplanted cells, tissues or organs are provided. These methods are directed to using one or more immunosuppressants in addition to an inhibitor of complement activity. Use of one or more immunosuppressants and an inhibitor of complement activity in the manufacture of one or more medicaments or medicament packages is also provided. Such medicaments or medicament packages are useful in prolonging survival of an allograft in a subject mammal.

In certain embodiments, the inhibition of complement activity is effected by chronic administration of a drug directed against complement C5. A preferred drug that inhibits complement activity is an antibody specific to one or more components of complement, for example, C5. In certain preferred embodiments, the antibody inhibits the cleavage of C5 and thereby inhibits the formation of both C5a and C5b-9. The antibody may be, e.g., a monoclonal antibody, a chimeric antibody (e.g., a humanized antibody), an antibody fragment (e.g., Fab), a single chain antibody, an Fv, or a domain antibody. The recipient is also treated with one or more immunosuppressive drugs, for example, cyclosporin A.

In certain embodiments, either an MHC mismatched recipient (i.e., a mammalian recipient of an MHC mismatched allograft), a presensitized recipient or an ABO mismatched recipient (i.e., a mammalian recipient of an AMB mismatched allograft) is treated. In this model, the recipient is again chronically treated with a complement inhibitor, preferably an anti-C5 monoclonal antibody, together with immunosuppressive drugs, preferably a chronic administration of cyclosporin A and a short-term administration of cyclophosphamide. This triple therapy results in extended graft survival in the presensitized allotransplant recipient.

The present disclosure also provides methods of prolonging survival of an allograft in a mammalian recipient by administering to the recipient agents that modulate the level and/or ratio of subclasses and/or isotypes of anti-donor immunoglobulins (Ig) in the recipient. In

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certain embodiments, an agent that reduces the level of anti-donor IgG1 in the recipient is preferred. In certain embodiments, an agent that increases the level of anti-donor IgG2a and/or IgG2b in the recipient is preferred. In certain embodiments, an agent that reduces the ratio of anti-donor IgG1/anti-donor IgG2a or IgG2b in the recipient is preferred.

The present disclosure also provides a method of prolonging survival of an allograft in a second mammalian recipient using an allograft that has been accommodated in a first mammalian recipient (i.e., the allograft has prolonged survival in the first recipient). The present disclosure further provides an allograft that is resistant to anti-donor antibodies in a mammalian recipient, and the allograft is prepared from a first recipient that has accommodated the allograft. In preferred embodiments, the first recipient has accommodated the allograft by receiving a treatment as described herein, such a triple therapy treatment involving administering to the first recipient a drug that inhibits complement activity and two immunosuppressive agents.

Further provided are pharmaceutical packages. A pharmaceutical package of the present disclosure may comprise a drug that inhibits complement activity and at least one immunosuppressive agent. The pharmaceutical package may further comprise a label for chronic administration. The pharmaceutical package may also comprise a label for self-administration by a patient, for example, a recipient of a transplant graft, or instructions for a caretaker of a recipient of a transplant graft. In certain embodiments, the drug and the agent in the pharmaceutical package are in a formulation or separate formulations that are suitable for chronic administration and/or self-administration.

The present disclosure also provides lyophilized formulations and formulations suitable for injection. Certain embodiments provide a lyophilized antibody formulation comprising an antibody that inhibits complement activity and a lyoprotectant. In preferred embodiments, the antibody formulation is suitable for chronic administration, for example, the antibody formulation is stable. Alternative embodiments provide an injection system comprising a syringe; the syringe comprises a cartridge containing an antibody that inhibits complement activity and is in a formulation suitable for injection.

An antibody employed in various embodiments of the present disclosure preferably inhibits the formation of terminal complement or C5a. In certain embodiments, antibody inhibits formation of terminal complement or C5a is a whole antibody or an antibody fragment. The whole antibody or antibody fragment may be a human, humanized,

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chimerized or deimmunized antibody or antibody fragment. In certain embodiments, the whole antibody or antibody fragment may inhibit cleavage of complement C5. In certain embodiments, the antibody fragment is a Fab, an F(ab')2, an Fv, a domain antibody, or a single-chain antibody. In preferred embodiments, the antibody fragment is pexelizumab. In alternative preferred embodiments, the whole antibody is eculizumab.

In certain embodiments, a drug, such as an antibody, that inhibits complement activity is present in unit dosage form, which can be particularly suitable for self-administration. Similarly, an immunosuppressive agent of the present disclosure may also be present in unit dosage form.

BRIEF DESCRIPTION OF THE DRAWINGS

Figures 1A-1D show anti-donor antibody levels in presensitized versus unsensitized recipients under different treatments.

Figures 2A and 2B show comparison between triple therapy using anti-C5 antibody, CsA and CyP in presensitized allograft recipients and combination therapy using only anti-C5 antibody and CsA in presensitized allograft recipients. Figure 2A compares heart-allograft survival in various recipients under different treatments as indicated. Figure 2B shows histology and immunohistology, for example, for lymphocyte infiltration in heart allografts of recipients in different groups.

Figure 3 shows blocked terminal complement activity by anti-C5 antibody as compared to immunosuppressive agents.

Figures 4A-4D compare levels of anti-donor antibodies in presensitized recipients of allografts under monotherapy with anti-C5 antibody alone, double combination therapy with anti-C5 antibody and CsA, and triple combination therapy with anti-C5 antibody, CsA and CyP.

Figures 5A and 5B show change of ratios of IgG isotypes in allograft recipients that were untreated or under different treatments.

Figure 6 shows high-level expression of Bcl-2 and Bcl-xl proteins in long-term surviving heart grafts as compared to heart grafts of untreated animals.

Figure 7 shows improved second transplantation (re-transplantation) of an accommodated graft from a first transplantation recipient.

Figure 8 shows results from re-transplantation experiments.

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Figure 9 shows results from re-transplantation experiments.

DETAILED DESCRIPTION

Overview: Rejection of Transplants or Grafts

Hyperacute rejection occurs within minutes to hours after transplant and is due to preformed antibodies to the transplanted tissue antigens. It is characterized by hemorrhage and thrombotic occlusion of the graft vasculature. The binding of antibody to endothelium activates complement, and antibody and complement induce a number of changes in the graft endothelium that promote intravascular thrombosis and lead to vascular occlusion, the result being that the grafted organ suffers irreversible ischemic damage (Abbas et al., 2000). Hyperacute rejection is often mediated by preexisting IgM alloantibodies, e.g., those directed against the ABO blood group antigens expressed on red blood cells. This type of rejection, mediated by natural antibodies, is the main reason for rejection of xenotransplants. Hyperacute rejection due to natural IgM antibodies is no longer a major problem with allografts because allografts are usually selected to match the donor and recipient ABO type. Hyperacute rejection of an ABO matched allograft may still occur, usually mediated by IgG antibodies directed against protein alloantigens, such as foreign MHC molecules, or against less well defined alloantigens expressed on vascular endothelial cells. Such antibodies may arise as a result of prior exposure to alloantigens through blood transfusion, prior transplantation, or multiple pregnancies (this prior exposure being referred to as "presensitization"). Abbas et al., 2000.

Acute rejection is a process of vascular and parenchymal injury mediated by T cells, macrophages, and antibodies that usually begins after the first week of transplantation. Abbas et al., 2001. T lymphocytes play a central role in acute rejection by responding to alloantigens, including MHC molecules, present on vascular endothelial and parenchymal cells. The activated T cells cause direct lysis of graft cells or produce cytokines that recruit and activate inflammatory cells, which cause necrosis. Both $CD4^+$ and $CD8^+$ cells may contribute to acute rejection. The destruction of allogeneic cells in a graft is highly specific and a hallmark of $CD8^+$ cytotoxic T lymphocyte killing. Abbas et al., 2000. $CD4^+$ T cells may be important in mediating acute graft rejection by secreting cytokines and inducing delayed-type hypersensitivity-like reactions in grafts, with some evidence available that indicates that $CD4^+$ T cells are sufficient to mediate acute rejection. Abbas et al., 2000. Antibodies can also mediate acute rejection after a graft recipient mounts a humoral immune

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response to vessel wall antigens and the antibodies that are produced bind to the vessel wall and activate complement. Abbas et al., 2000.

Chronic rejection is characterized by fibrosis with loss of normal organ structures occurring over a prolonged period. The pathogenesis of chronic rejection is less well understood than that of acute rejection. Graft arterial occlusion may occur as a result of the proliferation of intimal smooth muscle cells (Abbas et al., 2000). This process is called accelerated or graft arteriosclerosis and can develop in any vascularized organ transplant within 6 months to a year after transplantation.

For a transplant to be successful, the several modes of rejection must be overcome. Multiple approaches are utilized in preventing rejection. This may require administration of immunosuppressants, often several types to prevent the various modes of attack, e.g., inhibition of T-cell attack, antibodies, and cytokine and complement effects. Prescreening of donors to match them with recipients is also a major factor in preventing rejection, especially in preventing hyperacute rejection. Immunoadsorption of anti-HLA antibodies prior to grafting may reduce hyperacute rejection. Prior to transplantation the recipient or host may be administered anti-T cell reagents, e.g., the monoclonal antibody OKT3, Anti-Thymocyte Globulin (ATG), cyclosporin A, or tacrolimus (FK 506). Additionally, glucocorticoids and/or azathioprine may be administered to the host prior to transplant. Drugs used to aid in preventing transplant rejection include, but are not limited to, ATG or ALG, OKT3, daclizumab, basiliximab, corticosteroids, 15-deoxyspergualin, cyclosporins, tacrolimus, azathioprine, methotrexate, mycophenolate mofetil, 6-mercaptopurine, bredinin, brequinar, leflunamide, cyclophosphamide, sirolimus, anti-CD4 monoclonal antibodies, CTLA4-Ig, anti-CD154 monoclonal antibodies, anti-LFA1 monoclonal antibodies, anti-LFA-3 monoclonal antibodies, anti-CD2 monoclonal antibodies, and anti-CD45.

Allografts are rejected in part by the activation of T cells. The transplant recipient mounts a rejection response following $CD4^+$ T cell recognition of foreign antigens in the allograft. These antigens are encoded by the major histocompatibility complex (MHC). There are both Class I and Class II MHC molecules. In humans the class I MHC molecules are HLA-A, HLA-B, and HLA-C. The class II MHC molecules in humans are called HLA-DR, HLA-DQ and HLA-DP. In mice the class I MHC molecules are H-2K, H-2D and H-2L and the class II MHC molecules are I-A and I-E. When $CD4^+$ T cells bind the foreign MHC antigens they are activated and undergo clonal proliferation. The activated T cells secrete cytokines which aid in activating monocytes/macrophages, B cells and cytotoxic $CD8^+$ T

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cells. The activated monocytes/macrophages release agents which result in tissue damage, the B cells produce alloantibodies which lead to complement mediated tissue destruction, and the $CD8^+$ T cells kill graft cells in an antigen-specific manner through induction of apoptosis and cell lysis.

Immunosuppressive Agents

The numerous drugs utilized to delay graft rejection (i.e., to prolong their survival) work in a variety of ways. Immunosuppressive agents are widely used. See Stepkowski, 2000, for a review of the mechanism of action of several immunosuppressive drugs. Cyclosporin A is one of the most widely used immunosuppressive drugs for inhibiting graft rejection. It is an inhibitor of interleukin-2 or IL-2 (it prevents mRNA transcription of interleukin-2). More directly, cyclosporin inhibits calcineurin activation that normally occurs upon T cell receptor stimulation. Calcineurin dephosphorylates NFAT (nuclear factor of activated T cells) enabling it to enter the nucleus and bind to interleukin-2 promoter. By blocking this process, cyclosporin A inhibits the activation of the $CD4^+$ T cells and the resulting cascade of events which would otherwise occur. Tacrolimus is another immunosuppressant that acts by inhibiting the production of interleukin-2.

Rapamycin (Sirolimus), SDZ RAD, and interleukin-2 receptor blockers are drugs that inhibit the action of interleukin-2 and therefore prevent the cascade of events described above.

Inhibitors of purine or pyrimidine biosynthesis are also used to inhibit graft rejection. These prevent DNA synthesis and thereby inhibit cell division including the ability of T cells to divide. The result is the inhibition of T cell activity by preventing the formation of new T cells. Inhibitors of purine synthesis include azathioprine, methotrexate, mycophenolate mofetil (MMF) and mizoribine (bredinin). Inhibitors of pyrimidine synthesis include brequinar sodium and leflunomide. Cyclophosphamide is an inhibitor of both purine and pyrimidine synthesis.

Yet another method for inhibiting T cell activation is to treat the recipient with antibodies to T cells. OKT3 is a murine monoclonal antibody against CD3 which is part of the T cell receptor. This antibody inhibits the T cell receptor and suppresses T cell activation.

Numerous other drugs and methods for delaying allotransplant rejection are known to and used by those of skill in the art. One approach has been to deplete T cells, e.g., by irradiation. This has often been used in bone marrow transplants, especially if there is a

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partial mismatch of major HLA. Administration to the recipient of an inhibitor (blocker) of the CD40 ligand-CD40 interaction and/or a blocker of the CD28-B7 interaction has been used (U.S. Patent 6,280,957). Published PCT patent application WO 01/37860 teaches the administration of an anti-CD3 monoclonal antibody and IL-5 to inhibit the Th1 immune response. Published PCT patent application WO 00/27421 teaches a method for prophylaxis or treatment of corneal transplant rejection by administering a tumor necrosis factor-α antagonist. Glotz et al. (2002) show that administration of intravenous immunoglobulins (IVIg) can induce a profound and sustained decrease in the titers of anti-HLA antibodies thereby allowing a transplant of an HLA-mismatched organ. Similar protocols have included plasma exchanges (Taube et al., 1984) or immunoadsorption techniques coupled to immunosuppressive agents (Hiesse et al., 1992) or a combination of these (Montgomery et al., 2000). Changelian et al. (2003) teach a model in which immunosuppression is caused by an oral inhibitor of Janus kinase 3 (JAK3) which is an enzyme necessary for the proper signaling of cytokine receptors which use the common gamma chain (γc) (Interleukins-2, -4, -7, -9, -15, -21), the result being an inhibition of T cell activation. Antisense nucleic acids against ICAM-1 have been used alone or in combination with a monoclonal antibody specific for leukocyte-function associated antigen 1 (LFA-1) in a study of heart allograft transplantation (Stepkowski, 2000). Similarly, an anti-ICAM-1 antibody has been used in combination with anti-LFA-1 antibody to treat heart allografts (Stepkowski, 2000). Antisense oligonucleotides have additionally been used in conjunction with cyclosporin in rat heart or kidney allograft models, resulting in a synergistic effect to prolong the survival of the grafts (Stepkowski, 2000). Chronic transplant rejection has been treated by administering an antagonist of TGF-β which is a cytokine involved in differentiation, proliferation and apoptosis (U.S. Patent Application Publication US 2003/0180301).

Complement and Transplant/Graft Rejection

The role of complement in transplant rejection is well known. This is especially true in the case of xenotransplantation, but complement also plays a role in allotransplant rejection. For review, see Platt and Saadi, 1999. One aspect of complement's role is that ischemia-reperfusion injury may occur at the time that an organ graft is reperfused with the blood of the recipient. Complement may also cause some manifestations of allograft rejection.

The complement system is described in detail in U.S. Patent 6,355,245. The complement system acts in conjunction with other immunological systems of the body to

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defend against intrusion of cellular and viral pathogens. There are at least 25 complement proteins, which are found as a complex collection of plasma proteins and membrane cofactors. The plasma proteins make up about 10% of the globulins in vertebrate serum. Complement components achieve their immune defensive functions by interacting in a series of intricate but precise enzymatic cleavage and membrane binding events. The resulting complement cascade leads to the production of products with opsonic, immunoregulatory, and lytic functions.

The complement cascade progresses via the classical pathway or the alternative pathway. These pathways share many components and, while they differ in their initial steps, they converge and share the same "terminal complement" components (C5 through C9) responsible for the activation and destruction of target cells.

The classical complement pathway is typically initiated by antibody recognition of and binding to an antigenic site on a target cell. The alternative pathway is usually antibody independent and can be initiated by certain molecules on pathogen surfaces. Both pathways converge at the point where complement component C3 is cleaved by an active protease (which is different in each pathway) to yield C3a and C3b. Other pathways activating complement attack can act later in the sequence of events leading to various aspects of complement function.

C3a is an anaphylatoxin. C3b binds to bacterial and other cells, as well as to certain viruses and immune complexes, and tags them for removal from the circulation. C3b in this role is known as opsonin. The opsonic function of C3b is considered to be the most important anti-infective action of the complement system. Patients with genetic lesions that block C3b function are prone to infection by a broad variety of pathogenic organisms, while patients with lesions later in the complement cascade sequence, i.e., patients with lesions that block C5 functions, are found to be more prone only to Neisseria infection, and then only somewhat more prone (Fearon, 1983).

C3b also forms a complex with other components unique to each pathway to form classical or alternative C5 convertase, which cleaves C5 into C5a and C5b. C3 is thus regarded as the central protein in the complement reaction sequence since it is essential to both the alternative and classical pathways (Wurzner et al., 1991). This property of C3b is regulated by the serum protease Factor I, which acts on C3b to produce iC3b. While still functional as opsonin, iC3b cannot form an active C5 convertase.

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C5 is a 190 kDa beta globulin found in normal serum at approximately 75 μg/mL (0.4 μM). C5 is glycosylated, with about 1.5-3 percent of its mass attributed to carbohydrate. Mature C5 is a heterodimer of a 999 amino acid 115 kDa alpha chain that is disulfide linked to a 656 amino acid 75 kDa beta chain. C5 is synthesized as a single chain precursor protein product of a single copy gene (Haviland et al., 1991). The cDNA sequence of the transcript of this gene predicts a secreted pro-C5 precursor of 1659 amino acids along with an 18 amino acid leader sequence.

The pro-C5 precursor is cleaved after amino acid 655 and 659, to yield the beta chain as an amino terminal fragment (amino acid residues +1 to 655) and the alpha chain as a carboxyl terminal fragment (amino acid residues 660 to 1658), with four amino acids deleted between the two.

C5a is cleaved from the alpha chain of C5 by either alternative or classical C5 convertase as an amino terminal fragment comprising the first 74 amino acids of the alpha chain (i.e., amino acid residues 660-733). Approximately 20 percent of the 11 kDa mass of C5a is attributed to carbohydrate. The cleavage site for convertase action is at or immediately adjacent to amino acid residue 733. A compound that would bind at or adjacent to this cleavage site would have the potential to block access of the C5 convertase enzymes to the cleavage site and thereby act as a complement inhibitor.

C5 can also be activated by means other than C5 convertase activity. Limited trypsin digestion (Minta and Man, 1977; Wetsel and Kolb, 1982) and acid treatment (Yamamoto and Gewurz, 1978; Vogt et al., 1989) can also cleave C5 and produce active C5b.

C5a is another anaphylatoxin. C5b combines with C6, C7, and C8 to form the C5b-8 complex at the surface of the target cell. Upon binding of several C9 molecules, the membrane attack complex (MAC, C5b-9, terminal complement complex-TCC) is formed. When sufficient numbers of MACs insert into target cell membranes the openings they create (MAC pores) mediate rapid osmotic lysis of the target cells. Lower, non-lytic concentrations of MACs can produce other effects. In particular, membrane insertion of small numbers of the C5b-9 complexes into endothelial cells and platelets can cause deleterious cell activation. In some cases activation may precede cell lysis.

As mentioned above, C3a and C5a are anaphylatoxins. These activated complement components can trigger mast cell degranulation, which releases histamine and other mediators of inflammation, resulting in smooth muscle contraction, increased vascular

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permeability, leukocyte activation, and other inflammatory phenomena including cellular proliferation resulting in hypercellularity. C5a also functions as a chemotactic peptide that serves to attract pro-inflammatory granulocytes to the site of complement activation.

Complement-binding recipient antibodies to donor alloantigens are considered to be the main cause of hyperacute graft rejection. Owing to pretransplant crossmatch testing, this prototype of humoral rejection is now rarely observed (Regele et al., 2001). Data are now showing that humoral immune mechanisms might contribute to other types of allograft rejection (Regele et al., 2001). High levels of panel reactive antibodies indicating humoral presensitization were found to be associated with inferior kidney graft survival (Opelz, 1992), the appearance of alloantibodies during the post-transplant period has been reported to predict poor graft outcome (Jeannet et al., 1970; Halloran et al., 1992), and selective removal of recipient IgG by immunoadsorption reversed some rejection episodes indicating the contribution of humoral immune mechanisms to rejection (Persson et al., 1995; Böhmig et al., 2000). Complement activation within a graft might indicate antibody-mediated graft injury. The complement cleavage product C4d is a marker for activation of the antibody-dependent classical pathway. Capillary C4d deposits in kidney allograft biopsies were associated with poor graft outcome.

Recently increasing evidence indicates that complement activation significantly contributes to the sensitization of allograft recipients and the development of tissue injury in allografts (Platt et al., 1999). Antibodies are the most thoroughly investigated mediators of activating the classical complement pathway. Clinically, alloantibodies are known to activate complement (Baldwin et al., 2001). Halloran and Collins indicate that C4d deposition in peritubular capillaries of renal allografts is a sensitive and diagnostic marker of acute humoral rejection that correlates strongly with the presence of circulating donor-specific antibodies (Collins et al., 1999; Halloran, 2003). Further supporting evidence is seen in animals with complement inhibition (Pratt et al., 1996; Pruitt et al., 1991; Forbes et al., 1978) or deficiency (Pratt et al., 2000; Baurer et al., 1995) which exhibit significantly reduced inflammatory injury and lowered anti-donor immune responses. In ABMR, complement is suggested to be activated by the classical pathway and to play a key role in the pathogenesis (Collard et al., 1997). Although the role of complement in HAR or acute vascular rejection (AVR) following xenotransplantation has been well documented (Platt et al., 1999), precise mechanisms of complement in the pathogenesis of ABMR following allotransplantation has not yet been elucidated.

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The C5 component of complement is cleaved to form products with multiple proinflammatory effects and thus represents an attractive target for complement inhibition within the immune-mediated inflammatory response. As described above, C5a is a powerful anaphylatoxin and chemotactic factor. Cellular activation by C5a induces the release of multiple additional inflammatory mediators (Jose et al., 1983). The complement activation pathways (classical, alternative, or mannan-binding lectin pathway) ultimately lead to the formation of the cytolytic membrane attack complex C5b-9 (Kirschfunk, 2001), which can mediate both direct tissue injury by cell lysis, and proinflammatory cell activation at sublytic doses (Saadi et al., 1995; Papadimitriou et al., 1991). Therefore, blocking both C5a and C5b-9 generation may be required for the optimal inhibition of complement-mediated inflammatory response following transplantation. At the same time, inhibition of the complement cascade at C5 does not impair the generation of C3b, preserving C3b-mediated opsonization of pathogenic microorganisms as well as solubilization and clearance of immune complexes (Liszewski, 1993).

The beneficial effect of anti-C5 mAb has previously been reported in several experimental models including myocardial reperfusion (Vakeva et al., 1998), systemic lupus erythematosus (Wang et al., 1996) and rheumatoid arthritis (Wang et al., 1995); as well as in human clinical trials (Kirschfink, 2001) of autoimmune disease, cardiopulmonary bypass and acute myocardial infarction. In addition, complement inactivation by a functionally blocking anti-C5 monoclonal Ab (mAb) prevented HAR in xenotransplantation models (Kroshus et al., 1995; Wang et al., 1999).

Methods of delaying allotransplant rejection by administration of complement inhibitors have been tested. Published PCT patent application WO 92/10205 discloses the use of a combination of cyclosporin and a soluble complement receptor (sCR1) to inhibit rejection of a cardiac allotransplant in a presensitized rat model. Complement receptor 1 binds complements C3b and C4b. Soluble forms of complement receptor 1 occur naturally or can be generated via recombinant DNA procedures. These soluble complement receptors have inhibited in vitro the consequences of complement activation (U.S. Patent 6,057,131). In WO 92/10205, rats, which had been presensitized to the cardiac allograft they were receiving, were administered cyclosporin A intramuscularly at 10 mg/kg/day beginning two days prior to transplant and continued until the time of graft rejection. Additionally, soluble complement receptor 1 (sCR1) was administered as a single intravenous bolus at 15 mg/kg immediately prior to reperfusion of the graft. Control animals with no drug treatment had the

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graft rejected at an average of 3.8 days. Those administered cyclosporin A alone rejected the grafts at an average of 57 days (this was quite variable with two rats rejecting quickly at 2 and 4 days and a third rat rejecting at 166 days). Rats administered sCR1 alone rejected the grafts at an average of 44 days. Those rats administered the combination of cyclosporin A and sCR1 rejected the grafts at an average of 147 days. The combination of chronic cyclosporin A and single bolus sCR1 was seen to result in a synergistic effect greatly prolonging the time until graft rejection. Earlier studies by Pruitt and Bollinger (1991) used a similar model of a presensitized rat allograft to show that administration of sCR1 alone to inactivate complement resulted in increased time before graft rejection.

Sims et al. (U.S. Patent 5,135,916) suggest using inhibitors of complement, e.g., CD59 or antibodies against C7 or C9 to block the formation of the C5b-9 complex, to treat the vascular endothelium of organs and tissues to be transplanted. This would prevent the C5b-9 initiated cell necrosis. The C5b-9 inactivators would be added to the perfusate or storage medium to protect the vascular lining cells from ongoing complement activation during in vitro storage. Additionally the organ or tissue would be protected from the cytolytic and thrombotic effects arising from complement activation initiated upon transplantation, thereby circumventing complement mediated acute rejection. Sims et al. (U.S. Patent 5,573,940 and U.S. Patent 6,100,443) also teach a method of expressing CD59 in the transplanted tissue or organ to protect the transplanted organ from rejection. This can be accomplished by transfecting the cells being transplanted.

Although the several drugs developed to date in combination with methods of prescreening donors and recipients to match the donor allograft to the recipient have over time increased the average length of time of survival of allografts, many allografts are nonetheless rejected during the life-time of the recipient. In general, the prior art advances have mainly been directed to overcoming acute graft rejection. Further, the role of activated terminal complement components in antibody-mediated allograft rejection has not been examined using inhibitors that specifically target the complement cascade at the C5 protein level. The methods described herein and as exemplified in the Examples advance the allotransplant art by inhibiting chronic rejection of allografts, in particular, allografts in a presensitized recipient. New methods are presented for further prolonging allograft survival by using a proper combination of immunosuppressive drugs in combination with a chronic administration of a complement inhibitor.

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Methods and Uses

The methods disclosed herein are used to prolong allograft survival. The methods generally include administering an inhibitor of complement activity in combination with one or more immunosuppressants.

Suitable complement inhibitors are known to those of skill in the art. Antibodies can be made to individual components of activated complement, e.g., antibodies to C5a, C7, C9, etc. (see, e.g., U.S. Patent 6,534,058; published U.S. patent application US 2003/0129187; and U.S. Patent 5,660,825). Proteins are known which inhibit complement-mediated lysis, including CD59, CD55, CD46 and other inhibitors of C8 and C9 (see, e.g., U.S. Patent 6,100,443). U.S. Patent 6,355,245 teaches an antibody which binds to C5 and prevents it from being cleaved into C5a and C5b thereby preventing the formation not only of C5a but also the C5b-9 complex. Proteins known as complement receptors and which bind complement are also known (see, Published PCT Patent Application WO 92/10205 and U.S. Patent 6,057,131). Use of soluble forms of complement receptors, e.g., soluble CR1, can inhibit the consequences of complement activation such as neutrophil oxidative burst, complement mediated hemolysis, and C3a and C5a production. Those of skill in the art recognize the above as some, but not all, of the known methods of inhibiting complement and its activation.

Suitable immunosuppressants include, but are not limited to, ATG or ALG, OKT3, daclizumab, basiliximab, corticosteroids, 15-deoxyspergualin, cyclosporins, tacrolimus, azathioprine, methotrexate, mycophenolate mofetil, 6-mercaptopurine, bredinin, brequinar, leflunamide, cyclophosphamide, sirolimus, anti-CD4 monoclonal antibodies, CTLA4-Ig, anti-CD154 monoclonal antibodies, anti-LFA1 monoclonal antibodies, anti-LFA-3 monoclonal antibodies, anti-CD2 monoclonal antibodies, and anti-CD45.

An allograft can include a transplanted organ, part of an organ, tissue or cell. These include, but are not limited to, heart, kidney, lung, pancreas, liver, vascular tissue, eye, cornea, lens, skin, bone marrow, muscle, connective tissue, gastrointestinal tissue, nervous tissue, bone, stem cells, islets, cartilage, hepatocytes, and hematopoietic cells.

At least part of the reason for the failure of allografts is that one response by the recipient of an allograft is the activation of complement. This results in the formation of C5a and C5b-9 which are potent proinflammatory molecules which aid in causing graft failure. Without wishing to be bound by any proposed theory, Applicants theorized that inhibiting the

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formation of C5a and C5b-9 or inhibiting C5a and C5b-9 which was present would aid in preventing graft failure. Furthermore, it was theorized that so long as the allograft is present, the recipient will continue to attempt to mount an immune response against the graft, and this response will include attempts to produce C5a and C5b-9. If not prevented, this complement response will lead to acute vascular rejection in the short term and could contribute to chronic graft rejection in the long term. Prior art methods of using inhibitors of complement activity were limited to administering these inhibitors only at the time of transplant. This was helpful in preventing acute rejection, but as the results disclosed herein illustrate, improved results are obtained by administration of such inhibitors for a longer term. This long-term administration aids in preventing a chronic rejection of the allograft as opposed to only aiding in preventing an acute rejection. The result is a longer term survival of the allograft as compared to either not administering an inhibitor of complement activity or administering such an inhibitor only at the time of transplant of the allograft. Although very commonly it is desirable that the allograft will survive for the remaining lifetime of the recipient, there are times when the allograft is needed only for a shorter length of time, e.g., a bridge organ to bridge the time until the recipient's own organ can recover on its own, at which time the allograft will no longer be needed. The length of time such a graft will be needed will vary, but will usually be longer than the time at which acute rejection would occur and may be long enough for chronic rejection to occur. This period of desired survival for a bridge graft may be several months, e.g., six months.

To prove that long-term inhibition of complement activity will prolong allograft survival, experiments were performed in which complement activation was inhibited in a chronic fashion and not merely at the time of transplant. Chronic treatment means treatment during an extended period up to the lifetime of the allograft. This can be daily treatment but is not limited to daily treatment. Chronic treatment will maintain an effective amount of the drug in the allograft recipient. For example, a preferred method is to include the anti-C5 monoclonal antibody eculizumab in the treatment. In studies of persons suffering from paroxysmal nocturnal hemoglobinuria (PNH), eculizumab has been administered at a dose of 900 mg/patient once every 12-14 days. This dosing has been found to completely and consistently block terminal complement activity and has greatly inhibited the symptoms of PNH (Hillmen et al., 2004). The administered dose is able to block the effects of complement for approximately two weeks before the eculizumab is inactivated or removed from the body. Therefore, a chronic treatment of eculizumab may be, e.g., the administration

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of 900 mg to the allograft recipient once every two weeks for the remaining life-time of the patient. Similarly, other drugs can be delivered chronically as needed, whether this is on a daily basis or another schedule is required to maintain an effective amount of the drug in the allograft recipient. Because it is well known that graft rejection can be caused by more than just complement activation, e.g., by T cell activity, the experiments included immunosuppressants such as cyclosporin to further aid in preventing graft rejection.

A preferred method of inhibiting complement activity is to use a monoclonal antibody which binds to complement C5 and prevents C5 from being cleaved. This prevents the formation of both C5a and C5b-9 while at the same time allowing the formation of C3a and C3b which are beneficial to the recipient. Such antibodies that are specific to human complement are known (U.S. Patent 6,355,245). These antibodies disclosed in U.S. Patent 6,355,245 include both a whole or full-length antibody (now named eculizumab) and a single-chain antibody (now named pexelizumab). A similar antibody against mouse C5 is called BB5.1 (Frei et al., 1987). BB5.1 was utilized in the experiments set forth below. Antibodies to inhibit complement activity need not be monoclonal antibodies. They can be, e.g., polyclonal antibodies. They may additionally be antibody fragments. An antibody fragment includes, but is not limited to, an Fab, F(ab'), $F(ab')_2$, a single-chain antibody, a domain antibody and an Fv. Furthermore, it is well known by those of skill in the art that antibodies can be humanized (Jones et al., 1986), chimerized, or deimmunized. An antibody may also comprise a mutated Fc portion, such that the mutant Fc does not activate complement. The antibodies to be used in the present disclosure may be any of these. It is preferable to use humanized antibodies when the recipient of the allograft is a human.

Administration and Formulations

Administration of the inhibitor of complement activity is performed according to methods known to those of skill in the art. These inhibitors are administered preferably before the time of allograft transplantation or at the time of transplantation with administration continuing in a chronic fashion. These inhibitors can additionally be administered during a rejection episode in the event such an episode does occur.

The present disclosure also provides uses of a drug that inhibits complement activity and an immunosuppressive agent in the manufacture of a medicament or medicament package. Such medicament or medicament package is useful in prolonging allograft survival in a recipient, in particular, chronic survival of the allograft. In preferred embodiments, the

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medicament or medicament package is formulated and prepared such that it is suitable for chronic administration to the recipient of the allograft, for example, stable formulations are employed. In certain embodiments, the medicament or medicament package is formulated and prepared such that it is suitable for concurrent administration of the drug that inhibits complement activity and the immunosuppressive drug to the recipient of the allograft. In certain embodiments, the medicament or medicament package is formulated and prepared such that it is suitable for sequential (in either order) administration of the drug that inhibits complement activity and the immunosuppressive drug to the recipient of the allograft.

A pharmaceutical package of the present disclosure may comprise a drug that inhibits complement activity and at least one immunosuppressive agent. The pharmaceutical package may further comprise a label for chronic administration. The pharmaceutical package may also comprise a label for self-administration by a patient, for example, a recipient of a transplant graft, or instructions for a caretaker of a recipient of a transplant graft. In certain embodiments, the drug and the agent in the pharmaceutical package are in a formulation or separate formulations that are suitable for chronic administration and/or self-administration.

The present disclosure also provides lyophilized formulations and formulations suitable for injection. Certain embodiments provide a lyophilized antibody formulation comprising an antibody that inhibits complement activity and a lyoprotectant. In preferred embodiments, the antibody formulation is suitable for chronic administration, for example, the antibody formulation stable. Alternative embodiments provide an injection system comprising a syringe; the syringe comprises a cartridge containing an antibody that inhibits complement activity and is in a formulation suitable for injection.

An antibody employed in various embodiments of the present disclosure preferably inhibits the formation of terminal complement or C5a. In certain embodiments, antibody inhibits formation of terminal complement or C5a is a whole antibody or an antibody fragment. The whole antibody or antibody fragment may be a human, humanized, chimerized or deimmunized antibody or antibody fragment. In certain embodiments, the whole antibody or antibody fragment may inhibit cleavage of complement C5. In certain embodiments, the antibody fragment is a Fab, an F(ab')2, an Fv, a domain antibody, or a single-chain antibody. In preferred embodiments, the antibody fragment is pexelizumab. In alternative preferred embodiments, the whole antibody is eculizumab.

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In certain embodiments, a drug, such as an antibody, that inhibits complement activity is present in unit dosage form, which can be particularly suitable for self-administration. Similarly, an immunosuppressive agent of the present disclosure may also be present in unit dosage form. A formulated product of the present disclosure can be included within a container, typically, for example, a vial, cartridge, prefilled syringe or disposable pen. A doser such as the doser device described in U.S. Patent 6,302,855 may also be used, for example, with an injection system of the present disclosure.

A "stable" formulation is one in which the drug (e.g., an antibody) or agent therein essentially retains its physical and chemical stability and integrity upon storage. Various analytical techniques for measuring protein stability are available in the art and are reviewed in Peptide and Protein Drug Delivery, 247-301, Vincent Lee Ed., Marcel Dekker, Inc., New York, N.Y., Pubs. (1991) and Jones, A. Adv. Drug Delivery Rev. 10: 29-90 (1993). Stability can be measured at a selected temperature for a selected time period. For example, the extent of aggregation following lyophilization and storage can be used as an indicator of protein stability. For example, a "stable" formulation may be one wherein less than about 10% and preferably less than about 5% of the protein is present as an aggregate in the formulation. In other embodiments, any increase in aggregate formation following lyophilization and storage of the lyophilized formulation can be determined. For example, a "stable" lyophilized formulation may be one wherein the increase in aggregate in the lyophilized formulation is less than about 5% and preferably less than about 3%, when the lyophilized formulation is stored at 2-8 °C for at least one year. In other embodiments, stability of the protein formulation may be measured using a biological activity assay.

A "reconstituted" formulation is one which has been prepared by dissolving a lyophilized protein formulation in a diluent such that the protein is dispersed in the reconstituted formulation. The reconstituted formulation in suitable for administration (e.g. parenteral administration) to a patient to be treated with the protein of interest and, in certain embodiments of the invention, may be one which is suitable for subcutaneous administration.

An isotonic reconstituted formulation is preferable in certain embodiments. By "isotonic" is meant that the formulation of interest has essentially the same osmotic pressure as human blood. Isotonic formulations will generally have an osmotic pressure from about 250 to 350 mOsm. Isotonicity can be measured using a vapor pressure or ice-freezing type osmometer, for example.

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A "lyoprotectant" is a molecule which, when combined with a drug (e.g., antibody) of interest, significantly prevents or reduces chemical and/or physical instability of the drug (e.g., antibody) upon lyophilization and subsequent storage. Exemplary lyoprotectants include sugars such as sucrose or trehalose; an amino acid such as monosodium glutamate or histidine; a methylamine such as betaine; a lyotropic salt such as magnesium sulfate; a polyol such as trihydric or higher sugar alcohols, e.g. glycerin, erythritol, glycerol, arabitol, xylitol, sorbitol, and mannitol; propylene glycol; polyethylene glycol; Pluronics; and combinations thereof. The preferred lyoprotectant is a non-reducing sugar, such as trehalose or sucrose.

The lyoprotectant is added to the pre-lyophilized formulation in a "lyoprotecting amount" which means that, following lyophilization of the drug (e.g., antibody) in the presence of the lyoprotecting amount of the lyoprotectant, the drug (e.g., antibody) essentially retains its physical and chemical stability and integrity upon lyophilization and storage.

The "diluent" of interest herein is one which is pharmaceutically acceptable (safe and non-toxic for administration to a human) and is useful for the preparation of a reconstituted formulation. Exemplary diluents include sterile water, bacteriostatic water for injection (BWFI), a pH buffered solution (e.g. phosphate-buffered saline), sterile saline solution, Ringer's solution or dextrose solution.

A "preservative" is a compound which can be added to the diluent to essentially reduce bacterial action in the reconstituted formulation, thus facilitating the production of a multi-use reconstituted formulation, for example. Examples of potential preservatives include octadecyldimethylbenzyl ammonium chloride, hexamethonium chloride, benzalkonium chloride (a mixture of alkylbenzyldimethylammonium chlorides in which the alkyl groups are long-chain compounds), and benzethonium chloride. Other types of preservatives include aromatic alcohols such as phenol, butyl and benzyl alcohol, alkyl parabens such as methyl or propyl parahen, catechol, resorcinol, cyclohexanol, 3-pentanol, and m-cresol.

A "bulking agent" is a compound which adds mass to the lyophilized mixture and contributes to the physical structure of the lyophilized cake (e.g. facilitates the production of an essentially uniform lyophilized cake which maintains an open pore structure). Exemplary bulking agents include mannitol, glycine, polyethylene glycol and xorbitol.

Accordingly, a stable lyophilized antibody formulation can be prepared using a lyoprotectant (preferably a sugar such as sucrose or trehalose), which lyophilized formulation

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can be reconstituted to generate a stable reconstituted formulation having an antibody concentration which is significantly higher (e.g. from about 2-40 times higher, preferably 3-10 times higher and most preferably 3-6 times higher) than the antibody concentration in the pre-lyophilized formulation. Such high protein concentrations in the reconstituted formulation are considered to be particularly useful where the formulation is intended for subcutaneous administration. Despite the very high protein concentration in the reconstituted formulation, the reconstituted formulation can be stable (i.e. fails to display significant or unacceptable levels of chemical or physical instability of the protein) at 2-8 °C. for at least about 30 days. See U.S. Patent 6,821,515. In certain embodiments, the reconstituted formulation is isotonic.

When reconstituted with a diluent comprising a preservative (such as bacteriostatic water for injection, BWFI), the reconstituted formulation may be used as a multi-use formulation. Such a formulation is useful, for example, where a subject patient requires frequent administrations of the drug or antibody and/or agent to treat a chronic medical condition. The advantage of a multi-use formulation is that it facilitates ease of use for the patient, reduces waste by allowing complete use of vial contents, and results in a significant cost savings for the manufacturer since several doses are packaged in a single vial (lower filling and shipping costs).

The present disclosure also provides a method for preparing a formulation comprising the steps of: (a) lyophilizing a mixture of an antibody and a lyoprotectant; and (b) reconstituting the lyophilized mixture of step (a) in a diluent such that the reconstituted formulation is isotonic and stable.

An article of manufacture is also provided herein which comprises: (a) a container which holds a lyophilized mixture of an antibody and a lyoprotectant; and (b) instructions for reconstituting the lyophilized mixture with a diluent to a desirable antibody concentration in the reconstituted formulation. The article of manufacture may further comprise a second container which holds a diluent (e.g. bacteriostatic water for injection (BWFI) comprising an aromatic alcohol).

An injection system of the present disclosure may employ a medication delivery pen as described in U.S. Patent 5,308,341. Medication delivery pens have been developed to facilitate the self-administration of medication. A medication of the present disclosure can be a drug that inhibits complement activity, for example an antibody specific to complement C5,

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and/or an immunosuppressive agent. One medication delivery pen includes a vial holder into which a vial of insulin or other medication may be received. The vial holder is an elongate generally tubular structure with proximal and distal ends. The distal end of the vial holder includes mounting means for engaging a double-ended needle cannula. The proximal end also includes mounting means for engaging a pen body which includes a driver and dose setting apparatus. A disposable medication containing vial for use with the prior art vial holder includes a distal end having a pierceable elastomeric septum that can be pierced by one end of a double-ended needle cannula. The proximal end of this vial includes a stopper slidably disposed in fluid tight engagement with the cylindrical wall of the vial. This medication delivery pen is used by inserting the vial of medication into the vial holder. A pen body then is connected to the proximal end of the vial holder. The pen body includes a dose setting apparatus for designating a dose of medication to be delivery by the pen and a driving apparatus for urging the stopper of the vial distally for a distance corresponding to the selected dose.

The user of the pen mounts a double-ended needle cannula to the distal end of the vial holder such that the proximal point of the needle cannula pierces the septum on the vial. The patient then selects a dose and operates the pen to urge the stopper distally to deliver the selected dose. The dose selecting apparatus returns to zero upon injection of the selected dose. The patient then removes and discards the needle cannula, and keeps the prior art medication delivery pen in a convenient location for the next required medication administration. The medication in the vial will become exhausted after several such administrations of medication. The patient then separates the vial holder from the pen body. The empty vial may then be removed and discarded. A new vial can be inserted into the vial holder, and the vial holder and pen body can be reassembled and used as explained above.

Accordingly, a medication delivery pen generally has a drive mechanism for accurate dosing and ease of use. A dosage mechanism such as a rotatable knob allows the user to accurately adjust the amount of medication that will be injected by the pen from a prepackaged vial of medication. To inject the dose of medication, the user inserts the needle under the skin and depresses the knob once as far as it will depress. The pen may be an entirely mechanical device or it may be combined with electronic circuitry to accurately set and/or indicate the dosage of medication that is injected into the user. See U.S. Patent 6,192,891.

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The present disclosure also presents controlled-release or extended-release formulations suitable for chronic and/or self-administration of a medication.

The various formulations can be administered to a patient in need of treatment (e.g., a recipient of an allograft) with the medication (e.g., an antibody of the present disclosure and at least one immunosuppressive agent) by intravenous administration as a bolus or by continuous infusion over a period of time, by intramuscular, intraperitoneal, intracerobrospinal, subcutaneous, intra-articular, intrasynovial, intrathecal, oral, topical, or inhalation routes.

In certain embodiments, a formulation is administered to the patient by subcutaneous (i.e. beneath the skin) administration. For such purposes, the formulation may be injected using a syringe. However, other devices for administration of the formulation are available such as injection devices (e.g. the Inject-ease® and Genject® devices); injector pens (such as the GenPen®); needleless devices (e.g. MediJector® and BioJector®); and subcutaneous patch delivery systems.

The present methods and uses are described with reference to the following Examples, which are offered by way of illustration and are not intended to limit the disclosure in any manner. Standard techniques well known in the art or the techniques specifically described below are utilized. The following abbreviations are used herein: ABMR, antibody-mediated rejection; ACHR, accelerated humoral rejection; ACR, acute cellular rejection; AVR, acute vascular rejection; CsA, cyclosporin; CyP, cyclophosphamide; HAR, hyperacute rejection; MCP-1, monocyte chemotactic protein 1; MST, mean survival time; POD, postoperative day.

Example 1

Methods

Animals and Immunosuppressive Drugs Male adult C3H (H-2^k) mice and BALB/c (H-2^d) mice (Jackson Labs, Bar Harbor, Maine) weighing 25-30 g were chosen as donors and recipients, respectively. In the groups receiving immunosuppression, the recipients were injected with CsA (15 mg/kg/day, s.c., daily from day 0 to endpoint rejection or until day 100), or with CyP (40 mg/kg/day, i.v., on day 0 and 1), or with anti-C5 mAb (clone BB5.1, Alexion Pharmaceuticals Inc., 40 mg/kg/day, i.p., day 0–2, followed by twice a week, day 0-60). Animals were housed under conventional conditions at the Animal Care Facility,

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University of Western Ontario, and were cared for in accordance with the guidelines established by the Canadian Council on Animal Care. Olfert et al., 1993.

Skin Presensitization Full-thickness skin grafts taken from C3H donors were cut into square pieces of 1×1 cm^2 and transplanted onto the back of the BALB/c recipients' thorax one week prior to heart transplantation from the same donors. Rejection was defined as complete necrosis of the skin grafts.

Abdominal and Cervical Cardiac Transplantation Seven days after skin presensitization, C3H mouse hearts were transplanted into the abdomen of presensitized BALB/c recipients by anastomosing the donor aorta and recipient aorta, and the donor pulmonary artery and recipient inferior vena cava. In the groups with re-transplantation, second heart grafts harvested from either naive C3H mice or long-term surviving presensitized BALB/c recipients were transplanted into the cervical area of the recipients carrying a long-term surviving first abdominal heart graft by anastomosing the donor aorta and recipient carotid artery, and the donor pulmonary artery and recipient external jugular vein (end-to-side). The heart grafts were monitored daily until rejection unless otherwise indicated and rejection was defined as complete cessation of pulsation.

Experimental Groups Presensitized recipients were randomly assigned to eight groups, each consisting of eight animals: Group 1, mice with no treatment; Group 2, mice treated with CsA; Group 3, mice treated with CyP; Group 4, mice treated with CsA plus CyP; Group 5, mice treated with anti-C5 mAb; Group 6, mice treated with anti-C5 mAb plus CsA; Group 7, mice treated with anti-C5 mAb plus CyP; Group 8, mice treated with anti-C5 mAb in combination of CsA and CyP. When cardiac impulses were no longer palpable or at POD100, the grafts were removed for routine histology, immunohistochemistry and western blot analysis, serum samples were collected for flow cytometric analysis and complement hemolytic assay. Five additional animals were placed and sacrificed in groups 6 and 8 on POD3 (MST for groups 1-5, 7) to allow for comparisons at a uniform time point. Serum samples were also collected on POD 11, 21, 28 and 60 in Group 8 for detecting the sequential changes of anti-donor antibody levels and complement activity. In addition, when triple therapy treated presensitized recipients carried a first heart graft for 100 days, they were re-transplanted with a second heart. A naive C3H heart or a 100-day surviving C3H heart from another presensitized BALB/c recipient was used as the second heart. Eight animals were included in each re-transplant group.

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Graft Histology Tissue samples were fixed in 10% buffered formaldehyde. Specimens were then embedded in paraffin, and sectioned for H&E staining. The microscopic sections were examined in a blinded fashion for severity of rejection by a pathologist. Criteria for graft rejection included the presence of vasculitis, thrombosis, hemorrhage and lymphocyte infiltration. These changes were scored as: 0, no change; 1, minimum change; 2, mild change; 3, moderate change; or 4, marked change.

Immunohistochemistry Four micrometer sections were cut from tissue samples embedded in Tissue-Tek O.C.T gel (Optimum Cutting Temperature, Skura Finetek, Torrance, CA) mounted on gelatin-coated glass microscope slides and stained by a standard indirect avidin-biotin immunoperoxidase staining method using an Elite Vectastain ABC kit (Vector Laboratories Inc., Burlingame, CA). Specimens were stained for $CD4^+$ and $CD8^+$ cells with biotin-conjugated rat anti-mouse CD4 mAb (clone YTS 191.1.2, Cedarlane Laboratories Ltd., Hornby, Ontario, Canada) and biotin-conjugated rat anti-mouse CD8 mAb (clone 53-6.7, Pharmingen, Franklin Lakes, NJ), respectively. Intragraft monocyte/macrophage infiltration was detected by staining with biotin-conjugated rat anti-mouse Mac-1 mAb (Cedarlane Laboratories Ltd., Hornby, Ontario, Canada). Mouse IgG and IgM deposition in grafts was detected using biotin-conjugated goat anti-mouse-IgG and goat anti-mouse-IgM (Cedarlane). For identification of complement deposition, sections were serially incubated with goat anti-C3 or anti-C5 polyclonal Abs (Quidel, San Diego, CA), biotinylated rabbit anti-goat IgG (Vector Laboratories), and HRP-conjugated-streptavidin (Zymed Laboratories, South San Francisco, CA). Slides were washed with phosphate-buffered saline between steps, and examined under light microscopy. Negative controls were performed by omitting the primary antibodies. The immunostaining was scored in five high-power fields of each section, and five independent experiments were performed. The sections of immunoperoxidase staining were graded from 0 to 4+ according to the staining intensity: 0, negative; 1+, equivocal; 2+, weak staining; 3+, moderate staining; and 4+, very intensive staining.

Flow Cytometry The circulating anti-donor specific IgG and IgM antibodies were evaluated in the recipient serum by FACScan flow cytometry (Becton Dickinson, Mountain View, CA). Glotz et al., (1993); Tyan et al. (1994). Briefly, C3H mouse splenocytes were isolated and incubated at 37 °C for 30 minutes with serum from naive control and experimental groups. To stain for total IgG, IgG1, IgG2a, IgG2b and IgM, the cells were washed and incubated with FITC-conjugated goat antibody specific for the Fc portion of mouse IgG or with

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phycoerythrin-conjugated goat antibody specific for the μ-chain of mouse IgM (Jackson ImmunoResearch Laboratories, West Grove, PA), or with FITC-conjugated goat anti-mouse IgG1 (CALTAG Laboratories, Burlingame, CA), or with FITC-conjugated goat anti-mouse IgG2a (CALTAG), or with FITC-conjugated goat anti-mouse IgG2b (CALTAG). After 1 hour of staining at 4 °C, the cells were washed with PBS, resuspended at 5×10^6/mL, and analyzed by flow cytometry for mean channel fluorescence intensity, which represents the antibody-binding reactivity.

Complement Hemolytic Assay The purified anti-C5 mAb was serially diluted twofold (175-0.1 μg/ml) in GVB^{2+} buffer (gelatin Veronal-buffered saline: 0.1% gelatin, 141 mM NaCl, 0.5 mM $MgCl_2$, 0.15 mM $CaCl_2$, and 1.8 mM sodium barbital) and added in triplicate (50 μl/well) to a 96-well plate. BALB/c mouse serum was diluted to 40% v/v with GVB^{2+} buffer and added (50 μl/ml) to the rows of the same 96-well plate such that the final concentration of BALB/c mouse serum in each well was 20%. The plate was then incubated at room temperature for approximately 30 min while chicken erythrocytes were prepared. Chicken erythrocytes were washed 5×1 ml with GVB^{2+} buffer and resuspended to a final concentration of 5×10^7/ml in GVB^{2+}. Four milliliters of the chicken erythrocytes were sensitized by adding anti-chicken RBC polyclonal antibody (Intercell Technologies, Hopewell, NJ, 0.1% v/v) and the cells were incubated at 4 °C for 15 min with frequent vortexing. The cells were then washed 2×1 ml with GVB^{2+} and resuspended to a final volume of 2.4 ml in GVB^{2+}. The chicken erythrocytes (30 μl/well, 2.5×10^6 cells) were added to the plate containing serum and anti-C5 mAb as described above, mixed well, and incubated at 37 °C for 30 min. The plate was then centrifuged at 1000×g for 2 min, and 85 μl of the supernatant was transferred to a new 96-well microtiter plate. The plate was read at OD 415 nm using a microplate reader and the percentage of hemolysis was determined using this formula:

$$\%\ \text{hemolysis} = 100 \times \frac{(\text{OD sample}) - (\text{OD } GVB^{2+} \text{ control})}{(\text{OD 100\% lysed control}) - (\text{OD } GVB^{2+} \text{ control})}$$

with 100% lysed control obtained by the addition of 100 μl GVB^{2+} containing 0.1% NP-40 to the 30 μg/ml of chicken erythrocytes as prepared above.

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Western Blot Analysis Sonication of frozen heart samples was performed in RIPA lysis buffer (Santa Cruz Biotechnology, Inc.) at 4 °C for 1 minute at 10-second intervals, followed by microcentrifugation at 13,000 rpm for 10 minutes at 4 °C. Clarified supernatants were immediately quantitated in triplicate for protein content using Detergent-compatible protein assay kit (BIO-RAD). Heart lysates (10μg protein/well) were separated on NuPAGE, 4-12% gradient Bis-Tris gels and MES buffer system (Invitrogen) and transferred to polyvinylidene difluoride (PVDF) membrane (0.45 μm pore size; Invitrogen) using a semi-dry transfer apparatus (BIO-RAD). Membranes were cut appropriately at the correct molecular weights to allow the development of the blots with two different primary antibodies per blot such that each blot was exposed to a test antibody and an internal control antibody to insure equal sample loading. The test primary antibodies including anti-Bcl-2 (N-19) rabbit polyclonal sera (Santa Cruz Biotechnology, Inc.) and anti-Bcl-XS/L (M-125) rabbit polyclonal sera (Santa Cruz Biotechnology, Inc.) were used to detect intragraft expression of Bcl-2 and Bcl-xl proteins. Anti-calsequestrin rabbit polyclonal sera (Calbiochem) were used as internal control primary antibody (Kobayashi et al., 1999). Detection of primary antibody binding was performed as previously described (Arp et al., 1996) by exposing washed incubated blots to a polyclonal goat anti-rabbit IgG fraction conjugated to horseradish peroxidase (HRP; Roche Laboratories) and then appropriately developed by exposure to enhance chemiluminescence for HRP-conjugated antibodies (Roche Laboratories).

Statistical Analysis The data were reported as the mean ± SD. Allograft survival among experimental groups was compared using the rank-log test. Histological and immunohistological findings were analyzed using the Mann-Whitney U test. Flow cytometric data and western blot data were analyzed using one-way ANOVA. Differences with p values less than 0.05 were considered significant.

Example 2

Presensitization with C3H donor skin graft induces antibody-mediated ACHR in heart allografts of BALB/c recipients.

To develop a suitable small animal model that mimics presensitized patients in the clinic and to study ABMR, a novel, fully MHC-mismatched mouse ABMR model has been developed through presensitization of mouse recipients. In this model, BALB/c recipients were presensitized with C3H donor skin grafts one week prior to heart transplantation from the same donor. Seven days after donor skin presensitization, serum level of anti-donor IgG,

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but not IgM antibody was markedly elevated and reached to a peak level in the presensitized BALB/c recipients (Figure 1A). Heart transplantation from same donor was then performed in these highly sensitized recipients. Without immunosuppression, C3H heart grafts were rapidly rejected in 3.1 ± 0.4 days by ACHR, characterized by severe thrombosis, hemorrhage and infarction (Figure 1B-a). In contrast, same heart grafts in unsensitized BALB/c recipients (with mean survival time, MST of 8.2 ± 0.8 days) show the normal histology on post-operative day (POD) 3 (Figure 1B-b). When compared to unsensitized BALB/c recipients at the same day, heart grafts in presensitized animals revealed massive IgG antibody and complement (C3 and C5) deposition, but minimal $CD4^+$ and $CD8^+$ cell infiltration (Table 1). Furthermore, circulating anti-donor IgG levels in presensitized recipients were significantly higher than those of unsensitized same recipients receiving a heart graft on POD3 ($P< 0.01$, Figure 1C). However, anti-donor IgM remained at very low levels both in circulation (Figure 1C) and in heart grafts (Table 1) and it showed no significant difference between unsensitized and presensitized recipients. In addition, normal levels of complement hemolytic activity were shown in both presensitized and unsensitized heart recipients without treatment (Figure 1D). These data indicate that this is an ideal transplant model to study ABMR in presensitized recipients in which complement plays an important role in the pathogenesis.

Table 1.

Comparison of immunohistological changes of C3H heart allografts in unsensitized and presensitized BALB/c recipients on POD3

Groups	Unsensitized	Presensitized
IgG	1+	4+
IgM	1+	1+
C3	2+	3+
C5	2+	3+
CD4	0	1+
CD8	0	1+

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Grades for immunoperoxidase staining: 0, negative; 1+, equivocal; 2+, weak; 3+, moderate; 4+, intense.

Anti-C5 mAb in combination with CsA and CyP prevents ABMR and achieves indefinite heart allograft survival in presensitized mouse recipients.

Complement has been shown to play an important role in ABMR. However, the inhibitory effect of functionally blocking terminal complement cascade at the C5 level in highly sensitized recipients is unknown. In the study presented herein, the presensitized model was used to study the efficacy of anti-C5 mAb either alone or combined with CsA and /or CyP in prevention of ABMR. As presented in Figure 2A, treatment with either CsA or CyP or the two drugs in combination did not prevent ABMR and grafts were rejected in 3.0 ± 0.0 days, 3.3 ± 0.5 days and 3.5 ± 0.6 days, respectively with typical pathological features of ACHR including intravascular thrombosis and interstitial hemorrhage (Figure 2B-b, c, d), which were indistinguishable from heart grafts in untreated presensitized BALB/c recipients (Figure 2B-a). Anti-C5 monotherapy or combined with CyP was not able to improve graft survival and heart grafts were rejected by ACHR (Figure 2B-e, f) in 3.5 ± 0.6 days and 3.2 ± 0.4 days, respectively (Figure 2A). Although the combination therapy of anti-C5 mAb and CsA, the protocol capable of inducing long-term heart allograft survival in unsensitized animals, marginally prolonged graft survival in this presensitized model, heart grafts were also rejected by severe humoral rejection with vasculitis, thrombosis, hemorrhage and minimal cell infiltration (Figure 2B-g) in 11.9 ± 1.8 days (Figure 2A). In contrast, triple therapy of anti-C5 mAb in combination of CsA and CyP achieved indefinite heart graft survival over 100 days (Figure 2A) in presensitized animals ($P<0.01$ vs. the animals without treatment or treated with either monotherapy or two drugs in combination) with no evidence of rejection (Figure 2B-h). In this presensitized mouse model, as shown in Table 2, only minor intragraft $CD4^+$ and $CD8^+$ cell infiltration was observed in the recipients that rejected their heart grafts within 3 days. However, the number of these T cells was slightly increased if heart grafts survived longer in anti-C5 mAb plus CsA-treated recipients at the time of rejection (POD11) and in triple therapy-treated recipients at early stages of graft survival (e.g. POD11). Furthermore, with continuous treatment of CsA in the triple therapy group, $CD4^+$ and $CD8^+$ cell infiltration was inhibited in long-term surviving heart grafts on POD60 and 100. In addition, moderate intragraft Mac-1^+ cell infiltration, including monocytes and macrophages, was found in untreated and CsA-, CyP- or CsA plus CyP-treated animals,

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while the infiltration of these cells was significantly reduced in anti-C5 mAb treated animals (Table 2). These results indicate that functionally blocking anti-C5 mAb enables the use and efficacy of conventional immunosuppressive agents, thereby preventing ABMR and achieving indefinite heart graft survival in presensitized recipients.

Table 2.

Grades for immunoperoxidase staining of heart allografts

in presensitized mouse recipients at necropsy

Groups	Date for sample collection (POD)	C3	C5	**CD4**	CD8	Mac-1	IgG	IgM
Untreated	3	3+	3+	1+	1+	3+	4+	1+
CsA	3	3+	3+	1+	1+	3+	4+	1+
CyP	3	3+	3+	1+	1+	3+	3+	1+
CsA+CyP	3	3+	3+	1+	1+	3+	3+	1+
Anti-C5mAb	3	3+	0	1+	1+	2+	4+	1+
Anti-C5mAb+CsA	11	3+	0	2+	2+	2+	4+	1+
Anti-C5mAb+CyP	3	3+	0	1+	1+	2+	3+	1+
Anti-C5mAb+CsA+CyP	3	3+	0	1+	1+	2+	3+	1+
Anti-C5mAb+CsA+CyP	11	3+	0	2+	2+	1+	3+	1+
Anti-C5mAb+CsA+CyP	60	3+	0	1+	1+	0	2+	1+
Anti-C5mAb+CsA+CyP	100	3+	2+	0	0	0	2+	1+

Grades: 0, negative; 1+, equivocal; 2+, weak; 3+, moderate; 4+, intense.

Anti-C5 mAb completely inhibits total complement hemolytic activity and local C5 deposition in presensitized recipients receiving a heart allograft.

Anti-C5 mAb was previously shown to block the cleavage of complement protein C5 into the proinflammatory molecules C5a and C5b-9 (Kroshus et al., 1995), and to completely and consistently block terminal complement activity in mice (Wang et al., 1999). In the current study, terminal complement activity was measured by assessing the ability of

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recipient mouse sera to lyse antibody presensitized chicken erythrocytes and was compared at the same time-point (POD3). Treatment of mice with either CsA or CyP or the two drugs in combination had no effect on terminal complement activity, while treatment with anti-C5 mAb either alone or combined with CsA or/and CyP completely inhibited this activity (Figure 3; $P<0.01$, vs. naive and untreated animals, as well as CsA-, CyP-, or CsA plus CyP-treated animals). In addition, sera obtained from anti-C5 mAb treated animals at several earlier time points showed similarly diminished hemolytic activity, suggesting that serum terminal complement was inhibited throughout the treatment period. Furthermore, local C5 deposition in heart grafts was completely prevented in the anti-C5 mAb treated presensitized recipients, but not in untreated, or CsA-, CyP- and CsA plus CyP-treated presensitized animals (Table 2). As predicted, treatment with anti-C5 mAb did not prevent C3 deposition in the grafts (Table 2). These results suggest anti-C5 therapy completely blocks total complement activity after cardiac allografting in highly sensitized recipients.

Long-term surviving heart grafts in presensitized animals are resistant to humoral injury in the presence of low level of anti-donor antibodies and complement- a situation of accommodation.

To further investigate the role of anti-C5 mAb in humoral rejection, anti-donor alloantibody levels were measured in recipient sera by flow cytometry and intragraft antibody deposition by using immunostaining techniques in different groups. Figure 4A shows that on POD3 untreated presensitized BALB/c recipients had high levels of circulating anti-donor IgG antibodies. When presensitized recipients receiving either monotherapy or two drugs in combination, CsA and/or CyP partially down-regulated circulating anti-donor IgG levels, while treatment with anti-C5 mAb either alone or combined with CsA or CyP did not further affect anti-donor antibody levels at the same day. In contrast, with triple therapy of anti-C5 mAb, CsA and CyP, a high level of circulating anti-donor IgG was gradually downregulated and reached a low level on POD60, thereafter remaining at this level until day 100 (Figure 4B). Similar to levels of circulating antibodies in the different treatment groups, Table 2 shows that strong deposition of anti-mouse IgG was present in the rapidly rejected heart grafts of presensitized animals with no treatment or treated with monotherapy or two drugs in combination therapy. Interestingly, with triple therapy, IgG antibody deposition was gradually attenuated to a mild level in the long-term surviving heart grafts on POD 100 (Figure 4C-a, Table 2). In this model, IgM remained at very low levels in either circulation (Figure 4A, B) or transplanted heart grafts (Figure 4C-b, Table 2) in presensitized recipients

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with or without treatment. In addition, treatment with anti-C5 mAb eliminated complement activity to an undetectable level until day 60, followed by a progressive recovery to predepletion levels on POD 100 after discontinuation of anti-C5 therapy in presensitized mouse recipients receiving triple therapy (Figure 4D). Furthermore, intragraft C5 deposition was also detected in 100-day surviving presensitized animals (Table 2). These data demonstrate that ongoing transplant accommodation occurs in triple therapy treated presensitized recipients despite the presence of anti-graft antibodies and complement activation.

Anti-C5 mAb in combination with CsA and CyP reduces the IgG1/IgG2a ratio and leads to a shift in IgG subclass to IgG2b in recipients with accommodated grafts.

To determine whether anti-C5 mAb-based triple therapy would induce a shift in IgG subclass, which may be associated with accommodation, serum levels of anti-donor IgG subclasses of IgG1, IgG2a and IgG2b were compared between untreated recipients and the recipients with accommodated heart graft. Sera from untreated recipients contained predominant IgG1 isotype, indicated by a high ratio of IgG1/IgG2a (Figure 5A). In contrast, a significant reduction in the ratio of IgG1/IgG2a was observed in the recipients carrying accommodated grafts (Figure 5A, $P<0.01$). Furthermore, presensitized recipients with the accommodated heart grafts displayed an increased level of anti-donor IgG2b as compared to the same recipients with rejected grafts (Figure 5B, $P<0.01$). In addition, the pattern of IgG isotypes in the recipients treated with either monotherapy or two drugs in combination is indistinguishable from that of untreated animals. These data indicate that anti-donor IgG1 isotype may be associated with graft rejection, while production of anti-donor IgG2b subclass may function as a protective antibody and plays an important role in the induction of accommodation.

Anti-C5 mAb in combination with CsA and CyP induces intragraft Bcl-2 and Bcl-xl expression in highly sensitized mouse recipients.

To determine whether a causal relationship exists between intragraft expression of protective proteins and graft resistance to humoral injury in this model, western blot analysis was employed to detect proteins of interest in heart graft tissues from highly sensitized mouse recipients. Long-term surviving heart grafts were found to express high levels of Bcl-2 and Bcl-xl proteins on POD100, and these proteins were detected as early as 12 days after heart transplantation in highly sensitized recipients receiving anti-C5 mAb-based triple therapy

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(Figure 6). In contrast, there were no Bcl-2 and Bcl-xl proteins expressed on heart grafts of untreated animals (Figure 6) or animals treated with either monotherapy or two drugs in combination therapy. This result suggests that graft resistance to humoral injury in indefinite surviving animals is associated with the protection provided by Bcl-2 and Bcl-xl proteins in this presensitized model.

Presensitized recipients with an accommodating first heart graft accept a second accommodated heart graft but reject a second naive heart graft from the same donors.

The ability of accommodated grafts to resist rejection has not been tested directly under pathophysiological conditions where naive grafts undergo rejection following allotransplantation. In this model, to determine whether presensitized recipients with an accommodating first heart graft will accept a second accommodated graft but reject a second naive graft, we performed re-transplantation scenarios. After the accommodated C3H heart grafts have survived to the 100-day point, the time at which low levels of alloantibodies were detected (Figure 4B) and complement activity has returned to pretreatment levels (Figure 4D), in presensitized BALB/c recipient treated with anti-C5 mAb-based triple therapy, these recipients received a second heart graft. Specifically, either a naive (Figure 7A) or a 100-day accommodated C3H heart (Figure 7B) from another presensitized BALB/c recipient was transplanted into the neck of the presensitized recipients carrying an accommodating first C3H heart. These recipients rejected a second naive heart at 6.6 ± 1.1 days (Figure 8A) with severe AVR (Figure 8B-a) while the first heart continued to survive. In contrast, when the accommodated hearts that had been already surviving for 100 days in different presensitized mice were used as second grafts, these grafts were accepted by the presensitized recipients carrying an accommodating first heart graft (Figure 8A). There was no sign of rejection in those accommodated second heart grafts 90 days after second transplantation (Figure 8B-b). These data indicate that accommodated grafts become resistant to the effects of anti-donor antibodies and complement that normally mediate allograft rejection in these presensitized recipients. Furthermore, the fact that the host of the accommodated graft rejected a new graft suggests that accommodation involves changes to the graft.

Presensitized recipients being treated with CsA reject accommodated heart grafts.

Another re-transplantation was performed to determine whether accommodation in this presensitized model would be caused by the changes in the grafts and/or the recipients. Specifically, after C3H heart grafts have been accommodated in presensitized BALB/c mice

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for 100 days, the accommodated heart graft will then be re-transplanted into a second presensitized BALB/c recipient being treated with CsA alone (Figure 7C), a therapy that can prevent cellular rejection but cannot prevent accelerated humoral rejection of a fresh C3H heart in presensitized recipients. The accommodated C3H heart grafts were rapidly rejected in CsA treated presensitized BALB/c recipients. After re-transplantation, the pathology in accommodated heart grafts was changed from normal (Figure 9A) to severe ACHR with massive interstitial hemorrhage but few cell infiltrates (Figure 9B). In addition, high levels of anti-donor IgG and normal levels of complement hemolytic activity in these recipients receiving an accommodated C3H heart were similar to those of CsA treated presensitized recipients receiving a naive C3H heart. This result further indicates that accommodation induced by anti-C5 mAb-based triple therapy can originate from mechanisms involving changes not only to the graft, but also to the recipient.

Example 3

Acute Vascular Rejection in a Heart Transplantation Model

Experiments were performed to determine whether inclusion of an inhibitor of formation of terminal complement would attenuate acute vascular rejection and whether the use of such an inhibitor in conjunction with an immunosuppressant would achieve long-term allograft survival. In this set of experiments an anti-C5 monoclonal antibody was used in conjunction with cyclosporin. The model used was an allograft heterotopic heart transplant from C3H mice into BALB/c mice. This model is a stringent acute vascular rejection model with the C3H and BALB/c mice being strongly MHC mismatched. The transplantations and other methods were performed as described in Wang et al. (2003).

Heterotopic Cardiac Transplantation

Intra-abdominal heterotopic cardiac transplantation was performed as previously described by Wang et al. (2003). Briefly, a median sternotomy was performed on the donor, and the heart graft was slowly perfused in situ with 1.0 ml of cold heparinized Ringer's lactate solution through the inferior vena cava and aorta before the superior vena cava and pulmonary veins were ligated and divided. The ascending aorta and pulmonary artery were transected, and the graft was removed from the donor. The graft was then revascularized with end-to-side anastomoses between the donor's pulmonary artery and the recipient's inferior vena cava as well as the donor's aorta and the recipient's abdominal aorta using 11-0 nylon suture. The beating of the grafted heart was monitored daily by direct abdominal palpation.

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The degree of pulsation was scored as: A, beating strongly; B, noticeable decline in the intensity of pulsation; or C, complete cessation of cardiac impulses. When cardiac impulses were no longer palpable, the graft was removed for routine histology. In certain instances, mice in which the graft was still functioning were sacrificed to perform histology.

Results

Mice (male 8-12 week old mice weighing 25 – 30 g) were split into six experimental groups with six to eight mice per group. Transplant occurred on day 0. Histological changes were checked at the endpoint (the endpoint being graft failure) or in some cases a mouse was sacrificed prior to graft failure. The dosage of BB5.1 which was administered (40 mg/kg body weight three times per week) was known from prior studies to completely inhibit terminal complement activity.

Group 1' (control) - mice were administered 0.75 mL of saline intraperitoneally on days -1, 0, 1 and 2. Subsequently these mice were treated with 0.75 mL of saline intraperitoneally three times per week (Monday, Wednesday, Friday) until the endpoint.

Group 2' (cyclosporin A alone) - mice were administered 15 mg/kg body weight of cyclosporin A subcutaneously on a daily basis beginning at day 0 (day of transplant) until the endpoint.

Group 3' (anti-complement antibody alone) - mice were administered the anti-mouse C5 antibody BB5.1 (Frei et al., 1987) at 40 mg/kg body weight intraperitoneally on days -1, 0, 1 and 2 followed by 40 mg/kg body weight administered three times per week (Monday, Wednesday, Friday) until the endpoint.

Group 4' (anti-complement antibody until day 14 post-transplant plus cyclosporin A) - mice were administered the anti-mouse C5 antibody BB5.1 at 40 mg/kg body weight intravenously on days -1 through day 14 and were also administered cyclosporin A at 15 mg/kg of body weight on a daily basis beginning at day 0 until the endpoint. Note that this differs from the other groups in that the BB5.1 was administered intravenously and on a daily basis.

Group 5' (anti-complement antibody until day 28 post-transplant plus cyclosporin A) - mice were administered the anti-mouse C5 antibody BB5.1 at 40 mg/kg body weight intraperitoneally on days -1, 0, 1 and 2 followed by 40 mg/kg body weight administered three times per week (Monday, Wednesday, Friday) until day 28 and were also administered

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cyclosporin A at 15 mg/kg of body weight on a daily basis beginning at day 0 until the endpoint.

Group 6' (anti-complement antibody chronically until 100 days plus cyclosporin) - mice were administered the anti-mouse C5 antibody BB5.1 at 40 mg/kg body weight intraperitoneally on days -1, 0, 1 and 2 followed by 40 mg/kg body weight administered three times per week (Monday, Wednesday, Friday) until 100 days and were also administered cyclosporin A at 15 mg/kg of body weight on a daily basis beginning at day 0 until 100 days.

The results of this experiment are shown in Tables 3 and 4. Table 3 shows the survival time for the grafts. Table 4 sets forth the histological scores.

Table 3

Allograft Survival

Group (Treatment)	Individual Survival (days)	Mean Survival Time (days)
1'. Saline	8, 8, 8, 8, 8, 9	8.3 ± 0.5
2'. Cyclosporin A	14, 15, 15, 16, 16, 16, 17	15.5 ± 1.1
3'. BB5.1	7, 8, 8, 8, 8, 9	8.0 ± 0.6
4'. BB5.1 until day 14 + cyclosporin A	35, 38, 43, 45, 46, 47	42.3 ± 4.8
5'. BB5.1 until day 28 + cyclosporin A	77, 80, 80, 81, 82	80 ±1.9
6'. BB5.1 until day 100 + cyclosporin A	>100 days (7 mice; one sacrificed for histology)	> 100 days

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Table 4

Median Scores of Histological Changes of Heart Allografts at Necropsy

Groups	Vasc*	Infarc	Lymph	Throm	Hemo	Fibrin	PMN
1'. Saline (endpoint)	3.0	3.0	1.0	4.0	3.0	3.0	3.0
2'. Cyclosporin A (endpoint)	2.0	1.0	2.0	3.0	2.0	2.0	3.0
3'. BB5.1 (endpoint)	2.0	1.0	2.0	2.0	1.0	0.0	0.0
4'. BB5.1 until day 14 + cyclosporin A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
5'. BB5.1 28 days + Cyclosporin A (post-operative day 8)	0.0	0.0	0.0	0.0	0.0	0.0	0.0
5'. BB5.1 28 days + Cyclosporin A (endpoint)	0.0	0.0	1.0	1.0	2.0	1.0	0.0
6'. BB5.1 until day 100 + Cyclosporin A (post-operative day 100)	0.0	0.0	0.0	0.0	0.0	0.0	0.0

Median scores: 0 - normal; 1- minimum change; 2 - mild change; 3 - moderate change; 4 - marked change. N/A - not available.

*Vasc - vasculitis; Infar - infarction; Lymph - lymphocyte infiltration; Throm - thrombosis; Hemo - hemorrhage; Fibrin - fibrin deposition; PMN - polymorphonuclear cell infiltrate

The results indicate the synergistic effects of using a complement inhibiting drug in addition to an immunosuppressant. In untreated mice the grafts were rejected in about 8 davs. Use of the immunosuppressant cyclosporin A alone on a daily, chronic basis resulted

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in an increase in graft survival until approximately 15 days post-transplant. The use of the anti-C5 antibody BB5.1 to inhibit formation of terminal complement had no effect on its own, graft rejection occurring at 8 days post-transplant as in the control group (Group 1'). The combination of BB5.1 through day 28 post-transplant plus cyclosporin A showed a synergistic effect with graft survival being extended until approximately day 80. A more surprising result is that of Group 5' in which BB5.1 and cyclosporin A were each administered chronically post-transplant. In this case the graft survival was for more than 100 days (as much data as presently available). Additionally, the histological results shown in Table 4 indicate that the administration of both BB5.1 and cyclosporin A protected the graft from changes much better than either BB5.1 or cyclosporin A alone, and that the chronic administration of BB5.1 and cyclosporin A protected the graft to such an extent that even at 100 days post-transplant there were no histological changes seen in the engrafted hearts. A survival time of 100 days in these models is considered to be the gold standard. A survival of 100 days in the model is believed to indicate that there will be an indefinite survival of the allograft. When BB5.1 administration was stopped after 28 days, the grafts were protected but they did begin to show some minimal to mild histological changes by about day 80 which was the time at which graft failure occurred.

The Group 4' mice were treated differently in that they were administered BB5.1 on a daily basis by an intravenous administration. These animals became ill, showing weight loss and urine retention and were sacrificed at a time at which the grafted hearts were still beating although their function had declined. This was the first group of mice studied and it is unknown why these ill effects were seen. These ill effects were not seen when the BB5.1 was administered intraperitoneally with a schedule of three times per week. As seen below in Example 4, daily administration of BB5.1 via an intraperitoneal route did not cause ill effects. Also, intravenous administration was not necessarily the cause of the illness in these animals. Intravenous administration of eculizumab (a human equivalent antibody to BB5.1 in that it binds to human C5) has been successfully administered intravenously without ill effects to humans in a study of PNH (Hillmen et al., 2004). Complement inhibitors may be administered by other routes in addition to intravenous and intraperitoneal, with all such routes being well known by those skilled in the art.

Example 4

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Accelerated Rejection in a Presensitized Heart Transplantation Model

A second set of experiments similar to those of Example 3 was performed but the recipient mouse was presensitized to the donor organ. In these experiments, the presensitization was brought about by prior transplantation of a skin graft. In general, presensitization can occur not only as a result of having received an earlier allograft, but can also be caused by having received multiple blood transfusions or in women who have been pregnant. Besides such presensitization methods, allografts with an ABO mismatch will be rapidly attacked and rejected because of preformed antibodies to the ABO antigens unless steps are taken to prevent such an attack.

Some mice in these studies were administered cyclophosphamide in addition to BB5.1 and/or cyclosporin A. For these experiments BALB/c recipient mice were presensitized with C3H skin grafts one week prior to heart transplantation from the same donor (using the method of Pruitt and Bollinger, 1991). This model is designed to mimic presensitized transplantation in humans, especially in relation to accelerated humoral rejection. Recipient mice were split into eight groups of six to eight mice each. The treatments were as follow.

Group 1" (control) - mice (male 8-12 week old mice weighing 25 – 30 g) were administered 0.75 mL saline intraperitoneally on a daily basis beginning at day -1 and continuing until the endpoint (graft rejection).

Group 2" (cyclosporin A alone) - mice were administered cyclosporin A subcutaneously at a dose of 15 mg/kg body weight beginning on day 0 (day of transplant) until the endpoint.

Group 3" (BB5.1 alone) - mice were administered the anti-mouse complement monoclonal antibody BB5.1 at a dose of 40 mg/kg body weight delivered intraperitoneally on a daily basis beginning at day -1 and continuing until the endpoint.

Group 4" (cyclophosphamide alone) - mice were administered cyclophosphamide intravenously at a dose of 40 mg/kg body weight on each of days 0 and 1.

Group 5" (BB5.1 plus cyclosporin A) - mice were administered BB5.1 intraperitoneally at a dose of 40 mg/kg body weight on a daily basis beginning at day -1 and continuing until the endpoint. These mice were additionally administered cyclosporin A subcutaneously at a dose of 15 mg/kg body weight on a daily basis from day 0 until the endpoint.

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Group 6" (BB5.1 plus cyclophosphamide) - mice were administered BB5.1 intraperitoneally at a dose of 40 mg/kg body weight on a daily basis beginning at day -1 and continuing until the endpoint. These mice were additionally administered cyclophosphamide intravenously at a dose of 40 mg/kg body weight on each of days 0 and 1.

Group 7" (cyclosporin A plus cyclophosphamide) - mice were administered cyclosporin A subcutaneously at a dose of 15 mg/kg body weight on a daily basis from day 0 until the endpoint. These mice were additionally administered cyclophosphamide intravenously at a dose of 40 mg/kg body weight on each of days 0 and 1.

Group 8" (BB5.1 plus cyclosporin A plus cyclophosphamide) - mice were administered BB5.1 intraperitoneally at a dose of 40 mg/kg body weight on a daily basis beginning at day -1 and continuing until 100 days. These mice were also administered cyclosporin A subcutaneously at a dose of 15 mg/kg body weight on a daily basis from day 0 until 100 days. These mice were additionally administered cyclophosphamide intravenously at a dose of 40 mg/kg body weight on each of days 0 and 1. Two mice in this group were sacrificed at day 60 for histological studies (no rejection had yet occurred) and the four remaining mice still had not rejected their grafts by day 100.

Additionally a control group of mice which was not presensitized and received only the saline treatment as for Group 1" was tested.

The results of these experiments are shown in Tables 5 and 6. Table 5 lists survival times for the grafts and Table 6 summarizes the histological results.

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Table 5

Allograft Survival

Groups (Treatment)	Individual survival (days)	Mean survival time (days)
No presensitization	8, 8, 8, 8, 8, 9	8.3 ± 0.5*
1". One skin presensitization	3, 3, 3, 3, 3, 3, 3, 4	3.1 ± 0.4
2". Cyclosporin A	3, 3, 3, 3	3.0 ± 0.0
3". BB5.1	3, 3, 4, 4	3.5 ± 0.6
4". Cyclophosphamide	3, 3, 3, 4	3.3 ± 0.5
5". BB5.1 + Cyclosporin A	10, 10, 11, 11, 12, 12, 14, 15	11.9 ± 1.8**
6". BB5.1 + Cyclophosphamide	3, 3, 3, 3, 3, 4	3.2 ± 0.4
7". Cyclosporin A + Cyclophosphamide	3, 3, 3, 4, 4, 4	3.5 ± 0.6
8". BB5.1 + Cyclosporin A + Cyclophosphamide	> 100 days (4 mice)	> 100***

*P < 0.01 group 1" vs. no presensitization

**P < 0.01 group 5" vs. groups 1"-4" and 6"-7".

***P<0.01 group 8" vs. groups 1"-7".

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Table 6

Median Scores of Histological Changes of Heart Allografts at Necropsy

Groups	Vasc*	Infar	Lymph	Throm	Hemo	Fibrin	PMN
No presensitization (endpoint)	3.0	3.0	1.0	4.0	3.0	3.0	3.0
1". One skin presensitization (endpoint)	0.0	4.0	1.0	4.0	3.0	0.0	0.0
2". Cyclosporin A (endpoint)	0.0	4.0	0.0	3.0	3.0	N/A	N/A
3". BB5.1 (endpoint)	2.0	2.0	2.0	2.0	3.0	N/A	N/A
4". Cyclophosphamide (endpoint)	2.0	4.0	0.0	3.0	2.0	N/A	N/A
5". BB5.1 + Cyclosporin A (post-operative day 3)	0.0	1.0	1.0	0.0	0.0	0.0	0.0
5". BB5.1 + Cyclosporin A (endpoint)	2.0	2.0	2.0	2.0	2.0	0.0	0.0
6". BB5.1 + Cyclophosphamide (endpoint)	1.0	3.0	0.0	3.0	2.0	N/A	N/A
7". Cyclosporin A + Cyclophosphamide (endpoint)	0.0	1.0	1.0	2.0	3.0	N/A	N/A
8". BB5.1 + Cyclosporin A + Cyclophosphamide (post-operative day 3)	0.0	0.0	1.0	0.0	0.0	N/A	N/A
8. BB5.1 + Cyclosporin A + Cyclophosphamide (post-operative day 12)	0.0	0.0	1.0	0.0	0.0	N/A	N/A
8". BB5.1 + Cyclosporin A + Cyclophosphamide (post-	0.0	0.0	1.0	0.0	0.0	N/A	N/A

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operative day 60)							
8". BB5.1 + Cyclosporin A + Cyclophosphamide (post-operative day 100)	N/A	N/A	N/A	N/A	N/A	N/A	N/A

Median scores: 0 - normal; 1- minimum change; 2 - mild change; 3 - moderate change; 4 - marked change. N/A - not available.

*Vasc - vasculitis; Infar - infarction; Lymph - lymphocyte infiltration; Throm - thrombosis; Hemo - hemorrhage; Fibrin - fibrin deposition; PMN - polymorphonuclear cell infiltrate

The results shown in Table 5 indicate a difference between the presensitized mouse model and the nonpresensitized mouse model as used in Example 3. The results indicate that in the absence of presensitization, grafts are rejected in approximately 8 days in the absence of treatment with any drugs. Presensitizing the animals causes a more rapid rejection, the rejection of the graft in the presensitized animals being in approximately 3 days in the absence of any drug treatment. Treatment with either BB5.1, cyclosporin A or cyclophosphamide had no effect upon graft survival, with the grafts being rejected in approximately 3-4 days in each of these groups of animals. The combination of BB5.1 and cyclosporin A showed some effect with rejection occurring about day 12. The combination of BB5.1 and cyclophosphamide had no protective effect with rejection occurring about day 3. Similarly the combination of cyclosporin A and cyclophosphamide had essentially no protective effect with rejection occurring at 3-4 days. Very surprisingly, the combination of all three drugs (chronic administration of BB5.1 and cyclosporin plus administration of cyclophosphamide at the time of transplant) showed a highly synergistic effect with all of the mice surviving for more than 100 days. Again, a survival of 100 days in this model is considered to be the gold standard and assumes an indefinite survival.

These results as well as the histological results as shown in Table 6 indicate that the combination of chronic treatment with a complement inhibitor and an immunosuppressant such as cyclosporin A in treating a presensitized mouse results in some attenuation of accelerated rejection. Treatment of these animals additionally with cyclophosphamide at the time of transplant and on the first day after transplant results in a much greater time of survival, no rejection having been seen by at least day 100.

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It will be appreciated that the methods and compositions of the instant disclosure can be incorporated in the form of a variety of embodiments, only a few of which are disclosed herein. It will be apparent to the artisan that other embodiments exist and do not depart from the spirit of the disclosure. Thus, the described embodiments are illustrative and should not be construed as restrictive.

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LIST OF REFERENCES

The publications and other materials used herein to illuminate the background of the disclosure, and in particular, cases to provide additional details respecting the practice, are incorporated herein by reference in their entirety, and for convenience, are referenced by author and date in the text and respectively grouped in the following List of References.

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The contents of all references cited herein are incorporated by reference in their entirety.

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CLAIMS

1. A method to prolong survival of an MHC mismatched allograft in a recipient mammal, said method comprising administering to said mammal a) a drug which inhibits complement activity and b) at least one immunosuppressive drug, wherein said drug which inhibits complement activity is administered chronically.

2. The method of claim 1 wherein said mammal is a human.

3. The method of claim 2 wherein said MHC mismatched allograft is an HLA mismatched allograft.

4. The method of claim 1 wherein said drug which inhibits complement activity inhibits the formation of terminal complement or C5a.

5. The method of claim 4 wherein said drug which inhibits formation of terminal complement or C5a is a whole antibody or an antibody fragment.

6. The method of claim 5 wherein said whole antibody or antibody fragment is a human, humanized, chimerized or deimmunized antibody or antibody fragment.

7. The method of claim 5 wherein said whole antibody or antibody fragment inhibits cleavage of complement C5.

8. The method of claim 5 wherein said antibody fragment is selected from the group consisting of an Fab, an $F(ab')_2$, an Fv, a domain antibody, and a single-chain antibody.

9. The method of claim 5 wherein said antibody fragment is pexelizumab.

10. The method of claim 5 wherein said whole antibody is eculizumab.

11. The method claim 10 wherein said eculizumab is administered once every 2 weeks.

12. The method of claim 1 wherein said inhibitor of complement activity is selected from the group consisting of a i) soluble complement receptor, ii) CD59, iii) CD55, iv) CD46, and v) an antibody to C5, C6, C7, C8, or C9.

13. The method of claim 1 wherein said immunosuppressive drug inhibits T-cell activity or B-cell activity.

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14. The method of claim 1 wherein said immunosuppressive drug inhibits T-cell activity and B-cell activity.

15. The method of claim 1 wherein said immunosuppressive drug is selected from the group consisting of cyclosporin A, tacrolimus, sirolimus, OKT3, a corticosteroid, daclizumab, basiliximab, azathioprene, mycophenolate mofetil, methotrexate, 6-mercaptopurine, anti-T cell antibodies, cyclophosphamide, leflunamide, brequinar, ATG, ALG, 15-deoxyspergualin, and bredinin.

16. The method of claim 1 wherein more than one immunosuppressive drug is administered.

17. The method of claim 1 wherein said method comprises administering i) a drug which inhibits complement activity and ii) cyclosporin A.

18. The method of claim 17 wherein said drug which inhibits complement activity is an antibody which inhibits cleavage of complement C5.

19. The method of claim 1 wherein said allograft is selected from the group consisting of i) heart, ii) kidney, iii) lung, iv) pancreas, v) liver, vi) vascular tissue, vii) eye, viii) cornea, ix) lens, x) skin, xi) bone marrow, xii) muscle, xiii) connective tissue, xiv) gastrointestinal tissue, xv) nervous tissue, xvi) bone, xvii) stem cells, xviii) islets, xix) cartilage, xx) hepatocytes, and xxi) hematopoietic cells.

20. The method of claim 1 wherein said allograft survives for a time at least 20% longer than would occur if said method were to be performed without said drug which inhibits complement activity.

21. The method of claim 1 wherein said allograft survives for a time at least 40% longer than would occur if said method were to be performed without said drug which inhibits complement activity.

22. The method of claim 1 wherein said allograft survives for the remaining life-time of said mammal.

23. The method of claim 2 wherein said allograft survives for at least six months.

24. The method of claim 2 wherein said allograft survives for at least one year.

25. The method of claim 2 wherein said allograft survives for at least five years.

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26. The method of claim 2 wherein said allograft survives for the remaining life-time of said human.

27. The method of claim 1 wherein said drug which inhibits complement activity is administered chronically for at least 14 days.

28. The method of claim 1 wherein said drug which inhibits complement activity is administered chronically for at least 28 days.

29. The method of claim 1 wherein said drug which inhibits complement activity is administered chronically for at least 3 months.

30. The method of claim 1 wherein said drug which inhibits complement activity is administered chronically for at least 6 months.

31. The method of claim 1 wherein said drug which inhibits complement activity is administered chronically for at least 1 year.

32. The method of claim 1 wherein said drug which inhibits complement activity is administered chronically for at least 5 years.

33. The method of claim 1 wherein said drug which inhibits complement activity is administered chronically for the remaining life-time of said mammal.

34. The method of claim 1 wherein at least one immunosuppressive drug is administered chronically for the remaining life-time of said mammal.

35. The method of claim 34 wherein at least cyclosporin A is administered chronically for the remaining life-time of said mammal.

36. A method to prolong survival of an allograft in a recipient mammal presensitized to said allograft, said method comprising administering to said mammal a) a drug which inhibits complement activity and b) at least one immunosuppressive drug, wherein said drug which inhibits complement activity is administered chronically.

37. The method of claim 36 wherein said mammal is a human.

38. The method of claim 36 wherein said drug which inhibits complement activity inhibits the formation of terminal complement or C5a.

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39. The method of claim 38 wherein said drug that inhibits formation of terminal complement or C5a is a whole antibody or an antibody fragment.

40. The method of claim 39 wherein said whole antibody or antibody fragment is a human, humanized, chimerized or deimmunized antibody or antibody fragment.

41. The method of claim 39 wherein said whole antibody or antibody fragment inhibits cleavage of complement C5.

42. The method of claim 39 wherein said antibody fragment is selected from the group consisting of an Fab, an $F(ab')_2$, an Fv, a domain antibody, and a single-chain antibody.

43. The method of claim 39 wherein said antibody fragment is pexelizumab.

44. The method of claim 39 wherein said whole antibody is eculizumab.

45. The method claim 44 wherein said eculizumab is administered once every 2 weeks.

46. The method of claim 36 wherein said inhibitor of complement activity is selected from the group consisting of a i) soluble complement receptor, ii) CD59, iii) CD55, iv) CD46, and v) an antibody to C5, C6, C7, C8, or C9.

47. The method of claim 36 wherein said immunosuppressive drug inhibits T-cell activity or B-cell activity.

48. The method of claim 36 wherein said immunosuppressive drug inhibits T-cell activity and B-cell activity.

49. The method of claim 36 wherein said immunosuppressive drug is selected from the group consisting of cyclosporin A, tacrolimus, sirolimus, OKT3, a corticosteroid, daclizumab, basiliximab, azathioprene, mycophenolate mofetil, methotrexate, 6-mercaptopurine, anti-T cell antibodies, cyclophosphamide, leflunamide, brequinar, ATG, ALG, 15-deoxyspergualin, and bredinin.

50. The method of claim 36 wherein more than one immunosuppressive drug is administered.

51. The method of claim 36 wherein said method comprises administering i) a drug which inhibits complement activity and ii) cyclosporin A.

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52. The method of claim 51 wherein said method comprises administering i) a drug which inhibits complement activity, ii) cyclosporin A, and iii) cyclophosphamide.

53. The method of claim 51 wherein said drug which inhibits complement activity is an antibody which inhibits cleavage of complement C5.

54. The method of claim 36 wherein said allograft is selected from the group consisting of i) heart, ii) kidney, iii) lung, iv) pancreas, v) liver, vi) vascular tissue, vii) eye, viii) cornea, ix) lens, x) skin, xi) bone marrow, xii) muscle, xiii) connective tissue, xiv) gastrointestinal tissue, xv) nervous tissue, xvi) bone, xvii) stem cells, xviii) islets, xix) cartilage, xx) hepatocytes, and xxi) hematopoietic cells.

55. The method of claim 36 wherein said allograft survives for a time at least 20% longer than would occur if said method were to be performed without said drug which inhibits complement activity.

56. The method of claim 36 wherein said allograft survives for a time at least 40% longer than would occur if said method were to be performed without said drug which inhibits complement activity.

57. The method of claim 36 wherein said allograft survives for the remaining life-time of said mammal.

58. The method of claim 37 wherein said allograft survives for at least six months.

59. The method of claim 37 wherein said allograft survives for at least one year.

60. The method of claim 37 wherein said allograft survives for at least five years.

61. The method of claim 37 wherein said allograft survives for the remaining life-time of said human.

62. The method of claim 36 wherein said drug which inhibits complement activity is administered chronically for at least 14 days.

63. The method of claim 36 wherein said drug which inhibits complement activity is administered chronically for at least 28 days.

64. The method of claim 36 wherein said drug which inhibits complement activity is administered chronically for at least 3 months.

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65. The method of claim 36 wherein said drug which inhibits complement activity is administered chronically for at least 6 months.

66. The method of claim 36 wherein said drug which inhibits complement activity is administered chronically for at least 1 year.

67. The method of claim 36 wherein said drug which inhibits complement activity is administered chronically for at least 5 years.

68. The method of claim 36 wherein said drug which inhibits complement activity is administered chronically for the remaining life-time of said mammal.

69. The method of claim 36 wherein at least one immunosuppressive drug is administered chronically for the remaining life-time of said mammal.

70. The method of claim 69 wherein at least cyclosporin A is administered chronically for the remaining life-time of said mammal.

71. A method to prolong survival of an allograft in a recipient mammal which is an ABO mismatch to said allograft, said method comprising administering to said mammal a) a drug which inhibits complement activity and b) at least one immunosuppressive drug, wherein said drug which inhibits complement activity is administered chronically.

72. The method of claim 71 wherein said mammal is a human.

73. The method of claim 71 wherein said drug which inhibits complement activity inhibits the formation of terminal complement or C5a.

74. The method of claim 73 wherein said drug which inhibits formation of terminal complement or C5a is a whole antibody or an antibody fragment.

75. The method of claim 74 wherein said whole antibody or antibody fragment is a human, humanized, chimerized or deimmunized antibody or antibody fragment.

76. The method of claim 74 wherein said whole antibody or antibody fragment inhibits cleavage of complement C5.

77. The method of claim 74 wherein said antibody fragment is selected from the group consisting of an Fab, an $F(ab')_2$, an Fv, a domain antibody, and a single-chain antibody.

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78. The method of claim 74 wherein said antibody fragment is pexelizumab.

79. The method of claim 74 wherein said whole antibody is eculizumab.

80. The method claim 79 wherein said eculizumab is administered once every 2 weeks.

81. The method of claim 71 wherein said inhibitor of complement activity is selected from the group consisting of a i) soluble complement receptor, ii) CD59, iii) CD55, iv) CD46, and v) an antibody to C5, C6, C7, C8, or C9.

82. The method of claim 71 wherein said immunosuppressive drug inhibits T-cell activity or B-cell activity.

83. The method of claim 71 wherein said immunosuppressive drug inhibits T-cell activity and B-cell activity.

84. The method of claim 71 wherein said immunosuppressive drug is selected from the group consisting of cyclosporin A, tacrolimus, sirolimus, OKT3, a corticosteroid, daclizumab, basiliximab, azathioprene, mycophenolate mofetil, methotrexate, 6-mercaptopurine, anti-T cell antibodies, cyclophosphamide, leflunamide, brequinar, ATG, ALG, 15-deoxyspergualin, and bredinin.

85. The method of claim 71 wherein more than one immunosuppressive drug is administered.

86. The method of claim 71 wherein said method comprises administering i) a drug which inhibits complement activity and ii) cyclosporin A.

87. The method of claim 86 wherein said method comprises administering i) a drug which inhibits complement activity, ii) cyclosporin A, and iii) cyclophosphamide.

88. The method of claim 86 wherein said drug that inhibits complement activity is an antibody that inhibits cleavage of complement C5.

89. The method of claim 71 wherein said allograft is selected from the group consisting of i) heart, ii) kidney, iii) lung, iv) pancreas, v) liver, vi) vascular tissue, vii) eye, viii) cornea, ix) lens, x) skin, xi) bone marrow, xii) muscle, xiii) connective tissue, xiv) gastrointestinal tissue, xv) nervous tissue, xvi) bone, xvii) stem cells, xviii) islets, xix) cartilage, xx) hepatocytes, and xxi) hematopoietic cells.

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90. The method of claim 71 wherein said allograft survives for a time at least 20% longer than would occur if said method were to be performed without said drug that inhibits complement activity.

91. The method of claim 71 wherein said allograft survives for a time at least 40% longer than would occur if said method were to be performed without said drug that inhibits complement activity.

92. The method of claim 71 wherein said allograft survives for the remaining life-time of said mammal.

93. The method of claim 72 wherein said allograft survives for at least six months.

94. The method of claim 72 wherein said allograft survives for at least one year.

95. The method of claim 72 wherein said allograft survives for at least five years.

96. The method of claim 72 wherein said allograft survives for the remaining life-time of said human.

97. The method of claim 71 wherein said drug which inhibits complement activity is administered chronically for at least 14 days.

98. The method of claim 71 wherein said drug which inhibits complement activity is administered chronically for at least 28 days.

99. The method of claim 71 wherein said drug which inhibits complement activity is administered chronically for at least 3 months.

100. The method of claim 71 wherein said drug which inhibits complement activity is administered chronically for at least 6 months.

101. The method of claim 71 wherein said drug which inhibits complement activity is administered chronically for at least 1 year.

102. The method of claim 71 wherein said drug which inhibits complement activity is administered chronically for at least 5 years.

103. The method of claim 71 wherein said drug which inhibits complement activity is administered chronically for the remaining life-time of said mammal.

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104. The method of claim 71 wherein at least one immunosuppressive drug is administered chronically for the remaining life-time of said mammal.

105. The method of claim 104 wherein at least cyclosporin A is administered chronically for the remaining life-time of said mammal.

106. Use of a drug that inhibits complement activity and an immunosuppressive drug in the manufacture of a medicament or medicament package for prolong survival of an allograft in a mammal.

107. The use of claim 106, wherein more than one immunosuppressive drug is included in said medicament or medicament package.

108. The use of claim 106, wherein said drug that inhibits complement activity and said immunosuppressive drug are in a formulation suitable for concurrent administration to said mammal.

109. The use of claim 106, wherein said drug that inhibits complement activity and said immunosuppressive drug are in a formulation or formulations suitable for sequential administration to said mammal.

110. The use of claim 106, wherein said drug that inhibits complement activity is in a formulation suitable for chronic administration to said mammal.

111. The use of claim 106, wherein said immunosuppressive drug is in a formulation suitable for chronic administration to said mammal.

112. A method to prolong survival of allograft in a recipient mammal, comprising preparing an allograft from a first allograft accommodated by a first recipient mammal, wherein said first recipient mammal, after receiving said first allograft, has been treated with a drug that inhibits complement activity and at least one immunosuppressive agent.

113. An allograft that has prolonged survival in a recipient mammal, wherein said allograft is prepared from a first recipient mammal and was transplanted to the first recipient mammal that has been treated with a drug that inhibits complement activity and at least one immunosuppressive agent.

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114. A pharmaceutical package comprising a drug that inhibits complement activity and at least one immunosuppressive agent, wherein said drug and said agent are formulated for chronic administration.

115. The pharmaceutical package of claim 114, wherein said drug is an antibody in a lyophilized formulation comprising the antibody and a lyoprotectant.

116. The pharmaceutical package of claim 114, wherein said agent is in a lyophilized formulation comprising the agent and a lyoprotectant.

117. The pharmaceutical package of claim 114, wherein said drug and said agent are in the same lyophilized formulation comprising said drug, said agent, and a lyoprotectant.

118. The pharmaceutical package of claim 114, wherein said drug is in an injection system comprising a syringe that comprises a cartridge, wherein said cartridge contains said drug in a formulation suitable for injection.

119. The pharmaceutical package of claim 114, wherein said agent is in an injection system comprising a syringe that comprises a cartridge, wherein said cartridge contains said agent in a formulation suitable for injection.

120. The pharmaceutical package of claim 114, wherein said drug and said agent are in an injection system comprising a syringe that comprises a cartridge, wherein said cartridge contains said drug and said agent in a formulation suitable for injection.

121. The pharmaceutical package of claim 114, wherein said drug is present in unit dosage form.

122. The pharmaceutical package of claim 114, wherein said agent is present in unit dosage form.

123. A lyophilized antibody formulation comprising an antibody that inhibits complement activity and a lyoprotectant, wherein said antibody formulation is suitable for chronic administration.

124. The lyophilized antibody formulation of claim 123, wherein the antibody inhibits the formation of terminal complement or C5a.

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125. The lyophilized antibody formulation of claim 123, wherein the antibody is a whole antibody or an antibody fragment.

126. The lyophilized antibody formulation of claim 125, wherein the antibody wherein said whole antibody or antibody fragment is a human, humanized, chimerized or deimmunized antibody or antibody fragment.

127. The lyophilized antibody formulation of claim 125, wherein said whole antibody or antibody fragment inhibits cleavage of complement C5.

128. The lyophilized antibody formulation of claim 125, wherein said antibody fragment is selected from the group consisting of an Fab, an $F(ab')_2$, an Fv, a domain antibody, and a single-chain antibody.

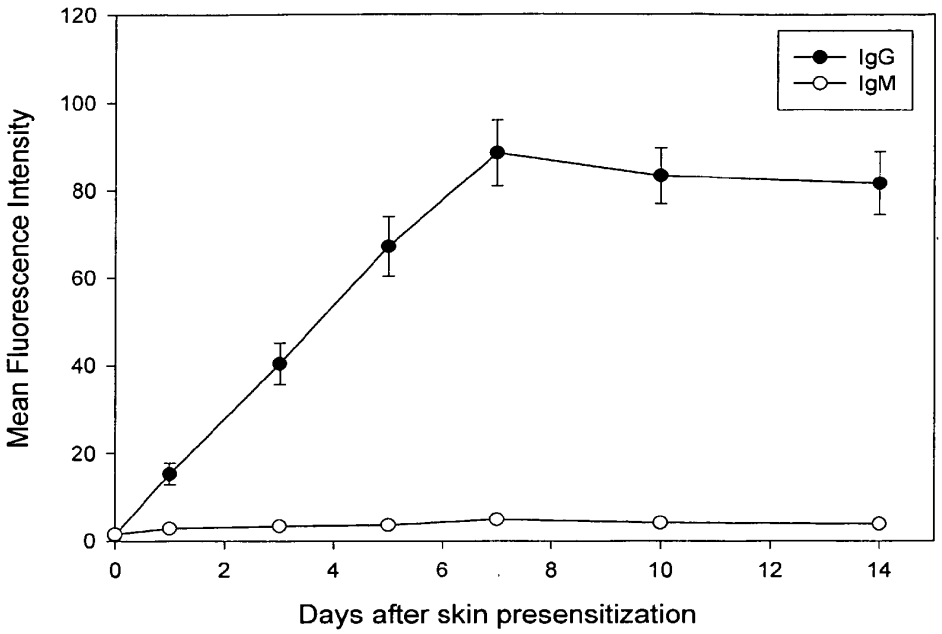
129. The lyophilized antibody formulation of claim 125, wherein said antibody fragment is pexelizumab.

130. The lyophilized antibody formulation of claim 125, wherein said whole antibody is eculizumab.

131. An injection system comprising a syringe, wherein said syringe comprises a cartridge containing an antibody that inhibits complement activity and is formulated suitable for injection.

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A



B

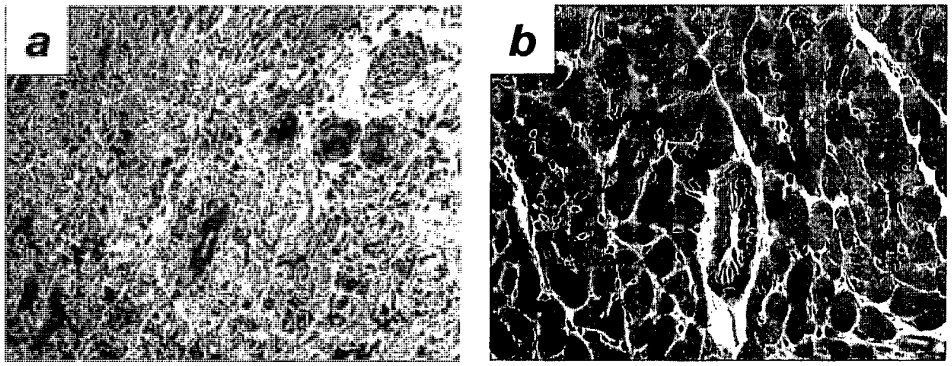


Figure 1A, B

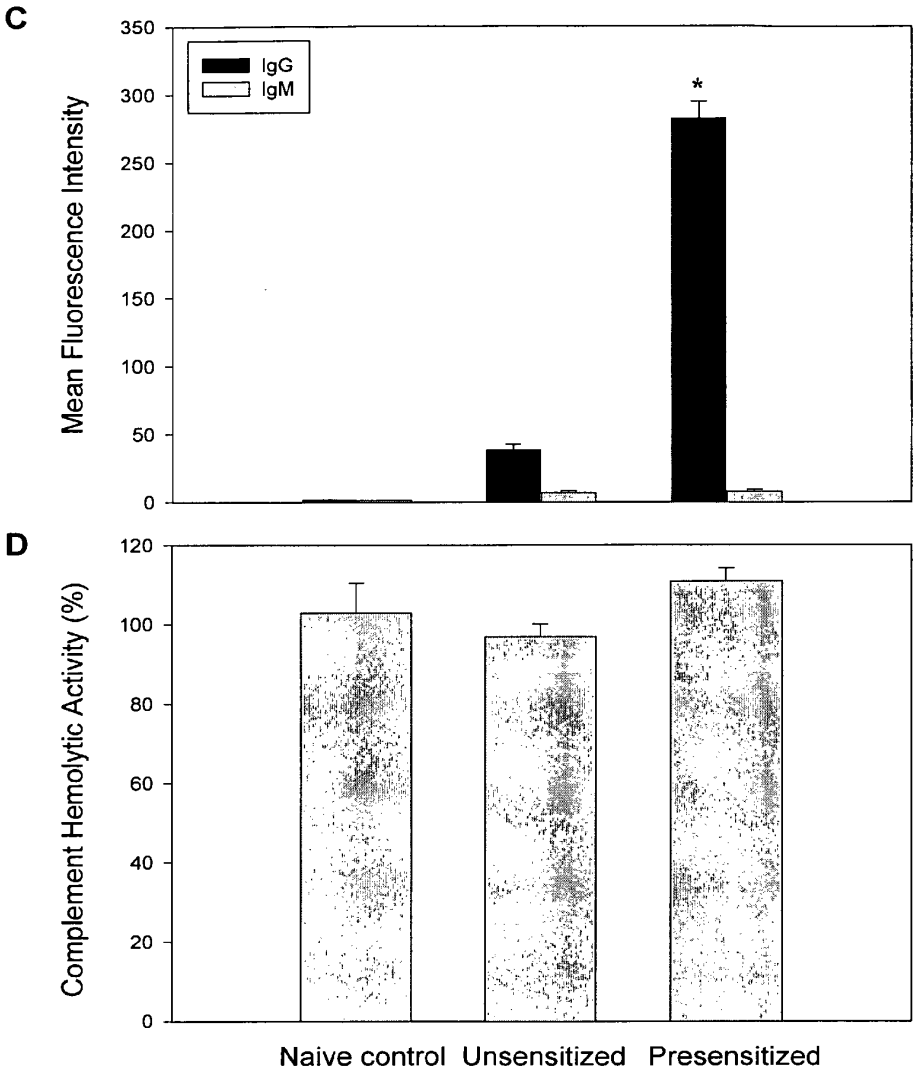


Figure 1C, D

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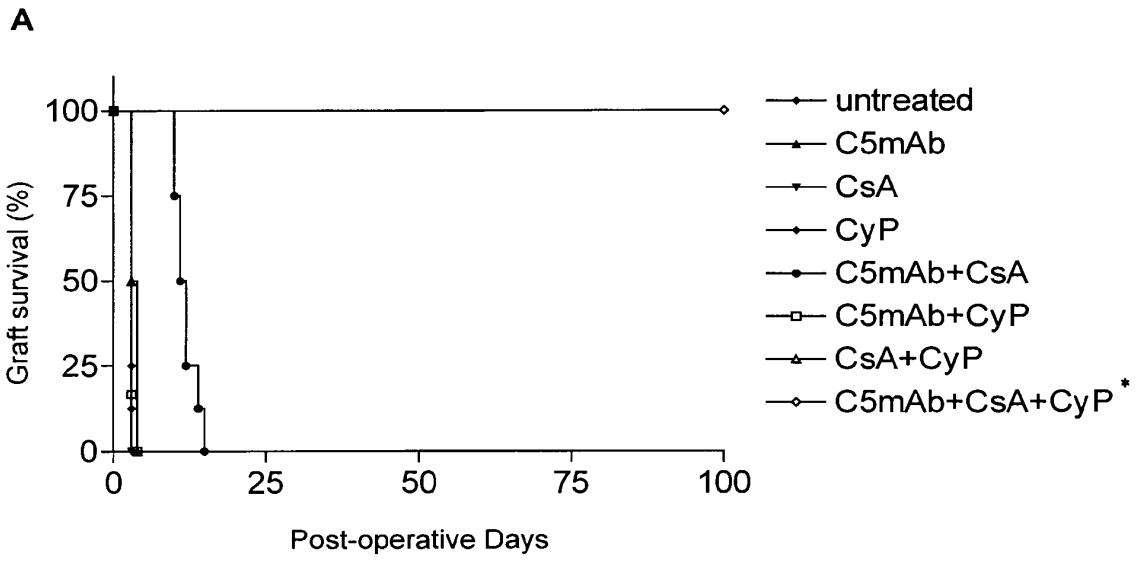

A
Graft survival (%)
100
75
50
25
0
0
25
50
75
100
Post-operative Days
untreated
C5mAb
CsA
CyP
C5mAb+CsA
C5mAb+CyP
CsA+CyP
C5mAb+CsA+CyP *

Figure 2A

B

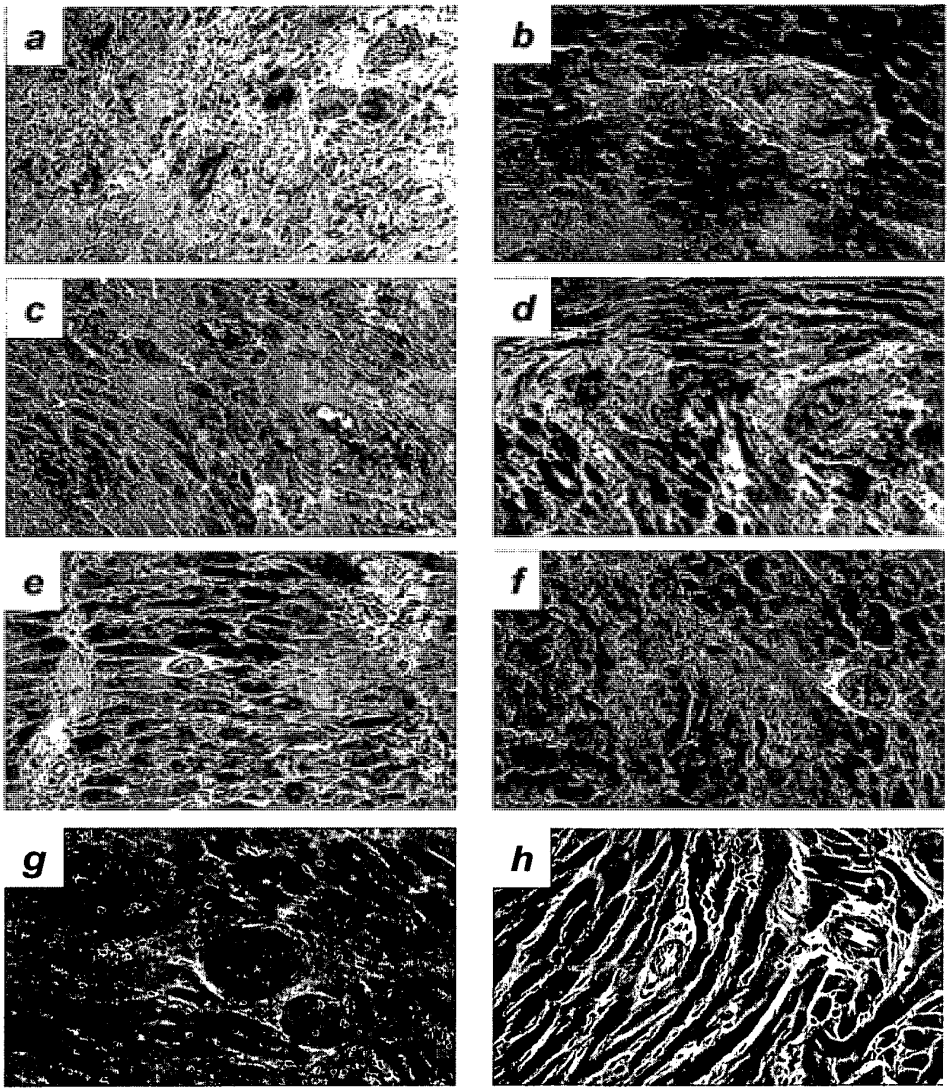


Figure 2B

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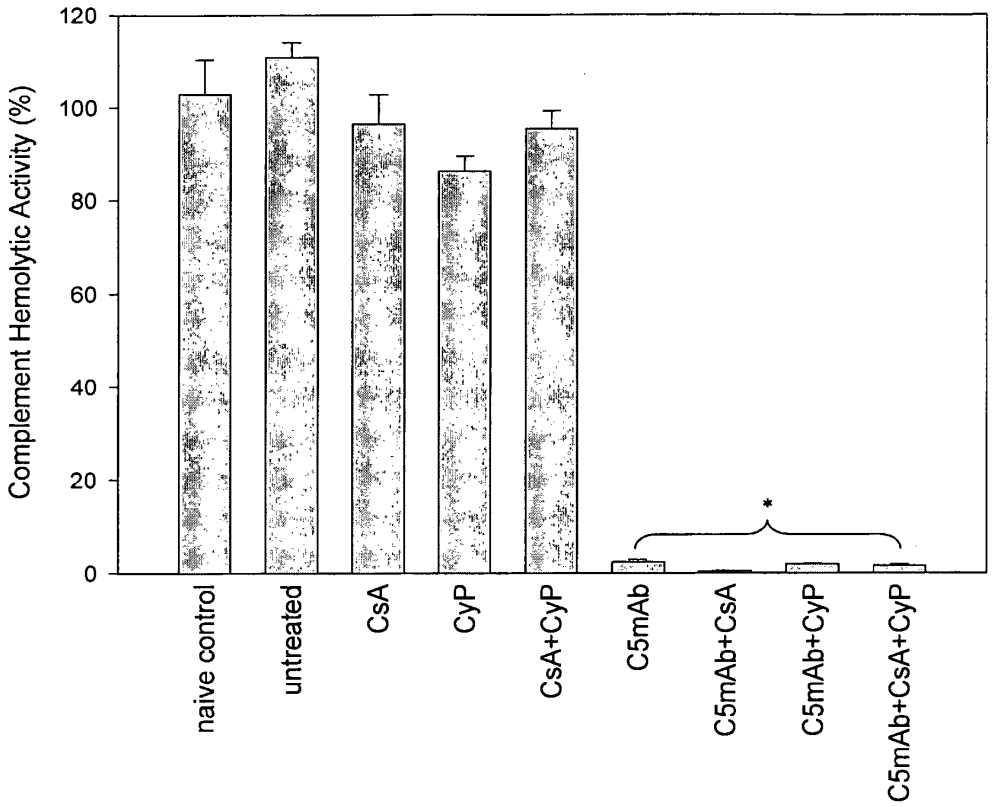


Figure 3

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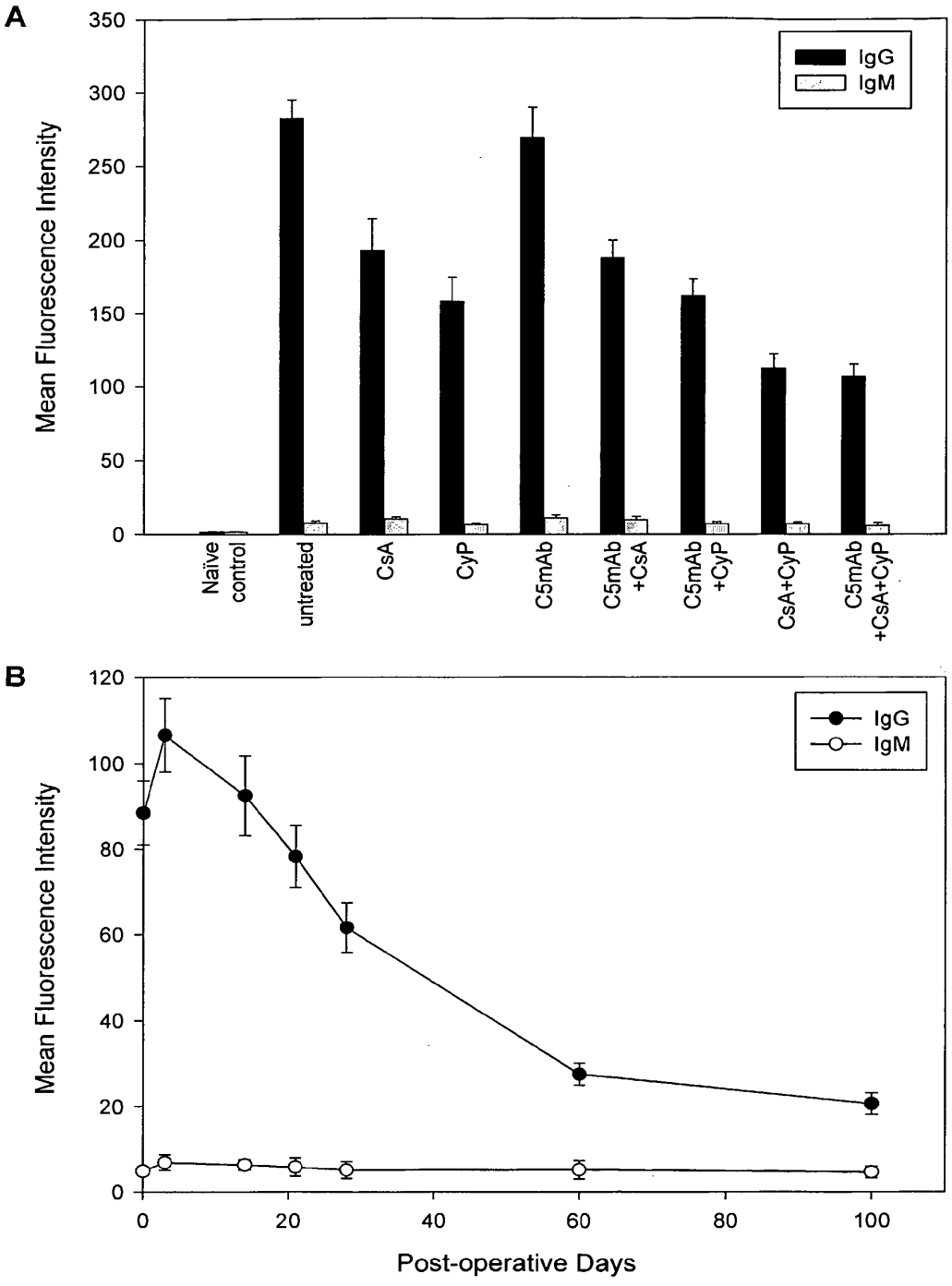
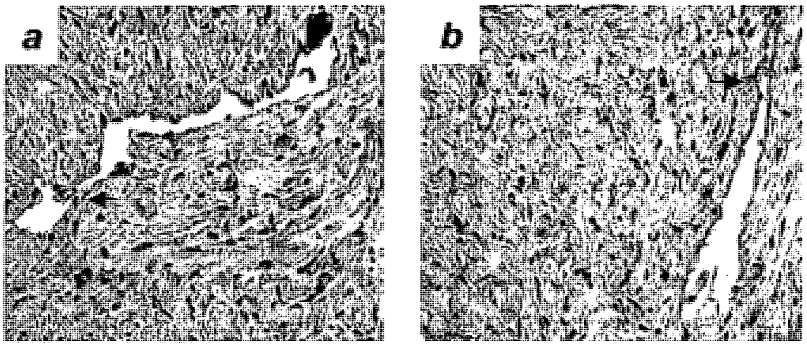


Figure 4A, B

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C



D

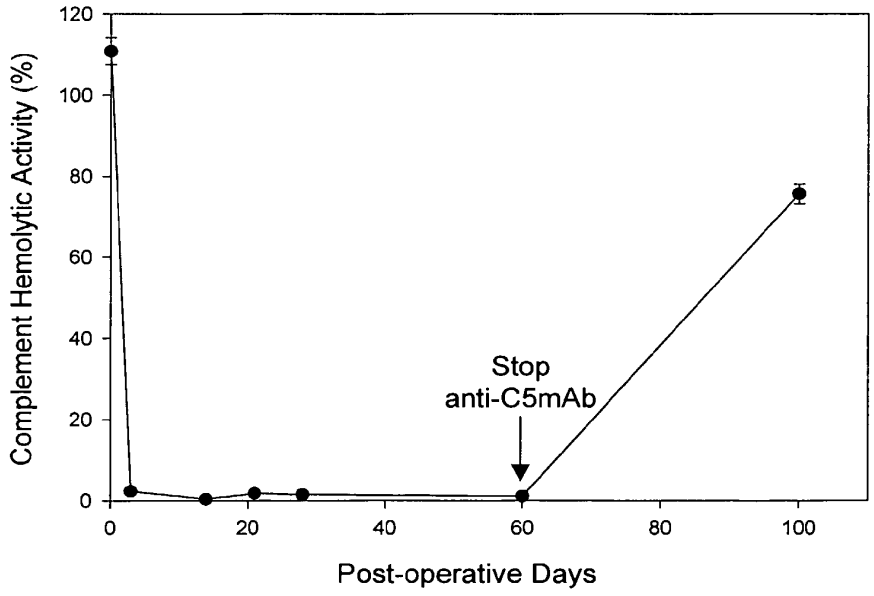


Figure 4C, D

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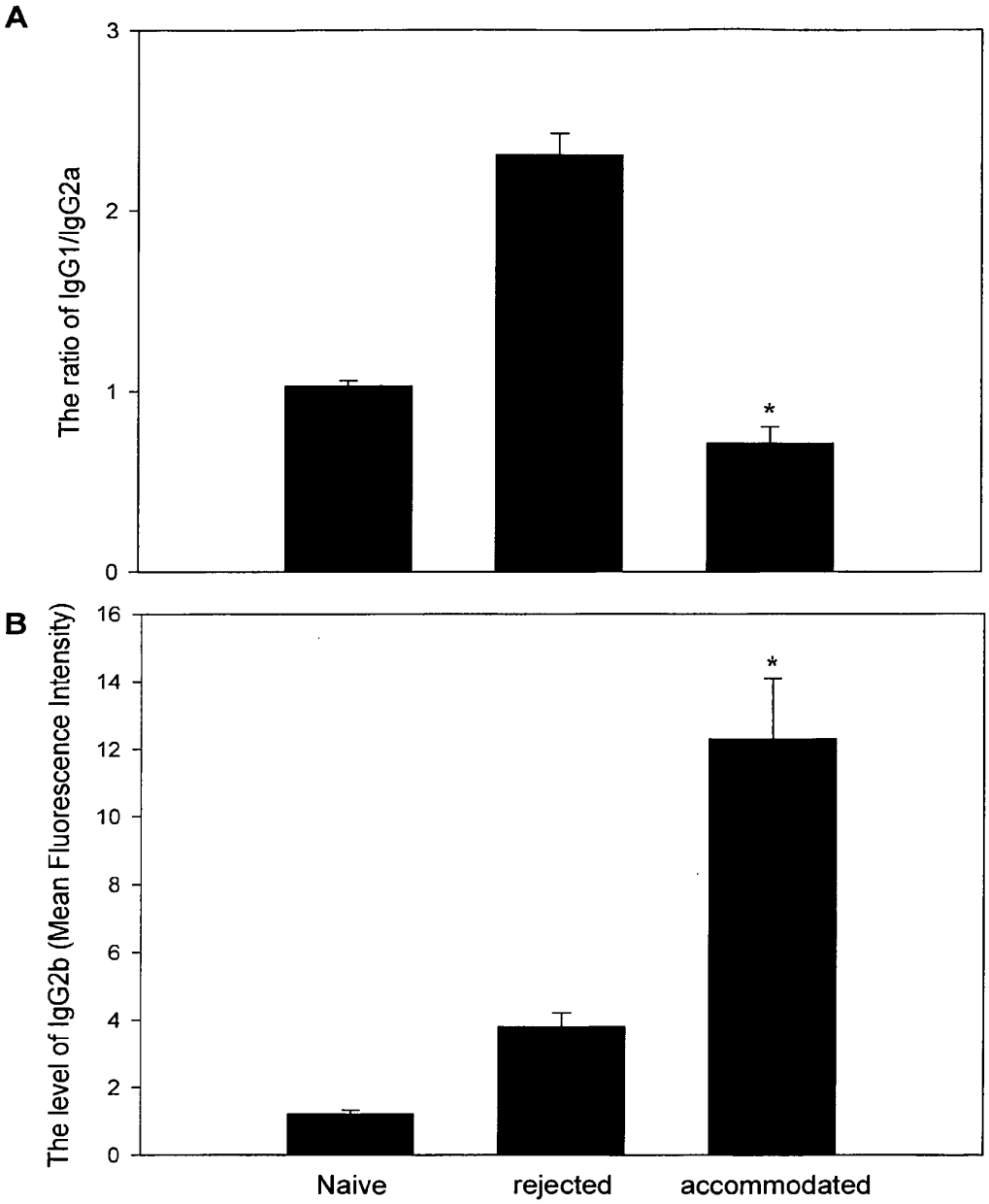


Figure 5A, B

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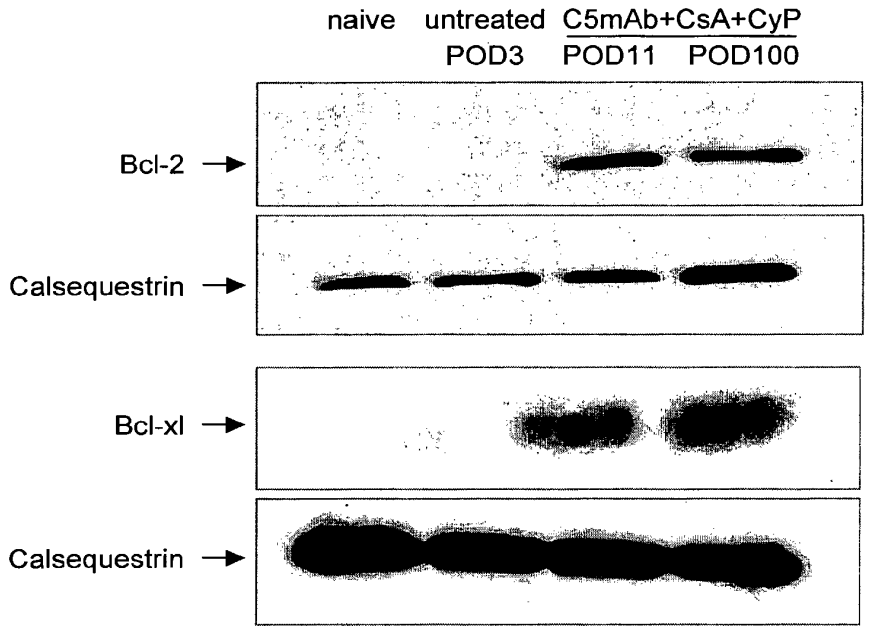


Figure 6

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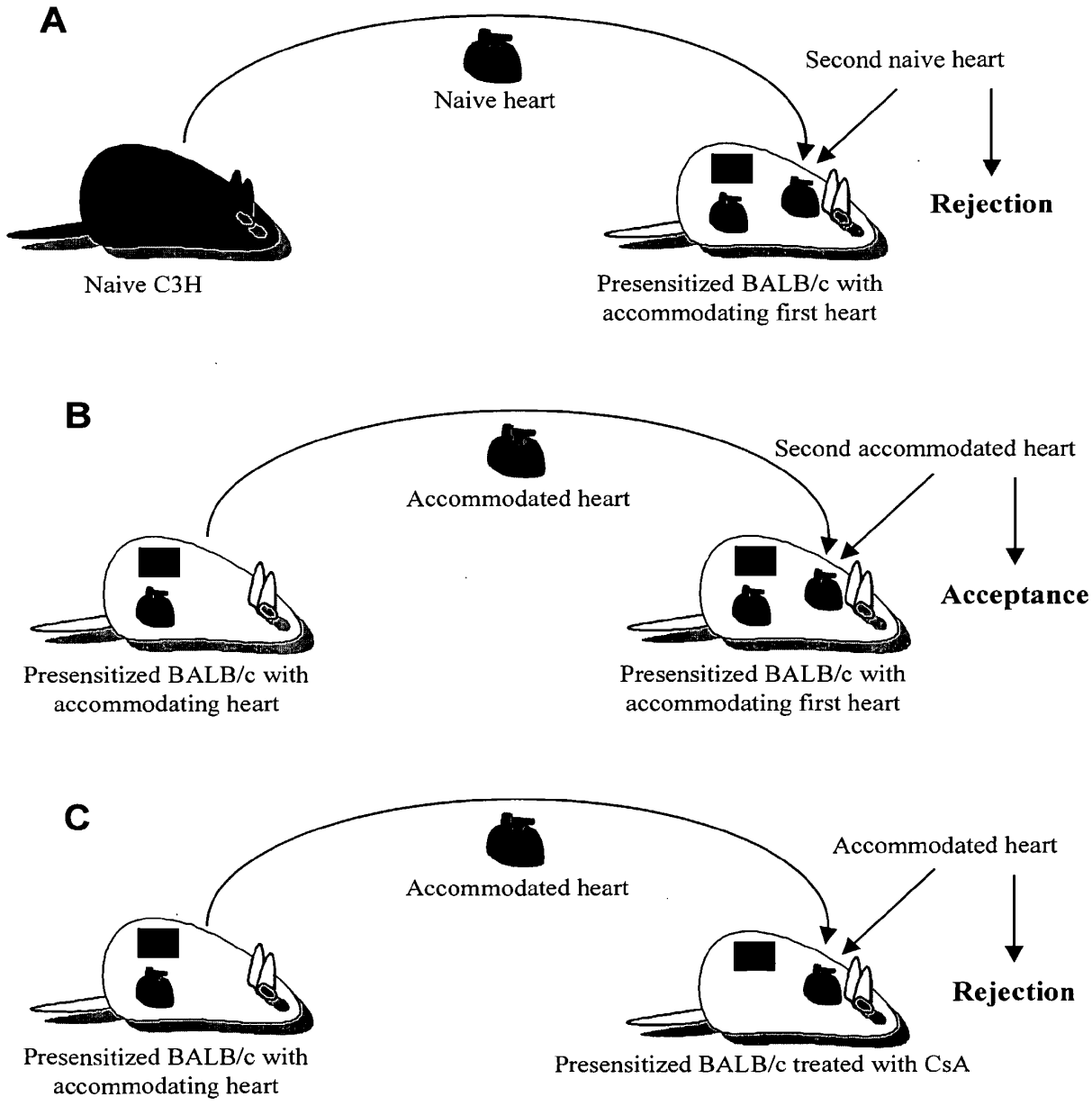
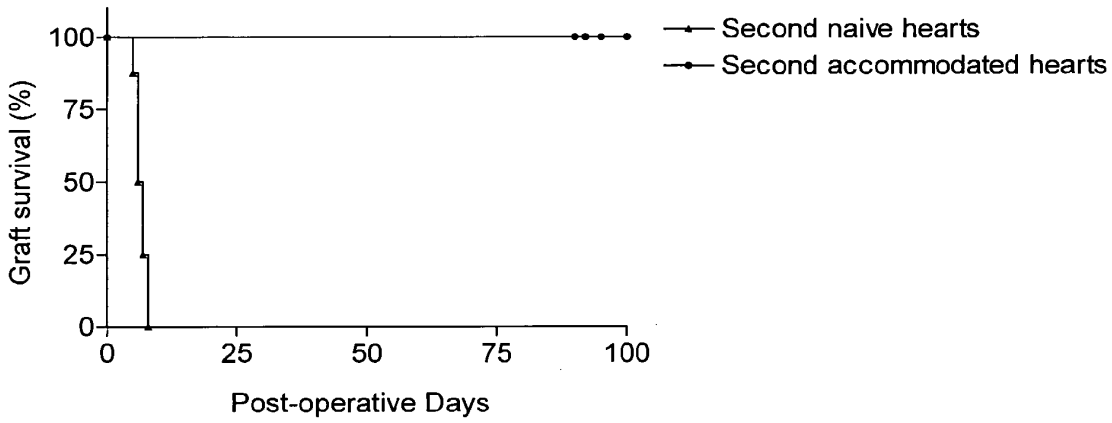


Figure 7

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A



B

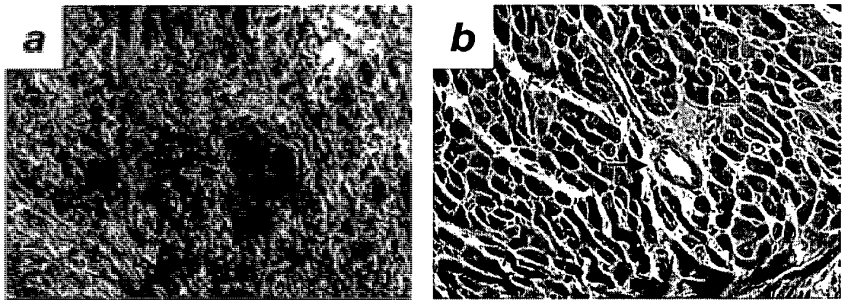


Figure 8

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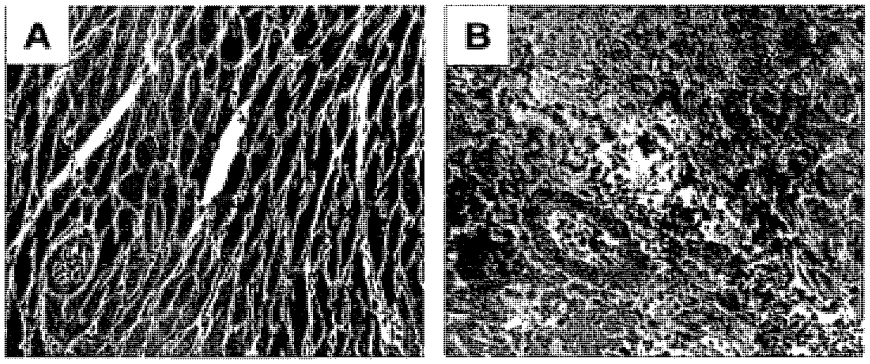


Figure 9

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A61K 39/395 (2006.01)

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(54) Title: USE OF A COMPLEMENT INHIBITOR TO TREAT PATIENTS WITH SICKLE CELL DISEASE

(57) Abstract: A method of treating a sickle cell patient with a complement inhibitor is disclosed. Treatment with an inhibitor of complement activation decreases the extent of red blood cell lysis and decreases the consequential clinical sequelae.

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USE OF A COMPLEMENT INHIBITOR TO TREAT PATIENTS WITH SICKLE CELL DISEASE

FIELD OF THE INVENTION

[0001] The present invention relates to methods for the treatment of sickle cell disease. In specific embodiments, the invention relates to the use of antibodies capable of inhibiting complement as therapeutic agents to treat sickle cell disease.

BACKGROUND OF THE INVENTION

[0002] Sickle cell disease (also called sickle cell anemia) is an inherited form of anemia. The red blood cells are affected by a mutation in the beta globin gene which affects hemoglobin structure. The mutant hemoglobin causes red blood cells, which normally are smooth and round, to become hard, sticky, and shaped like sickles or crescents. These red cells tend to get stuck and block the flow of blood in small blood vessels and to lyse which in turn leads to pain, damage and a low blood count or anemia.

[0003] Sickle cell disease affects about 72,000 Americans, predominantly those of African ancestry. One in every 600 African-American births is a baby with sickle cell disease. One in every 1,000-1,400 Hispanic-American births is a baby with sickle cell disease. Those with the disease usually show some signs and symptoms after four months of age. These include: anemia because the sickle cells are fragile and break apart easily and die leaving a shortage of red blood cells to carry oxygen; periodic episodes of pain referred to as crises which develop when sickle-shaped red blood cells block blood flow through tiny blood vessels to the chest, abdomen and joints, with the pain sometimes occurring in the bones; hand-foot syndrome wherein swollen hands and feet occur when sickle-shaped red blood cells block blood flow out of the hands and feet; jaundice resulting from the liver being overwhelmed by the rapid breakdown of red blood cells; frequent infections because of damage to the spleen caused by the sickle cells; stunted growth because of a shortage of oxygen and nutrients due to a lack of healthy red blood cells; and vision problems which result from damage to blood vessels in the eye caused by sickle cells plugging those blood vessels. Other complications include stroke (caused by sickle cells blocking

blood flow to the brain), acute chest syndrome (chest pain, fever and difficulty breathing caused by trapped sickle cells in the lungs); organ damage to not only the spleen and eyes but also the kidneys and liver due to chronic deprivation of oxygen-rich blood; and ulcers on the legs due to a lack of blood vessels to nourish the skin. Gallstones are a possible complication resulting from high levels of bilirubin due to the high level of breakdown of red blood cells. Priapism may also develop if sickle cells prevent blood flow out of an erect penis and this can lead to impotence. Persons with sickle cell disease may also experience fatigue, joint pain, breathlessness, rapid heart rate, abdominal pain, bloody urine (hematuria), excessive urination, and excessive thirst.

[0004] Presently the only cure for sickle cell disease is a bone marrow transplantation. Unfortunately very few sickle cell patients have a suitable donor for transplant. Consequently, treatment of sickle cell patients is usually aimed at avoiding crises, relieving symptoms and preventing complications. Antibiotics such as penicillin are given to children beginning when they are 2-4 months old to help prevent infections such as pneumonia. Vaccines are also given to prevent bacterial infections. Pain relievers, sometimes including narcotics, are commonly administered during a sickle crisis. Red blood cell transfusions are used to increase the number of normal red blood cells in circulation, helping to relieve anemia and its resulting symptoms and helping to prevent stroke. Blood transfusions do, however, include some risk such as a buildup of excess iron which can damage the heart, liver and other organs. Administration of supplemental oxygen via a breathing mask can be useful during an acute chest syndrome or a sickle cell crisis. Hydroxyurea, a prescription drug normally used to treat cancer, is sometimes administered to adults with severe disease. It reduces the frequency of painful crises and may reduce the need for blood transfusions. It appears to work by stimulating production of fetal hemoglobin. Patients who took hydroxyurea over a 9-year period experienced a 40% reduction in deaths. There is concern that long-term use of this drug may cause tumors or leukemia. Other drugs used to activate the production of fetal hemoglobin include 5-azacytidine and 5-aza-2'-deoxycytidine (decitabine) which hypomethylate DNA but, as with hydroxyurea, these can be toxic carcinogens.

[0005] Experimental treatments are being performed in an attempt to either cure or better treat sickle cell disease. Because sickle cell disease is caused by a mutation in a single gene, gene therapy is being considered as a treatment to cure the disease. However, gene therapy studies in general for other diseases have not worked well and are fraught with the possibility that the therapy will in turn cause some type of cancer due to indiscriminate insertion of the gene into the genome. Drugs being tested include butyric acid (which may increase the amount of fetal hemoglobin in the blood), clotrimazole (normally used to treat fungal infections but which may prevent loss of water from red blood cells and thereby reduce the number of sickle cells that form), and nitric oxide (a gas which helps keep blood vessels open and reduces the stickiness of red blood cells). A search of the ClinicalTrials.gov website using the search term "sickle cell" gave a listing of 55 clinical trials (including completed studies, studies no longer recruiting, studies still recruiting patients, terminated studies, and studies not yet recruiting) related to sickle cell disease or sickle cell trait. This listing is shown as Table 1.

Table 1

1. **Completed**	A study of the efficacy and safety of ICA-17043 (with or without hydroxyurea) in patients with sickle cell anemia. Conditions: Sickle Cell Disease; Sickle Cell Anemia
2. **Completed**	Mobilization and Handling of Stem Cells for Transplant from Healthy Volunteers with Sickle Cell Trait Condition: Sickle Cell Trait
3. **Recruiting**	Nitric Oxide Inhalation to Treat Sickle Cell Pain Crises Condition: Anemia, Sickle Cell
4. **Recruiting**	Evaluation of Hydroxyurea Plus L-arginine or Sildenafil to Treat Sickle Cell Anemia Condition: Sickle Cell Anemia
5. **Recruiting**	Natural History of Sickle Cell Disease and Other Hemolytic Disorders Conditions: Sickle Cell Anemia; Hemolytic Anemia; Hemoglobin SC Disease; Hematologic Diseases
6. **Recruiting**	Study of Oral ICL670 (Deferasirox) Relative to Subcutaneous Deferoxamine in Sickle Cell Disease Patients Conditions: Sickle Cell Disease; Iron Overload; Hemolytic Anemia
7. **Recruiting**	Collection and Storage of Umbilical Cord Stem Cells for Treatment of Sickle Cell Disease

Conditions: Healthy; Sickle Cell Anemia

8. **Completed** Effects of Nitric Oxide and Nitroglycerin in Patients with Sickle Cell Anemia
Conditions: Chest Pain; Sickle Cell Anemia

9. **Recruiting** Secondary Pulmonary Hypertension in Adults with Sickle Cell Anemia
Conditions: Pulmonary Hypertension; Sickle Cell Anemia

10. **Completed** Nitric Oxide to Improve Blood Flow in Sickle Cell Disease
Condition: Sickle Cell Anemia

11. **Recruiting** Bone Marrow Transplantation in Treating Children With Sickle Cell Disease
Condition: Sickle Cell Anemia

12. **No longer recruiting** Hydroxyurea for the Treatment of Patients with Sickle Cell Anemia
Condition: Sickle Cell Anemia

13. **No longer recruiting** Safety of ICL670 vs. Deferoxamine in Sickle Cell Disease Patients with Iron Overload due to Blood Transfusions
Condition: Anemia, Sickle Cell

14. **No longer recruiting** Decompression Coring Versus Conservative Therapy in Patients With Avascular Necrosis of the Hip Related to Sickle Cell Disease
Conditions: Bone Avascular Necrosis; Sickle Cell Anemia

15. **Recruiting** Inhaled Nitric Oxide and Transfusion Therapy for Patients with Sickle Cell Anemia and Secondary Pulmonary Hypertension
Conditions: Sickle Cell Anemia; Pulmonary Hypertension

16. **Recruiting** Arginine Treatment of Acute Chest Syndrome (Pneumonia) in Sickle Cell Disease Patients
Conditions: Anemia, Sickle Cell; Pneumonia

17. **Recruiting** Therapeutic Application of Intravascular Nitrite for Sickle Cell Disease
Condition: Sickle Cell Anemia

18. **Recruiting** Atorvastatin Therapy to Improve Endothelial Function in Sickle Cell Disease
Condition: Sickle Cell Disease

19. **Completed** Cerebrovascular Involvement in Sickle Cell Disease - Comprehensive Sickle Cell Center
Conditions: Anemia, Sickle Cell; Blood Disease; Cerebrovascular Accident

20. **Completed** Prevention of Cerebral Infarction in Sickle Cell Anemia - Comprehensive Sickle Cell Center
Conditions: Anemia, Sickle Cell; Blood Disease; Cerebrovascular Disorders; Cerebrovascular Accident

21. **Completed** A Phase I/II Trial of Recombinant-Methionyl Human Stem Cell Factor (SCF) in Adult Patients with Sickling Disorders

Conditions: hemoglobin SC disease; sickle cell anemia

22. **Recruiting** Home Based Massage and Relaxation for Sickle Cell Pain
Condition: Sickle Cell Disease

23. **Recruiting** A Stratified Sickle Event Randomized Trial (ASSERT)
Condition: Sickle Cell Disease

24. **Recruiting** Study of Clotrimazole and Hydroxyurea in Patients With Sickle Cell Syndromes
Condition: Sickle Cell Anemia

25. **No longer recruiting** Phase III Randomized Study of Poloxamer 188 for Vaso-Occlusive Crisis of Sickle Cell Disease
Condition: Sickle Cell Anemia

26. **Recruiting** Phase II Randomized Trial of Arginine Butyrate Plus Standard Local Therapy in Patients With Refractory Sickle Cell Ulcers
Conditions: Skin Ulcers; Sickle Cell Anemia

27. **Recruiting** Phase I/II Randomized Study of Hydroxyurea With or Without Clotrimazole in Patients With Sickle Cell Anemia
Condition: Sickle Cell Anemia

28. **Completed** Pilot Study of Fructose for Sickle Cell Crisis
Condition: Sickle Cell Anemia

29. **Completed** Investigation of Selected Patient Groups From The Cooperative Study of Sickle Cell Disease
Conditions: Anemia, Sickle Cell; Blood Disease

30. **Completed** Neuropsychological Studies of Children with Sickle Cell
Conditions: Blood Disease; Anemia, Sickle Cell; Neurologic Manifestations

31. **Recruiting** Stem Cell Transplantation after Reduced-Dose Chemotherapy for Patients with Sickle Cell Disease or Thalassemia
Conditions: Hemoglobinopathies; Anemia, Sickle Cell; Hemoglobin SC Disease; Thalassemia; Thalassemia Major

32. **Recruiting** Induction of Stable Chimerism for Sickle Cell Anemia
Conditions: Blood Disease; Hematopoietic Stem Cell Transplantation; Anemia, Sickle Cell

33. **Recruiting** L-glutamine Therapy for Sickle Cell Anemia
Conditions: Anemia, Sickle Cell; Thalassemia

34. **Completed** Penicillin Prophylaxis in Sickle Cell Disease (PROPS)
Conditions: Anemia, Sickle Cell; Hematologic Diseases; Hemoglobinopathies; Infection (S. pneumoniae); Pneumonia

35. **No longer recruiting** Multicenter Study of Hydroxyurea in Patients With Sickle Cell Anemia (MSH)
Conditions: Anemia, Sickle Cell; Hematologic Diseases; Hemoglobinopathies

36. **Completed** Stroke Prevention in Sickle Cell Anemia (STOP 1)
Conditions: Anemia, Sickle Cell; Cerebral Embolism and Thrombosis; Cerebrovascular Disorders; Hematologic

Diseases; Hemoglobinopathies

37. **Completed** Pediatric Hydroxyurea in Sickle Cell Anemia (PED HUG)
Conditions: Anemia, Sickle Cell; Hematologic Diseases; Hemoglobinopathies

38. **Completed** Cooperative Study of The Clinical Course of Sickle Cell Disease
Conditions: Anemia, Sickle Cell; Blood Disease

39. **Completed** Indices of Severity and Prognosis for Sickle Cell Disease
Conditions: Anemia, Sickle Cell; Blood Disease

40. **Completed** Hemostasis in Sickle Cell Disease--Infancy to Adulthood
Conditions: Anemia, Sickle Cell; Blood Disease

41. **Recruiting** Pediatric Hydroxyurea in Sickle Cell Anemia (BABY HUG)
Conditions: Blood Disease; Anemia, Sickle Cell

42. **No longer recruiting** Pain in Sickle Cell Epidemiologic Study
Conditions: Blood Disease; Anemia, Sickle Cell

43. **No longer recruiting** Pediatrics:Chlamydia, Sickle Cell Anemia and Stroke Risk - Ancillary to STOP II
Conditions: Blood Disease; Anemia, Sickle Cell; Chlamydia Infections; Cerebrovascular Accident

44. **Recruiting** Silent Cerebral Infarct Multi-Center Clinical Trial
Conditions: Sickle Cell Anemia; Stroke

45. **No longer recruiting** Stroke Prevention in Sickle Cell Anemia (STOP 2)
Conditions: Blood Disease; Cerebrovascular Accident; Anemia, Sickle Cell

46. **Completed** Study of Allogeneic Bone Marrow Transplantation Using Matched, Related Donors in Patients With Nonmalignant Hematologic Disorders
Conditions: Neutropenia; Sickle Cell Anemia; Thalassemia Major; Red-Cell Aplasia, Pure

47. **Recruiting** Phase I/II Study of Nonmyeloablative Allogeneic Bone Marrow Transplantation in Patients With High Risk Hemoglobinopathy
Conditions: Graft Versus Host Disease; Sickle Cell Anemia; Thalassemia

48. **No longer recruiting** Transcranial Doppler (TCD) Ultrasound of Subjects Enrolled in BABY HUG - Ancillary to BABY HUG
Conditions: Blood Disease; Anemia, Sickle Cell; Cerebrovascular Disorders; Cerebral Embolism and Thrombosis

49. **Terminated** Bone marrow transplant from donor using less toxic conditioning for patient with high risk hemoglobinopathies
Conditions: Sickle Cell Anemia; Hemoglobinopathy; Thalassemia

50. **Terminated** Bone Marrow transplant from related donor for patients with high risk hemoglobinopathies

		Conditions: Sickle Cell Anemia; Hemoglobinopathy; Thalassemia
51.	Recruiting	Improving the Results of Bone Marrow Transplantation for Patients with Severe Congenital Anemias Conditions: Congenital Hemolytic Anemia; Diamond-Blackfan Anemia
52.	Not yet recruiting	Sibling Donor Cord Blood Banking and Transplantation Conditions: Blood Disease; Anemia, Sickle Cell; Anemia (Cooley's); Leukemia; Bone Marrow Transplantation; Hematopoietic Stem Cell Transplantation
53.	Recruiting	Development of a Hospital-Based Home Program for the Use of Inhaled Nitric Oxide in the Chronic Management of Severe Cardiopulmonary Diseases Conditions: Pulmonary Hypertension; Lung Disease; Sickle Cell Disease; Cardiac transplant; Lung transplant
54.	Recruiting	The Effect of Oral Magnesium Pidolate on How Often Painful Crises Happens in Patients with Hemoglobin SC Disease Condition: Hemoglobin SC Disease
55.	No longer recruiting	Surgery With or Without Chemotherapy in Treating Patients With Stage I Non-small Cell Lung Cancer Condition: stage I non-small cell lung cancer

[0006] It is seen that numerous of these studies concern the use of hydroxyurea (either alone or in combination with another drug), bone marrow transplantation, nitric oxide, or clotrimazole. A small number of the listed studies are testing other drugs, e.g., hydroxyurea plus L-arginine or sildenafil; nitric oxide plus nitroglycerin; ICA-17043; ICL60 (Deferasirox) as compared to deferoxamine; poloxamer 188; atorvastatin; arginine; L-glutamine; arginine butyrate; fructose; and oral magnesium pidolate.

[0007] In addition to the studies listed above, numerous articles have been published concerning the use of other drugs to treat sickle cell patients. These drugs work in a large variety of ways. Abdulmalik et al. (Br. J. Haematol. 128:552-561 (2005)) used 5-hydroxymethyl-2-furfural which binds to intracellular sickle hemoglobin and inhibits sickling. Vanillin is known to bind to sickle hemoglobin and inhibit sickling, but given orally it is rapidly decomposed. Zhang et al. (Br. J. Haematol. 125:788-795 (2004)) used a vanillin prodrug, MX-1520, which is not rapidly decomposed and found that it reduced the percentage of sickled cells in the blood. DeBellis et al. (Blood Cells Mol. Dis. 31:286-290 (2003)) tested three

purine-based antiviral agents (ganciclovir, valacyclovir, and penciclovir) and found that valacyclovir and ganciclovir show anti-sickling activity similar to acyclovir which was known to inhibit aggregation of hemoglobin S and the sickling of erythrocytes. Cordeiro and Oniyangi (Cochrane Database Syst. Rev. 3:CD004448 (2004)) found that a phytomedicine (Niprisan) was effective in reducing episodes of sickle cell disease crisis associated with severe pain. Iyamu et al. (Br. J. Haematol. 122:1001-1008 (2003)) also studied Niprisan (Nix-0699) in mice and found that it inhibited sickling. Manion et al. (Clin. Pharmacol. Ther. 69:346-355 (2001)) studied the use of aspartame for treating sickle cell disease. Aspartame binds to two human Bence Jones proteins (Mcg and Sea). In vivo studies in persons showed that aspartame treatment led to decreased sickling. Beddell et al. (Br. J. Pharmacol. 82:397-407 (1984)) designed substituted benzaldehydes to bind preferentially to the oxy conformation of human hemoglobin to stabilize the oxygenated form of hemoglobin and thereby increase its oxygen affinity. At least one such compound was a potent inhibitor at low oxygen pressure of the sickling of erythrocytes. Related work by Arya et al. (Br. J. Haematol. 93:817-821 (1996)) involved the study of Tucaresol (589C80;4[2-formyl-3-hydroxyphenoxymethyl]benzoic acid) which is a substituted benzaldehyde. Administration of tucaresol to sickle cell patients resulted in decreased hemolysis, a decrease in lactate dehydrogenase, and a halving of the irreversibly sickled cell counts. However, 3 of 6 patients developed fever and cervical lymphadenopathy. Riddington and De Franceschi (Cochrane Database Syst. Rev. 4:CD003426 (2002)) reviewed the literature of controlled trials to find trials related to using drugs which aimed to prevent sickle cell related crises by reducing red blood cell dehydration. They found two trials. These tested zinc sulfate and piracetam. The zinc trial showed a significant reduction in the total number of pain, hemolytic, aplastic and sequestration crises over one and a half years. The piracetam trial showed a reduction in pain crises over a one year time span, although blood counts were not significantly changed. Dehydration of red blood cells can occur through the Ca-activated K channel which depends on the parallel movement of Cl ions. Bennekou et al. (Blood 97:1451-1457 (2001)) studied whether Cl-conductance block might prevent dehydration of sickle red blood cells. They used a novel Cl-conductance inhibitor (NS3623). Mice treated with NS3623

showed an increase in hematocrit, a decrease in the mean corpuscular hemoglobin concentration, and a loss of the densest red cell population with a shift from a high proportion of sickled to well-hydrated discoid erythrocytes. Kocak et al. (Br. J. Haematol. 92:329-331 (1996)) used the vasodilating Ca^{+2} channel blocker bencyclane in 18 patients with sickle cell disease. The patients' blood contained fewer irreversibly sickled cells. Inhibition of the sickling-induced fluxes of Na^{+}, K^{+} and Ca^{+2} was studied by Joiner et al. using dipyridamole (Blood 97:3976-3983 (2001)). The dipyridamole was found to inhibit sickling by inhibiting the ion flux. Shartava et al. (Am. J. Hematol. 62:19-24 (1999)) studied both clotrimazole (which is a specific inhibitor of the Ca^{+2} activated potassium channel) and the antioxidant N-acetylcysteine. Both were found to inhibit the in vitro formation of high-density sickle cells. The authors concluded that N-acetylcysteine protects the potassium channel from oxidative damage caused by diminished levels of reduced glutathione. Another drug which protects against K^{+} efflux is bepridil and this was found to significantly inhibit the formation of irreversibly sickled cells in a study by Johnston et al. (Br. J. Haematol. 73:522-526 (1989)). A recent review of established and experimental treatments for sickle cell disease was published by De Franceschi and Corrocher (Haematologica 89:348-356 (2004)), the contents of which are incorporated herein by reference.

[0008] In addition to the numerous studies listed above, basic research has been performed which shows a possible relationship between sickle cell disease and complement. The complement system is described in detail in U.S. Patent 6,355,245. The complement system acts in conjunction with other immunological systems of the body to defend against intrusion of cellular and viral pathogens. There are at least 25 complement proteins, which are found as a complex collection of plasma proteins and membrane cofactors. The plasma proteins make up about 10% of the globulins in vertebrate serum. Complement components achieve their immune defensive functions by interacting in a series of intricate but precise enzymatic cleavage and membrane binding events. The resulting complement cascade leads to the production of products with opsonic, immunoregulatory, and lytic functions.

[0009] The complement cascade progresses via the classical pathway or the alternative pathway. These pathways share many components and, while they differ in their initial steps, they converge and share the same "terminal complement" components (C5 through C9) responsible for the activation and/or destruction of target cells.

[0010] The classical complement pathway is typically initiated by antibody recognition of and binding to an antigenic site on a target cell. The alternative pathway is usually antibody independent and can be initiated by certain molecules on pathogen surfaces. Both pathways converge at the point where complement component C3 is cleaved by an active protease (which is different in each pathway) to yield C3a and C3b. Complement activation can also occur via the lectin complement pathway (LCP). Lectins are carbohydrate-binding proteins that recognize oligosaccharide structures present on cell surfaces, the extracellular matrix, and secreted glycoproteins. As with the classical complement pathway and the alternative pathway, the LCP also converges at the point of cleavage of complement component C3. Other pathways activating complement attack can act later in the sequence of events leading to various aspects of complement function.

[0011] C3a is an anaphylatoxin. C3b binds to bacterial and other cells, as well as to certain viruses and immune complexes, and tags them for removal from the circulation. C3b in this role is known as opsonin. The opsonic function of C3b is considered to be the most important anti-infective action of the complement system. Patients with genetic lesions that block C3b function are prone to infection by a broad variety of pathogenic organisms, while patients with lesions later in the complement cascade sequence, i.e., patients with lesions that block C5 functions, are found to be more prone only to Neisseria infection, and then only somewhat more prone (Fearon (1983). In Intensive Review of Internal Medicine, 2nd Ed. Fanta and Minaker, eds. Brigham and Women's and Beth Israel Hospitals).

[0012] C3b also forms a complex with other components unique to each pathway to form classical or alternative C5 convertase, which cleaves C5 into C5a and C5b. C3 is thus regarded as the central protein in the complement reaction sequence since it is essential to both the alternative and classical pathways (Wurzner et al., Complement Inflamm. 8:328-340 (1991)). This property of C3b is regulated

by the serum protease Factor I, which acts on C3b to produce iC3b. While still functional as opsonin, iC3b cannot form an active C5 convertase.

[0013] C5 is a 190 kDa beta globulin found in normal serum at approximately 75 μg/mL (0.4 μM). C5 is glycosylated, with about 1.5-3 percent of its mass attributed to carbohydrate. Mature C5 is a heterodimer of a 999 amino acid 115 kDa alpha chain that is disulfide linked to a 656 amino acid 75 kDa beta chain. C5 is synthesized as a single chain precursor protein product of a single copy gene (Haviland et al., J. Immunol. 146:362-368 (1991)). The cDNA sequence of the transcript of this gene predicts a secreted pro-C5 precursor of 1659 amino acids along with an 18 amino acid leader sequence.

[0014] The pro-C5 precursor is cleaved after amino acid 655 and 659, to yield the beta chain as an amino terminal fragment (amino acid residues +1 to 655) and the alpha chain as a carboxyl terminal fragment (amino acid residues 660 to 1658), with four amino acids deleted between the two.

[0015] C5a is cleaved from the alpha chain of C5 by either alternative or classical C5 convertase as an amino terminal fragment comprising the first 74 amino acids of the alpha chain (i.e., amino acid residues 660-733). Approximately 20 percent of the 11 kDa mass of C5a is attributed to carbohydrate. The cleavage site for convertase action is at or immediately adjacent to amino acid residue 733. A compound that would bind at or adjacent to this cleavage site would have the potential to block access of the C5 convertase enzymes to the cleavage site and thereby act as a complement inhibitor. C5 can also be activated by means other than C5 convertase activity. Limited trypsin digestion (Minta and Man, J. Immunol. 119:1597-1602 (1977); Wetsel and Kolb, J. Immunol. 128:2209-2216 (1982)) and acid treatment (Yamamoto and Gewurz, J. Immunol. 120:2008-2015 (1978); Vogt et al., Molec. Immunol. 26:1133-1142 (1989)) can also cleave C5 and produce active C5b.

[0016] C5a is another anaphylatoxin. C5b combines with C6, C7, and C8 to form the C5b-8 complex at the surface of the target cell. Upon binding and polymerization of several C9 molecules, the membrane attack complex (MAC, C5b-9, terminal complement complex-TCC) is formed. When sufficient numbers of MACs insert into target cell membranes the openings they create (MAC pores)

mediate rapid osmotic lysis of the target cells. Lower, non-lytic concentrations of MACs can produce other effects. In particular, membrane insertion of small numbers of the C5b-9 complexes into endothelial cells and platelets can cause deleterious cell activation. In some cases activation may precede cell lysis. As mentioned above, C3a and C5a are anaphylatoxins. These activated complement components can trigger mast cell degranulation, which releases histamine and other mediators of inflammation, resulting in smooth muscle contraction, increased vascular permeability, leukocyte activation, and other inflammatory phenomena including cellular proliferation resulting in hypercellularity. C5a also functions as a chemotactic peptide that serves to attract pro-inflammatory granulocytes to the site of complement activation.

[0017] In 1994 Chudwin et al. (Clin. Immunol. Immunopathol. 71:199-202 (1994)) reported that red blood cells from sickle cell patients activated complement to a greater extent than did red blood cells from control patients. Additionally they reported that the activation was via the alternative pathway and not the classical pathway. In 1995 Mold et al. (Clin. Immunol. Immunopathol. 76:314-320 (1995)) demonstrated that the alternative pathway activation is initiated by membrane phospholipid changes which occur in sickled erythrocytes. They found that in patients with intermittent pain there was little evidence of complement activation and that there was an increased plasma concentration of C3a during a painful crisis. Also, elevated C3a and C4d levels were observed in patients with continuous pain. Earlier, Tomasko and Chudwin had shown that changes in phospholipid organization in sickle cells may contribute to the chronic alternative complement pathway activation seen in sickle cell disease patients (J. Lab. Clin. Med. 112:248-253 (1988)). In 1986 De Ceulaer et al. (J. Clin. Lab. Immunol. 21:37-41 (1986)) published a paper concerning complement levels in sickle cell disease patients and the relation to infection. They reported that complement component C3 levels were consistently lower in sickle cell children and levels of C3d were significantly higher, but they found no difference in the prevalence of infections between the groups. Dieye et al. (Dakar Med. 44:175-179 (1999)) also studied the relationship between complement and infection in sickle cell patients. They found that C3c complement (indicative of the alternative pathway) levels were decreased significantly whereas

C4c (indicative of the classical pathway) levels were not. They conclude there is a direct involvement of the complement system in sickle cell disease and the depletion of C3 is a possible cause of increased susceptibility to infections in patients with sickle cell disease.

[0018] Mohamed et al. (Am. J. Trop. Med. Hyg. 49:799-803 (1993)) found that C3d levels are elevated in sickle cell disease patients. They noted that this was not accompanied by altered complement activity in serum in vitro or in C3 reduction. They state that the underlying mechanism of this activation may be the triggering of the complement reaction by the sickled cell, the phospholipid organization of which appears to promote the alternative pathway complement activation. They conclude that the complement activation may contribute to impaired host defense against bacterial infections.

[0019] Test and Woolworth (Blood 83:842-852 (1994)) further studied the relationship between sickle cell disease and complement. They first noted that prior work concluded that intravascular hemolysis of sickle cells resulted in complement activation. Test and Woolworth took the opposite view that possibly complement activation was leading to hemolysis. They showed in a series of in vitro assays that regulation of complement in sickle cells was abnormal, especially in that increased binding of C5b-7 and C9 to denser sickle cells was seen and this appeared to increase the susceptibility of sickle cells to lysis. They believe that the increased binding is most likely caused by changes in MIRL (also referred to as CD59) brought about by the sickling process and which is a membrane protein which inhibits lysis by the membrane attack complex. CD59 is a human glycosylphosphatidylinositol-anchored membrane glycoprotein that serves as the principle inhibitor of the cytolytic and pore forming activities of the C5b-9 membrane attack complex (MAC) of human complement. By inhibiting MAC, CD59 protects human blood cells, vascular endothelium and other cells from complement, which is normally present in human plasma and other body fluids. Although the exact mechanism of its complement inhibitory function remains to be elucidated, CD59 is known to bind peptide segments of C8 and C9 that become exposed when these complement proteins incorporate into the C5b-9 complex, thereby preventing initiation or propagation of the membrane-inserted C9 polymer

that is responsible for membrane damage. Blood cells from patients with paroxysmal nocturnal hemoglobinuria (PNH) lack the ability to anchor CD59 in their membranes and these cells are very susceptible to lysis via complement. Transducing these cells with a recombinant transmembrane form of CD59 results in the surface expression of CD59 and these transduced cells are protected against classical complement-mediated membrane damage by human serum (Rother et al., Blood 84:2604-2611 (1994)).

[0020] This work was followed up by Liu et al. (Blood 93:2297-2301 (1999)) who inserted various types of lipids into human erythrocyte membranes. They found that neutral lipids had no effect on C5b-7 uptake or hemolysis by C5b-9, but acidic phospholipids did cause a dose-dependent increase in both lysis and C5b-7 uptake. They concluded that the presence of anionic lipids on the exterior of the membrane increases C5b-7 uptake and subsequent hemolysis. They point out that it is known that sickle cell erythrocytes have increased exposure of phophatidylserine on their external face and are abnormally sensitive to lysis by C5b-9.

[0021] Concerning the issue of hemolysis, it is known that in autoimmune hemolytic anemia red blood cell destruction is primarily extravascular. This is largely mediated through either Fc and/or complement receptors expressed by phagocytic effector cells. Experimentally induced autoimmune hemolytic anemia occurs even in the absence of the complement components C3, C4 and C5 but requires the presence of Fc receptors in association with the common FcR γ-chain (Meyer et al., Blood 92:3997-4002 (1998)).

[0022] The prior art as a whole leaves the field quite uncertain as to what role, if any, complement plays in sickle cell disease and more specifically complement's role in lysis of red blood cells in sickle cell disease patients. Mohamed et al. (Am. J. Trop. Med. Hyg. 49:799-803 (1993)) state, "Although some investigators have reported defects in the complement system as the cause for the increased susceptibility to infections, others have not found such defects." They also state that intravascular hemolysis accounts for the destruction of one-third of the sickled erythrocytes, while two-thirds are removed by macrophages in the spleen and other locations and that the hemolytic process in sickle cell anemia may involve several components, including activation of complement, macrophages, and neutrophils.

[0023] The publications and other materials used herein to illuminate the background of the disclosure, and in particular, cases to provide additional details respecting the practice, are incorporated herein by reference.

SUMMARY

[0024] Methods for treating patients suffering from sickle cell disease are presented. A method of treating sickle cell disease in a mammal comprising treating said mammal with a therapeutically effective amount of an anti-C5 antibody, wherein said treatment results in decreased lysis of red blood cells in said mammal. In certain embodiments, said mammal is a human.

[0025] In certain embodiments, said antibody is a whole antibody or an antibody fragment. In certain embodiments, said whole antibody or antibody fragment is selected from the group consisting of: a polyclonal antibody, a monoclonal antibody or antibody fragment, a diabody, a chimerized or chimeric antibody or antibody fragment, a humanized antibody or antibody fragment, a deimmunized human antibody or antibody fragment, a fully human antibody or antibody fragment, a single chain antibody, an Fv, an Fab, an Fab', or an $F(ab')_2$.

[0026] In certain embodiments, said treatment is chronic. In certain embodiments, said treatment comprises treating an acute episode. In certain embodiments, said mammal is treated by administering said antibody intravenously.

[0027] In certain embodiments, said mammal is treated to inhibit or decrease the amount and/or extent of an undesirable physiological condition resulting from excess lysis of red blood cells. In certain embodiments, said undesirable physiological condition is selected from the group consisting of dystonia, a clotting disorder, pulmonary hypertension, systemic hypertension, gastrointestinal contractions, abdominal pain, sternal pain, erectile dysfunction, priapism, inflammation, esophageal spasm, dysphagia, thrombosis, decreased organ perfusion, platelet activation and death.

[0028] In certain embodiments, said antibody inhibits activation of the classical pathway, the alternative pathway or the lectin complement pathway. In certain embodiments, said antibody is an antibody against a member of the complement cascade components such as for example, C5, C5b, C6, C7, C8, and C9. In certain

embodiments, said antibody is an inhibitor of C5 cleavage. In certain embodiments, said antibody decreases the availability of downstream complement components.

[0029] In certain embodiments, said antibody is pexelizumab. In certain embodiments, said antibody is eculizumab.

DETAILED DESCRIPTION

[0030] Sickle cell disease is an extremely serious disease affecting approximately 72,000 Americans and many more persons in other countries. At present a cure is almost nonexistent, the only cure being a bone marrow transplant. Gene therapy is a possible cure but is not being performed. In general sickle cell disease patients have their symptoms treated but are not cured. Treatments include treating or preventing infections by administration of antibiotics, blood transfusions to increase the supply of normal red blood cells, drugs to increase the level of fetal hemoglobin which is able to carry oxygen, drugs to prevent loss of water from erythrocytes thereby helping to prevent sickling, and drugs to aid in keeping blood vessels open. Despite these treatments, many patients continue to suffer greatly and many patients die as a result of the disease. More effective treatments are needed.

[0031] Several studies dating back several years have shown that complement activation may be affected in sickle cell disease patients. These date back to at least 1967 (Francis and Womack, Am. J. Med. Technol. 33:77-86 (1967)). However the role of complement activation is still unclear. There are conflicting reports as to whether changes in complement result in greater infection. Even if it is proved that infection is greater because of effects to the complement system, such infections are normally treated with inexpensive antibiotics such as penicillin. Other work shows conflicting results as to whether sickle cell disease causes complement activation or whether complement activation causes some of the problems of sickle cell disease.

[0032] Applicant here proposes that treatment of a sickle cell disease patient with a complement inhibitor will decrease lysis of red blood cells and at least some of the symptoms seen in sickle cell patients. Many of the symptoms are a direct result of the lysis of red blood cells. One aspect of the lysis of red blood cells is the consequent excess free hemoglobin in the bloodstream. This can lead to smooth muscle dystonias involving the gastrointestinal, cardiovascular, pulmonary, and

urogenital systems, as well as clotting disorders, these symptoms including gastrointestinal contractions, erectile dysfunction such as priapism, and pulmonary hypertension as well as to clot formation (Rother et al., JAMA 293:1653-1662 (2005), the contents of which are specifically incorporated herein by reference). Approximately one-third of sickled red blood cells are lysed via intravascular hemolysis (Mohamed et al., Am. J. Trop. Med. Hyg. 49:799-803 (1993)). Applicant here proposes that inhibition of complement activation will decrease the amount of lysis and thereby decrease the amount and/or extent of symptoms related to the lysis of red blood cells in sickle cell disease patients. Inhibitors of members of the complement cascade including for example antibodies to components such as C5, C5b, C6, C7, C8, and C9. In particular embodiments, this application contemplates the use of the anti-C5 antibody eculizumab (a whole antibody) which is known to inhibit cleavage of C5 into C5a and C5b. Treatment of patients with such inhibitors thereby decreases complement mediated lysis of red blood cells. Long lasting inhibitors are preferable. Eculizumab, being a whole antibody, is longer lasting in vivo than is a single-chain antibody and is preferably used although shorter acting inhibitors may be used, especially if used in time of a crisis and is used to relieve the crisis. Eculizumab has been used in clinical studies and found to be well tolerated with minimal side effects. Eculizumab has been administered to patients with paroxysmal nocturnal hemoglobinuria which is a disease in which red blood cells are easily lysed due to a lack of a protein in the red blood cell membrane which protects against lysis by activated complement. Most patients are administered a dose once every two weeks. See Hillmen et al., New Engl. J. Med. 350:552-559 (2004), the contents of which are specifically incorporated herein by reference.

[0033] Suitable anti-C5 antibodies are known to those of skill in the art. Antibodies can be made to individual components of activated complement, e.g., antibodies to C7, C9, etc. (see, e.g., U.S. Patent 6,534,058; published U.S. patent application US 2003/0129187; and U.S. Patent 5,660,825). U.S. Patent 6,355,245 teaches an antibody which binds to C5 and inhibits cleavage into C5a and C5b thereby decreasing the formation not only of C5a but also the down stream complement components.

[0034] Additional proteins are known which inhibit complement-mediated lysis, including CD59, CD55, CD46 and other inhibitors of C8 and C9 (see, e.g., U.S. Patent 6,100,443). Proteins known as complement receptors and which bind complement are also known (see, Published PCT Patent Application WO 92/10205 and U.S. Patent 6,057,131). Use of soluble forms of complement receptors, e.g., soluble CR1, can inhibit the consequences of complement activation such as neutrophil oxidative burst, complement mediated hemolysis, and C3a and C5a production. Those of skill in the art recognize the above as some, but not all, of the known methods of inhibiting complement and its activation.

[0035] A preferred method of inhibiting complement activity is to use a monoclonal antibody which binds to complement C5 and inhibits cleavage. This decreases the formation of both C5a and C5b while at the same time allowing the formation of C3a and C3b which are beneficial to the recipient. Such antibodies which are specific to human complement are known (U.S. Patent 6,355,245). These antibodies disclosed in U.S. Patent 6,355,245 include a preferred whole antibody (now named eculizumab). A similar antibody against mouse C5 is called BB5.1 (Frei et al., Mol. Cell. Probes. 1:141-149 (1987)). Antibodies to inhibit complement activity need not be monoclonal antibodies. They can be, e.g., polyclonal antibodies. They may additionally be antibody fragments. An antibody fragment includes, but is not limited to, an Fab, F(ab'), $F(ab')_2$, single-chain antibody, and Fv. Furthermore, it is well known by those of skill in the art that antibodies can be humanized (Jones et al., Nature 321:522-5 (1986)), chimerized, or deimmunized. The antibodies to be used in the present disclosure may be any of these. It is preferable to use humanized antibodies.

[0036] In specific embodiments, a therapeutic agent of the disclosure comprises an antibody or antibody fragment. Antibodies and fragments thereof may be made by any conventional method, such as those methods described herein. Antibodies are found in multiple forms, e.g., IgA, IgG, IgM, etc. Additionally, antibodies can be engineered in numerous ways. They can be made as single-chain antibodies (including small modular immunopharmaceuticals or SMIPs™), Fab and $F(ab')_2$ fragments, etc. Antibodies can be humanized, chimerized, deimmunized, or fully human. Numerous publications set forth the many types of antibodies and the

methods of engineering such antibodies. For example, see U.S. Patent Nos. 6,355,245; 6,180,370; 5,693,762; 6,407,213; 6,548,640; 5,565,332; 5,225,539; 6,103,889; and 5,260,203.

[0037] This invention provides fragments of anti-C5 antibodies, which may comprise a portion of an intact antibody, preferably the antigen-binding or variable region of the intact antibody. Examples of antibody fragments include Fab, Fab', $F(ab')_2$, and Fv fragments; diabodies; linear antibodies (Zapata et al., Protein Eng. 8:1057-1062 (1995)); single-chain antibody molecules; and multispecific antibodies formed from antibody fragments.

[0038] Papain digestion of antibodies produces two identical antigen-binding fragments, called "Fab" fragments, each with a single antigen-binding site, and a residual "Fc" fragment, whose name reflects its ability to crystallize readily. Pepsin treatment of an antibody yields an $F(ab')_2$ fragment that has two antigen-combining sites and is still capable of cross-linking antigen.

[0039] "Fv" usually refers to the minimum antibody fragment that contains a complete antigen-recognition and -binding site. This region consists of a dimer of one heavy- and one light-chain variable domain in tight, non-covalent association. It is in this configuration that the three CDRs of each variable domain interact to define an antigen-binding site on the surface of the V_H-V_L dimer. Collectively, the six CDRs confer antigen-binding specificity to the antibody. However, even a single variable domain (or half of an Fv comprising only three CDRs specific for an antigen) has the ability to recognize and bind antigen, although likely at a lower affinity than the entire binding site.

[0040] The Fab fragment also contains the constant domain of the light chain and the first constant domain (CH1) of the heavy chain. Fab' fragments differ from Fab fragments by the addition of a few residues at the carboxy terminus of the heavy chain CH1 domain including one or more cysteines from the antibody hinge region. Fab'-SH is the designation herein for Fab' in which the cysteine residue(s) of the constant domains bear a free thiol group. $F(ab')_2$ antibody fragments originally were produced as pairs of Fab' fragments that have hinge cysteines between them. Other chemical couplings of antibody fragments are also known.

[0041] This disclosure also provides monoclonal anti-C5 antibodies. A monoclonal antibody can be obtained from a population of substantially homogeneous antibodies, i.e., the individual antibodies comprising the population are identical except for possible naturally-occurring mutations that may be present in minor amounts. Monoclonal antibodies are highly specific, being directed against a single antigenic site. Furthermore, in contrast to conventional (polyclonal) antibody preparations that typically include different antibodies directed against different determinants (epitopes), each monoclonal antibody is directed against a single determinant on the antigen. In addition to their specificity, the monoclonal antibodies are advantageous in that they are often synthesized by the hybridoma culture, uncontaminated by other immunoglobulins. Monoclonal antibodies may also be produced in transfected cells, such as CHO cells and NS0 cells. The modifier "monoclonal" indicates the character of the antibody as being obtained from a substantially homogeneous population of antibodies and does not require production of the antibody by any particular method. For example, the monoclonal antibodies to be used in accordance with the present disclosure may be made by the hybridoma method first described by Kohler et al., Nature 256:495-497 (1975), or may be made by recombinant DNA methods (*see, e.g.*, U.S. Patent Nos. 4,816,567 and 6,331,415). The "monoclonal antibodies" may also be isolated from phage antibody libraries using the techniques described in Clackson et al., Nature 352:624-628 (1991) and Marks et al., J. Mol. Biol. 222:581-597 (1991), for example.

[0042] General methods for the immunization of animals (in this case with C5 and/or C5b, etc.), isolation of antibody producing cells, fusion of such cells with immortal cells (e.g., myeloma cells) to generate hybridomas secreting monoclonal antibodies, screening of hybridoma supernatants for reactivity of secreted monoclonal antibodies with a desired antigen (in this case the immunogen or a molecule containing the immunogen), the preparation of quantities of such antibodies in hybridoma supernatants or ascites fluids, and for the purification and storage of such monoclonal antibodies, can be found in numerous publications. These include: Coligan, et al., eds. Current Protocols In Immunology, John Wiley & Sons, New York, 1992; Harlow and Lane, Antibodies, A Laboratory Manual, Cold Spring Harbor Laboratory, New York, 1988; Liddell and Cryer, A Practical Guide

To Monoclonal Antibodies, John Wiley & Sons, Chichester, West Sussex, England, 1991; Montz et al., Cellular Immunol. 127:337-351 (1990); Wurzner et al., Complement Inflamm. 8:328-340 (1991); and Mollnes et al., Scand. J. Immunol. 28:307-312 (1988).

[0043] A description of the preparation of a mouse anti-human-C5 monoclonal antibody with specific binding characteristics is presented in U.S. Patent Application Publication No. 20050226870. Wurzner et al., Complement Inflamm. 8:328-340 (1991), describe the preparation of other mouse anti-human-C5 monoclonal antibodies referred to as N19-8 and N20-9.

[0044] Other antibodies specifically contemplated are "oligoclonal" antibodies. As used herein, the term "oligoclonal" antibodies" refers to a predetermined mixture of distinct monoclonal antibodies. *See, e.g.*, PCT publication WO 95/20401; U.S. Patent Nos. 5,789,208 and 6,335,163. In one embodiment, oligoclonal antibodies consisting of a predetermined mixture of antibodies against one or more epitopes are generated in a single cell. In other embodiments, oligoclonal antibodies comprise a plurality of heavy chains capable of pairing with a common light chain to generate antibodies with multiple specificities (*e.g.,* PCT publication WO 04/009618). Oligoclonal antibodies are particularly useful when it is desired to target multiple epitopes on a single target molecule (*e.g.,* C5). In view of the assays and epitopes disclosed herein, those skilled in the art can generate or select antibodies or mixture of antibodies that are applicable for an intended purpose and desired need.

[0045] In certain embodiments that include a humanized and/or chimeric antibody, one or more of the CDRs are derived from an anti-human C5 antibody. In a specific embodiment, all of the CDRs are derived from an anti-human C5 antibody. In another specific embodiment, the CDRs from more than one anti-human C5 antibody are mixed and matched in a chimeric antibody. For instance, a chimeric antibody may comprise a CDR1 from the light chain of a first anti-human C5 antibody combined with CDR2 and CDR3 from the light chain of a second anti-human C5 antibody, and the CDRs from the heavy chain may be derived from a third anti-human C5 antibody. Further, the framework regions may be derived from one of the same anti-human C5 antibodies, from one or more different antibodies,

such as a human antibody, or from a humanized antibody. Human or humanized antibodies are specific for administration to human patients.

[0046] "Single-chain Fv" or "scFv" antibody fragments comprise the V_H and V_L domains of an antibody, wherein these domains are present in a single polypeptide chain. Preferably, the Fv polypeptide further comprises a polypeptide linker between the V_H and V_L domains that enables the scFv to form the desired structure for antigen binding. For a review of scFv see Pluckthun in The Pharmacology of Monoclonal Antibodies, vol. 113, Rosenburg and Moore, eds. (Springer-Verlag: New York, 1994), pp. 269-315.

[0047] SMIPs are a class of single-chain peptide engineered to include a target binding region, effector domain (CH2 and CH3 domains). *See, e.g.*, U.S. Patent Application Publication No. 20050238646. The target binding region may be derived from the variable region or CDRs of an antibody, e.g., an anti-C5 antibody of the invention. Alternatively, the target binding region is derived from a protein that binds C5.

[0048] The term "diabodies" refers to small antibody fragments with two antigen-binding sites, which fragments comprise a heavy-chain variable domain (V_H) connected to a light-chain variable domain (V_L) in the same polypeptide chain (V_H-V_L). By using a linker that is too short to allow pairing between the two domains on the same chain, the domains are forced to pair with the complementary domains of another chain and create two antigen-binding sites. Diabodies are described more fully in, for example, EP 404,097; WO 93/11161; and Hollinger et al., Proc. Natl. Acad. Sci. USA, 90: 6444-6448 (1993).

[0049] An "isolated" antibody is one that has been identified and separated and/or recovered from a component of its natural environment. Contaminant components of its natural environment are materials that would interfere with diagnostic or therapeutic uses for the antibody, and may include enzymes, hormones, and other proteinaceous or nonproteinaceous solutes. In specific embodiments, the antibody will be purified to greater than 95% by weight of antibody as determined by the Lowry method, or greater than 99% by weight, to a degree that complies with applicable regulatory requirements for administration to human patients (e.g., substantially pyrogen-free), to a degree sufficient to obtain at

least 15 residues of N-terminal or internal amino acid sequence by use of a spinning cup sequenator, or to homogeneity by SDS-PAGE under reducing or nonreducing conditions using Coomassie blue or, preferably, silver stain. Isolated antibody includes the antibody in situ within recombinant cells, since at least one component of the antibody's natural environment will not be present. Ordinarily, however, isolated antibody will be prepared by at least one purification step, for example, an affinity chromatography step, an ion (anion or cation) exchange chromatography step, or a hydrophobic interaction chromatography step.

[0050] It is well known that the binding to a molecule (or a pathogen) of antibodies with an Fc region assists in the processing and clearance of the molecule (or pathogen). The Fc portions of antibodies are recognized by specialized receptors expressed by immune effector cells. The Fc portions of IgG1 and IgG3 antibodies are recognized by Fc receptors present on the surface of phagocytic cells such as macrophages and neutrophils, which can thereby bind and engulf the molecules or pathogens coated with antibodies of these isotypes (C. A. Janeway et al., Immunobiology 5th edition, page 147, Garland Publishing (New York, 2001)).

[0051] In certain embodiments, single chain antibodies, and chimeric, humanized or primatized (CDR-grafted) antibodies, as well as chimeric or CDR-grafted single chain antibodies, comprising portions derived from different species, are also encompassed by the present disclosure as antigen-binding fragments of an antibody. The various portions of these antibodies can be joined together chemically by conventional techniques, or can be prepared as a contiguous protein using genetic engineering techniques. For example, nucleic acids encoding a chimeric or humanized chain can be expressed to produce a contiguous protein. See, e.g., U.S. Pat. Nos. 4,816,567 and 6,331,415; U.S. Pat. No. 4,816,397; European Patent No. 0,120,694; WO 86/01533; European Patent No. 0,194,276 B1; U.S. Pat. No. 5,225,539; and European Patent No. 0,239,400 B1. See also, Newman et al., BioTechnology 10:1455-1460 (1992), regarding primatized antibody. See, e.g., Ladner et al., U.S. Pat. No. 4,946,778; and Bird et al., Science 242:423-426 (1988), regarding single chain antibodies.

[0052] In addition, functional fragments of antibodies, including fragments of chimeric, humanized, primatized or single chain antibodies, can also be produced.

Functional fragments of the subject antibodies retain at least one binding function and/or modulation function of the full-length antibody from which they are derived. Preferred functional fragments retain an antigen-binding function of a corresponding full-length antibody (such as for example, ability of anti-C5 antibody to bind C5).

Pharmaceutical Formulations and Uses

[0053] Methods of administration of antibodies are well-known to those of skill in the art. To achieve the desired inhibition, the antibodies can be administered in a variety of unit dosage forms. The dose will vary according to the particular antibody. For example, different antibodies may have different masses and/or affinities, and thus require different dosage levels. Antibodies prepared as Fab fragments will also require differing dosages than the equivalent intact immunoglobulins, as they are of considerably smaller mass than intact immunoglobulins, and thus require lower dosages to reach the same molar levels in the patient's blood. The dose will also vary depending on the manner of administration, the particular symptoms of the patient being treated, the overall health, condition, size, and age of the patient, and the judgment of the prescribing physician. Dosage levels of the antibodies for human subjects are generally between about 1 mg per kg and about 100 mg per kg per patient per treatment, and preferably between about 5 mg per kg and about 50 mg per kg per patient per treatment. In terms of plasma concentrations, the antibody concentrations are preferably in the range from about 25 μg/mL to about 500 μg/mL. However, greater amounts may be required for extreme cases and smaller amounts may be sufficient for milder cases.

[0054] Administration of the antibodies will generally be performed by an intravascular route, e.g., via intravenous infusion by injection. Other routes of administration may be used if desired but an intravenous route will be the most preferable. Formulations suitable for injection are found in Remington's Pharmaceutical Sciences, Mack Publishing Company, Philadelphia, Pa., 17th ed. (1985). Such formulations must be sterile and non-pyrogenic, and generally will include a pharmaceutically effective carrier, such as saline, buffered (e.g., phosphate buffered) saline, Hank's solution, Ringer's solution, dextrose/saline, glucose solutions, and the like. The formulations may contain pharmaceutically acceptable

auxiliary substances as required, such as, tonicity adjusting agents, wetting agents, bactericidal agents, preservatives, stabilizers, and the like. Although antibodies are preferred, especially anti-C5 antibodies which have already been shown to be safe and effective at decreasing the accumulation of downstream complement components in persons, the use of other complement inhibitors is also contemplated by this disclosure. The pharmaceutical formulations and uses of the disclosure may be combined with any known complement inhibitors or sickle cell treatments known in the art (supra).

INCORPORATION BY REFERENCE

[0055] All publications and patents mentioned herein are hereby incorporated by reference in their entirety as if each individual publication or patent was specifically and individually indicated to be incorporated by reference. In case of conflict, the present application, including any definitions herein, will control.

[0056] The present methods are described with reference to the following Examples, which are offered by way of illustration and are not intended to limit the disclosure in any manner. Standard techniques well known in the art or the techniques specifically described below are utilized.

EXAMPLE

PROPHYLACTIC TREATMENT OF A

SICKLE CELL DISEASE PATIENT WITH ECULIZUMAB

[0057] Sickle cell disease patients have episodes of hemolysis in which large amounts of red blood cells are lysed and hemoglobin is released into the plasma. Because of the recurring nature of this disease, such patients will be treated prophylactically by administering anti-C5 antibodies at regular intervals such that active antibody is present in the plasma at any time and can bind to C5 and inhibit its activation, thereby decreasing the amount of lysis of red blood cells. The amount of antibody required will depend upon the severity of the disease. Antibodies are degraded over time and must be replaced. As an example to be used as guidance, PNH patients are administered an anti-C5 antibody at a dose of 900 mg

approximately once every two weeks to maintain an active level of that antibody (Hillmen et al., N. Engl. J. Med. 350:552-559 (2004)) to decrease lysis of red blood cells. The amount delivered depends upon the form of the antibody and its *in vivo* half-life.

[0058] While the invention has been disclosed by reference to the details of preferred embodiments of the invention, it is to be understood that the disclosure is intended in an illustrative rather than in a limiting sense, as it is contemplated that modifications will readily occur to those skilled in the art, within the spirit of the invention and the scope of the appended claims.

CLAIMS:

1. A method of treating sickle cell disease in a mammal comprising treating said mammal with a therapeutically effective amount of an anti-C5 antibody, wherein said treatment results in decreased lysis of red blood cells in said mammal.

2. The method of claim 1 wherein said mammal is a human.

3. The method of claim 1 wherein said antibody is a whole antibody or an antibody fragment.

4. The method of claim 3 wherein said whole antibody or antibody fragment is selected from the group consisting of: a polyclonal antibody, a monoclonal antibody or antibody fragment, a diabody, a chimerized or chimeric antibody or antibody fragment, a humanized antibody or antibody fragment, a deimmunized human antibody or antibody fragment, a fully human antibody or antibody fragment, a single chain antibody, an Fv, an Fab, an Fab', or an $F(ab')_2$.

5. The method of claim 1 wherein said treatment is chronic.

6. The method of claim 1 wherein said treatment comprises treating an acute episode.

7. The method of claim 1 wherein said mammal is treated by administering said antibody intravenously.

8. The method of claim 1 wherein said mammal is treated to inhibit or decrease the amount and/or extent of an undesirable physiological condition resulting from excess lysis of red blood cells.

9. The method of claim 8 wherein said undesirable physiological condition is selected from the group consisting of dystonia, a clotting disorder, pulmonary hypertension, systemic hypertension, gastrointestinal contractions, abdominal pain, sternal pain, erectile dysfunction, priapism,

inflammation, esophageal spasm, dysphagia, thrombosis, decreased organ perfusion, and death.

10. The method of claim 1 wherein said antibody inhibits activation of the classical pathway, the alternative pathway or the lectin complement pathway.

11. The method of claim 1 wherein said antibody is an antibody against any member of the group consisting of the complement components C5, C5b, C6, C7, C8, and C9.

12. The method of claim 1 wherein said antibody is an inhibitor of C5 cleavage.

13. The method of claim 1 wherein said antibody is pexelizumab.

14. The method of claim 1 wherein said antibody is eculizumab.

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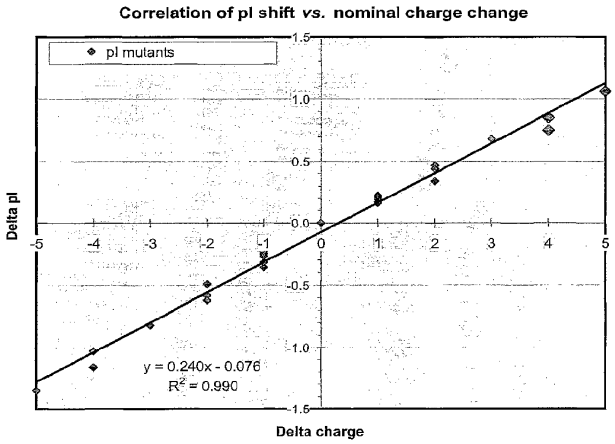
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(54) **Title:** AN INTEGRATED APPROACH FOR GENERATING MULTIDOMAIN PROTEIN THERAPEUTICS



(57) **Abstract:** The invention provides method for therapeutic protein drug development that incorporates therapeutic and/or formulation and/or manufacturing considerations in the early screening process. The approach involves screening a plurality of different variants of a domain that have been determined to have the desired therapeutic property to identify one or more variants that have desired therapeutic and/or formulation characteristics, and constructing the full multidomain proteins using the identified domain variants. The present invention also provides a method for determining the shelf life of multidomain proteins in formulations. The method comprises determining a thermal denaturation and/or renaturation curve of a domain of the protein whose unfolding leads to aggregation of the protein in a solution. The method evaluates the shelf life of the multidomain protein based on the denaturation/renaturation curve. The invention also provides methods for engineering multidomain proteins to improve their therapeutic and/or formulation characteristics.

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AN INTEGRATED APPROACH FOR GENERATING MULTIDOMAIN PROTEIN THERAPEUTICS

1. FIELD OF THE INVENTION

[0001] The invention relates to a method for therapeutic protein development that allows generation of proteins of both high therapeutic efficacy and optimal formulation characteristics, *e.g.*, high solubility and long shelf life. The present invention also relates to a method for evaluating one or more metrics, which provide an indication of the shelf life of a multidomain protein formulation.

2. BACKGROUND OF THE INVENTION

[0002] A wide variety of biologically active proteins and polypeptides can now be produced in sufficiently large quantities for use as drugs. For example, the development of the hybridoma method and recombinant DNA techniques have made it possible to produce antibodies on large scale. This has allowed wide use of pharmaceutical compositions containing proteins, such as antibodies, for treating a variety of diseases. Such treatments normally require administering to a patient the proteins at high concentrations.

[0003] However, a protein that has desired therapeutic properties may not have sufficiently high solubility. Even for those proteins that have high solubility, high concentration liquid formulations tend to have short shelf lives and may lose biological activity as a result of chemical and physical instabilities during the storage. Additionally, proteins are generally more viscous at high concentrations, which can complicate packaging, storage and delivery of the protein therapeutic. Furthermore, chemical instability may be caused by deamidation, racemization, hydrolysis, oxidation, beta elimination or disulfide exchange, and physical instability may be caused by protein denaturation, aggregation, precipitation or adsorption. Among those, aggregation, deamidation and oxidation are known to be the most common causes of antibody degradation (Wang *et al.*, 1988, *J. of Parenteral Science & Technology* 42 (Suppl.):S4-S26; Cleland *et al.*, 1993, *Critical Reviews in Therapeutic Drug Carrier Systems* 10(4):307-377; Manning *et al.*, 1989, Pharm. Res. 6:903-918). Aggregate formation during storage of a liquid protein composition can adversely affect the biological activity of the protein, resulting in loss of therapeutic efficacy and/or an increase in immunogenicity in humans. Aggregate formation may also cause other problems

such as blockage of tubing, membranes, or pumps when the protein composition is administered using an infusion system.

[0004] Due to the instability of proteins in liquid pharmaceutical formulations, protein therapeutics are often packaged in the lyophilized form along with a suitable liquid medium for reconstitution. Although lyophilization improves storage stability of the composition, many proteins exhibit decreased activity, either due to storage in the dried state (Pikal, 1990, Biopharm. 27:26-30) or as a result of aggregate formation or loss of catalytic activity upon reconstitution as a liquid formulation (see, for example, Carpenter *et al.*, 1991, Develop. Biol. Standard 74:225-239; Broadhead *et al.*, 1992, Drug Devel. Ind. Pharm. 18:1169-1206; Mumenthaler *et al.*, 1994, Pharm. Res. 11:12-20; Carpenter *et al.*, 1988, Cryobiology 25:459-470; and Roser, 1991, Biopharm. 4:47-53). Lyophilized formulations of antibodies also require a prolonged process for lyophilization and high cost for manufacturing. A lyophilized formulation has to be reconstituted aseptically and accurately by healthcare practitioners prior to administering to patients. The reconstitution procedure is cumbersome and the time limitation after the reconstitution can cause great inconveniences in administering the formulation to patients, leading to significant waste, if not reconstituted properly or if the reconstituted dose is not used within six (6) hours and must be discarded. Reconstitution may also increase the possibility of incorrect dosing. Thus, a lyophilized formulation which is more stable and is readily reconstituted with little loss in potency is desirable.

[0005] A desirable alternative to lyophilized formulations is liquid formulations of protein therapeutics having concentrations comparable to or higher than the reconstituted lyophilized formulations. Such liquid formulations of protein therapeutics can be administered to a subject without the need of reconstitution, thereby allowing healthcare practitioners much quicker and easier administration of protein therapeutics to a patient. In addition, the manufacturing process of the liquid formulation protein therapeutics is simpler and more efficient than the manufacturing process for the lyophilized version because all stages of the manufacturing of the liquid formulations are carried out in an aqueous solution, involving no drying process, such as lyophilization. Accordingly, it is also more cost effective. The development of high concentration, ready-to-use, liquid formulations of protein therapeutics has thus attracted great attention in the biopharmaceutical industry.

[0006] Stability of proteins and polypeptides in pharmaceutical formulations, both liquid and lyophilized, can be affected, for example, by factors such as pH, ionic strength,

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temperature, repeated cycles of freeze-thaw, and exposure to mechanical shear forces such as occur during processing. Various highly stable, high concentration liquid formulations have been successfully developed. For example, liquid formulations of antibodies that are stable for more than 5 years when stored at 4°C have been reported. U.S. Patent No. 6,525,102 discloses a stabilized liquid polypeptide-containing pharmaceutical composition. The composition comprises an amino acid base, which serves as the primary stabilizing agent of the polypeptide, and an acid and/or its salt form to buffer the solution within an acceptable pH range for stability of the polypeptide. The compositions are near isotonic. The '102 patent also discloses methods for increasing stability of a polypeptide in a liquid pharmaceutical composition and for increasing storage stability of such a pharmaceutical composition. Lyophilized formulations are common and their stability and reconstitution characteristics may be modified by the addition of stabilizers and/or excipients. However, the development of such liquid and lyophilized formulations depends on the particular protein therapeutics, and often requires significant optimization efforts. Thus, improving the stability of pharmaceutical compositions containing protein therapeutics of a pharmaceutically effective concentration remains a challenge. An additional challenge is providing for formulations which have low enough viscosity to be readily manufactured and/or administered at high concentrations.

[0007] In a traditional approach to therapeutic protein (*e.g.*, antibody) development, the protein that has a desired activity and/or property (*e.g.*, binding affinity) is first generated. The protein is then submitted for formulation development to determine the optimal formulation and storage conditions. Traditional screening and optimization processes require lengthy stability studies which are both time consuming and can only examine a limited number of potential formulations. If the protein should fail to meet the formulation requirements, the whole drug development process essentially fails. Thus, there is a need for methods that allow incorporating formulation considerations into early stages of the drug development process. In addition, since the desired shelf life can be as long as one year or longer, methods relying monitoring the formulations in real time are inefficient. Attempts have been made to develop methods for rapidly screening formulations. For example, U.S. Patent No. 6,232,085 discloses a multi-variable method for optimizing the shelf life of a protein which is capable of denaturing due to a thermal change. The method comprises contacting the target molecule with one or more of a multiplicity of different molecules or different biochemical conditions in each of a multiplicity of containers, simultaneously

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heating the multiplicity of containers, measuring in each of the containers a physical change associated with the thermal denaturation of the target molecule resulting from heating, generating a thermal denaturation curve for the target molecule as a function of temperature for each of the containers, comparing each of the denaturation curves to (i) each of the other thermal denaturation curves and to (ii) the thermal denaturation curve obtained for the target under a reference set of biochemical conditions, and ranking the efficacies of multiplicity of different molecules or the different biochemical conditions according to the change in each of the thermal denaturation curves. However, such methods are cumbersome and do not address the address the intrinsic properties or characteristics, such as, pI and Tm, of the protein to be formulated.

[0008] The intrinsic properties of proteins not only affect their formulation characteristics but may have serious implications for their therapeutic use as well. For example, studies have shown that recombinant toxins made up of a cell-targeting Fv portion of an antibody fused to a toxin have non-specific dose limiting toxicities (*e.g.*, non-specific liver toxicities) which are attributable to the high isoelectric point (pI) of the Fv portion of the molecule. Lowering the pI of the Fv portion of these recombinant toxins by site directed mutagenesis reduced their non-specific toxicity in animal models without altering reducing their antitumor activity (Onda *et al.*, 1999, J. Immunol., 163: 6072-77, Onda *et al.*, 2001, Cancer Res., 61: 5070-77). Likewise, lowering the pI of a radiolabelled anti-tumor dsFv (disulfide stabilized Fv) by chemical modification increased renal clearance thereby decreasing the buildup of radioactivity in the kidney (Kim *et al.*, 2002, Nucl. Med. Biol., 29: 795-801).

[0009] In other studies the transendothelial migration and endocytosis of antibodies was enhanced by cationization to increase the pI. The cationized antibodies retained their binding affinity and were rapidly internalized into cells with minimal non-specific toxicity or immunogenicity (Pardrige *et al.*, 1998, J. Pharmaol. Exp. Therap., 286: 548-54). Cationization of antibodies has also been shown to enhance the delivery of antibodies across the blood brain barrier (Triguero *et al.*, 1989, PNAS, 86: 4761-4765) These data indicate that there may be an optimal pI for certain therapeutic proteins, such as antibodies or chimeric proteins made up of antibody domains. Particularly those proteins which carry a toxin, are required in large doses for optimal therapeutic response or those which are required intracellularly or in extravascular compartments.

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[0010] Thus, there is a need for more efficient methods that allow quick indication of the shelf life and/or clinical properties of protein formulations based on the intrinsic properties of the protein. Additionally, because certain intrinsic properties, such as pI and Tm, are generally not selection criterion when therapeutic proteins (*e.g.*, antibodies) are developed, proteins which are therapeutically active may have suboptimal formulation or clinical properties. Methods to engineer certain intrinsic properties, such as pI and Tm, downstream of, or concurrently with development would allow the rapid production of proteins with preferred formulation and therapeutic characteristics.

[0011] Discussion or citation of a reference herein shall not be construed as an admission that such reference is prior art to the present invention.

3. SUMMARY OF THE INVENTION

[0012] The invention is based in part on the discovery of the inventors that certain therapeutic and/or formulation and/or manufacturing characteristics of a multidomain protein can be evaluated by examining individual domains that form the protein. One or more metrics representing the physical and/or chemical and/or structural characteristics of protein domains are determined and individual domains are then selected based on their metrics. The individual domains may be examined in the context of the intact multidomain protein or as isolated domains. For example, the physical/chemical (including structural) characteristics of a Fab or an Fc domain in an antibody may determine the biodistribution and/or non-specific toxicity and/or stability and/or solubility and/or viscosity of the antibody. An approach incorporating selecting appropriate domains having optimal therapeutic and/or formulation characteristics prior to or concurrently with the generation of the full protein improves the overall drug development efficiency. This approach thus allows generation of proteins of both high therapeutic efficacy and optimal formulation characteristics, *e.g.*, high solubility and long shelf life.

[0013] The invention provides an integrated approach to therapeutic protein development which incorporates therapeutic and/or formulation and/or manufacturing considerations in the early screening and development process. The approach involves evaluating one or more individual domains of a protein to identify domains that have both the desired biological activity and desired therapeutic and/or formulation characteristics. For example, a plurality of different variants of a domain that have been determined to have the desired biological activity can be screened to identify one or more variants that have certain

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desired therapeutic and/or formulation characteristics, *e.g.*, having desired stability and/or solubility. The identified domain variants are then used in the construction of the full multidomain proteins. For example, in therapeutic antibody development, after affinity screening of an expression library (*e.g.*, a phage display library), Fab domains having high binding affinity can be screened for their formulation characteristics, *e.g.*, solubility and/or stability. One or more Fab domains having desired formulation characteristics, *e.g.*, having high solubility and/or stability, are selected and each used with an appropriate Fc domain in the construction of the full antibodies. Different candidate (including variant/modified domains) Fc domains can also be screened for formulation characteristics, *e.g.*, solubility and stability, to select an Fc domain that has the desired formulation characteristics. The constructed antibodies are then submitted for further formulation development.

[0014] The invention further provides methods for the development of a therapeutic multidomain protein by engineering one or more domains of the multidomain protein to have the desired therapeutic and/or formulation characteristics such as for example, biodistribution, non-specific toxicity, solubility and/or stability. For example, a domain having a desired biological activity can be modified by replacing one or more amino acid residues in said domain to generated a modified domain or a population of modified domains which are then screened for their therapeutic characteristics, *e.g.*, biodistribution and/or non-specific toxicity. One or more modified domains having desired therapeutic characteristics are selected and each used in the construction of the full multidomain protein.

[0015] The present invention also provides a method for evaluating the shelf life, i.e., the long term stability, of a protein preparation comprising a multidomain protein based on a thermal denaturation and/or renaturation behavior of a multidomain protein in a liquid protein preparation. It is contemplated that the multidomain protein may comprise a domain whose unfolding leads to aggregation of the multidomain protein in the liquid protein preparation. The liquid protein preparation can be a solution of the multidomain protein of a particular concentration, *e.g.*, a concentration from about 5 to 300 mg/ml. The liquid protein preparation can also comprise other substances, including but not limited to, salts, ligands, co-factors, and so on. The method thus can also be used for determining the optimal conditions, *e.g.*, the constituents and the optimal concentration of each such constituent.

[0016] The invention provides a method of generating one or more multidomain proteins, comprising (a) evaluating for each of a plurality of candidate domains one or more metrics representing one or more therapeutic and/or formulation and/or manufacturing

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characteristics of the domain, wherein the plurality of candidate domains exhibits a biological activity above a predetermined threshold level; (b) selecting one or more domains from the plurality based on the metrics; and (c) optionally, constructing a full multidomain protein using each domain selected in step (b) and one or more other domains. In one embodiment, the method of the invention is used to generate one or more antibodies. In a specific embodiment, the domain is an antigen binding domain (*e.g.*, Fab domain). In one embodiment, the metrics of the invention include one or more parameters characterizing the stability of a candidate domain. In another embodiment, the metrics of the invention include one or more parameters characterizing the solubility, biodistribution or non-specific toxicity of a candidate domain. In a specific embodiment, the parameters characterizing stability of a candidate domain include the Tm value of the domain, and the parameters characterizing solubility, biodistribution or non-specific toxicity of a candidate domain include the pI value of the domain. The metrics of the invention may further include metrics characterizing stability of a candidate domain under one or more different conditions selected from the group consisting of different pH values, different temperatures, different shear stresses, and different freeze/thaw cycles.

[0017] The plurality of candidate domains can be an antigen binding domains (*e.g.*, Fab domains). In such cases, the biological activity may be the antigen binding domain's binding affinity to a target antigen. In certain embodiments, at least some of the antigen binding domains bind different epitopes of the antigen. In a specific embodiment, the plurality of antigen binding domains are obtained by screening an expression library (*e.g.*, a phage display library) with the antigen. In another specific embodiment, the plurality of antigen binding domains are obtained by digesting a plurality of monoclonal antibodies. Each selected antigen binding is then combined with one or more other domains (*e.g.*, constant region domains) to generate one or more multidomain proteins.

[0018] The plurality of candidate domains can be constant region domains. In such cases, the biological activity may be the constant region domain's binding affinity to constant region domain receptors and/or ligands (*e.g.*, FcRn, C1q, FcγRs) and/or ability to mediate effector functions (*e.g.*, ADCC, CDC). In a specific embodiment, the plurality of constant region domains are obtained by screening an expression library with a constant region domain ligand. Each selected constant region domain is then combined with another domain (*e.g.*, a antigen binding domain, a cellular receptor domain) to generate one or more multidomain proteins.

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[0019] In one embodiment, metrics of the invention include one or more parameters characterizing stability of an antigen binding domain (*e.g.*, Fab domain). In another embodiment, metrics include one or more parameters characterizing solubility, biodistribution or non-specific toxicity of an antigen binding domain. In a specific embodiment, the parameters characterizing stability of an antigen binding domain include a Tm value of the antigen binding domain, and the parameters characterizing solubility, biodistribution or non-specific toxicity of an antigen binding domain comprise a pI value of the antigen binding domain. The metrics of the invention may further include metrics characterizing stability of the antigen binding domain under one or more different conditions selected from the group consisting of different pH values, different temperatures, different shear stresses, and different freeze/thaw cycles.

[0020] In one embodiment, metrics of the invention include one or more parameters characterizing stability of a constant region domain (*e.g.*, Fc domain). In another embodiment, metrics include one or more parameters characterizing solubility, biodistribution or non-specific toxicity of a constant region domain. In a specific embodiment, said the parameters characterizing stability of said constant region domain include a Tm value of the constant region domain, and the parameters characterizing solubility, biodistribution or non-specific toxicity of the constant region domain include a pI value of the constant region domain. The metrics of the invention may further include metrics characterizing stability of the constant region domain under one or more different conditions selected from the group consisting of different pH values, different temperatures, different shear stresses, and different freeze/thaw cycles.

[0021] In one embodiment, the method of generating one or more multidomain proteins further comprises, before using the selected domain to construct a full multidomain protein (prior to said step (c)), the steps of (i) evaluating for each of a plurality of other candidate domains one or more metrics; and (ii) selecting another domain from the plurality of other candidate domains based on the metrics. In one embodiment, the metrics comprise one or more parameters characterizing stability of the second domain. In another embodiment, the metrics of the invention include one or more parameters characterizing solubility, biodistribution or non-specific toxicity of the second domain. In one embodiment, the parameters characterizing stability of the second domain include a Tm value of the second domain, and the parameters characterizing solubility, biodistribution or non-specific toxicity of said second domain include a pI value of the second domain. The metrics of the invention

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may further include metrics characterizing stability of the second domain under one or more different conditions selected from the group consisting of different pH values, different temperatures, different shear stresses, and different freeze/thaw cycles. In one embodiment, the second domain is a constant region domain. In a specific embodiment, the first domain is an antigen binding domain (*e.g.*, Fab domain) and the second domain is an antibody constant region domain (*e.g.*, Fc domain).

[0022] In a specific embodiment, the invention provides a method of generating one or more antibodies which bind to a given target, comprising (a) identifying a plurality of candidate antigen binding domains exhibiting a binding affinity for the target above a predetermined threshold level; (b) determining the Tm and/or pI values for each of the plurality of candidate antigen binding domains; (c) selecting one or more antigen binding domains from the plurality based on their Tm and/or pI values; and (d) constructing an antibody using each antigen binding domain selected in step (c) and one or more other domains. In one embodiment, at least some of the antigen binding domains bind different epitopes of the target.

[0023] The invention also provides a method of screening one or more multidomain proteins, such as antibodies, which bind to a given target, comprising (a) evaluating for each of a plurality of multidomain proteins one or more metrics of the invention representing one or more therapeutic and/or formulation and/or manufacturing characteristics of candidate domains of the multidomain proteins, wherein the plurality of multidomain proteins exhibits a biological activity above a predetermined threshold level; and (b) selecting one or more multidomain proteins from the plurality based on the metrics representing one or more therapeutic and/or formulation and/or manufacturing characteristics of said multidomain proteins.

[0024] The invention also provides a method of engineering a multidomain protein to improve one or more therapeutic and/or formulation and/or manufacturing characteristics without significantly altering other biological activities. The method comprises making one or more modifications (*e.g.*, amino acid substitutions), wherein the modifications (*e.g.*, amino acid substitutions) are such that they improve one or more of the characteristics of the multidomain protein.

[0025] In the method of engineering a multidomain protein to have improved improve one or more therapeutic and/or formulation and/or manufacturing characteristics without significantly altering other biological activities, the multidomain protein can be an antibody

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and the biological activities include, but are not limited to, one or more of the following biological activities: antigen binding, serum half-life, complement fixation, Fc receptor binding and antigen-dependent cytotoxicity of the antibody.

[0026] The invention also provides a method of evaluating long term stability of a multidomain protein in a solution, wherein long term stability is defined as less than 5%, 10%, or 20% aggregation upon storage for a predetermined period of time (*e.g.*, 1 to 6 months) at a predetermined temperature (*e.g.*, 4°C). The method comprises (a) providing a solution of a multidomain protein; (b) denaturing one or more domains of a multidomain protein by heating the solution of the multidomain protein; (c) determining if the domains refold upon cooling; and (d) classifying the multidomain protein as having long term stability in the solution if the domains are determined to refold in step (c).

[0027] The invention also provides a method of identifying in a multidomain protein one or more domains, the unfolding of which causes aggregation of the multidomain protein in a solution, comprising (a) denaturing the one or more domains by heating the solution of the multidomain protein; (b) determining if one or more of the domains refold upon cooling; and (c) identifying one or more domains that do not refold upon cooling in step (b), thereby identifying a domain or domains, the unfolding of which causes aggregation of the multidomain protein in the solution.

[0028] The invention also provides a method of engineering a multidomain protein to have improved long term stability in a solution, wherein said long term stability is defined as less than 5%, less than 10%, or less than 20% aggregation upon storage for a predetermined period of time at a predetermined temperature. The method comprises (a) modifying a domain of a multidomain protein by replacing one or more amino acid residues in the domain to generated a modified domain; (b) denaturing the modified domain by heating a solution of a multidomain protein comprising the modified domain; (c) determining if the modified domain in the multidomain protein refolds upon cooling; and (d) classifying the multidomain protein containing the modified domain as having improved long term stability if the modified domain is determined to refold in step (c). In certain embodiments, the unfolding of the domain prior to modification causes the aggregation of the multidomain protein. In the method of engineering a multidomain protein to have improved long term stability, the multidomain protein can be an antibody. It is contemplated that steps (a) to (d) may be performed on an isolated domain. For example, a Fab domain may be isolated, modified denatured, renatured and classified. In one embodiment, the identified domain having

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improved long term stability is used in the generation of a multidomain protein. In another embodiment, the modified domain is an antigen binding domain (*e.g.*, Fab domain). In still another embodiment, the modified domain is a constant region domain (*e.g.*, Fc domain).

[0029] The invention further provides a method of screening for a multidomain protein which has improved long term stability in a solution, wherein long term stability is defined as less than 5%, 10%, or 20% aggregation upon storage for a predetermined period of time at a predetermined temperature comprising (a) denaturing respectively two or more multidomain proteins that are members of a population of multidomain proteins, wherein each multidomain protein comprises a different modified domain, the modified domains having one or more amino acid residues substituted, wherein the denaturing is accomplished by heating a solution of one of the multidomain proteins comprising a modified domain; (b) determining if the modified domain in each of the multidomain proteins denatured in step (a) refolds upon cooling; and (c) identifying the multidomain proteins containing a modified domain determined to refold in step (b) as having improved long term stability. In one embodiment, the method further comprises generating the population of multidomain proteins comprising different modified domains. In certain embodiments the unfolding of the domain prior to modification causes aggregation of the multidomain protein.

[0030] In the method of screening for a multidomain protein which has improved long term stability, the multidomain protein can be an antibody. In one embodiment, the domain is an antigen binding domain (*e.g.*, a Fab domain). In another embodiment, the domain is a constant region domain (*e.g.*, a Fc domain). It is contemplated that the methods of the invention may be performed on an isolated domain or domains. In one embodiment, the modified domain determined to refold upon cooling is used in the generation of a multidomain protein. In one embodiment, said denaturation and renaturation steps are carried out by generating a thermal denaturation/renaturation curve, *e.g.*, using differential scanning calorimetry.

[0031] The invention provides a method of engineering a multidomain protein to have improved stability. The method comprises (a) modifying a domain of a multidomain protein by replacing one or more amino acid residues in the domain to generated a modified domain; (b) determining the Tm of the modified domain; and (c) classifying the multidomain protein containing the modified domain as having improved stability if the domain is determined to have a higher Tm in step (b). Accordingly, the invention also provides engineered multidomain proteins which have a higher Tm than the multidomain protein prior to being

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engineered. The invention also provides engineered multidomain proteins which have improved stability than the multidomain protein prior to being engineered. In certain embodiments, the Tm of the domain prior to modification is either low or contributes to the multidomain protein have a low Tm.

[0032] The invention provides a method of engineering a multidomain protein to have improved solubility and/or lower viscosity. The method comprises (a) modifying a domain of a multidomain protein by replacing one or more amino acid residues in the domain to generated a modified domain; (b) determining the pI of the modified domain; and (c) classifying the multidomain protein containing the modified domain as having improved solubility and/or viscosity if the modified domain is determined to have a higher pI in step (b). In another embodiment of the method, the pI of the multidomain protein containing the modified domain is determined in step (b) and the multidomain protein containing the modified domain is classified as having improved solubility and/or viscosity if the multidomain protein containing the modified domain is determined to have a higher pI in step (b). Accordingly, the invention also provides engineered multidomain proteins which have a higher pI relative to the multidomain protein prior to being engineered. The invention also provides engineered multidomain proteins which have improved solubility and/or lower viscosity relative to the multidomain protein prior to being engineered. In certain embodiments, the pI of the domain prior to modification is either low or contributes to the multidomain protein have a low pI.

[0033] The invention further provides a method of engineering a multidomain protein to have reduced non-specific toxicity. The method comprises (a) modifying a domain of a multidomain protein by replacing one or more amino acid residues in the domain to generated a modified domain; (b) determining the pI of the modified domain; and (c) classifying the multidomain protein containing the modified domain as having reduced non-specific toxicity if the modified domain is determined to have a lower pI in step (b). In another embodiment of the method, the pI of the multidomain protein containing the modified domain is determined in step (b) and the multidomain protein containing the modified domain is classified as having reduced non-specific toxicity if the multidomain protein containing the modified domain is determined to have a lower pI in step (b). Accordingly, the invention also provides engineered multidomain proteins which have a lower pI relative to the multidomain protein prior to being engineered. The invention also provides engineered multidomain proteins which have reduced non-specific toxicity relative to the multidomain

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protein prior to being engineered. In certain embodiments, the domain prior to modification either has a pI or contributes to the multidomain protein having a pI which results in non-specific toxicity.

[0034] In addition, the invention provides a method of engineering a multidomain protein to have a specific biodistribution (*e.g.*, intracellular, extravascular, extracellular). The method comprises (a) modifying a domain of a multidomain protein by replacing one or more amino acid residues in the domain to generated a modified domain; (b) determining the pI of the modified domain; and (c) classifying the multidomain protein containing the modified domain as having reduced intracellular localization if the modified domain is determined to have a lower pI in step (b) or as having increased intracellular and/or extravascular localization if the modified domain is determined to have a higher pI in step (b). In another embodiment of the method, the pI of the multidomain protein containing the modified domain is determined in step (b) and the multidomain protein containing the modified domain is classified as having reduced intracellular localization if the multidomain protein containing the modified domain is determined to have a lower pI in step (b) or as having increased intracellular and/or extravascular localization if the multidomain protein containing the modified domain is determined to have a higher pI in step (b). Accordingly, the invention also provides engineered multidomain proteins which have a specific biodistribution. Specifically, the invention provides engineered multidomain proteins which have increased intracellular and/or extravascular localization relative to the multidomain protein prior to being engineered. The invention also provides engineered multidomain proteins which have reduced intracellular localization relative to the multidomain protein prior to being engineered. In certain embodiments, the domain prior to modification either has a pI or contributes to the multidomain protein having a pI which determines the biodistribution.

4. BRIEF DESCRIPTION OF THE FIGURES

[0035] FIG. 1. The DSC thermogram of the full length Ca-hG1 Mab molecule is shown in the top panel, while the bottom panel is an overlay of the thermograms obtained from purified Fab and Fc fragments of Ca-hG1 Mab molecule. Two discrete peaks are seen for the Fc domain at approximately 68°C and 83°C. A single peak is seen for the Fab fragment at approximately 87°C.

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[0036] FIG. 2. Deconvolution of the DSC thermogram of the full length Ca-hG1 Mab (see Fig. 1). Three discrete peaks are seen with Tm values of 60°C, 83°C and 87°C.

[0037] FIG. 3. Overlay of multiple DSC scans of the full length Ca-hG1 Mab, demonstrating reversibility over multiple heating and cooling cycles when heated to 72°C.

[0038] FIG. 4. Overlay of multiple DSC scans of the full length Ca-hG1 Mab, demonstrating less reversibility over multiple heating and cooling cycles when heated to 87°C than seen for heating to 72°C (see FIG. 3).

[0039] FIG. 5. Overlay of multiple DSC scans of the Fab fragment of Ca-hG1 Mab, demonstrating less reversibility over multiple heating and cooling cycles when heated to 85°C than seen for heating to 72°C (see FIG. 3).

[0040] FIG. 6. Overlay of multiple DSC scans of the Fab fragment of Ca-hG1 Mab, demonstrating less reversibility over multiple heating and cooling cycles when heated to 87°C than seen for heating to 68°C (see FIG. 7).

[0041] FIG. 7. Overlay of multiple DSC scans of the Fc fragment of Ca-hG1 Mab, demonstrating reversibility over multiple heating and cooling cycles when heated to 68°C.

[0042] FIG. 8. Overlay of multiple DSC scans of the Fc fragment of Ca-hG1 Mab, demonstrating poor reversibility over multiple heating and cooling cycles when heated to 83°C than seen for heating to 68°C (see FIG. 7).

[0043] FIG. 9. Overlay of DSC scans of full length Mabs Ba-hG1 and Ca-hG1 showing dramatically different profiles. Ba-hG1 has a major peak at ~72°C while the major peak for Ca-hG1 is seen at ~87°C.

[0044] FIG. 10. The DSC thermogram of the full length Ba-hG1 Mab molecule is shown in the top panel, while the bottom panel is an overlay of the thermograms obtained from purified Fab and Fc fragments of Ba-hG1 Mab molecule. Two discrete peaks are seen for the Fc domain at approximately 67°C and 83°C. Two overlapping peaks are seen for the Fab fragment at approximately 72°C and 76°C.

[0045] FIG. 11. Deconvolution of the DSC thermogram of the full length Ba-hG1 Mab (see Fig. 10). Three discrete peaks are seen with Tm values of 71°C, 82°C and 93°C.

[0046] FIG. 12. Overlay of multiple DSC scans of full length Ba-hG1 Mab, demonstrating less reversibility over multiple heating and cooling cycles when heated to 70°C than seen for the Fab fragment alone heated to 71°C (see FIG. 14).

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[0047] FIG. 13. Overlay of multiple DSC scans of full length Ba-hG1 Mab, demonstrating less reversibility over multiple heating and cooling cycles when heated to 73°C than seen for the Fab fragment alone heated to 71°C (see FIG. 14).

[0048] FIG. 14. Overlay of multiple DSC scans of the Fab fragment of Ba-hG1 Mab, demonstrating reversibility over multiple heating and cooling cycles when heated to 71°C.

[0049] FIG. 15. Overlay of multiple DSC scans of the Fab fragment of Ba-hG1 Mab, demonstrating less reversibility over multiple heating and cooling cycles when heated to 76°C than seen for heating to 71°C (see FIG. 14).

[0050] FIG. 16. Overlay of multiple DSC scans of the Fc fragment of Ba-hG1 Mab, demonstrating reversibility over multiple heating and cooling cycles when heated to 67°C.

[0051] FIG. 17. Graphical representation of the IEF and DSC analysis for a different panel of antibodies. Antibodies Ca-hG1, Ca1-hG1 and Ca1-hG1a are highly related, recognizing the same protein epitope and differing by only a few amino acids. The remaining antibodies, As-hG1, Ba-hG1 and Da-hG1 are unrelated.

[0052] FIG. 18. Analysis of a panel of different antibodies which bind to a variety of epitopes present on a single protein. These antibodies have a common Fc domain and vary only in their Fab regions A) Isoelectric focusing (IEF) demonstrate that there is a wide range of pI values (*e.g.*, ~7.8 to ~9.2) for the different antibodies. B) Differential scanning calorimetry (DSC) analysis indicates that there is a wide range of Tm values (*e.g.*, ~66°C to ~90°C) for the different antibodies. C) Graphical representation of the IEF and DSC analysis for the panel of antibodies.

[0053] FIG. 19. Graphical representation of the IEF and DSC analysis for a different panel of antibodies which bind to a variety of epitopes present on a single protein. Also plotted are several antibodies used in earlier studies and two chimeric antibodies generated by combining the heavy and light chains from two different antibodies. All of these antibodies have a common Fc domain and vary only in their Fab regions.

[0054] FIG. 20. Graphical representation of the IEF and DSC analysis of a panel of antibodies which are identical except for mutations in their hinge region.

[0055] FIG. 21. Viscosity analysis for several of the antibodies analyzed in Fig 17. Each antibody was analyzed at 100 mg/ml, in addition Ba-hG1 was analyzed at 126 mg/ml, 138 mg/ml and 150 mg/ml.

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[0056] FIG. 22. Aggregation rate vs. Fab Tm. Panel A plots the aggregation rate of several Ba-hG1, Da-hG1, Ca-hG1 and Ca1-hG1 in relation to the Tm of the Fab region. Panel B plots the aggregation over time for the isolated Fc region and Fab domains of Ca-hG1 and Ba-hG1.

[0057] FIG. 23. Antibody naming scheme used in this application. First 3 characters identify the antigen binding domain: the capital letter designates the target, the lower case letter designates a particular epitope of the target, the number designates the variant of the antibody (for simplicity reasons, 0 is often omitted). The last 4 characters identify the Fc domain: the first 3 characters identify the Fc domain, the last lower case letter designates the Fc variant. The example in FIG. 23, Aa1-hG1a, thus identifies variant "1" of an antibody that binds epitope "a" of target "A" and has variant "a" of a human gamma-1 (hG1) as its Fc domain.

[0058] FIG. 24. Ribbon diagram of CH2 and CH3 of the human Fc showing the location of the initial five residues where substitutions were made. This illustration is a side view of a human Fc showing only one CH2 domain (top) and one CH3 domain (bottom). Residues that were substituted are spacefilled. The red indicates a region where mutations may affect C1q, FcγR, FcRn, and protein A binding, the blue indicates a region where mutations may affect FcγR and FcRn binding, and the green indicates a region where mutations may affect FcRn and protein A binding. The yellow region is where the two CH3 domains pack against each other.

[0059] FIG. 25. Ribbon diagram of CH2 and CH3 of the human Fc showing the location of six additional residues where substitutions were made. The orientation is the same as in Figure 1 and the coloration conveys the same meaning as described in Figure 1. Substituted residues are spacefilled.

[0060] FIG. 26. IEF gel of the first ten single substitutions made. The pI was determined by measuring the migration of the band with the highest intensity in a given lane. The wild type antibody control (WT) was produced in NSO cells.

[0061] FIG. 27. IEF gel of the double and triple substitutions. The triple substitutions E345K Q362K D401N and E345K Q362K D401K probably have too high of a pI to be resolved on this gel and ran off. WT antibody produced both in 293H and NSO cells were run for comparison.

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[0062] FIG. 28. IEF gel of the second 12 single substitutions made. The pI was determined by measuring the migration of the band with the highest intensity in a given lane. wild type (WT) antibody produced both in 293H and NSO cells were run for comparison.

[0063] FIG 29. Correlation of pI shift vs. nominal charge change. Plotted are the values for the delta change in pI vs. the delta change in the charge for each of the substituted antibodies. The correlation is largely linear.

[0064] FIG 30. Overlay of DSC thermograms of the wild type and single substituted anti-IL9 antibodies with altered pI. The Tm profiles of E345Q, E345K, R355Q, R355E, Q362E and Q362K(in the left panel) are very similar to that of the wild type antibody each having one major peak at ~76°C. The Tm profiles of K340Q, K340E and D401K have a distinct peak between about 62°C and ~70°C in addition to the major peak at ~76°C.

[0065] FIG 31. Overlay of DSC thermograms of the wild type and triple substituted anti-IL9 antibodies with altered pI.

[0066] FIG 32. Overlay of DSC thermograms of the wild type Fa-hG1 antibody and the two variants Fa-hG1b and Fa-hG4a. The major peak representing the Tm of the Fab domain is at 70.4°C for both Fa-hG1 and Fa-hG4a and at 70.9°C for Fa-hG1b.

[0067] FIG 33. IEF gel of the wild type Fa-hG1 antibody and the two variants Fa-hG1b and Fa-hG4a. The pI of the major protein bands are 8.35, 8.18 and 713 for Fa-hG1, Fa-hG1b and Fa-hG4a, respectively.

5. DETAILED DESCRIPTION OF THE INVENTION

[0068] The invention is based in part on the discovery of the inventors that certain therapeutic and/or formulation and/or manufacturing characteristics of a multidomain protein (*e.g.*, antibody) can be evaluated by examining individual domains that form the protein. One or more metrics representing the physical and/or chemical and/or structural characteristics of protein domains are determined and individual domains are then selected based on their metrics. The individual domains may be examined in the context of the intact multidomain protein or as isolated domains. For example, the physical/chemical (including structural) characteristics of a Fab or an Fc domain in an antibody may determine the biodistribution and/or non-specific toxicity and/or stability and/or solubility and/or viscosity of the antibody. An approach incorporating selecting appropriate domains having optimal therapeutic and/or formulation characteristics prior to or concurrently with the generation of the full protein improves the overall drug development efficiency. This approach thus allows generation of

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proteins of both high therapeutic efficacy and optimal formulation characteristics, *e.g.*, high solubility and long shelf life.

[0069] The invention provides an integrated approach to therapeutic protein development which incorporates therapeutic and/or formulation and/or manufacturing considerations in the early screening and development process. The approach involves evaluating one or more individual candidate domains of a protein to identify domains that have both the desired biological activity and desired therapeutic and/or formulation characteristics. For example, a plurality of different variants of a domain (also encompassed by the terms "domain variant(s)," "variant domain(s)" and "candidate domain(s)") that have been determined to have the desired biological activity can be screened to identify one or more variants that have certain desired therapeutic and/or formulation characteristics based on certain metrics (*e.g.*, Tm and/or pI). The identified domain variants are then used in the construction of the full multidomain proteins. For example, in therapeutic antibody development, after affinity screening of an expression library (*e.g.*, a phage display library), candidate Fab domains having high binding affinity can be screened for their formulation characteristics, *e.g.*, solubility and/or stability. One or more Fab domains having desired formulation characteristics, *e.g.*, having high solubility and/or stability, are selected and each used with an appropriate Fc domain in the construction of the full antibodies. Different candidate Fc domains can also be screened for formulation characteristics, *e.g.*, solubility and stability, to select an Fc domain that has the desired formulation characteristics. The constructed antibodies are then submitted for further formulation development.

[0070] The invention further provides methods for the development of a therapeutic multidomain protein by engineering one or more domains of the multidomain protein to have the desired therapeutic and/or formulation characteristics such as for example, biodistribution, non-specific toxicity, solubility and/or stability. For example, a domain having a desired biological activity can be modified by replacing one or more amino acid residues in said domain to generated a modified domain (also encompassed by the terms "domain variant(s)," "variant domain(s)" and "candidate domain(s)") or a population of modified domains which are then screened for their therapeutic characteristics, *e.g.*, biodistribution and/or non-specific toxicity by comparing certain metrics (*e.g.*, Tm and/or pI) of the modified domains to those of the unmodified domain. One or more modified domains having desired therapeutic characteristics based on their metrics (*e.g.*, having a desired Tm and/or pI) are selected and each used in the construction of the full multidomain protein.

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[0071] The present invention also provides a method for evaluating the shelf life, i.e., the long term stability, of a protein preparation comprising a multidomain protein based on a thermal denaturation and/or renaturation behavior of a multidomain protein in a liquid protein preparation. It is contemplated that the multidomain protein may comprise a domain whose unfolding leads to aggregation of the multidomain protein in the liquid protein preparation. The liquid protein preparation can be a solution of the multidomain protein of a particular concentration, *e.g.*, a concentration from about 5 to 300 mg/ml. The liquid protein preparation can also comprise other substances, including but not limited to, salts, ligands, co-factors, and so on. The method thus can also be used for determining the optimal conditions, *e.g.*, the constituents and the optimal concentration of each such constituent.

[0072] The inventor has discovered that the aggregation of a multidomain protein in a solution is the result of thermal unfolding (also referred to herein as "thermal denaturation" or simply "denaturation") of a particular domain or domains in the protein, and that thermal denaturation and/or renaturation behavior of a multidomain protein comprising the particular domain or domains provides an indication of the long term stability and, thus, the shelf life, of a liquid formulation of the multidomain protein.

[0073] The pI of certain therapeutic multidomain proteins is known to affect their biodistribution and/or their non-specific toxicity profiles. The inventor has further discovered that the viscosity and solubility of a multidomain protein in a solution correlates with the pI of the multidomain protein and/or a particular domain or domains in the protein, relative to the pH of the solution. Thus, the pI of a multidomain protein and/or one or more individual domains provides an indication of viscosity and solubility of a liquid formulation of the multidomain protein in addition to other therapeutic characteristics. Additionally, the inventor has discovered that the pI of multidomain proteins can be modified to alter those characteristics which are governed by the pI of a protein.

5.1. Methods For Development Of Multidomain Protein Therapeutics

[0074] The invention provides a method for protein drug development that incorporates therapeutic and/or formulation and/or manufacturing considerations in the early screening process. A protein drug is a formulated drug form of a therapeutic protein which can be used in the treatment or prevention of a disease. The formulation of the drug aids and/or optimizes the clinical effect of the protein, i.e., the pharmacological effect of the protein. The development of a therapeutic protein depends on the physical, chemical, and

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pharmacokinetic properties of the protein. The manufacturing process of a protein drug, including production, purification, storage, and any downstream processing of the protein, also depends on the physical and chemical properties of the protein.

[0075] As used herein, the "therapeutic characteristics" of a protein include physical, chemical, and pharmacokinetic properties of the protein which affect the pharmacological effect of the protein drug form. Examples of therapeutic characteristics of a protein include, but are not limited to, biodistribution, non-specific toxicity and clearance profiles of the protein.

[0076] As used herein, the formulation and/or manufacturing characteristics of a protein include physical, chemical, and pharmacokinetic properties of the protein which affect the pharmacological effect of the protein drug form and/or the production, purification, storage and any downstream processing of the protein. For simplicity reasons, the formulation and/or manufacturing characteristics of a protein are often referred to herein jointly as simply the "formulation characteristics." Examples of formulation characteristics of a protein include, but are not limited to, stability (*e.g.*, thermal stability and/or storage stability, also termed shelf life), solubility and viscosity of the protein.

[0077] The invention provides a method for the generation of multidomain proteins having both high biological activities and optimal therapeutic and/or formulation and/or manufacturing characteristics. The method comprises evaluating the biological activities and the therapeutic and/or formulation and/or manufacturing characteristics of individual domains of a multidomain protein, and identifying domains that exhibit both desired biological activities, *e.g.*, desired level of target binding affinity and/or desired serum half-life, etc., and desired therapeutic and/or formulation and/or manufacturing characteristics, *e.g.*, desired level of solubility and/or stability. In certain embodiments, the therapeutic and/or formulation and/or manufacturing characteristics of individual domains of a multidomain protein are evaluated by metrics of the invention which include one or more parameters characterizing therapeutic and/or formulation characteristics including but not limited to stability, solubility, biodistribution and non-specific toxicity. In certain embodiments, individual domains that exhibits an optimal combination of biological activities and therapeutic and/or formulation and/or manufacturing characteristics are identified. In certain other embodiments, different domains which when combined in a protein exhibit an optimal combination of biological activities and therapeutic and/or formulation and/or manufacturing

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characteristics are identified. The identified domains are then used to construct the full protein.

[0078] In one embodiment, the method of generating one or more multidomain proteins for therapeutic uses, comprises (a) evaluating for each of a plurality of candidate domains one or more metrics representing one or more therapeutic and/or formulation and/or manufacturing characteristics of the first domain, wherein the plurality of candidate domains exhibits a biological activity above a predetermined threshold level; (b) selecting one or more domains from the plurality based on the metrics; and (c) optionally, constructing a full multidomain protein using each domain selected in step (b) and one or more other domains. In one embodiment, the metrics include one or more parameters characterizing stability of the candidate domain. In another embodiment, the metrics include one or more parameters characterizing solubility, biodistribution or non-specific toxicity of the candidate domain.

[0079] Thus, the present invention provides a method comprising screening a plurality of candidate domains to identify one or more domains that have both the desired biological activities, *e.g.*, desired target binding affinity, and desired therapeutic and/or formulation characteristics, *e.g.*, biodistribution, non-specific toxicity, stability, solubility and viscosity. Each of the candidate domains is also referred to as a variant of the domain. The method comprises evaluating the candidate domains for both their biological activities and their therapeutic and/or formulation properties. One or more candidate domains which exhibit an optimal combination of biological activities and therapeutic and/or formulation characteristics are selected for constructing the full multidomain proteins.

[0080] In one embodiment, the method of generating one or more multidomain proteins for therapeutic uses further comprises, before using the selected domain to construct a full multidomain protein (prior to said step (c)), the steps of (i) evaluating for each of a plurality of other candidate domains one or more metrics; and (ii) selecting a another domain from the plurality of other candidate domains based on the metrics. In one embodiment, the metrics include one or more parameters characterizing stability of the other candidate domain. In another embodiment, the metrics include one or more parameters characterizing solubility, biodistribution or non-specific toxicity of the other candidate domain.

[0081] The present invention also provides a method for screening a plurality of candidate domains to identify one or more domains that have both the desired biological activities, *e.g.*, desired target binding affinity, and desired metrics representing their therapeutic and/or formulation characteristics. in the context of the full multidomain protein.

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Thus, the present invention provides a method to evaluate one or more domains of a multidomain protein in an intact multidomain protein. By screening a plurality of intact multidomain proteins for one or more candidate domains which exhibit an optimal combination of biological activities therapeutic and/or formulation characteristics, the need to construct the full multidomain protein is eliminated. In one embodiment, the method comprises screening a plurality of antigen binding domains that bind a given target antigen in the context of an intact full length antibody molecule, to identify one or more antigen binding domains that have desired therapeutic and/or formulation characteristics.

[0082] The present invention further provides a method to engineer a domain to improve one or more therapeutic and/or formulation characteristic. In one embodiment, specific modifications (*e.g.,* amino acids substitutions, additions or deletions) are engineered into a domain to modify one or more desired therapeutic and/or formulation characteristics.

[0083] In one embodiment, the formulation characteristics of a candidate protein domain is evaluated by evaluating one or more metrics of the invention (also referred to herein as simply "metrics") characterizing the formulation characteristics of the candidate domain. In one embodiment, the metrics include one or more parameters characterizing the stability of a domain. In another embodiment, the metrics include one or more parameters characterizing the solubility, biodistribution or non-specific toxicity of a domain. In a specific embodiment, the one or more parameters characterizing stability of the domain include a Thermal melting temperature (Tm) value of the domain. The Tm of a candidate domain, *e.g.*, a Fab domain, can be a good indicator of the thermal stability of a protein containing the domain and may further provide an indication of the shelf-life of a protein containing the domain. A lower Tm indicates more aggregation/less stability, whereas a higher Tm indicates less aggregation/ more stability. Thus, candidate domains having higher Tm are preferable for incorporation into a full multidomain protein (*e.g.*, an antibody). In one embodiment, candidate domains having a Tm greater than a predetermined threshold value are selected. In some embodiments, one or more candidate domains that have a Tm value higher than at least 50°C, 55°C, 60°C, 65°C, 70°C, 75°C, 80°C, 85°C, 90°C, 95°C, 100°C, 105°C, 110°C, 115°C or 120°C are selected for construction of the full multidomain protein. In specific embodiments, the candidate domains are antigen binding domains (*e.g.*, Fab domain, scFv, etc.).

[0084] Thermal melting temperatures (Tm) of a protein domain can be measured using any standard method known in the art. For example, Vermeer *et al.* studied the

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unfolding and denaturation of a monoclonal mouse anti-rat IgG of isotype 2b by differential scanning calorimetry (DSC) and circular dichroism (CD) spectroscopy (Vermeer *et al.*, 2000, Biophys. J. 78:394-404; Vermeer *et al.*, 2000, Colloids Surfaces A: Physicochem. Eng. Aspects. 161:139-150; Vermeer *et al.*, 2000, J. Colloid Interface Sci. 225:394-397; Vermeer *et al.*, 2000, Biophys. J. 79:2150-2154). They showed that the folding/unfolding of the IgG can be characterized by two main transitions that are themselves superpositions of various steps. The bimodal distribution observed in both DSC and CD experiments did not depend on the scan rate in the experiments. The two transitions appeared to be independent, and the unfolding was irreversible. The IgG was then digested into isolated Fab and Fc fragments (Vermeer *et al.*, 2000, Biophys. J. 79: 2150-2154). The secondary structure as well as the thermodynamic stability of the two isolated fragments were studied and compared with those of the intact immunoglobulin. It was shown that the two peaks observed for intact IgG can be assigned to the Fab and Fc fragments, respectively. Vermeer *et al.* also showed that, in addition to induction by heat, the structural perturbation of IgG in general could also be triggered by changing the pH (Vermeer *et al.*, 2000, Biophys. J. 78:394-404) or by interaction with a hydrophobic environment, *e.g.*, adsorption onto Teflon surfaces or interaction with surfactants (Vermeer *et al.*, 1998, Biochim. Biophys. Acta. 1425:1-12; Vermeer *et al.*, 2000, Colloids Surfaces A: Physicochem. Eng. Aspects. 161:139-150; Vermeer *et al.*, 2000, J. Colloid Interface Sci. 225:394-397).

[0085] In one embodiment, the Tm of a protein domain is measured using a sample containing isolated protein domain molecules. In another embodiment, the Tm of a protein domain is measured using a sample containing an intact multidomain protein that contains the domain to be analyzed. In the latter case, the Tm of the domain is deduced from the data of the protein by analyzing only those data points corresponding to the domain of interest. In one embodiment, the Tm of a protein or protein domain is measured with a VP-DSC (MicroCal, LLC) using a scan rate of 1.0°C/min and a temperature range of 25 –120°C. A filter period of 8 seconds is used along with a 5 minute pre-scan thermostating. In a specific example, samples are prepared by dialysis into 25 mM Histidine-HCl, pH 6 using Pierce dialysis cups (3.5 kD). Average Mab concentrations are 50 μg/mL as determined by A280. Melting temperatures are determined following manufacturer procedures using Origin software supplied with the system. Briefly, multiple baselines are run with buffer in both the sample and reference cell to establish thermal equilibrium. After the baseline is subtracted from the sample thermogram, the data are concentration normalized and fitted using the

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deconvolution function. In another embodiment, stability of the candidate domains are evaluated using a method described in Section 5.2. The one or more metrics may further include metrics characterizing stability of the domain under one or more different conditions selected from the group consisting of different pH values, different temperatures, different shear stresses, and different freeze/thaw cycles.

[0086] In another specific embodiment, the one or more parameters characterizing the solubility, biodistribution or non-specific toxicity of the domain includes an Isoelectric Point (pI) value of the domain. The pI of a protein is defined as the pH at which a polypeptide carries no net charge. It is known in the art that protein solubility is typically lowest when the pH of the solution is equal to the isoelectric point (pI) of the protein. It is thus possible to evaluate the solubility of a protein for a given pH, *e.g.*, pH 6, based on its pI. The pI of a protein is also a good indicator of the viscosity of the protein in a liquid formulation. High pI indicates high solubility and low viscosity (especially important for high concentration formulations). In one embodiment, candidate domains having a pI greater than a predetermined threshold value are selected. As described above, the pI of a protein also plays a role in biodistribution and non-specific toxicity of multidomain proteins. For example, it is known in the art that reducing the pI of recombinant toxins results in lower non-specific toxicity and renal accumulation. Alternatively, increases the pI of antibodies is known to increase their intracellular and/or extravascular localization. One of skill in the art can readily determine which therapeutic characteristics are most desirable for a particular multidomain protein. In some embodiments, one or more candidate domains that have a pI value higher than about 5.0, 5.5, 6.0, 6.5, 7.0, 7.5, 8.0, 8.5, or 9.0 are selected for construction of the full multidomain protein. In other embodiments, one or more candidate domains that have a pI value less than about 9.0, 8.5, 8.0, 7.5, 7.0, 6.5, 6.0, 5.5, or 5.0 are selected for construction of the full multidomain protein. It will be understood by one skilled in the art that a single protein will have multiple charge forms. Without wishing to be bound by any particular theory, the charge of a protein can be modified by a number of different mechanisms including but not limited to, amino acid substitution, cationization, deamination, carboxyl-terminal amino acid heterogeneity, phosphorylation and glycosylation. As used herein the pI value is defined as the pI of the predominant charge form.

[0087] The pI of a protein may be determined by a variety of methods including but not limited to, isoelectric focusing and various computer algorithms (see for example Bjellqvist *et al.*, 1993, *Electrophoresis* 14:1023). In one embodiment, pI is determined using

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a Pharmacia Biotech Multiphor 2 electrophoresis system with a multi temp 3 refrigerated bath recirculation unit and an EPS 3501 XL power supply. Pre-cast ampholine gels (Amersham Biosciences, pI range 2.5-10) are loaded with 5 μg of protein. Broad range pI marker standards (Amersham, pI range 3-10, 8 μL) are used to determine relative pI for the Mabs. Electrophoresis is performed at 1500 V, 50 mA for 105 minutes. The gel is fixed using a Sigma fixing solution (5x) diluted with purified water to 1x. Staining is performed overnight at room temperature using Simply Blue stain (Invitrogen). Destaining is carried out with a solution that consisted of 25% ethanol, 8% acetic acid and 67% purified water. Isoelectric points are determined using a Bio-Rad Densitometer relative to calibration curves of the standards. The one or more metrics may further include metrics characterizing stability of the domain under one or more different conditions selected from the group consisting of different pH values, different temperatures, different shear stresses, and different freeze/thaw cycles.

[0088] It will be understood by one skilled in the art that the evaluation of candidate domains may be performed on isolated domains or alternatively, each domain may be evaluated in the context of the intact multidomain protein. The latter approach is particularly useful when a plurality of multidomain proteins differ from each other in a single domain. It will be further understood, that an intact multidomain protein comprising a modified domain may be evaluated to determine the effect of a modified domain on one or more metrics of the invention representing one or more therapeutic and/or formulation and/or manufacturing characteristics. It will also be understood by one skilled in the art that the selected domains, whether evaluated as isolated domains or in the context of an intact multidomain protein, may be incorporated into multidomain proteins. For example, a Fab fragment evaluated and selected in the context of an intact antibody may be utilized in the generation of a chimeric protein comprising a toxin. As used herein, the term "evaluate candidate domains" and grammatical variations thereof, specifically encompass the evaluation of both isolated candidate domains and the evaluation of candidate domains in the context of an intact multidomain protein or fragment thereof.

[0089] Thus, the invention provides a method of screening a plurality of multidomain proteins to identify one or more multidomain proteins that have both the desired biological activities and the desired therapeutic and/or formulation characteristics comprising (a) evaluating for each of a plurality of different multidomain proteins one or more metrics representing one or more therapeutic and/or formulation and/or manufacturing characteristics

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of candidate domains of the multidomain proteins, wherein the plurality of different multidomain proteins exhibits a biological activity above a predetermined threshold level; and (b) selecting one or more multidomain proteins from the plurality based on the metrics of the candidate domains. In one embodiment, the method further comprises generating the population of different multidomain proteins. In certain embodiments, the multidomain protein is an antibody. In other embodiments the modified domain is an antigen binding domain. In still other embodiments, the modified domain is an Fc domain or fragment thereof.

[0090] The invention also provides a method for engineering a multidomain protein for preferred therapeutic and/or formulation properties. In one embodiment, the method comprises engineering one or more domains to improve the protein's formulation characteristics. In another embodiment, the method comprises engineering one or more domains to improve the multidomain protein's therapeutic characteristics. In still another embodiment, the method comprises engineering one or more domains to improve both the multidomain protein's therapeutic and formulation characteristics. In specific embodiments, the engineered domain exhibits improved therapeutic and/or formulation characteristics without reducing significantly the protein's pharmacological characteristics. In another specific embodiment, the engineered domain exhibits improved therapeutic and/or formulation characteristics without substantially affecting the protein's pharmacological characteristics. Accordingly, the invention also provides engineered multidomain proteins having preferred therapeutic and/or formulation properties. In certain embodiments, the engineered multidomain proteins having preferred therapeutic and/or formulation properties comprise a modified domain. In specific embodiment, the engineered multidomain proteins having preferred therapeutic and/or formulation properties comprise a modified antibody domain (*e.g.*, antigen binding domain, Fc domain).

[0091] In a specific embodiment, the invention provides a method of engineering a multidomain protein to have improved stability. In certain embodiments, the multidomain protein comprises a domain which either has a low Tm or contributes to the multidomain protein having a low Tm. In one embodiment, a domain of a multidomain protein is modified by substituting one or more amino acid residues in the domain such that the stability of the domain is increased. In another embodiment, a domain is modified such that its Tm value is increased. The method comprises (a) modifying a domain of a multidomain protein by replacing one or more amino acid residues in the domain to generated a modified domain; (b)

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determining the Tm of the modified domain; and (c) classifying a multidomain protein containing the modified domain as having improved stability if the modified domain is determined to have a higher Tm in step (b). In some embodiments a domain is modified such that it has a Tm greater than the Tm of the domain prior to modification. In certain embodiments, the Tm of the modified domain is increased by at least 2°C, at least 4°C, at least 6°C, at least 8°C, at least 10°C, at least 15°C, at least 20°C, at least 25°C, at least 30°C, or least 40°C. In some embodiments, a domain is engineered such that it has a Tm greater than a predetermined threshold value. In certain embodiments, the predetermined Tm threshold value is at least 50°C, 55°C, 60°C, 65°C, 70°C, 75°C, 80°C, 85°C, 90°C, 95°C, 100°C, 105°C, 110°C, 115°C, or 120°C. In certain embodiments, the multidomain protein is an antibody. In other embodiments said modified domain is an antigen binding domain. In still other embodiments, said modified domain is an Fc domain or fragment thereof.

[0092] As described above, the Tm of a domain may be evaluated in an intact multidomain protein. Accordingly, the present invention provides method of engineering a multidomain protein to have improved stability in which the Tm of intact multidomain protein comprising a modified domain is determined. Optionally, or alternatively, the method of engineering a multidomain protein to have improved stability comprises (a) modifying the domain by replacing one or more amino acid residues in the domain to generated a modified domain; (b) determining the Tm of the multidomain protein containing the modified domain; and (c) classifying a multidomain protein containing the modified domain based on the Tm of the multidomain protein containing the modified domain determined in step (b).

[0093] The non-specific toxicity and/or biodistribution and/or solubility and/or viscosity of a protein may be optimized by altering the number and location of ionizable residues in the protein to adjust the pI. For example the pI of a polypeptide can be manipulated by making the appropriate amino acid substitutions. For example, at each amino acid residue of a protein, there are several possible changes that can be made: charged residues can be changed to uncharged residues or residues with the opposite charge and uncharged residues can be changed to residues with either a positive or negative charge. The maximum change in charge that can occur is where a charged amino acid is substituted with another amino acid of opposite charge (*e.g.*, by substituting an aspartic acid for a lysine or arginine). Replacing a charged residue with an uncharged residue (*e.g.*, by substituting a charged amino acid such as a lysine, for an uncharged residue such as alanine) serves will

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remove a charge but not add opposite charge and thus will result in a smaller pI change. The acidic amino acids aspartic acid (D) and glutamic acid (E) are deprotonated at or near physiological pH and carry a negative charge. The basic amino acids lysine (K) and arginine (R) are protonated at or near physiological pH and carry a positive charge. Substitutions of D and E with either K or R, or vice versa, are likely to have the greatest impact on pI. Specific amino acid substitutions are described below and detailed in Example 4.

[0094] Without wishing to be bound by any particular theory, amino acid substitutions of a protein that result in changes of the pI of said protein may improve non-specific toxicity and/or biodistribution and/or solubility and/or the viscosity of the protein. One skilled in the art would be able to determine amino acid substitutions that is most appropriate for a particular protein to achieve a desired pI. The pI of a protein may be determined by a variety of methods including but not limited to isoelectric focusing. It can also be estimated using any one of the various computer algorithms (see for example Bjellqvist *et al.*, 1993, *Electrophoresis* 14:1023). In certain embodiments, the invention provides engineered multidomain proteins that have improved non-specific toxicity and/or biodistribution and/or solubility and/or lower viscosity. In a specific embodiment, the engineered multidomain proteins that have improved non-specific toxicity and/or biodistribution solubility and/or lower viscosity comprise a modified domain having different pI than the same domain prior to modification.

[0095] In a specific embodiment, the invention provides a method of engineering a multidomain protein to have improved solubility and/or lower viscosity. In certain embodiments, the multidomain protein comprises a domain which either has a low pI or contributes to the multidomain protein having a low pI. The method comprises (a) modifying a domain of the multidomain protein by replacing one or more amino acid residues in the domain to generated a modified domain; (b) determining the pI of the modified domain; and (c) classifying a multidomain protein containing the modified domain as having improved solubility and/or viscosity if the modified domain is determined to have a higher pI in step (b). In one embodiment a domain is engineered such that it has a pI greater than the pI of the domain prior to modification. In some specific embodiments, the pI of the modified domain is increased by at least 0.5, at least 1.0, at least 2.0, at least 3.0, at least 4.0, at least 5.0, or at least 10.0. In one embodiment, a domain is engineered such that it has a pI greater than a predetermined threshold value. In some specific embodiments, the predetermined pI threshold value is about 5.0, 5.5, 6.0, 6.5, 7.0, 7.5, 8.0, 8.5, or 9.0.

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[0096] In certain embodiments, the invention provides engineered multidomain proteins that have improved solubility and/or lower viscosity. In a specific embodiment, the engineered multidomain proteins that have improved solubility and/or lower viscosity comprise a modified domain having a higher pI than the same domain prior to modification. In certain embodiments, the multidomain protein is an antibody. In other embodiments said modified domain is an antigen binding domain. In still other embodiments, said modified domain is an Fc domain or fragment thereof.

[0097] In other specific embodiments, the invention provides a method of engineering a multidomain protein to have reduced non-specific toxicity. In certain embodiments, the multidomain protein comprises a domain which either has a pI or contributes to the multidomain protein having a pI which results in non-specific toxicity. The method comprises (a) modifying a domain of a multidomain protein by replacing one or more amino acid residues in the domain to generated a modified domain; (b) determining the pI of the modified domain; and (c) classifying the multidomain protein containing the modified domain as having reduced non-specific toxicity if the modified domain is determined to have a lower pI in step (b). In one embodiment a domain is engineered such that it has a pI less than the pI of the domain prior to modification. In some specific embodiments, the pI of the modified domain is decreased by at least 0.5, at least 1.0, at least 2.0, at least 3.0, at least 4.0, at least 5.0, or at least 10.0. In one embodiment, a domain is engineered such that it has a pI less than a predetermined threshold value. In some specific embodiments, the predetermined pI threshold value is about 9.0, 8.5, 8.0, 7.5, 7.0, 6.5, 6.0, 5.5 or 5.0.

[0098] In certain embodiments, the invention provides engineered multidomain proteins that have reduced non-specific toxicity. In a specific embodiment, the engineered multidomain proteins that have reduced non-specific toxicity comprises a modified domain having a lower pI than the same domain prior to modification. In certain embodiments, the multidomain protein is an antibody. In other embodiments said modified domain is an antigen binding domain. In still other embodiments, said modified domain is an Fc domain or fragment thereof.

[0099] In additional embodiments, the invention provides a method of engineering a multidomain protein to have a specific biodistribution (*e.g.*, intracellular, extravascular, extracellular). In certain embodiments, the multidomain protein comprises a domain which either has a pI or contributes to the multidomain protein having a pI which determines the biodistribution. The method comprises (a) modifying a domain of a multidomain protein by

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replacing one or more amino acid residues in the domain to generated a modified domain; (b) determining the pI of the modified domain; and (c) classifying a multidomain protein containing the modified domain as having reduced intracellular localization if the modified domain is determined to have a lower pI in step (b) or as having increased intracellular and/or extravascular localization if the modified domain is determined to have a higher pI in step (b). In one embodiment a domain is modified such that it has a pI greater than the pI of the domain prior to modification. In some specific embodiments, the pI of the modified domain is increased by at least 0.5, at least 1.0, at least 2.0, at least 3.0, at least 4.0, at least 5.0, or at least 10.0. In one embodiment, a domain is modified such that it has a pI greater than a predetermined threshold value. In another embodiment a domain is modified such that it has a pI less than the pI of the domain prior to modification. In some specific embodiments, the pI of the modified domain is decreased by at least 0.5, at least 1.0, at least 2.0, at least 3.0, at least 4.0, at least 5.0, or at least 10.0. In another embodiment, a domain is engineered such that it has a pI less than a predetermined threshold value. In some specific embodiments, the predetermined pI threshold value is about 9.0, 8.5, 8.0, 7.5, 7.0, 6.5, 6.0, 5.5 or 5.0.

[0100] In certain embodiments, the invention provides engineered multidomain proteins that have increased intracellular and/or extravascular localization. In a specific embodiment, the engineered multidomain proteins that have increased intracellular and/or extravascular localization comprise a modified domain having a higher pI than the same domain prior to modification. In other embodiments, the invention provides engineered multidomain proteins that have reduced intracellular localization. In a specific embodiment, the engineered multidomain proteins that have reduced intracellular localization comprise a modified domain having a lower pI than the same domain prior to modification. In certain embodiments, the multidomain protein is an antibody. In other embodiments said modified domain is an antigen binding domain. In still other embodiments, said modified domain is an Fc domain or fragment thereof.

[0101] As described above, the pI of a domain may be evaluated in an intact multidomain protein. Accordingly, the present invention provides methods of engineering a multidomain protein to have improved non-specific toxicity and/or biodistribution solubility and/or lower viscosity in which the pI of intact multidomain protein comprising a modified domain is determined. Optionally, or alternatively, the methods of engineering a multidomain protein to have improved non-specific toxicity and/or biodistribution solubility and/or lower viscosity described above comprise: (a) modifying a domain of a multidomain

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protein by replacing one or more amino acid residues in the domain to generated a modified domain; (b) determining the pI of the multidomain protein containing the modified domain; and (c) classifying a multidomain protein containing the modified domain based on the pI of the multidomain protein containing the modified domain determined in step (b).

[0102] In certain embodiments, the modified Fc domain comprises a replacement at one or more amino acid residues selected from the group consisting of K338, A339, K340, G341, Q342, R344, E345, R355, E356, E357, M358, T359, K360, N361, Q362, L365, T366, K370, N390, Y391, K392, T393, T394, V397, L398, D399, S400, D401, F405, K409, L410, D413 and K414 as numbered by the EU index as set forth in Kabat. In specific embodiments, the modified Fc domain comprises one or more amino acid replacements from the group consisting of K338 to any uncharged residue (*e.g.*, Q but generally not P or C), K338D, K338E, A339D, A339E, A339K, A339R, K340 to any uncharged residue (*e.g.*, Q but generally not P or C), K340D, K340E, G314D, G314E, G314K, G314R, Q342D, Q342E, Q342K, Q342R, R344 to any uncharged residue (*e.g.*, Q but generally not P or C), R344D, R344E, E345 to any uncharged residue (*e.g.*, Q but generally not P or C), E345K, E345R, R355 to any uncharged residue (*e.g.*, Q but generally not P or C), R355D, R355E, E356 to any uncharged residue (*e.g.*, Q but generally not P or C), E356K, E356R, E357 to any uncharged residue (*e.g.*, Q but generally not P or C), E357K, E357R, M358D, M358E, M358K, M358R, T359D, T359E, T359K, T359R, K360 to any uncharged residue (*e.g.*, Q but generally not P or C), K360D, K360E, N361D, N361E, N361K, N361R, Q362D, Q362E, Q362K, Q362R, L365D, L365E, L365K, L365R, T366D, T366E, T366K, T366R, K370 to any uncharged residue (*e.g.*, Q but generally not P or C), K370D, K370E, N390D, N390E, N390K, N390R, Y391D, Y391E, Y391K, Y391R, K392 to any uncharged residue (*e.g.*, Q but generally not P or C), K392D, K392E, T393D, T393E, T393K, T393R, T394D, T394E, T394K, T394R, V397D, V397E, V397K, V397R, L398D, L398E, L398K, L398R, D399 to any uncharged residue (*e.g.*, Q but generally not P or C), D399K, D399R, S400D, S400E, S400K, S400R, D401 to any uncharged residue (*e.g.*, Q but generally not P or C), D401K, D401R, F405D, F405E, F405K, F405R, K409 to any uncharged residue (*e.g.*, Q but generally not P or C), K409D, K409E, L410D, L410E, L410K, L410R, D413 to any uncharged residue (*e.g.*, Q but generally not P or C), D413K, D413R, K414 to any uncharged residue (*e.g.*, Q but generally not P or C), K414D and K414E as numbered by the EU index as set forth in Kabat.

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[0103] In certain embodiments, the engineered Fc domain with a higher pI comprises a replacement at one or more amino acid residues selected from the group consisting of A339, G341, Q342, E345, E356, E357, M358, T359, N361, Q362, L365, T366, N390, Y391, T393, T394, V397, L398, D399, S400, D401, F405, L410 and D413 as numbered by the EU index as set forth in Kabat. In specific embodiments, the engineered Fc domain with a higher pI comprises one or more amino acid replacements selected from the group consisting of A339K, A339R, G314K, G314R, Q342K, Q342R, E345 to any uncharged residue (*e.g.*, Q but generally not P or C), E345K, E345R, E356 to any uncharged residue (*e.g.*, Q but generally not P or C), E356K, E356R, E357 to any uncharged residue (*e.g.*, Q but generally not P or C), E357K, E357R, M358K, M358R, T359K, T359R, N361K, N361R, Q362K, Q362R, L365K, L365R, T366K, T366R, N390K, N390R, Y391K, Y391R, T393K, T393R, T394K, T394R, V397K, V397R, L398K, L398R, D399 to any uncharged residue (*e.g.*, Q but generally not P or C), D399K, D399R, S400K, S400R, D401 to any uncharged residue (*e.g.*, Q but generally not P or C), D401K, D401R, F405K, F405R, L410K, L410R, D413 to any uncharged residue (*e.g.*, Q but generally not P or C), D413K and D413R as numbered by the EU index as set forth in Kabat.

[0104] In certain embodiments, the engineered Fc domain with a lower pI comprises a replacement at one or more amino acid residues selected from the group consisting of K338, A339, K340, G341, Q342, R344, R355, M358, T359, K360, N361, Q362, L365, T366, K370, N390, Y391, K392, T393, T394, V397, L398, S400, F405, K409, L410, and K414 as numbered by the EU index as set forth in Kabat. In specific embodiments, the engineered Fc domain with a lower pI comprises one or more amino acid replacements selected from the group consisting of K338 to any uncharged residue (*e.g.*, Q but generally not P or C), K338D, K338E, A339D, A339E, K340 to any uncharged residue (*e.g.*, Q but generally not P or C), K340D, K340E, G314D, G314E, Q342D, Q342E, R344 to any uncharged residue (*e.g.*, Q but generally not P or C), R344D, R344E, R355 to any uncharged residue (*e.g.*, Q but generally not P or C), R355D, R355E, M358D, M358E, T359D, T359E, K360 to any uncharged residue (*e.g.*, Q but generally not P or C), K360D, K360E, N361D, N361E, Q362D, Q362E, L365D, L365E, T366D, K370 to any uncharged residue (*e.g.*, Q but generally not P or C), K370D, K370E, N390D, N390E, Y391D, Y391E, K392 to any uncharged residue (*e.g.*, Q but generally not P or C), K392D, K392E, T393D, T393E, T394D, T394E, V397D, V397E, L398D, L398E, S400D, S400E, F405D, F405E, K409 to any uncharged residue (*e.g.*, Q but generally not P or C), K409D, K409E, L410D, L410E, K414 to any uncharged residue (*e.g.*,

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Q but generally not P or C), K414D and K414E as numbered by the EU index as set forth in Kabat.

[0105] It is contemplated that evaluation of candidate domains is generally to be performed under substantially similar conditions. For example, each candidate domain, evaluated as an intact multidomain protein or as an isolated domain thereof, is preferably at a similar or identical concentration and is in a similar or identical buffer. Furthermore, all manipulations (*e.g.*, pipetting, mixing, heating, cooling, etc.) are to be performed in a substantially similar manner for each candidate domain being evaluated whenever possible.

[0106] In another embodiment, candidate domains are further evaluated under one or more particular biochemical conditions, *e.g.*, conditions under which the formulated drug is stored and/or used. For example, pH affects the shelf life of a protein. The composition of the solvent, *e.g.*, water, also affects the shelf life of a protein. Glycerol alters the solvation properties of water to favor the native conformation of proteins. Ligands and cofactors in the solution may also affect the shelf life of a protein. Other biochemical parameters that have been shown to affect protein shelf life are: protein concentration, temperature, glutathione redox buffers (GSH, GSSG), the presence of detergents, and the presence of other additives, such as glycerol, arginine-HCl, polyethylene glycol (PEG), and organic solvents. Thus, the candidate domains can be evaluated under various conditions to gain more insights into the domains formulation characteristics, such pH dependence, ionic strength dependence, concentration of salts of the Hofmeister series, glycerol concentration, sucrose concentration, arginine concentration, dithiothreitol concentration, metal ion concentration, shear stress, and freeze/thaw stress, etc. For example, the stability of the candidate domains can be determined under a plurality of different biochemical conditions, either different levels of a particular type of conditions, such as different pH values, different temperatures, different sucrose concentrations, or a combination of different types and levels of conditions.

[0107] Some exemplary biochemical conditions described below are of particular interest. In some embodiments, the formulation may contain histidine with a concentration ranging from about 1 mM to about 100 mM, about 10 mM to about 50 mM, or about 20 mM to about 30 mM. Histidine can be in the form of L-histidine, D-histidine, or a mixture thereof, but L-histidine is the most preferable. Histidine can be also in the form of hydrates. Histidine may be used in a form of pharmaceutically acceptable salt, such as hydrochloride (*e.g.*, monohydrochloride and dihydrochloride), hydrobromide, sulfate, acetate, etc. The purity of histidine should be at least 98%, or at least 99%, or at least 99.5%.

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[0108] The pH of the formulation should not be equal to the isoelectric point of the particular multidomain protein (*e.g.*, antibody) to be used in the formulation and may range from about 5.0 to about 7, or about 5.5 to about 6.5, or about 5.8 to about 6.2, and or about 6.0.

[0109] In addition to histidine and a multidomain protein (*e.g.*, an antibody) , the formulations may further comprise one or more amino acids (*e.g.*, glycine) at a concentration of less than 100 mM, less than 50 mM, less than 3.0 mM, less than 2.0 mM, or less than 1.8 mM, and most preferably 1.6 mM. The amount of amino acid in the formulation should not cause a significant buffering effect so that protein precipitation at its isoelectric point can be avoided. An amino acid may be also used in a form of pharmaceutically acceptable salt, such as hydrochloride, hydrobromide, sulfate, acetate, etc. The purity of the amino acid should be at least 98%, or at least 99%, or 99.5%. In a specific embodiment, glycine is included in the formulations of the present invention.

[0110] Optionally, the formulations may further comprise other excipients, such as saccharides (*e.g.*, sucrose, mannose, trehalose, etc.), polyols (*e.g.*, Tween) and sugar alcohols (*e.g.*, mannitol, sorbitol, etc.). In one embodiment, the other excipient is a saccharide. In a specific embodiment, the saccharide is sucrose, which is at a concentration ranging from between about 1% to about 20%, or about 5% to about 15%, or about 8% to 10%. In another embodiment, the other excipient is a polyol. Preferably, however, the formulations of the present invention do not contain mannitol. In a specific embodiment, the polyol is polysorbate (*e.g.*, Tween 20), which is at a concentration ranging from between about 0.001% to about 1%, or about 0.01 to about 0.1.

[0111] In one embodiment, candidate domains are evaluated by one or more particular physical manipulations. For example candidate domains can be repeatedly subjected to shearing forces such as pumping, shaking, vortexing and the like to determine their ability to withstand shear stress such as those encountered during manufacture and shipping.

[0112] In a specific embodiment, the present invention provides a method for therapeutic antibody development. As used herein, the terms "antibody" and "antibodies" refer to monoclonal antibodies, multispecific antibodies, human antibodies, humanized antibodies, camelised antibodies, chimeric antibodies and anti-idiotypic (anti-Id) antibodies. The terms "antibody fragment" and "antibody domain" refer to any distinct region of antibody including but not limited to, "antigen binding domains" which bind an epitope, such

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as, Fab fragments, F(ab') fragments, Fv domains, Fd domain, "constant region domains" such as, CH1, hinge domain and Fc domains and any portions thereof, including for example, CH2 and CH3 domains. Single-chain Fvs (scFv), disulfide-linked Fvs (sdFv), and similar recombinantly generated antigen binding domains are also encompassed by the terms "antibody fragment" and "antibody domain". In particular, antibodies include immunoglobulin molecules and immunologically active fragments of immunoglobulin molecules, as well as antibody domain fusion proteins *i.e.*, molecules that contain an antigen binding site or other antibody domain, fused to another protein domain including but not limited to non-immunoglobulin proteins, an Fc domain or fragment thereof. As outlined herein, the terms "antibody" and "antibodies" specifically include the Fc variants described herein, full length antibodies and variant Fc-Fusions comprising Fc domains, or fragments thereof, comprising at least one novel amino acid residue described herein fused to an immunologically active fragment of an immunoglobulin or to other proteins as described herein. Such variant Fc fusions include but are not limited to, scFv-Fc fusions, variable region (*e.g.*, VL and VH) –Fc fusions, scFv-scFv-Fc fusions. Immunoglobulin molecules can be of any type (*e.g.*, IgG, IgE, IgM, IgD, IgA and IgY), class (*e.g.*, IgG1, IgG2, IgG3, IgG4, IgA1 and IgA2) or subclass.

[0113] The present invention also specifically encompasses antibodies with multiple specificities (*e.g.*, an antibody with specificity for two or more discrete antigens (reviewed in Cao et al., 2003, *Adv Drug Deliv Rev* 55:171; Hudson et al., 2003, *Nat Med* 1:129)). For example, bispecific antibodies contain two different binding specificities fused together. In the simplest case a bispecific antibody would bind to two adjacent epitopes on a single target antigen, such an antibody would not cross-react with other antigens. Alternatively, bispecific antibodies can bind to two different antigens, such an antibody specifically binds to two different molecules such as a heterologous polypeptide or solid support material, but not to other unrelated molecules (*e.g.*, BSA). *See, e.g.*, PCT publications WO 93/17715; WO 92/08802; WO91/00360; WO 92/05793; Tutt, et al., J. Immunol. 147:60-69 (1991); U.S. Pat. Nos. 4,474,893; 4,714,681; 4,925,648; 5,573,920; 5,601,819; Kostelny et al., J. Immunol. 148:1547-1553 (1992). While such molecules normally will only bind two antigens (*i.e.* bispecific antibodies), antibodies with additional specificities such as trispecific antibodies are encompassed by the instant invention. Accordingly, the multidomain proteins of the present invention may be antibodies that are monospecific, bispecific, trispecific or of greater multispecificity.

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[0114] It will be understood that Fc domain as used herein includes the polypeptides comprising the constant region of an antibody excluding the first constant region immunoglobulin domain. Thus Fc refers to the last two constant region immunoglobulin domains of IgA, IgD, and IgG, and the last three constant region immunoglobulin domains of IgE and IgM, and the flexible hinge N-terminal to these domains. For IgA and IgM Fc may include the J chain. For IgG, the Fc domain comprises immunoglobulin domains Cgamma2 and Cgamma3 (Cγ2 and Cγ3) and the hinge between Cgamma1 (Cγ1) and Cgamma2 (Cγ2). Although the boundaries of the Fc domain may vary, the human IgG heavy chain Fc domain is usually defined to comprise residues C226 or P230 to its carboxyl-terminus, wherein the numbering is according to the EU index as in Kabat et al. (1991, NIH Publication 91-3242, National Technical Information Service, Springfield, VA). The "EU index as set forth in Kabat" refers to the residue numbering of the human IgG1 EU antibody as described in Kabat et al. *supra*. Fc may refer to this domain in isolation, or this region in the context of an antibody, antibody fragment, or Fc fusion protein. An Fc containing protein may be an antibody, Fc fusion, or any protein or protein domain that comprises an Fc domain. The present invention also encompasses proteins comprising variant Fc domains, which are non naturally occurring variants of an Fc. Note: Polymorphisms have been observed at a number of Fc positions, including but not limited to Kabat 270, 272, 312, 315, 356, and 358, and thus slight differences between the presented sequence and sequences in the prior art may exist.

[0115] The method for therapeutic antibody development comprises screening a plurality of candidate antibody domains (*e.g.*, Fab, Fc and Fv) that have high biological activity (*e.*g., binding affinity to a target antigen (*e.g.*, antigen, Fc-receptor), effector function (*e.g.*, ADCC, CDC)) for one or more metrics characterizing the therapeutic and/or formulation characteristics. In one embodiment, the metrics include one or more parameters characterizing stability of said antibody domain. In another embodiment, the metrics include one or more parameters characterizing solubility, biodistribution or non-specific toxicity of said antibody domain. In a specific embodiment, said one or more parameters characterizing stability of said antibody domain comprise a Tm value of said antibody domain, and said one or more parameters characterizing solubility, biodistribution or non-specific toxicity of said antibody domain comprise a pI value of said antibody domain.

[0116] The present invention also provides a method of generating one or more antibodies for therapeutic uses. In one embodiment, the method of generating one or more antibodies for therapeutic uses, comprises (a) evaluating for each of a plurality of candidate

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antibody domains one or more metrics representing one or more therapeutic and/or formulation and/or manufacturing characteristics of the antibody domain, wherein the plurality of candidate antibody domains exhibits a biological activity above a predetermined threshold level; (b) selecting one or more antibody domains from the plurality based on the metrics; and (c) optionally, constructing an antibody using each antibody domain selected in step (b) and one or more other domains.

[0117] In another embodiment, the method of generating one or more antibodies for therapeutic uses further comprises, before using the selected antibody domain to construct an antibody (prior to step (c)), the steps of (i) evaluating for each of a plurality of candidate other antibody domains one or more metrics; and (ii) selecting another antibody domain from the plurality of candidate other antibody domains based on the metrics.

[0118] In one embodiment, the plurality of candidate antibody domains can be an antigen binding domains (*e.g.*, Fab domains). In such cases, the biological activity may be the antigen binding domain's binding affinity to a target antigen. In certain embodiments, at least some of the antigen binding domains bind different epitopes of the target antigen. In a specific embodiment, the plurality of antigen binding domains are obtained by screening an expression library (*e.g.,* a phage display library) with the target antigen. In another specific embodiment, the plurality of antigen binding domains are obtained by digesting a plurality of monoclonal antibodies. Each selected antigen binding domain is then combined with another protein domain (*e.g.*, Fc domain) to generate one or more multidomain proteins. In a specific embodiment, each selected antigen binding domain is combined with another antigen binding domain which may bind to the same or a different target antigen. In another specific embodiment, each selected antigen binding domain is combined with an antibody constant domain.

[0119] In another embodiment, the plurality of candidate antibody domains can be Fc domains. In such cases, the biological activity may be the Fc domain's binding affinity to constant region domain receptors an/or ligands (*e.g.*, FcRn, C1q, FcγRs) and/or ability to mediate effector functions (*e.g.*, ADCC, CDC). In a specific embodiment, the plurality of Fc domains are obtained by screening an expression library (*e.g.,* a phage display library) with one or more of the constant region domain receptors an/or ligands. Each selected Fc is then combined with another protein domain (*e.g.*, a Fab domain, a cellular receptor domain) to generate one or more multidomain proteins.

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[0120] The methods described above for screening and/or engineering protein domains for their non-specific toxicity, biodistribution, solubility and thermal stability can be used. One or more antibody domains having reduced non-specific toxicity and/or desired biodistribution and/or high solubility and/or thermal stability are selected and used for constructing the full antibodies by combining them with the appropriate domain(s) to generate a full antibody. In one embodiment, one or more candidate antibody domains that have a Tm value higher than at least 50°C, 55°C, 60°C, 65°C, 70°C, 75°C, 80°C, 85°C, 90°C, 95°C, 100°C, 105°C, 110°C, 115°C, or 120°C are selected for construction of the full antibody. In another embodiment, one or more candidate antibody domains that have a pI value higher than about 5.0, 5.5, 6.0, 6.5, 7.0, 7.5, 8.0, 8.5 or 9.0 are selected for construction of the full antibody domain containing multidomain protein. In another embodiment, one or more candidate antibody domains that have a pI value less than about 9.0, 8.5, 8.0, 7.5, 7.0, 6.5, 6.0, 5.5 or 5.0 are selected for construction of the full antibody domain containing multidomain protein

[0121] In a specific embodiment, a plurality of antigen binding domains (*e.g.*, Fab, scFv, etc.) that bind a given target antigen with an affinity above a chosen threshold level are obtained by affinity screening of an expression library (*e.g.,* a phage display library). One or more metrics characterizing the antigen binding domains' therapeutic and/or formulation properties are then evaluated for each of the antigen binding domains. The plurality of antigen binding domains are ranked according to the one or more metrics. In one embodiment, the plurality of antigen binding domains are ranked according to their Tm values, and one or more antigen binding domains are selected from the top of the ranked list. In another embodiment, the plurality of antigen binding domains are ranked according to their pI values, and one or more antigen binding domains are selected from the top of the ranked list. In still another embodiment, the plurality of antigen binding domains are ranked according to a combined Tm and pI rank, and one or more antigen binding domains are selected from the top of the ranked list. The selected antigen binding domains are then used for construction of the full antigen binding domain containing multidomain proteins (*e.g.,* antibodies, diabodies, etc.).

[0122] In another specific embodiment, a plurality of antibody constant region domains (*e.g.*, Fc, CH2, CH3, etc) are evaluated for one or more metrics characterizing the constant region domains' therapeutic and/or formulation properties (*e.g.*, solubility and thermal stability). The plurality of antigen binding domains are ranked according to the one

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or more metrics. In one embodiment, the plurality of constant region domains are ranked according to their Tm values, and one or more constant region domains are selected from the top of the ranked list. In another embodiment, the plurality of constant region domains are ranked according to their pI values, and one or more constant region domains are selected from the top of the ranked list. In still another embodiment, the plurality of constant region domains are ranked according to a combined Tm and pI rank, and one or more constant region domains are selected from the top of the ranked list. The selected constant region domains are then used for construction of the full antigen binding domain containing multidomain proteins (*e.g.,* antibodies, diabodies, etc.). In certain embodiments, one or more candidate antibody constant region domains that have a Tm value higher than at least 50°C, 55°C, 60°C, 65°C, 70°C, 75°C, 80°C, 85°C, 90°C, 95°C, 100°C, 105°C, 110°C, 115°C, or 120°C are selected for construction of the full antibody constant region domain containing multidomain protein (*e.g.*, antibody). In other embodiments, one or more candidate antibody constant region domains that have a pI value higher than about 5.0, 5.5, 6.0, 6.5, 7.0, 7.5, 8.0, 8.5 or 9.0 are selected for construction of the full antibody constant region domain containing multidomain protein (*e.g.*, antibody, Fc-fusion protein, etc.). In still other embodiments, one or more candidate antibody constant region domains that have a pI value lower than about 9.0, 8.5, 8.0, 7.5, 7.0, 6.5, 6.0, 5.5, or 5.0 are selected for construction of the full antibody constant region domain containing multidomain protein.

[0123] In a specific embodiment, the invention provides a method for engineering an antibody for preferred therapeutic and/or formulation properties. In one embodiment, the method comprises engineering the antigen binding (*e.g.,* Fab) and/or constant region (*e.g.*, Fc) domains to improve the protein's therapeutic and/or formulation characteristics. The method comprises making one or more modification (*e.g.*, amino acid substitutions), the modifications are such that they improve one or more of the characteristics of said antibody.

[0124] In addition to binding antigen, antibodies are known to bind to a number of ligands via their constant region domain including, Fc receptors (*e.g.,* FcRn, FcγRs) and the complement protein C1q. The binding interactions of the constant region domain are essential for a variety of effector functions and downstream signaling events such as antibody dependent cell-mediated cytotoxicity (ADCC) activity and complement dependent cytotoxicity (CDC). In certain embodiments, the engineered antibody exhibits improved therapeutic and/or formulation characteristics without reducing significantly the antibody's pharmacological characteristics, *e.g.*, the antibody's binding specificity, binding affinity

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and/or avidity to its target, or the antibody's effector functions, *e.g.*, Fc-receptor (FcR) and/or C1q binding, antibody dependent cellular cytotoxicity (ADCC), complement dependent cytotoxicity (CDC), and/or serum half life. In another embodiment, the engineered antibody exhibits improved therapeutic and/or formulation characteristics and improved pharmacological characteristics, *e.g.*, the antibody's binding specificity, binding affinity and/or avidity to its target, or the antibody's Fc effector functions, *e.g.*, FcR binding, ADCC, CDC, and/or serum half life.

[0125] "Antibody-dependent cell-mediated cytotoxicity" or "ADCC" refers to a form of cytotoxicity in which secreted Ig bound onto Fc receptors (FcRs) present on certain cytotoxic cells (e.g., Natural Killer (NK) cells, neutrophils, and macrophages) enables these cytotoxic effector cells to bind specifically to an antigen-bearing target cell and subsequently kill the target cell with cytotoxins. Specific high-affinity IgG antibodies directed to the surface of target cells "arm" the cytotoxic cells and are absolutely required for such killing. Lysis of the target cell is extracellular, requires direct cell-to-cell contact, and does not involve complement. It is contemplated that, in addition to antibodies, other proteins comprising Fc domain, specifically Fc fusion proteins, having the capacity to bind specifically to an antigen-bearing target cell will be able to effect cell-mediated cytotoxicity. For simplicity, the cell-mediated cytotoxicity resulting from the activity of an Fc fusion protein is also referred to herein as ADCC activity.

[0126] The ability of any particular protein comprising an Fc to mediate lysis of the target cell by ADCC can be assayed. To assess ADCC activity a protein comprising an Fc is added to target cells in combination with immune effector cells, which may be activated by the antigen antibody complexes resulting in cytolysis of the target cell. Cytolysis is generally detected by the release of label (*e.g.* radioactive substrates, fluorescent dyes or natural intracellular proteins) from the lysed cells. Useful effector cells for such assays include peripheral blood mononuclear cells (PBMC) and Natural Killer (NK) cells. Specific examples of *in vitro* ADCC assays are described in Wisecarver et al., 1985 79:277-282; Bruggemann et al., 1987, *J Exp Med* 166:1351-1361; Wilkinson et al., 2001, *J Immunol Methods* 258:183-191; Patel et al., 1995 *J Immunol Methods* 184:29-38 and herein (see Example 3). Alternatively, or additionally, ADCC activity of the protein comprising an Fc may be assessed *in vivo, e.g.,* in an animal model such as that disclosed in Clynes et al., 1998, PNAS *USA* 95:652-656.

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[0127] "Complement dependent cytotoxicity" and "CDC" refer to the lysing of a target cell in the presence of complement. The complement activation pathway is initiated by the binding of the first component of the complement system (C1q) to a molecule, an antibody for example, complexed with a cognate antigen. To assess complement activation, a CDC assay, *e.g.* as described in Gazzano-Santoro et al., 1996, *J. Immunol. Methods,* 202:163, may be performed.

[0128] In one embodiment, the pI of an engineered antibody binding domain is between pH 5.0 and pH 10.0. In one embodiment, substitutions resulting in alterations in the pI of the antigen binding domain will not significantly diminish its binding affinity for an antigen. In one embodiment, the pI of an engineered antibody constant region domain is between pH 5.0 and pH 10.0. In still another embodiment, substitutions resulting in alterations in the pI of the constant region domain will not significantly diminish its effector binding and/or function. It is also contemplated that substitutions resulting in alterations in the pI in an antibody domain may be selected such that both the pI and other pharmacological characteristics of the antibody domain, *e.g.*, the antibody's binding specificity, binding affinity and/or avidity to its target, or the antibody's Fc effector functions are improved. The inventors have found that certain modifications of the hinge region do not change the pI and Tm of the antibody significantly. Thus, in one embodiment, the invention provides a method for engineering an antibody to improve the antibody's biological activity without reducing the antibody's therapeutic and/or formulation properties.

[0129] In one embodiment, the modifications of an antibody domain as described herein may be combined with known modifications of the Fc domain such as those disclosed in Duncan et al, 1988, *Nature* 332:563-564; Lund *et al.*, 1991, *J. Immunol* 147:2657-2662; Lund et al, 1992, *Mol Immunol* 29:53-59; Alegre et al, 1994, *Transplantation* 57:1537-1543; Hutchins *et al.*, 1995, *Proc Natl. Acad Sci U S A* 92:11980-11984; Jefferis et al, 1995, *Immunol Lett.* 44:111-117; Lund *et al.*, 1995, *Faseb J* 9:115-119; Jefferis et al, 1996, *Immunol Lett* 54:101-104; Lund et al, 1996, *Immunol* 157:4963-4969; Armour *et al.*, 1999, *Eur J Immunol* 29:2613-2624; Idusogie et al, 2000, *J Immunol* 164:4178-4184; Reddy et al, 2000, *J Immunol* 164:1925-1933; Xu *et al.*, 2000, *Cell Immunol* 200:16-26; Idusogie et al, 2001, *J Immunol* 166:2571-2575; Shields *et al.*, 2001, *J Biol Chem* 276:6591-6604; Jefferis et al, 2002, *Immunol Lett* 82:57-65; Presta *et al.*, 2002, *Biochem Soc Trans* 30:487-490); U.S. Pat. Nos. 5,624,821; 5,885,573; 5,677,425; 6,165,745; 6,277,375; 5,869,046; 6,121,022; 5,624,821; 5,648,260; 6,528,624; 6,194,551; 6,737,056; 6,821,505; 6,277,375; U.S. Patent

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Publication No. 2004/0002587; PCT Publication Nos. WO 00/42072 and WO 99/58572; WO 94/29351; WO 02/060919; WO 04/029207; WO 04/099249; WO 04/063351. Also encompassed by the present invention are Fc domains which comprise deletions, additions and/or modifications. Still other modifications/substitutions/additions/deletions of the Fc domain will be readily apparent to one skilled in the art.

[0130] In one embodiment, the antibodies may be engineered to include modifications in the Fc domain, typically to alter one or more functional properties of the antibody, such as serum half-life, complement fixation, Fc receptor binding, and/or antigen-dependent cellular cytotoxicity, without reducing the antibodies' pI and Tm. Furthermore, an antibody may be chemically modified (*e.g.*, one or more chemical moieties can be attached to the antibody) or be modified to alter its glycosylation, again to alter one or more functional properties of the antibody.

[0131] In one embodiment, the amino acid sequence of the Fc domain is modified by deleting, adding and/or substituting at least amino acid residue to alter one or more of the functional properties of the antibody described above. This approach is described further in Duncan et al, 1988, *Nature* 332:563-564; Lund *et al.*, 1991, *J. Immunol* 147:2657-2662; Lund et al, 1992, *Mol Immunol* 29:53-59; Alegre et al, 1994, *Transplantation* 57:1537-1543; Hutchins *et al.*, 1995, *Proc Natl. Acad Sci U S A* 92:11980-11984; Jefferis et al, 1995, *Immunol Lett.* 44:111-117; Lund *et al.*, 1995, *Faseb J* 9:115-119; Jefferis et al, 1996, *Immunol Lett* 54:101-104; Lund et al, 1996, *J Immunol* 157:4963-4969; Armour *et al.*, 1999, *Eur J Immunol* 29:2613-2624; Idusogie et al, 2000, *J Immunol* 164:4178-4184; Reddy et al, 2000, *J Immunol* 164:1925-1933; Xu *et al.*, 2000, *Cell Immunol* 200:16-26; Idusogie et al, 2001, *J Immunol* 166:2571-2575; Shields *et al.*, 2001, *J Biol Chem* 276:6591-6604; Jefferis et al, 2002, *Immunol Lett* 82:57-65; Presta *et al.*, 2002, *Biochem Soc Trans* 30:487-490); U.S. Patent Nos. 5,624,821; 5,885,573; 5,677,425; 6,165,745; 6,277,375; 5,869,046; 6,121,022; 5,624,821; 5,648,260; 6,194,551; 6,737,056 U.S. Patent Application Nos. 10/370,749 and PCT Publications WO 94/2935; WO 99/58572; WO 00/42072; WO 04/029207.

[0132] In still another embodiment, the glycosylation of antibodies is modified. For example, an aglycoslated antibody can be made (*i.e.*, the antibody lacks glycosylation). Glycosylation can be altered to, for example, increase the affinity of the antibody for a target antigen. Such carbohydrate modifications can be accomplished by, for example, altering one or more sites of glycosylation within the antibody sequence. For example, one or more amino acid substitutions can be made that result in elimination of one or more variable region

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framework glycosylation sites to thereby eliminate glycosylation at that site. Such aglycosylation may increase the affinity of the antibody for antigen. Such an approach is described in further detail in U.S. Patent Nos. 5,714,350 and 6,350,861.

[0133] Additionally or alternatively, an antibody can be made that has an altered type of glycosylation, such as a hypofucosylated antibody having reduced amounts of fucosyl residues or an antibody having increased bisecting GlcNAc structures. Such altered glycosylation patterns have been demonstrated to increase the ADCC ability of antibodies. Such carbohydrate modifications can be engineered by, for example, expressing the antibody in a host cell with altered glycosylation machinery. Cells with altered glycosylation machinery have been described in the art and can be used as host cells in which to express recombinant antibodies of the invention to thereby produce an antibody with altered glycosylation. See, for example, Shields, R.L. *et al.* (2002) *J. Biol. Chem.* 277:26733-26740; Umana *et al.* (1999) *Nat. Biotech.* 17:176-1, as well as, European Patent No: EP 1,176,195; PCT Publications WO 03/035835; WO 99/54342. Additional, methods for generating engineered glycoforms are known in the art, and include but are not limited to those described in Davies et al., 20017 *Biotechnol Bioeng* 74:288-294; Shields et al, 2002, *J Biol Chem* 277:26733-26740; Shinkawa et al., 2003, *J Biol Chem* 278:3466-3473) U.S. Pat. No. 6,602,684; U.S. Ser. No. 10/277,370; U.S. Ser. No. 10/113,929; PCT WO 00/61739A1; PCT WO 01/292246A1; PCT WO 02/311140A1; PCT WO 02/30954A1; Potillegent™ technology (Biowa, Inc. Princeton, N.J.); GlycoMAb™ glycosylation engineering technology (GLYCART biotechnology AG, Zurich, Switzerland). See, e.g., WO 00061739; EA01229125; US 20030115614; Okazaki et al., 2004, *JMB*, 336: 1239-49.

[0134] In another embodiment, the antibodies may be engineered to include modifications in the antigen binding domain to alter the therapeutic and/or formulation characteristics of the antibody, without reducing the binding characteristics of the antibody for its antigen. The method comprises making one or more modification (*e.g.*, amino acid substitutions), said modifications are such that they improve said one or more of the therapeutic and/or formulation characteristics of said antibody. One skilled in the art will understand that amino acid substitutions and other modifications of an antibody may alter its binding characteristics (examples of binding characteristics include but are not limited to, binding specificity, equilibrium dissociation constant (K_D), dissociation and association rates (K_{off} and K_{on} respectively), binding affinity and/or avidity) and that certain alterations are more or less desirable. For example a modification that preserves or enhances antigen

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binding would generally be more preferable then one that diminished or altered antigen binding. It will be further understood, that antibodies may be engineered to include modifications in the constant region domain to alter the therapeutic and/or formulation characteristics of the antibody, without reducing the binding characteristics of the constant region to its receptors or ligands (*e.g.*, FcRs, C1q). The binding characteristics of an antibody for a target antigen or constant region domain ligand may be determined by a variety of methods including but not limited it, equilibrium methods (*e.g.*, enzyme-linked immunoabsorbent assay (ELISA) or radioimmunoassay (RIA)), or kinetics (*e.g.*, BIACORE® analysis; see Example 2), for example. Other commonly used methods to examine the binding characteristics of antibodies are described in *Using Antibodies: A Laboratory Manual*, Cold Spring Harbor Laboratory Press, NY, Harrow *et al.*, 1999 and *Antibodies: A Laboratory Manual*, Cold Spring Harbor Laboratory Press, NY; Harlow *et al.*, 1989.

[0135] It is well known in the art that the affinity constant (K_a) is defined as k_{on}/k_{off} and that the equilibrium dissociation constant (K_D) is defined as k_{off}/k_{on}. It is generally understood that an antibody with a high K_a is preferable to an antibody with a low K_a and that an antibody with a low K_D is preferable to an antibody with a high K_D. However, in some instances the value of the k_{on} or k_{off} may be more relevant than the value of the K_D. One skilled in the art can determine which kinetic parameter is most important for a given antigen binding domain and application. In one embodiment, the methods of the invention will result in modified antigen binding and/or constant region domains with improved therapeutic and/or formulation characteristics and one or more binding characteristics (*e.g.*, binding specificity, K_D, K_{off}, K_{on}, binding affinity and/or avidity) that are improved by at least 2%, or by at least 5%, or by at least 10%, or by at least 20 %, or by at least 30%, or by at least 40%, or by at least 50%, or by at least 60%, or by at least 70%, or by at least 80% when compared to kinetic parameters of the antigen binding and/or constant region domain without said modification.

[0136] In another embodiment, the methods of the invention will result in modified antigen binding and/or constant region domains that have improved therapeutic and/or formulation characteristics, but do not have substantially diminished binding characteristics. For example, the methods of the invention will generate antigen binding and/or constant region domains that exhibit improved formulation characteristics, but preferably have no reduction in any binding characteristic (*e.g.*, binding specificity, K_D, K_{off}, K_{on}, binding

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affinity and/or avidity), or have one or more antigen binding characteristics that are reduced by less than 1%, or by less than 5%, or by less than 10%, or by less than 20 %, or by less than 30%, or by less than 40%, or by less than 50%, or by less than 60%, or by less than 70%, or by less than 80% when compared to antigen binding of the antibody without said substitution.

[0137] In yet another embodiment, the methods of the invention will result in the selection of antigen binding and/or constant region domains with a binding activity above a predetermined threshold having improved therapeutic and/or formulation characteristics. In certain embodiments, the binding activity is the affinity constant or K_a (k_{on}/k_{off}) of the domain for a particular target/ligand/receptor. In a specific embodiment, the K_a is at least 10^2M^{-1}, at least $5\times10^2M^{-1}$, at least 10^3M^{-1}, at least $5\times10^3M^{-1}$, at least 10^4M^{-1}, at least $5\times10^4M^{-1}$, at least 10^5M^{-1}, at least $5\times10^5M^{-1}$, at least 10^6M^{-1}, at least $5\times10^6M^{-1}$, at least 10^7M^{-1}, at least $5\times10^7M^{-1}$, at least 10^8M^{-1}, at least $5\times10^8M^{-1}$, at least 10^9M^{-1}, at least $5\times10^9M^{-1}$, at least $10^{10}M^{-1}$, at least $5\times10^1M^{-1}$, at least $10^{11}M^{-1}$, at least $5\times10^{11}M^{-1}$, at least $10^{12}M^{-1}$, at least $5\times10^{12}M$, at least $10^{13}M^{-1}$, at least $5\times10^{13}M^{-1}$, at least $10^{14}M^{-1}$, at least $5\times10^{14}M^{-1}$, at least $10^{15}M^{-1}$, or at least $5\times10^{15}M^{-1}$. In other embodiments, the binding activity is the equilibrium dissociation constant (K_D) of the domain for a particular target/ligand/receptor. As described above, one of skill in the art will recognize that a molecule having a higher binding affinity will generally have a lower K_D value. Accordingly, in a specific embodiment the K_D is less than 10^{-5} M, or less than 10^{-6} M, or less than 10^{-7} M, or less than 10^{-8} M, or less than 10^{-9} M, or less than 10^{-10} M, or less than 10^{-11} M, or less than 10^{-12} M, or less than 10^{-13} M.

[0138] In one embodiment, selected or engineered antigen binding and/or constant region domains are then used to construct a full antigen binding and/or antibody constant domain containing multidomain protein (*e.g.*, antibody) using methods known in the art. Such multidomain proteins can then be submitted to formulation development to determine the optimal formulations.

[0139] There are various methods available for assessing the stability of protein drug formulations (*e.g.*, multidomain protein formulations), based on the physical and chemical structures of the proteins (*e.g.*, antibodies or fragments thereof) as well as on their biological activities. For example, to study denaturation of proteins, methods such as charge-transfer absorption, thermal analysis, fluorescence spectroscopy, circular dichroism, NMR, and HPSEC, are available. *See*, for example, Wang *et al.*, 1988, J. of Parenteral Science & Technology 42 (Suppl):S4-S26.

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[0140] The rCGE and HPSEC are the most common and simplest methods to assess the formation of protein aggregates, protein degradation, and protein fragmentation. Accordingly, the stability of the formulations may be assessed by these methods.

[0141] In certain embodiments, the concentration of the multidomain protein formulations is at least 15 mg/ml, at least 20 mg/ml, at least 25 mg/ml, at least 30 mg/ml, at least 35 mg/ml, at least 40 mg/ml, at least 45 mg/ml, at least 50 mg/ml, at least 55 mg/ml, at least 60 mg/ml, at least 65 mg/ml, at least 70 mg/ml, at least 75 mg/ml, at least 80 mg/ml, at least 85 mg/ml, at least 90 mg/ml, at least 95 mg/ml, at least 100 mg/ml, at least 105 mg/ml, at least 110 mg/ml, at least 115 mg/ml, at least 120 mg/ml, at least 125 mg/ml, at least 130 mg/ml, at least 135 mg/ml, at least 140 mg/ml, at least 150 mg/ml, at least 200 mg/ml, at least 250 mg/ml, or at least 300 mg/ml.

[0142] In certain embodiments, the formulations of the multidomain protein exhibit stability at the temperature ranges of 38°C-42°C for at least 30 days, at least 45 days, or at least 60 days and, in some embodiments, not more than 120 days, of 20°C-24°C for at least 6 months, or at least 1 year, of 2°C-8°C (in particular, at 4°C) for at least 6 months, at least 1 year, at least 2 years, at least 3 years, at least 4 years, or at least 5 years and at -20°C for at least 1 year, at least 2 years, at least 3 years, at least 4 years, or at least 5 years, as assessed by high performance size exclusion chromatography (HPSEC). Namely, the formulations have low to undetectable levels of aggregation and/or fragmentation, as defined herein, after the storage for the defined periods as set forth above. Preferably, no more than 5%, no more than 4%, no more than 3%, no more than 2%, no more than 1%, no more than 0.5% of the protein or protein fragment forms an aggregate as measured by HPSEC, after the storage for the defined periods as set forth above. In specific embodiments, formulations of the multidomain protein exhibit almost no loss in biological activities of the multidomain protein during the prolonged storage under the condition described above, as assessed by various assays including, but not limited to, enzyme-linked immunosorbent assay (ELISA) and radioimmunoassay to measure the ability of, for example, an antibody or antibody fragment to specifically bind to a target antigen, by a C3a/C4a assay to measure the complement activating ability of the antibody and by chromium release assay to measure the ADCC activity of the antibody. The formulations retain after the storage for the above-defined periods more than 80%, more than 85%, more than 90%, more than 95%, more than 98%, more than 99%, or more than 99.5% of the initial biological activities of the formulation prior to the storage.

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[0143] For example, the stability of the formulations may be evaluated by HPSEC or rCGE, wherein the percent area of the peaks represents the non-degraded protein. In particular, approximately 250 μg of, for example, the antibody or antibody fragment that specifically binds to a target antigen (approximately 25 μl of a liquid formulation comprising 10 mg/ml said antibody or antibody fragment) is injected onto a TosoH Biosep TSK G3000SWXL column (7.8 mm x 30 cm) fitted with a TSK SW x1 guard column (6.0 mm CX 4.0 cm). The antibody or antibody fragment is eluted isocratically with 0.1 M disodium phosphate containing 0.1 M sodium sulfate and 0.05% sodium azide, at a flow rate of 0.8 to 1.0 ml/min. Eluted protein is detected using UV absorbance at 280 nm. A suitable reference standard is run in the assay as a control, and the results are reported as the area percent of the product monomer peak compared to all other peaks excluding the included volume peak observed at approximately 12 to 14 minutes. Peaks eluting earlier than the monomer peak are recorded as percent aggregate.

[0144] In certain embodiments, the formulations of the multidomain protein exhibit low to undetectable levels of aggregation as measured by HPSEC or rCGE, that is, no more than 5%, no more than 4%, no more than 3%, no more than 2%, no more than 1%, or no more than 0.5% aggregate by weight protein, and low to undetectable levels of fragmentation, that is, 80% or higher, 85% or higher, 90% or higher, 95% or higher, 98% or higher, or 99% or higher, or 99.5% or higher of the total peak area in the peak(s) representing intact protein. In the case of SDS-PAGE, the density or the radioactivity of each band stained or labeled with radioisotope can be measured and the % density or % radioactivity of the band representing non-degraded multidomain protein can be obtained.

[0145] The stability of the formulations can be also assessed by any assays that measure the biological activity of the multidomain protein in the formulation. For example, the biological activities of antibodies include, but are not limited to, antigen-binding activity, complement-activation activity, Fc-receptor binding activity, and so forth. Antigen-binding activity of the antibodies can be measured by any method known to those skilled in the art, including but not limited to ELISA, radioimmunoassay, Western blot, BIAcore, and the like. Complement-activation activity can be measured by a C3a/C4a assay in the system where the antibody which specifically binds to an antigen is reacted in the presence of the complement components with the cells expressing the antigen. Also see Harlow *et al.*, Antibodies: A Laboratory Manual, (Cold Spring Harbor Laboratory Press, 2nd ed. 1988). An ELISA based assay, *e.g.*, may be used to compare the ability of an antibody or fragment thereof to

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specifically bind to a target antigen to a suitable reference standard. In this assay, plates are coated with the target antigen and the binding signal of a set concentration of a suitable reference standard is compared to the binding signal of the same concentration of a test antibody or antibody fragment.

[0146] The purity of the multidomain protein formulations may be measured by any method well-known to one of skill in the art such as, *e.g.*, HPSEC. The sterility of the multidomain protein formulations may be assessed by methods well known in the art. For example, sterile soybean-casein digest medium and fluid thioglycollate medium are inoculated with a test protein formulation by filtering a liquid protein formulation through a sterile filter having a nominal porosity of 0.45 μm. When using the Sterisure™ or Steritest™ method, each filter device is aseptically filled with approximately 100 ml of sterile soybean-casein digest medium or fluid thioglycollate medium. When using the conventional method, the challenged filter is aseptically transferred to 100 ml of sterile soybean-casein digest medium or fluid thioglycollate medium. The media are incubated at appropriate temperatures and observed three times over a 14 day period for evidence of bacterial or fungal growth.

[0147] The methods described above can be used to generate antibody therapeutics targeting any infectious organisms, including but not limited to any viruses and bacteria.

[0148] The methods described above can also be used to generate antibody therapeutics targeting other antigens, including but not limited to 17-1A, $\alpha 4\beta 7$ integrin receptor, AFP, CBL, CD11, CD11a, CD14, CD147, CD18, CD20, CD22, CD23, CD25, CD3, CD33, CD4, CD40, CD40L, CD44, CD52, CD64 (FcR), CD80, CEA, Complement (C5), CTLA-4, EGF receptor, Ep-CAM, E-selectin, Factor VII, FcRI receptors, Gamma Interferon, GD2-ganglioside, gp IIIb/IIIa, gp72, HER-2, HLA-DR 10 beta, HLA-DR antigen, ICAM-3, IgE, IL-4, IL5, IL-5, IL-8, inhibitor of P38MAP kinase, inosine monophosphate dehydrogenase, ganglioside GD3, MUC-1, nuC242, PEM antigen, SK-1 antigen, TNF alpha, VEGF, VEGF-receptor, and VLA-4.

[0149] In certain specific embodiments, the methods described above can also be used to generate antibody therapeutics that specifically binds to an antigen of RSV, an antigen of human metapneumovirus (hMPV), integrin $\alpha_v\beta_3$, CD2, CD19, EphA2, EphA4, or IL-9. Additional nonlimiting therapeutic targets are described in section 5.3 below.

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5.2. Methods For Evaluating And/Or Improving The Shelf Life Of A Formulations Comprising A Multidomain Protein

[0150] The invention also provides a method for evaluating the shelf-life of a multidomain protein formulation. The methods of the invention involves evaluating the thermal denaturation and/or renaturation behavior of a multidomain protein in a liquid preparation, which comprises a multidomain protein of interest having a domain the unfolding of which leads to aggregation of the multidomain protein in the liquid protein preparation. In one embodiment, the denaturation/renaturation behavior of the liquid protein preparation is determined by measuring a thermal denaturation/renaturation curve. The method then provides an indicator for the shelf life of the preparation based on the thermal denaturation and/or renaturation curve. For example, if the domain does not refold upon cooling or denatures at a low temperature, the multidomain protein is likely to have a short shelf life.

[0151] The invention also provides a method of evaluating long term stability of a multidomain protein in a solution, wherein the long term stability is defined as less than 5%, less than 10%, or less than 20% aggregation upon storage for a predetermined period of time at a predetermined temperature. The method comprises (a) providing a solution of a multidomain protein; (b) denaturing one or more domains of the multidomain protein by heating the solution of the multidomain protein; (c) determining if the domains refold upon cooling; and (d) classifying the multidomain protein as having long term stability in the solution if the domains are determined to refold in step (c). It is contemplated that the stability of a multidomain protein may be evaluated in a number of different solutions thereby identifying a particular solution useful for stabilizing a multidomain protein. Alternatively, or optionally, the method may be utilized to compare several different multidomain proteins having a desired biological activity above a predetermined threshold level, wherein each multidomain protein is formulated in a solution having identical components with the exception of the multidomain protein.

[0152] It is contemplated that a multidomain protein may comprise a domain the unfolding of which causes aggregation of the multidomain protein. Accordingly, the invention also provides a method for identifying a domain in a multidomain protein, which domain is responsible for aggregation of the protein. In one embodiment, the method of identifying one or more domain in a multidomain protein, which is responsible for aggregation comprises (a) denaturing one or more domains of the multidomain protein by

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heating said solution; (b) determining if one or more of said domains refold upon cooling; and (c) identifying one or more domains that do not refold upon cooling in step (b), thereby identifying a domain or domains, the unfolding of which causes aggregation of said multidomain protein in said solution.

[0153] The invention also provides a method of engineering a multidomain protein to have improved long term stability in a solution, wherein said long term stability is defined as less than 5%, less than 10%, or less than 20% aggregation upon storage for a predetermined period of time at a predetermined temperature. The method of engineering a multidomain protein to have improved long term stability in a solution comprises (a) modifying a domain of the multidomain protein by replacing one or more amino acid residues in the domain to generated a modified domain; (b) denaturing the modified domain by heating a solution of a multidomain protein comprising the modified domain; (c) determining if said modified domain in the multidomain protein refolds upon cooling; and (d) classifying the multidomain protein containing the modified domain as having improved long term stability if the modified domain is determined to refold in step (c). In one embodiment, the multidomain protein is an antibody. It is contemplated that steps (a) to (d) may be performed on an isolated domain. For example, a Fab domain, the unfolding of which causes aggregation of an antibody, may be isolated, modified denatured, renatured and classified. In one embodiment, the identified domain having improved long term stability is used in the generation of a multidomain protein. In one embodiment, the multidomain protein is an antibody. In another embodiment, the domain is an antigen binding domain. In yet another embodiment, the domain is a constant region domain. In certain embodiments, the multidomain protein comprises a domain the unfolding of which causes aggregation of the multidomain protein in the solution.

[0154] The invention further provides a method of screening for a multidomain protein which has improved long term stability in a solution, wherein the long term stability is defined as less than 5%, less than 10%, or less than 20% aggregation upon storage for a predetermined period of time at a predetermined temperature. In certain embodiments, a multidomain protein comprises a domain the unfolding of which causes aggregation of the multidomain protein in a solution. In one embodiment, the method comprises (a) denaturing respectively two or more multidomain proteins that are members of a population multidomain proteins, wherein each multidomain proteins comprises a different modified domain, the modified domain having one or more amino acid residues substituted, wherein the denaturing

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is accomplished by heating a solution of one of the multidomain proteins comprising the modified domain; (b) determining if the different modified domains in each multidomain protein denatured in step (a) refolds upon cooling; and (c) identifying the multidomain proteins containing a modified domain that is determined to refold in step (b) as having improved long term stability. In one embodiment, the method further comprises generating the population of different multidomain proteins. It is contemplated that steps (a) to (c) may be performed on isolated domains. For example, a Fab domain, the unfolding of which causes aggregation of an antibody, may be isolated and modified to generate a population of different modified domains two or more of which may then be screened by the method. In one embodiment, the identified domain having improved long term stability is used in the generation of a multidomain protein. In a specific embodiment the multidomain protein is an antibody. In one embodiment, the domain is an antigen binding domain (e.g., a Fab domain). In another embodiment, the domain is a constant region domain.

[0155] In certain embodiments, the denaturation and renaturation (i.e., refolding upon cooling) steps are carried out by generating a thermal denaturation/renaturation curve, e.g., using differential scanning calorimetry. The magnitude of the change in a physical property associated with the thermal denaturation of the multidomain protein as a result of heating is measured over a range of temperatures to generate a thermal denaturation/renaturation curve. It is contemplated that the temperature range encompasses the desired storage temperature range.

[0156] As used herein, a "thermal denaturation/renaturation curve" is a plot of a change in a physical property associated with the denaturation or renaturation of a protein as a function of temperature. See, for example, Davidson et al., Nature Structure Biology 2:859 (1995); Clegg, R. M. et al., Proc. Natl. Acad. Sci. U.S.A. 90:2994-2998 (1993). Any physical property of the protein which changes during denaturation, e.g., the emission of light or heat, the absorption of light or heat, scattering of light, and dichroism, may be used for monitoring the structural change of the protein. Examples of such physical properties include fluorescent emission, fluorescent energy transfer, absorption of ultraviolet or visible light, changes in polarization of light, and light scattering. Fluorescence emission can be intrinsic to a protein or can be due to a fluorescence reporter molecule.

[0157] As used herein, "aggregation" refers to a physical interaction between the protein or polypeptide molecules that result in formation of multimers. The multimers may remain soluble, or precipitate out of solution.

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[0158] The multidomain protein formulation can be a solution of the multidomain protein of a suitable concentration, e.g., a concentration of 20, 30, 40, 50, 100 mg/ml or higher. The liquid multidomain protein formulation can also comprise other constituents, including but are not limited to, salts, ligands, co-factors, etc. The concentration and constituents of the liquid multidomain protein formulation are selected such that the thermal denaturation/renaturation behavior of the multidomain protein in the liquid multidomain protein formulation reflects the long term stability of the liquid multidomain protein formulation whose shelf life is to be evaluated. In one embodiment, the concentration of the multidomain protein in the liquid multidomain protein formulation being analyzed differs from the concentration of the multidomain protein in a liquid protein formulation by no more than 50%, 20%, 10%, 5% or 1%. In a specific embodiment, the concentration of the multidomain protein in the liquid multidomain protein formulation being analyzed is substantially the same as the concentration of the multidomain protein in a multidomain protein formulation.

[0159] The multidomain protein can comprise other amino acid residues or domains in addition to the aggregation-causing domain.

[0160] The concentration of a multidomain protein in a liquid formulation is at least 15 mg/ml, at least 20 mg/ml, at least 25 mg/ml, at least 30 mg/ml, at least 35 mg/ml, at least 40 mg/ml, at least 45 mg/ml, at least 50 mg/ml, at least 55 mg/ml, at least 60 mg/ml, at least 65 mg/ml, at least 70 mg/ml, at least 75 mg/ml, at least 80 mg/ml, at least 85 mg/ml, at least 90 mg/ml, at least 95 mg/ml, at least 100 mg/ml, at least 105 mg/ml, at least 110 mg/ml, at least 115 mg/ml, at least 120 mg/ml, at least 125 mg/ml, at least 130 mg/ml, at least 135 mg/ml, at least 140 mg/ml, at least 150 mg/ml, at least 200 mg/ml, at least 250 mg/ml, or at least 300 mg/ml.

[0161] The formulations may also comprise other substances, e.g., histidine, glycine, saccharides (e.g., sucrose, mannose, trehalose, etc.), polyols, (e.g., Tween) and sugar alcohols (e.g., mannitol, sorbitol, etc.). The concentration of histidine which is included in the formulations ranges from 1 mM to 100 mM, or from 5 mM to 50 mM. Histidine can be in the form of L-histidine, D-histidine, or a mixture thereof, but L-histidine is generally preferred. Histidine can be also in the form of hydrates. Histidine may be used in a form of pharmaceutically acceptable salt, such as hydrochloride (e.g., monohydrochloride and dihydrochloride), hydrobromide, sulfate, acetate, etc. The purity of histidine should be at least 98%, preferably at least 99%, and most preferably at least 99.5%.

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[0162] The concentration of an amino acid to be used in a formulation can be at a concentration of less than 150 mM, less than 100 mM, less than 75 mM, less than 50 mM, less than 25 mM, less than 10 mM, less than 5.0 mM, or less than 2.0 mM. The amount of amino acid in the formulation should not cause a significant buffering effect so that protein precipitation at its isoelectric point can be avoided. An amino acid may be also used in a form of pharmaceutically acceptable salt, such as hydrochloride, hydrobromide, sulfate, acetate, etc. The purity of the amino acid should be at least 98%, or at least 99%, or at least 99.5%.

[0163] The saccharide can be sucrose at a concentration ranging from between about 1% to about 20%, preferably about 5% to about 15%, and more preferably about 8% to 10%. The polyol can be polysorbate (e.g., Tween 20) at a concentration ranging from between about 0.001% to about 1%, or about 0.01% to about 0.1%.

[0164] The pH of the formulation should not be equal to the isoelectric point of the particular multidomain protein to be used in the formulation and may range from about 5.0 to about 8.0, or about 5.5 to about 6.5, or about 6.0 to about 7.0, or about 6.5 to about 7.5, or about 7.0 to about 8.0, or about 5.8 to about 6.2, and or about 6.0.

[0165] Liquid formulations preferably exhibit stability at the temperature ranges of 38oC-42oC for at least 15 days and, in some embodiments, not more than 25 days, of 20oC-24oC for at least 1 month, at least 2 months, at least 4 months, or at least 6 months, of 2oC-8oC (in particular, at 4oC) for at least 6 months, at least 1 year, at least 1.5 years, at least 2 years, at least 3 years or at least 4 years and at -20oC for at least 1 year, at least 2 years, at least 3 years, at least 4 years, or at least 5 years, as assessed by high performance size exclusion chromatography (HPSEC). Namely, the formulations, more specifically liquid formulations, have low to undetectable levels of aggregation and/or fragmentation, as defined herein, after the storage for the defined periods as set forth above. In certain embodiments, no more than 5%, no more than 4%, no more than 3%, no more than 2%, no more than 1%, and or no more than 0.5% of the multidomain protein forms an aggregate as measured by HPSEC, after the storage for the defined periods as set forth above.

[0166] In one embodiment, a suitable solution of a multidomain protein that comprises a domain whose unfolding leads to aggregation of the multidomain protein whose shelf life is of interest is provided, wherein the solution stabilizes the domain. In another embodiment, a suitable solution of a multidomain protein comprising an engineered domain having improved long term stability is provided.

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[0167] A lyophilized formulation preferably exhibits no significant changes observed at a refrigerated temperature (2-8°C) for at least 12 months, preferably 2 years, and more preferably 3 years; or at room temperature (23-27°C) for at least 3 months, preferably 6 months, and more preferably 1 year. The criteria for stability are as follows: No more than 10%, or no more than 5%, of the protein domain is degraded as measured by HPSEC. The rehydrated solution is colorless, or clear to slightly opalescent by visual analysis. The concentration, pH and osmolality of the formulation have no more than +/- 10% change. Potency is within 70-130, preferably 80- 120 % of the control. No more than 10%, preferably 5% of clipping is observed. No more than 10%, or no more than 5% of aggregation is formed.

[0168] The methods of screening and/or evaluating the long term stability of a multidomain protein in a solution of the invention can provide an indicator of the shelf life of a plurality of formulations of different multidomain proteins, e.g., a plurality of different monoclonal antibodies. In one embodiment, a suitable solution of a multidomain protein is provided for each multidomain protein. Alternatively, the methods of screening and/or evaluating the long term stability of a multidomain protein in a solution of the invention can provide an indicator of the shelf life of a plurality of different solutions comprising the same multidomain protein. In another embodiment, a multidomain protein is formulated in a number of different solutions. In certain embodiments, each multidomain protein comprises a domain whose unfolding leads to aggregation of the corresponding multidomain protein. In other embodiments, each multidomain protein comprises a variant of a domain whose unfolding leads to aggregation of the corresponding multidomain protein. A thermal denaturation curve is measured for each of such multidomain proteins. The multidomain proteins are then ranked based on the denaturation temperatures of the multidomain proteins. The lower denaturation temperature corresponds to lower stability, and thus is indicative of a shorter shelf life.

[0169] In one embodiment, the methods of screening and/or evaluating the long term stability of a multidomain protein in a solution is used as an indicator of the shelf life of a plurality of formulations of different modified multidomain proteins. Each of the plurality of modified multidomain proteins comprises a domain in a modified form, e.g., having one or more amino acid residues in the domain substituted. A suitable solution of a multidomain protein comprising a modified domain is provided for each modified multidomain protein. A thermal denaturation curve is measured for each of such multidomain proteins. The modified

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multidomain proteins are then ranked based on the denaturation temperatures of the multidomain proteins. One or more modified monoclonal multidomain protein may be selected based on the rank order. In a specific embodiment, the multidomain protein is an antibody.

[0170] The methods of screening and/or evaluating the long term stability of a multidomain protein in a solution can also be used for identifying biochemical conditions that optimize the stability of, and hence the shelf life of, a formulation of a multidomain protein. For example, pH affects the shelf life of a protein. For a liquid formulation the composition of the solvent, e.g., water, also affect the shelf life of a protein. For example, glycerol alters the solvation properties of water to favor the native conformation of proteins. Ligands and cofactors in the solution may also affect the shelf life of a protein. Other biochemical parameters that have been shown to affect protein folding are: protein concentration, temperature, glutathione redox buffers (GSH, GSSG), the presence of detergents, and the presence of other additives, such as glycerol, arginine-HCl, polyethylene glycol (PEG), and organic solvents. Various conditions can be optimized, including pH optimum, ionic strength dependence, concentration of salts of the Hofmeister series, glycerol concentration, sucrose concentration, arginine concentration, dithiothreitol concentration, metal ion concentration, etc. Such biological conditions can be evaluated based on the thermal denaturation curve of the multidomain protein under the conditions. In one embodiment, a plurality of different conditions are ranked, and the optimal one is selected.

[0171] In one embodiment, the thermal denaturation/renaturation curve is obtained using differential scanning calorimetry (DSC). In this embodiment, a DSC thermogram of the denaturation/renaturation of the multidomain protein is obtained. Methods of using DSC to study the denaturation of proteins are well known in the art (see, e.g., Vermeer et al., 2000, Biophys. J. 78:394-404; Vermeer et al., 2000, Biophys. J. 79: 2150-2154). DSC can detect fine-tuning of interactions between the individual domains of a protein (Privalov et al., 1986, Methods Enzymol. 131:4-51).

[0172] In one embodiment, DSC measurements are performed using a Setaram Micro-DSC III (Setaram, Caluire, France). The samples are placed in the calorimeter in a 1 ml sample cell against a 1 ml reference cell containing the appropriate blank solution. The cells are stabilized for 4 h at 25°C inside the calorimeter before heating up to the final temperature at a selected heating rate. The transition temperature and enthalpy are determined using the Setaram software (Setaram, Version 1.3).

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[0173] In another embodiment, DSC measurements are performed using a VP-DSC (MicroCal, LLC). In one embodiment, a scan rate of 1.0°C/min and a temperature range of 25 –120°C are employed. A filter period of 8 seconds is used along with a 5 minute pre-scan thermostating. Multiple baselines are run with buffer in both the sample and reference cell to establish thermal equilibrium. After the baseline is subtracted from the sample thermogram, the data are concentration normalized and fitted using the deconvolution function. Melting temperatures are determined following manufacturer procedures using Origin software supplied with the system.

[0174] In another embodiment, the thermal denaturation/renaturation curve is obtained using circular dichroism (CD) spectroscopy. Changes in the secondary structure of IgG as a function of temperature and/or, e.g., pH, can be studied by CD spectroscopy (Fasman, 1996, Circular Dichroism and the Conformational Analysis of Biomolecules. Plenum Press, New York). The advantage of this technique are that the spectroscopic signal is not affected by the presence of the surrounding solution and that well-defined procedures are available to elucidate the secondary structure based on reference spectra of the different structure elements (de Jongh et al., 1994, Biochemistry. 33:14521-14528). The fractions of the secondary structural elements can be obtained from the CD spectra.

[0175] In one embodiment, the CD spectra are measured with a JASCO spectropolarimeter, model J-715 (JASCO International Co., Tokyo, Japan). A quartz cuvette of 0.1 cm light path length is used. Temperature regulation is carried out using a JASCO PTC-348WI (JASCO International) thermocouple. Temperature scans are recorded at a selected heating rate using the Peltier thermocouple with a resolution of 0.2°C and a time constant of 16 s. Wavelength scans, in the far-UV region (0.2 nm resolution) are obtained by accumulation of a plurality of scans with a suitable scan rate

[0176] The thermal denaturation/renaturation curve can also be measured by light spectrophotometry. When a protein in a solution denatures in response to heating, the molecules aggregate and the solution scatters light more strongly. Aggregation leads to changes in the optical transparency of the sample, and can be measured by monitoring the change in absorbance of visible or ultraviolet light of a defined wavelength.

[0177] In still another embodiment, fluorescence spectroscopy is used to obtain the thermal denaturation/renaturation curve. In one embodiment, intrinsic protein fluorescence, e.g., intrinsic tryptophan fluorescence, is monitored. In another embodiment, fluorescence probe molecules are monitored. Methods of performing fluorescence spectroscopy

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experiments are well known to those skilled in the art. See, for example, Bashford, C. L. et al., Spectrophotometry and Spectrofluorometry: A Practical Approach, pp. 91-114, IRL Press Ltd. (1987); Bell, J. E., Spectroscopy in Biochemistry, Vol. I, pp. 155-194, CRC Press (1981); Brand, L. et al., Ann. Rev. Biochem. 41:843 (1972).

[0178] The methods of the invention can be practiced using an array format, in which a plurality of different liquid multidomain protein preparations is evaluated simultaneously (see, U.S. Patent No. 6,232,085). The array format is particular useful for evaluating the potential shelf life of a plurality of formulations of different multidomain proteins, *e.g.*, a plurality of modified monoclonal antibodies, or the shelf life of a multidomain protein under a plurality of different biochemical conditions.

5.3. Multidomain Proteins

[0179] In one embodiment the methods of the present invention are useful for the generation of multidomain proteins with improved manufacturing characteristics (referred to herein as "multidomain proteins of the invention") that specifically bind to a target molecule. Such multidomain proteins include but are not limited to antibodies including antibody domain fusion proteins. In one embodiment, a multidomain protein of the invention specifically binds a nonpolypeptide target. In another embodiment, a multidomain protein of the invention specifically binds a polypeptide target. In another embodiment, administration of a multidomain protein of the invention to a mammal suffering from a disease or disorder can result in a therapeutic benefit in that mammal.

[0180] Antibody domain fusion proteins include Fc fusion proteins, which combines an Fc domain or fragment thereof, with a fusion partner, which in general can be any protein, polypeptide, peptide, including, but not limited to, the target-binding region of a receptor, an adhesion molecule, a ligand, an enzyme, or some other protein or protein domain. Antibody domain fusion proteins also include antigen binding domain fusion proteins, which combines an antigen binding domain or fragment thereof, with a fusion partner, which in general can be any protein, polypeptide, peptide, including, but not limited to, another antigen binding domain, the target-binding region of a receptor, an adhesion molecule, a ligand, an enzyme, a toxin or some other protein or protein domain. It will be understood that the role of the fusion partner is determined by the therapeutic goal. For example the role of the non-Fc part of an Fc fusion is generally to mediate target binding, and thus it is functionally analogous to the variable regions of an antibody while the role of the fusion partner of an antigen binding

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domain fusion protein may be to mediate binding to a second target in the case of a second antigen binding domain or to provide a cytotoxic agent in the case of a toxin.

[0181] Virtually any molecule may be targeted by and/or incorporated into a multidomain protein of the invention including, but not limited to, following list of proteins, subunits, domains, motifs, and epitopes belonging to the following list of cellular proteins: renin; a growth hormone, including human growth hormone and bovine growth hormone; growth hormone releasing factor; parathyroid hormone; thyroid stimulating hormone; lipoproteins; alpha- 1 - antitrypsin; insulin A-chain; insulin B-chain; proinsulin; follicle stimulating hormone; calcitonin; luteinizing hormone; glucagon; clotting factors such as factor VII, factor VIIIC, factor IX, tissue factor (TF), and von Willebrands factor; anti-clotting factors such as Protein C; atrial natriuretic factor; lung surfactant; a plasminogen activator, such as urokinase or human urine or tissue-type plasminogen activator (t-PA); bombesin; thrombin; hemopoietic growth factor; tumor necrosis factor (TNF) proteins such as TNF-alpha, TNF-beta, TNFbeta2, TNFc, TNFalphabeta, 4-1BBL as well as members of the TNF superfamily members such as, TNF-like weak inducer of apoptosis (TWEAK), and LIGHT, B lymphocyte stimulator (BlyS); members of the TNF receptor superfamily including TNF-RI, TNF-RII, TRAIL receptor-1, Transmembrane activator and CAML interactor (TACI) and OX40L; Fas ligand (FasL); enkephalinase; RANTES (regulated on activation normally T-cell expressed and secreted); human macrophage inflammatory protein (MIP-1-alpha); a serum albumin such as human serum albumin; Muellerian-inhibiting substance; relaxin A-chain; relaxin B-chain; prorelaxin; mouse gonadotropin-associated peptide; a microbial protein, such as beta-lactamase; DNase; IgE; a cytotoxic T-lymphocyte associated antigen (CTLA), such as CTLA-4; inhibin; activin; vascular endothelial growth factor (VEGF); receptors for hormones or growth factors such as, for example, EGFR (ErbB-1), VGFR; interferons such as alpha interferon (α-IFN), beta interferon (β-IFN) and gamma interferon (γ-IFN); interferon alpha receptor (IFNAR) subunits 1 and/or 2 and other receptors such as, A1, Adenosine Receptor, Lymphotoxin Beta Receptor, BAFF-R, endothelin receptor; protein A or D; rheumatoid factors; a neurotrophic factor such as bone-derived neurotrophic factor (BDNF), neurotrophin-3,-4,-5, or -6 (NT-3, NT-4, NT-5, or NT-6), or a nerve growth factor; platelet-derived growth factor (PDGF); fibroblast growth factor such as αFGF and βFGF; epidermal growth factor (EGF); transforming growth factor (TGF) such as TGF-alpha and TGF-beta, including TGF-1, TGF-2, TGF-3, TGF-4, or TGF-5; insulin-like growth factor-I and-II (IGF-I and IGF-II); des (1-3)-IGF-I (brain IGF-I), insulin-like growth

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factor binding proteins, keratinocyte growth factor; growth factor receptors such as, FGFR-3, IGFR; CD proteins such as CD2, CD3, CD3E, CD4, CD 8, CD11, CD11a, CD14, CD16, CD18, CD19, CD20, CD22, CD23, CD25, CD27, CD27L, CD28, CD29, CD30, CD30L, CD32, CD33 (p67 protein), CD34, CD38, CD40, CD40L, CD52, CD54, CD56, CD63, CD64, CD80 and CD147; erythropoietin; osteoinductive factors; immunotoxins; a bone morphogenetic protein (BMP); an interferon such as interferon-alpha,-beta, and-gamma; colony stimulating factors (CSFs), such as M-CSF, GM-CSF, and G-CSF; interleukins (ILs), e.g., IL-1 to IL-13 and IL-15, IL-18, IL-23; EPO; superoxide dismutase; T-cell receptors alpha/beta; surface membrane proteins; decay accelerating factor; transport proteins; homing receptors; addressins; regulatory proteins; chemokine family members such as the eotaxins, the MIPs, MCP-1, RANTES; cell adhesion molecules such as selectins (L-selectin, P-selectin, E-selectin) LFA-1, LFA-3, Mac 1, p150.95, VLA-1, VLA-4, ICAM-1, ICAM-3, EpCAM and VCAM, a4/p7 integrin, and Xv/p3 integrin, integrin alpha subunits such as CD49a, CD49b, CD49c, CD49d, CD49e, CD49f, alpha7, alpha8, alpha9, alphaD, CD11a, CD11b, CD51, CD11c, CD41, alphaIIb, alphaIELb; integrin beta subunits such as, CD29, CD 18, CD61, CD104, beta5, beta6, beta7 and beta8; Integrin subunit combinations including but not limited to, $\alpha V\beta 3$, $\alpha V\beta 5$ and $\alpha 4\beta 7$; cellular ligands such as, TNF-related apoptosis-inducing ligand (TRAIL), A proliferation-inducing ligand (APRIL), B Cell Activating Factor (BAFF), a member of an apoptosis pathway; IgE; blood group antigens; flk2/flt3 receptor; obesity (OB) receptor; mpl receptor; CTLA-4; protein C; an Eph receptor such as EphA2, EphA4, EphB2, etc.; immune system markers, receptors and ligands such as CTLA-4, T cell receptor, B7-1, B7-2, IgE, Human Leukocyte Antigen (HLA) such as HLA-DR, CBL; complement proteins such as complement receptor CR1, C1Rq and other complement factors such as C3, and C5; blood factors including tissue factor, factor VII; a glycoprotein receptor such as GpIbα, GPIIb/IIIa and CD200; and fragments of any of the above-listed polypeptides.

[0182] Also contemplated are multidomain proteins of the invention that specifically bind cancer antigens including, but not limited to, ALK receptor (pleiotrophin receptor), pleiotrophin; KS 1/4 pan-carcinoma antigen; ovarian carcinoma antigen (CA125); prostatic acid phosphate; prostate specific antigen (PSA); melanoma-associated antigen p97; melanoma antigen gp75; high molecular weight melanoma antigen (HMW-MAA); prostate specific membrane antigen; carcinoembryonic antigen (CEA); carcinoembryonic antigen-related cell adhesion molecule (CEACAM1); cytokeratin tumor-associated antigen; human milk fat globule (HMFG) antigen; tumor-associated antigen expressing Lewis Y related

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carbohydrate; colorectal tumor-associated antigens such as: CEA, tumor-associated glycoprotein-72 (TAG-72), CO17-1A, GICA 19-9, CTA-1 and LEA; Burkitt's lymphoma antigen-38.13; CD19; human B-lymphoma antigen-CD20; CD33; melanoma specific antigens such as ganglioside GD2, ganglioside GD3, ganglioside GM2 and ganglioside GM3; tumor-specific transplantation type cell-surface antigen (TSTA); virally-induced tumor antigens including T-antigen, DNA tumor viruses and Envelope antigens of RNA tumor viruses; oncofetal antigen-alpha-fetoprotein such as CEA of colon, 5T4 oncofetal trophoblast glycoprotein and bladder tumor oncofetal antigen; differentiation antigen such as human lung carcinoma antigens L6 and L20; antigens of fibrosarcoma; human leukemia T cell antigen-Gp37; neoglycoprotein; sphingolipids; breast cancer antigens such as EGFR (Epidermal growth factor receptor); NY-BR-16; NY-BR-16 and HER2 antigen (p185HER2); Her2/neu (ErbB-2), Her3 (ErbB-3), Her4 (ErbB-4), polymorphic epithelial mucin (PEM) antigen; epithelial membrane antigen (EMA); Melanoma-associated antigen MUC18; MUC1; malignant human lymphocyte antigen-APO-1; differentiation antigen such as I antigen found in fetal erythrocytes; primary endoderm I antigen found in adult erythrocytes; preimplantation embryos; I(Ma) found in gastric adenocarcinomas; M18, M39 found in breast epithelium; SSEA-1 found in myeloid cells; VEP8; VEP9; Myl; VIM-D5; D156-22 found in colorectal cancer; TRA-1-85 (blood group H); SCP-1 found in testis and ovarian cancer; C14 found in colonic adenocarcinoma; F3 found in lung adenocarcinoma; AH6 found in gastric cancer; Y hapten; Ley found in embryonal carcinoma cells; TL5 (blood group A); EGF receptor found in A431 cells; E1 series (blood group B) found in pancreatic cancer; FC10.2 found in embryonal carcinoma cells; gastric adenocarcinoma antigen; CO-514 (blood group Lea) found in Adenocarcinoma; NS-10 found in adenocarcinomas; CO-43 (blood group Leb); G49 found in EGF receptor of A431 cells; MH2 (blood group ALeb/Ley) found in colonic adenocarcinoma; 19.9 found in colon cancer; gastric cancer mucins; T5A7 found in myeloid cells; R24 found in melanoma; 4.2, GD3, D1.1, OFA-1, GM2, OFA-2, GD2, and M1:22:25:8 found in embryonal carcinoma cells and SSEA-3 and SSEA-4 found in 4 to 8-cell stage embryos; Cutaneous Tcell Lymphoma antigen; MART-1 antigen; Sialy Tn (STn) antigen; Anaplastic lymphoma kinase (ALK) found in large cell lymphoma; Colon cancer antigen NY-CO-45; Lung cancer antigen NY-LU-12 variant A; Adenocarcinoma antigen ART1; Paraneoplastic associated brain-testis-cancer antigen (onconeuronal antigen MA2; paraneoplastic neuronal antigen); Neuro-oncological ventral antigen 2 (NOVA2); Hepatocellular carcinoma antigen gene 520; TUMOR-ASSOCIATED ANTIGEN CO-029; Tumor-associated antigens MAGE-C1 (cancer/testis antigen CT7), MAGE-B1 (MAGE-XP

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antigen), MAGE-B2 (DAM6), MAGE-2, MAGE-4a, MAGE-4b and MAGE-X2; Cancer-Testis Antigen (NY-EOS-1); placental alkaline phosphatase (PLAP) and testicular PLAP-like alkaline phosphatase, transferrin receptor; Heparanase I; EphA2 associated with numerous cancers and fragments of any of the above-listed polypeptides.

[0183] Other exemplary polypeptide targets include but not limited to the following list of proteins, subunits, domains, motifs, and epitopes belonging to the following list of microbial proteins: human cytomegalovirus (HCMV) proteins such as, envelope glycoprotein, gB, internal matrix proteins of the virus, pp65 and pp150, immediate early (IE) proteins; human immunodeficiency virus (HIV) proteins such as, Gag, Pol, Vif and Nef (Vogt et al., 1995, Vaccine 13: 202-208); HIV antigens gp120 and gp160 (Achour et al., 1995, Cell. Mol. Biol. 41: 395-400; Hone et al., 1994, Dev. Biol. Stand. 82: 159-162); gp41 epitope of human immunodeficiency virus (Eckhart et al., 1996, J. Gen. Virol. 77: 2001-2008); hepatitis C virus (HCV) proteins such as, nucleocapsid protein in a secreted or a nonsecreted form, core protein (pC); E1 (pE1), E2 (pE2) (Saito et al., 1997, Gastroenterology 112: 1321-1330), NS3, NS4a, NS4b and NS5 (Chen et al., 1992, Virology 188:102-113); severe acute respiratory syndrome (SARS) corona virus proteins include but are not limited to, the S (spike) glycoprotein, small envelope protein E (the E protein), the membrane glycoprotein M (the M protein), the hemagglutinin esterase protein (the HE protein), and the nucleocapsid protein (the N-protein) See, e.g., Marra et al., "The Genome Sequence of the SARS-Associated Coronavirus," Science Express, May 2003); Mycobacterium tuberculosis proteins such as the 30-35 kDa (a.k.a. antigen 85, alpha-antigen) that is normally a lipoglycoprotein on the cell surface, a 65-kDa heat shock protein, and a 36-kDa proline-rich antigen (Tascon et al. (1996) Nat. Med. 2: 888-92), Ag85A, Ag85b (Huygen et al., 1996, Nat. Med. 2: 893-898), 65-kDa heat shock protein, hsp65 (Tascon et al., 1996, Nat. Med. 2: 888-892), MPB/MPT51 (Miki et al., 2004, Infect. Immun. 72:2014-21), MTSP11, MTSP17 (Lim et al., 2004, FEMS Microbiol. Lett. 232:51-9 and supra); Herpes simplex virus (HSV) proteins such as gD glycoprotein, gB glycoprotein; proteins from intracellular parasites such as Leishmania include LPG, gp63 (Xu and Liew, 1994, Vaccine 12: 1534- 1536; Xu and Liew, 1995, Immunology 84: 173-176), P-2 (Nylen et al., 2004, Scand. J. Immunol. 59:294-304), P-4 (Kar et al. 2000, J Biol. Chem. 275:37789-97), LACK (Kelly et al., 2003, J Exp. Med. 198:1689-98); microbial toxin proteins such as Clostridium perfringens toxin; in addition, exemplary antigen peptides of human respiratory syncytial virus (hRSV), human

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metapneumovirus (HMPV) and Parainfluenza virus (PIV) are detailed in: Young et al., in Patent publication WO04010935A2.

[0184] One skilled in the art will appreciate that the aforementioned lists of targets refers not only to specific proteins and biomolecules, but the biochemical pathway or pathways that comprise them. For example, reference to CTLA-4 as a target antigen implies that the ligands and receptors that make up the T cell co-stimulatory pathway, including CTLA-4, B7-1, B7-2, CD28, and any other undiscovered ligands or receptors that bind these proteins, are also targets. Thus target, as used herein, refers not only to a specific biomolecule, but the set of proteins that interact with the target and the members of the biochemical pathway to which the target belongs. One skilled in the art will further appreciate that any of the aforementioned target antigens, the ligands or receptors that bind them, or other members of their corresponding biochemical pathway, may be operably linked to the multidomain proteins or a portion thereof of the present invention in order to generate a fusion protein. Thus for example, a multidomain fusion that targets EGFR could be constructed by operably linking a multidomain protein or portion thereof to EGF, TGFα, or any other ligand, discovered or undiscovered, that binds EGFR. Accordingly, a multidomain protein or portion thereof of the present invention could be operably linked to EGFR in order to generate an fusion that binds EGF, TGFα, or any other ligand, discovered or undiscovered, that binds EGFR. Thus virtually any polypeptide, whether a ligand, receptor, or some other protein or protein domain, including but not limited to the aforementioned targets and the proteins that compose their corresponding biochemical pathways, may be operably linked to the multidomain proteins of the present invention or a portion thereof to develop a fusion.

[0185] In one embodiment the multidomain protein of the invention is an antibody or an antibody domain fusion protein. Numerous methods useful for the generation of antibodies or antibody domain fusion proteins are well known in the art. Several nonlimiting examples are described below in section 5.4. In a specific embodiment the methods of the present invention are utilized to generate and/or screen antibody or antibody domain fusion proteins which have preferred/improved manufacturing characteristics.

[0186] A number of specific multidomain proteins, namely antibodies and antibody domain fusion proteins (e.g., Fc fusions) that are approved for use, in clinical trials, or in development may benefit from the methods of the present invention. Said antibodies and antibody domain fusion proteins (e.g., Fc fusions) are herein referred to as "clinical products and candidates". Thus in specific embodiments, the methods of the present invention may

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find use in a range of clinical products and candidates. For example the engineering and screening methods of the present invention may find use developing an antibody with improved manufacturing characteristics that has binding and functional characteristics substantially similar to rituximab (Rituxan®, IDEC/Genentech/Roche) (see for example U.S. Pat. No. 5,736,137), a chimeric anti-CD20 IgG1 antibody approved to treat Non-Hodgkin's lymphoma; HuMax-CD20 (Genmab), an anti-CD20 (see for example PCT WO 04/035607); an anti-CD20 antibody described in U.S. Pat. No. 5,500,362; AME-I33 (Applied Molecular Evolution) humanized and optimized anti-CD20 Mab; hA20 (Immunomedics, Inc.) a humanized anti-CD20 Mab; HumaLYM™ (Intracel) a fully human anti-CD20 Mab; trastuzumab (Herceptin®, Genentech) a humanized anti-Her2/neu antibody approved to treat breast cancer (see for example U.S. Pat. No. 5,677,171); pertuzumab (rhuMab-2C4, Omnitarg™, Genentech); an anti-Her2 antibody described in U.S. Pat. No. 4,753,894; cetuximab (Erbitux®, Imclone) (U.S. Pat. No. 4,943,533; PCT WO 96/40210), a chimeric anti-EGFR antibody in clinical trials for a variety of cancers; ABX-EGF (Abgenix/Immunex/Amgen) described in U.S. Pat. No. 6,235,883; HuMax-EGFr (Genmab) described in U.S. patent application No. 10/172,317; 425, EMD55900, EMD62000, and EMD72000 (Merck KGaA) (U.S. Pat. No. 5,558,864); ICR62 (Institute of Cancer Research) (PCT WO 95/20045); TheraCIM hR3 (YM Biosciences, Canada and Centro de Immunologia Molecular, Cuba) (U.S. Pat. Nos. 5,891,996; 6,506,883); mAb-806 (Ludwig Institute for Cancer Research, Memorial Sloan-Kettering) (Jungbluth et al. 2003, Proc Natl Acad Sci USA. 100(2):639-44); KSB-102 (KS Biomedix); MR1-1 (IVAX, National Cancer Institute) (PCT WO 01/62931); and SC100 (Scancell) (PCT WO 01/88138); alemtuzumab (Campath®, Genzyme), a humanized monoclonal anti CD52 IgG1 antibody currently approved for treatment of B-cell chronic lymphocytic leukemia; muromonab-CD3 (Orthoclone OKT3®, Ortho Biotech/Johnson & Johnson), an anti-CD3 antibody; OrthoClone OKT4A (Ortho Biotech), a humanized anti-CD4 IgG antibody; ibritumomab tiuxetan (Zevalin®, IDEC/Schering AG), a radiolabeled anti-CD20 antibody; gemtuzumab ozogamicin (Mylotarg®, Celltech/Wyeth), an anti-CD33 (p67 protein) antibody; alefacept (Amevive®, Biogen), an anti-LFA-3 Fc fusion; abciximab (ReoPro®, Centocor/Lilly), a anti-glycoprotein IIb/IIIa receptor on the platelets for the prevention of clot formation; basiliximab (Simulect®, Novartis) an anti-CD25 antibody; infliximab (Remicade®, Centocor), an anti-TNFalpha antibody; adalimumab (Humira®, Abbott), an anti-TNFalpha antibody; Humicade™ (CellTech), an anti-TNFalpha antibody; etanercept (Enbrel®, Immunex/Amgen), an anti-TNFalpha Fc fusion; ABX-CBL (Abgenix), an anti-CD147 antibody; ABX-IL8 (Abgenix),

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an anti-lL8 antibody; ABX-MA1 (Abgenix), an anti-MUC18 antibody; Pemtumomab (R1549, 90Y-muHMFG1, Antisoma), an anti-MUC1 antibody; Therex (R1550, Antisoma), an anti-MUC1 antibody; AngioMab (AS1405, Antisoma), HuBC-1 and Thioplatin (AS1407) being developed by Antisoma; natalizumab (Antegren®, Biogen), an anti-alpha-4-beta-1 (VLA-4) and alpha-4-beta-7 antibody; ANTOVA™ (Biogen). a humanized anti-CD40L IgG antibody; VLA-1 mAb (Biogen), an anti-VLA-1 integrin antibody; LTBR mAb (Biogen), an anti-lymphotoxin beta receptor (LTBR) antibody; CAT-152 (Cambridge Antibody Technology), an anti-TGFβ2 antibody; J695 (Cambridge Antibody Technology/Abbott), an anti-IL-12 antibody; CAT-192 (Cambridge Antibody Technology/Genzyme); an anti-TGFβ1 antibody; CAT-213 (Cambridge Antibody Technology), an anti-Eotaxin1 antibody; LymphoStat-B™ an anti-Blys antibody and TRAIL-R1mAb, an anti-TRAIL-R1 antibody both being developed by Cambridge Antibody Technology and Human Genome Sciences, Inc.; bevacizumab (Avastin™, rhuMAb-VEGF, Genentech) an anti-VEGF antibody; an anti-HER receptor family antibody (Genentech); Anti-Tissue Factor antibody (Genentech); Omalizumab (Xolair™, Genentech) an anti-IgE antibody; Efalizumab (Raptiva™, Genentech/Xoma), an anti-CD11a antibody; MLN-02 Antibody (formerly LDP-02, Genentech /Millenium Pharmaceuticals), a humanized anti-α4β7 antibody; HuMax CD4 (Genmab), an anti-CD4 antibody being; HuMax-IL 15 (Genmab and Amgen), an anti-IL15 antibody; HuMax-Inflam (Genmab/Medarex),; HuMax-Cancer (Genmab/Medarex/Oxford GcoSciences), an anti-Heparanase I antibody; HuMax-Lymphoma (Genmab/Amgen); HuMax-TAC (Genmab); IDEC-131 (IDEC Pharmaceuticals), an anti-CD40L antibody; Clenoliximab (IDEC-151, IDEC Pharmaceuticals), an anti-CD4 antibody; IDEC-114 (IDEC Pharmaceuticals), an anti-CD80 antibody; IDEC-152 (IDEC Pharmaceuticals), an anti-CD23; anti-macrophage migration factor (MIF) antibodies being developed by IDEC Pharmaceuticals; BEC2 (Imclone), an anti-idiotypic antibody; IMC-1C11 (Imclone), an anti-KDR antibody; DC101 (Imclone), an anti-flk-1 antibody; anti-VE cadherin antibodies being developed by Imclone; labetuzumab (CEA-Cide™, Immunomedics), an anti-carcinoembryonic antigen (CEA) antibody; Epratuzumab (LymphoCide™, Immunomedics), an anti-CD22 antibody; AFP-Cide (Immunomedics); MyelomaCide (Immunomedics); LkoCide (Immunomedics); ProstaCide (Immunomedics); MDX-010 (Medarex), an anti-CTLA4 antibody; MDX-060 (Medarex), an anti-CD30 antibody; MDX-070 (Medarex); MDX-018 (Medarex); MDX-CD4 (Medarex/Eisai/Genmab), a human anti-CD4 IgG antibody; Osidem™ (IDM-1, Medarex/Immuno-Designed Molecules), an anti-Her2 antibody; HuMax™-CD4 (Medarex/Genmab), an anti-CD4 antibody; HuMax-IL15

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(Medarex/Genmab); CNTO 148 (Medarex/Centocor/J&J), an anti-TNFα antibody; CNTO 1275 (Centocor/J&J), an anti-cytokine antibody; CNTO 95 (Centocor/J&J), a human Integrin αv antibody (PCT publication WO 02/12501); MOR101 and MOR102 (MorphoSys), anti-intercellular adhesion molecule-1 (ICAM-1) (CD54) antibodies; MOR201 (MorphoSys), an anti-fibroblast growth factor receptor 3 (FGFR-3) antibody; visilizumab (Nuvion®, Protein Design Labs), an anti-CD3 antibody; HuZAF™ (Protein Design Labs), an anti-gamma interferon antibody; Anti-α5β1 Integrin (Protein Design Labs); anti-IL-12 (Protein Design Labs); ING-1 (Xoma), an anti-Ep-CAM antibody; MLN01 (Xoma), an anti-Beta2 integrin antibody; ZENAPAX® (daclizumab, Roche Pharmaceuticals) an immunosuppressive, humanized anti-CD25 monoclonal antibody for the prevention of acute renal allograft rejection; CDP860 (Celltech, UK), a humanized, PEGylated anti-CD18 F(ab')2; PRO542 (Progenics/Genzyme Transgenics), an anti-HIV gp120 antibody fused with CD4; C14 (ICOS Pharm), an anti-CD14 antibody; OVAREX™ (Altarex), a murine anti-CA 125 antibody; PANOREX™ (Glaxo Wellcome/Centocor), a murine anti-17-IA cell surface antigen IgG2a antibody; VITAXIN™ (MedImmune, PCT publication No. WO 2003/075957), a humanized anti-αVβ3 integrin antibody; siplizumab (MEDI-507, MedImmune, WO 99/03502), a humanized form of the murine monoclonal anti-CD2 antibody, BTI-322; palivizumab (Synagis®, MedImmune), a humanized neutralizing anti-RSV antibody; MEDI-524 (Numax, MedImmune), an affinity optimized humanized anti RSV antibody; Zamyl (Smart M195, Protein Design Lab/Kanebo), a humanized anti-CD33 IgG antibody; Remitogen (Smart 1D10, Protein Design Lab/Kanebo) which is a humanized anti-HLA antibody; ONCOLYM™ (Lym-1, Techniclone) is a radiolabelled murine anti-HLA DR antibody; Efalizumab (Genetech/Xoma), a humanized monoclonal anti-CD11a antibody; ICM3 (ICOS Pharm), a humanized anti-ICAM3 antibody; IDEC-114 (IDEC Pharm/Mitsubishi), a primatized anti-CD80 antibody; eculizumab (5G1.1, Alexion Pharm) a humanized anti-complement factor 5 (C5) antibody; pexelizumab (5G1.1-SC, Alexion Pharm) a fully humanized single chain monoclonal antibody; LDP-01 (Millennium/Xoma), a humanized anti-β2-integrin IgG antibody. In specific embodiments, the multidomain proteins of the invention are not Numax® or an antigen-binding fragment thereof (*e.g.*, a Fab fragment of Numax®).

5.4. Generation Of Antibodies

[0187] In one embodiment, the multidomain proteins of the invention are antibodies that specifically bind to a target molecule. Nonlimiting examples of target molecules are

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described above (see section 5.3). Antibodies that specifically bind any target (also referred to herein as "antigen") can be produced by any method known in the art for the synthesis of antibodies, in particular, by chemical synthesis or preferably, by recombinant expression techniques.

[0188] Polyclonal antibodies specific for an antigen can be produced by various procedures well-known in the art. For example, a human antigen can be administered to various host animals including, but not limited to, rabbits, mice, rats, etc. to induce the production of sera containing polyclonal antibodies specific for the human antigen. Various adjuvants may be used to increase the immunological response, depending on the host species, and include but are not limited to, Freund's (complete and incomplete), mineral gels such as aluminum hydroxide, surface active substances such as lysolecithin, pluronic polyols, polyanions, peptides, oil emulsions, keyhole limpet hemocyanins, dinitrophenol, and potentially useful human adjuvants such as BCG (bacille Calmette-Guerin) and corynebacterium parvum. Such adjuvants are also well known in the art.

[0189] Monoclonal antibodies can be prepared using a wide variety of techniques known in the art including the use of hybridoma, recombinant, and phage display technologies, or a combination thereof. For example, monoclonal antibodies can be produced using hybridoma techniques including those known in the art and taught, for example, in Harlow et al., Antibodies: A Laboratory Manual, (Cold Spring Harbor Laboratory Press, 2nd ed. 1988); Hammerling, et al., in: Monoclonal Antibodies and T-Cell Hybridomas 563-681 (Elsevier, N.Y., 1981) . The term "monoclonal antibody" as used herein is not limited to antibodies produced through hybridoma technology. The term "monoclonal antibody" refers to an antibody that is derived from a single clone, including any eukaryotic, prokaryotic, or phage clone, and not the method by which it is produced.

[0190] Methods for producing and screening for specific antibodies using hybridoma technology are routine and well known in the art. Briefly, mice can be immunized with a non-murine antigen and once an immune response is detected, e.g., antibodies specific for the antigen are detected in the mouse serum, the mouse spleen is harvested and splenocytes isolated. The splenocytes are then fused by well known techniques to any suitable myeloma cells, for example cells from cell line SP20 available from the ATCC. Hybridomas are selected and cloned by limited dilution. The hybridoma clones are then assayed by methods known in the art for cells that secrete antibodies capable of binding the antigen. Ascites fluid,

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which generally contains high levels of antibodies, can be generated by immunizing mice with positive hybridoma clones.

[0191] Monoclonal antibodies can be generated by the method comprising culturing a hybridoma cell secreting an antibody of the invention wherein, preferably, the hybridoma is generated by fusing splenocytes isolated from a mouse immunized with a non-murine antigen with myeloma cells and then screening the hybridomas resulting from the fusion for hybridoma clones that secrete an antibody able to bind to the antigen.

[0192] Antibody fragments which recognize specific particular epitopes (referred to herein as "antigen binding domain(s)") may be generated by any technique known to those of skill in the art. For example, Fab and F(ab')2 fragments of the invention may be produced by proteolytic cleavage of immunoglobulin molecules, using enzymes such as papain (to produce Fab fragments) or pepsin (to produce F(ab')2 fragments). F(ab')2 fragments contain the variable region, the light chain constant region and the CH1 domain of the heavy chain. Further, the antibodies of the present invention can also be generated using various phage display methods known in the art.

[0193] In phage display methods, functional antibody domains are displayed on the surface of phage particles which carry the polynucleotide sequences encoding them. In particular, DNA sequences encoding VH and VL domains are amplified from animal cDNA libraries (e.g., human or murine cDNA libraries of affected tissues). The DNA encoding the VH and VL domains are recombined together with an scFv linker by PCR and cloned into a phagemid vector. The vector is electroporated in E. coli and the E. coli is infected with helper phage. Phage used in these methods are typically filamentous phage including fd and M13 and the VH and VL domains are usually recombinantly fused to either the phage gene III or gene VIII. Phage expressing an antigen binding domain that binds to a particular antigen can be selected or identified with antigen, e.g., using labeled antigen or antigen bound or captured to a solid surface or bead. Examples of phage display methods that can be used to make the antibodies of the present invention include those disclosed in Brinkman et al., 1995, J. Immunol. Methods 182:41-50; Ames et al., 1995, J. Immunol. Methods 184:177-186; Kettleborough et al., 1994, Eur. J. Immunol. 24:952-958; Persic et al., 1997, Gene 187:9-18; Burton et al., 1994, Advances in Immunology 57:191-280; International application No. PCT/GB91/O1 134; International publication Nos. WO 90/02809, WO 91/10737, WO 92/01047, WO 92/18619, WO 93/11236, WO 95/15982, WO 95/20401, and WO97/13844; and U.S. Patent Nos. 5,698,426, 5,223,409, 5,403,484, 5,580,717, 5,427,908,

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5,750,753, 5,821,047, 5,571,698, 5,427,908, 5,516,637, 5,780,225, 5,658,727, 5,733,743 and 5,969,108.

[0194] As described in the above references, after phage selection, the antibody coding regions from the phage can be isolated and used to generate whole antibodies, including human antibodies, or any other desired antigen binding fragment, and expressed in any desired host, including mammalian cells, insect cells, plant cells, yeast, and bacteria, e.g., as described below. Techniques to recombinantly produce Fab, Fab' and F(ab')2 fragments can also be employed using methods known in the art such as those disclosed in PCT publication No. WO 92/22324; Mullinax et al., 1992, BioTechniques 12(6):864-869; Sawai et al., 1995, AJRI 34:26-34; and Better et al., 1988, Science 240:1041-1043.

[0195] To generate whole antibodies, PCR primers including VH or VL nucleotide sequences, a restriction site, and a flanking sequence to protect the restriction site can be used to amplify the VH or VL sequences in scFv clones. Utilizing cloning techniques known to those of skill in the art, the PCR amplified VH domains can be cloned into vectors expressing a VH constant region, e.g., the human gamma 4 constant region, and the PCR amplified VL domains can be cloned into vectors expressing a VL constant region, e.g., human kappa or lamba constant regions. Preferably, the vectors for expressing the VH or VL domains comprise a promoter, a secretion signal, a cloning site for the variable domain, constant domains, and a selection marker such as neomycin. The VH and VL domains may also cloned into one vector expressing the necessary constant regions. The heavy chain conversion vectors and light chain conversion vectors are then co-transfected into cell lines to generate stable or transient cell lines that express full-length antibodies, e.g., IgG, using techniques known to those of skill in the art.

[0196] Methods for making bispecific antibodies are known in the art. Traditional production of full-length bispecific antibodies is based on the coexpression of two immunoglobulin heavy chain-light chain pairs, where the two chains have different specificities (Millstein et al.,1983, Nature, 305:537-539). Because of the random assortment of immunoglobulin heavy and light chains, these hybridomas (quadromas) produce a potential mixture of different antibody molecules, of which only one has the correct bispecific structure. Purification of the correct molecule, which is usually done by affinity chromatography steps, is rather cumbersome, and the product yields are low. Similar procedures are disclosed in WO 93/08829, and in Traunecker et al., 1991, EMBO J., 10:3655-3659. A more directed approach is the generation of a Di-diabody a tetravalent

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bispecific antibody. Methods for producing a Di-diabody are known in the art (see e.g., Lu et al., 2003, J Immunol Methods 279:219-32; Marvin et al., 2005, Acta Pharmacolical Sinica 26:649).

[0197] According to a different approach, antibody variable domains with the desired binding specificities (antibody-antigen combining sites) are fused to immunoglobulin constant domain sequences. The fusion preferably is with an immunoglobulin heavy chain constant domain, comprising at least part of the hinge, CH2, and CH3 regions. It is preferred to have the first heavy-chain constant region (CH1) containing the site necessary for light chain binding, present in at least one of the fusions. DNAs encoding the immunoglobulin heavy chain fusions and, if desired, the immunoglobulin light chain, are inserted into separate expression vectors, and are co-transfected into a suitable host organism. This provides for great flexibility in adjusting the mutual proportions of the three polypeptide fragments in embodiments when unequal ratios of the three polypeptide chains used in the construction provide the optimum yields. It is, however, possible to insert the coding sequences for two or all three polypeptide chains in one expression vector when, the expression of at least two polypeptide chains in equal ratios results in high yields or when the ratios are of no particular significance.

[0198] In one embodiment of this approach, the bispecific antibodies are composed of a hybrid immunoglobulin heavy chain with a first binding specificity in one arm, and a hybrid immunoglobulin heavy chain-light chain pair (providing a second binding specificity) in the other arm. It was found that this asymmetric structure facilitates the separation of the desired bispecific compound from unwanted immunoglobulin chain combinations, as the presence of an immunoglobulin light chain in only one half of the bispecific molecule provides for a facile way of separation. This approach is disclosed in WO 94/04690. For further details of generating bispecific antibodies see, for example, Suresh et al., 1986, Methods in Enzymology, 121:210. According to another approach described in WO96/27011, a pair of antibody molecules can be engineered to maximize the percentage of heterodimers which are recovered from recombinant cell culture. The preferred interface comprises at least a part of the CH3 domain of an antibody constant domain. In this method, one or more small amino acid side chains from the interface of the first antibody molecule are replaced with larger side chains (e.g. tyrosine or tryptophan). Compensatory "cavities" of identical or similar size to the large side chain(s) are created on the interface of the second antibody molecule by replacing large amino acid side chains with smaller ones (e.g. alanine

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or threonine). This provides a mechanism for increasing the yield of the heterodimer over other unwanted end-products such as homodimers.

[0199] Bispecific antibodies include cross-linked or "heteroconjugate" antibodies. For example, one of the antibodies in the heteroconjugate can be coupled to avidin, the other to biotin. Such antibodies have, for example, been proposed to target immune system cells to unwanted cells (U.S. Pat. No. 4,676,980), and for treatment of HIV infection (WO 91/00360, WO 92/200373, and EP 03089). Heteroconjugate antibodies may be made using any convenient cross-linking methods. Suitable cross-linking agents are well known in the art, and are disclosed in U.S. Pat. No. 4,676,980, along with a number of cross-linking techniques.

[0200] For some uses, including in vivo use of antibodies in humans and in vitro detection assays, it may be preferable to use humanized antibodies or chimeric antibodies. Completely human antibodies and humanized antibodies are particularly desirable for therapeutic treatment of human subjects. Human antibodies can be made by a variety of methods known in the art including phage display methods described above using antibody libraries derived from human immunoglobulin sequences. See also U.S. Patent Nos. 4,444,887 and 4,716,111; and International publication Nos. WO 98/46645, WO 98/50433, WO 98/24893, WO98/16654, WO 96/34096, WO 96/33735, and WO 91/10741.

[0201] Human antibodies can also be produced using transgenic mice which are incapable of expressing functional endogenous immunoglobulins, but which can express human immunoglobulin genes. For example, the human heavy and light chain immunoglobulin gene complexes may be introduced randomly or by homologous recombination into mouse embryonic stem cells. Alternatively, the human variable region, constant region, and diversity region may be introduced into mouse embryonic stem cells in addition to the human heavy and light chain genes. The mouse heavy and light chain immunoglobulin genes may be rendered non-functional separately or simultaneously with the introduction of human immunoglobulin loci by homologous recombination. In particular, homozygous deletion of the JH region prevents endogenous antibody production. The modified embryonic stem cells are expanded and microinjected into blastocysts to produce chimeric mice. The chimeric mice are then bred to produce homozygous offspring which express human antibodies. The transgenic mice are immunized in the normal fashion with a selected antigen, e.g., all or a portion of a polypeptide. Monoclonal antibodies directed against the antigen can be obtained from the immunized, transgenic mice using conventional

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hybridoma technology. The human immunoglobulin transgenes harbored by the transgenic mice rearrange during B cell differentiation, and subsequently undergo class switching and somatic mutation. Thus, using such a technique, it is possible to produce therapeutically useful IgG, IgA, IgM and IgE antibodies. For an overview of this technology for producing human antibodies, see Lonberg and Huszar (1995, Int. Rev. Immunol. 13:65-93). For a detailed discussion of this technology for producing human antibodies and human monoclonal antibodies and protocols for producing such antibodies, see, e.g., International publication Nos. WO 98/24893, WO 96/34096, and WO 96/33735; and U.S. Patent Nos. 5,413,923, 5,625,126, 5,633,425, 5,569,825, 5,661,016, 5,545,806, 5,814,318, and 5,939,598. In addition, companies such as Abgenix, Inc. (Freemont, CA) and Genpharm (San Jose, CA) can be engaged to provide human antibodies directed against a selected antigen using technology similar to that described above.

[0202] A chimeric antibody is a molecule in which different portions of the antibody are derived from different immunoglobulin molecules. Methods for producing chimeric antibodies are known in the art. See e.g., Morrison, 1985, Science 229:1202; Oi et al., 1986, BioTechniques 4:214; Gillies et al., 1989, J. Immunol. Methods 125:191-202; and U.S. Patent Nos. 5,807,715, 4,816,567, 4,8 16397, and 6,311,415.

[0203] A humanized antibody is an antibody or its variant or fragment thereof which is capable of binding to a predetermined antigen and which comprises a framework region having substantially the amino acid sequence of a human immunoglobulin and a CDR having substantially the amino acid sequence of a non-human immunoglobulin. A humanized antibody comprises substantially all of at least one, and typically two, variable domains (Fab, Fab', F(ab').sub.2, Fabc, Fv) in which all or substantially all of the CDR regions correspond to those of a non-human immunoglobulin (i.e., donor antibody) and all or substantially all of the framework regions are those of a human immunoglobulin consensus sequence. Preferably, a humanized antibody also comprises at least a portion of an immunoglobulin constant region (Fc), typically that of a human immunoglobulin. Ordinarily, the antibody will contain both the light chain as well as at least the variable domain of a heavy chain. The antibody also may include the CH1, hinge, CH2, CH3, and CH4 regions of the heavy chain. The humanized antibody can be selected from any class of immunoglobulins, including IgM, IgG, IgD, IgA and IgE, and any isotype, including IgG1, IgG2, IgG3 and lgG4. Usually the constant domain is a complement fixing constant domain where it is desired that the humanized antibody exhibit cytotoxic activity, and the class is typically IgG1. Where such

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cytotoxic activity is not desirable, the constant domain may be of the IgG2 class. The humanized antibody may comprise sequences from more than one class or isotype, and selecting particular constant domains to optimize desired effector functions is within the ordinary skill in the art. The framework and CDR regions of a humanized antibody need not correspond precisely to the parental sequences, e.g., the donor CDR or the consensus framework may be mutagenized by substitution, insertion or deletion of at least one residue so that the CDR or framework residue at that site does not correspond to either the consensus or the import antibody. Such mutations, however, will not be extensive. Usually, at least 75% of the humanized antibody residues will correspond to those of the parental framework and CDR sequences, more often 90%, and most preferably greater than 95%. A humanized antibody can be produced using variety of techniques known in the art, including but not limited to, CDR-grafting (see e.g., European Patent No. EP 239,400; International Publication No. WO 91/09967; and U.S. Patent Nos. 5,225,539, 5,530,101, and 5,585,089), veneering or resurfacing (see e.g., European Patent Nos. EP 592,106 and EP 519,596; Padlan, 1991, Molecular Immunology 28(4/5):489-498; Studnicka et al., 1994, Protein Engineering 7(6):805-814; and Roguska et al., 1994, PNAS 91:969-973), chain shuffling (see e.g., U.S. Patent No. 5,565,332), and techniques disclosed in, e.g., U.S. Pat. No. 6,407,213, U.S. Pat. No. 5,766,886, International Publication No. WO 9317105, Tan et al., J. Immunol. 169:1119-25 (2002), Caldas et al., Protein Eng. 13(5):353-60 (2000), Morea et al., Methods 20(3):267-79 (2000), Baca et al., J. Biol. Chem. 272(16):10678-84 (1997), Roguska et al., Protein Eng. 9(10):895-904 (1996), Couto et al., Cancer Res. 55 (23 Supp):5973s - 5977s (1995), Couto et al., Cancer Res. 55(8):1717-22 (1995), Sandhu JS, Gene 150(2):409-10 (1994), and Pedersen et al., J. Mol. Biol. 235(3):959-73 (1994). Often, framework residues in the framework regions will be substituted with the corresponding residue from the CDR donor antibody to alter, preferably improve, antigen binding. These framework substitutions are identified by methods well known in the art, e.g., by modeling of the interactions of the CDR and framework residues to identify framework residues important for antigen binding and sequence comparison to identify unusual framework residues at particular positions. (See, e.g., Queen et al., U.S. Patent No. 5,585,089; and Riechmann et al., 1988, Nature 332:323.)

[0204] Further, the antibodies of the invention can, in turn, be utilized to generate anti-idiotype antibodies that "mimic" a receptor using techniques well known to those skilled in the art. (See, e.g., Greenspan & Bona, 1989, FASEB J. 7(5): 437-444; and Nissinoff,

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1991, J. Immunol. 147(8): 2429-2438). For example, antibodies of the invention which bind to and competitively inhibit the binding of an receptor (as determined by assays well known in the art and disclosed infra) to its ligands can be used to generate anti-idiotypes that "mimic" the ligand and, as a consequence, bind to and neutralize the receptor and/or its ligands. Such neutralizing anti-idiotypes or Fab fragments of such anti-idiotypes can be used in therapeutic regimens to neutralize a ligand and/or its receptor. The invention provides methods employing the use of polynucleotides comprising a nucleotide sequence encoding an antibody of the invention or a fragment thereof.

[0205] The invention provides polynucleotides comprising a nucleotide sequence encoding an antibody or fragment thereof that specifically binds to an antigen and having one or more amino acid substitutes for improved therapeutic and/or formulation and/or manufacturing characteristics. The invention also encompasses polynucleotides that hybridize under high stringency, intermediate or lower stringency hybridization conditions to polynucleotides that encode an antibody of the invention.

[0206] The polynucleotides may be obtained, and the nucleotide sequence of the polynucleotides determined, by any method known in the art. The nucleotide sequence of antibodies specific for a desired antigen can be obtained, e.g., from the literature or a database such as GenBank. Nucleotide or alternatively, if the amino acid sequence of an antibody or fragment thereof that specifically binds to an antigen is known, the nucleotide sequences encoding the antibody or a fragment thereof (e.g., a CDR) can be determined using methods well known in the art, i.e., nucleotide codons known to encode particular amino acids are assembled in such a way to generate a nucleic acid that encodes the antibody. Such a polynucleotide encoding the antibody may be assembled from chemically synthesized oligonucleotides (e.g., as described in Kutmeier et al., 1994, BioTechniques 17:242), which, briefly, involves the synthesis of overlapping oligonucleotides containing portions of the sequence encoding the antibody, annealing and ligating of those oligonucleotides, and then amplification of the ligated oligonucleotides by PCR.

[0207] Alternatively, a polynucleotide encoding an antibody may be generated from nucleic acid from a suitable source. If a clone containing a nucleic acid encoding a particular antibody is not available, but the sequence of the antibody molecule is known, a nucleic acid encoding the immunoglobulin may be chemically synthesized or obtained from a suitable source (e.g., an antibody cDNA library, or a cDNA library generated from, or nucleic acid, preferably poly A+ RNA, isolated from, any tissue or cells expressing the antibody, such as

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hybridoma cells selected to express an antibody of the invention) by PCR amplification using synthetic primers hybridizable to the 3' and 5' ends of the sequence or by cloning using an oligonucleotide probe specific for the particular gene sequence to identify, e.g., a cDNA clone from a cDNA library that encodes the antibody. Amplified nucleic acids generated by PCR may then be cloned into replicable cloning vectors using any method well known in the art.

[0208] Once the nucleotide sequence of the antibody is determined, the nucleotide sequence of the antibody may be manipulated using methods well known in the art for the manipulation of nucleotide sequences, e.g., recombinant DNA techniques, site directed mutagenesis, PCR, etc. (see, for example, the techniques described in Current Protocols in Molecular Biology, F.M. Ausubel et al., ed., John Wiley & Sons (Chichester, England, 1998); Molecular Cloning: A Laboratory Manual, 3rd Edition, J. Sambrook et al., ed., Cold Spring Harbor Laboratory Press (Cold Spring Harbor, NY, 2001); Antibodies: A Laboratory Manual, E. Harlow and D. Lane, ed., Cold Spring Harbor Laboratory Press (Cold Spring Harbor, NY, 1988); and Using Antibodies: A Laboratory Manual, E. Harlow and D. Lane, ed., Cold Spring Harbor Laboratory (Cold Spring Harbor, NY, 1999)), to generate antibodies having a different amino acid sequence, for example to create amino acid substitutions, deletions, and/or insertions.

[0209] In a specific embodiment, one or more of the CDRs is inserted within framework regions using routine recombinant DNA techniques. The framework regions may be naturally occurring or consensus framework regions, and preferably human framework regions (see, e.g., Chothia et al., 1998, J. Mol. Biol. 278: 457-479 for a listing of human framework regions). Preferably, the polynucleotide generated by the combination of the framework regions and CDRs encodes an antibody that specifically binds to a particular antigen. Preferably, as discussed supra, one or more amino acid substitutions may be made within the framework regions, and, preferably, the amino acid substitutions improve binding of the antibody to its antigen. Additionally, such methods may be used to make amino acid substitutions or deletions of one or more variable region cysteine residues participating in an intrachain disulfide bond to generate antibody molecules lacking one or more intrachain disulfide bonds. Other alterations to the polynucleotide are encompassed by the present invention and within the skill of the art.

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5.5. Generation Of Antibody Domain Fusion Proteins Conjugates And Derivatives

[0210] As described above multidomain proteins include but are not limited to antibodies which also encompasses antibody-like and antibody-domain fusion proteins. An antibody-like molecule is any molecule that has been generated with a desired binding property, see, e.g., PCT Publication Nos. WO 04/044011; WO 04/058821; WO 04/003019 and WO 03/002609. Antibody-domain fusion proteins may incorporate one or more antibody domains or fragments thereof, such as the Fc domain or the variable domain with a fusion partner which in general can be an protein, including, but not limited to, a ligand, an enzyme, the ligand portion of a receptor, an adhesion protein, or some other protein or domain. For example, the heterologous polypeptides may be fused or conjugated to a Fab fragment, Fd fragment, Fv fragment, F(ab)2 fragment, a VH domain, a VL domain, a VH CDR, a VL CDR, or fragment thereof. A large number of antibody-domain molecules are known in the art including, but not limited to, diabodies (dsFv)2 (Bera et al., 1998, J. Mol. Biol. 281:475-83); minibodies (homodimers of scFv-CH3 fusion proteins)(Pessi et al., 1993, Nature 362:367-9), tetravalent di-diabody (Lu et al., 2003 J. Immunol. Methods 279:219-32), tetravalent bi-specific antibodies called Bs(scFv)4-IgG (Zuo et al., 2000, Protein Eng. 13:361-367) and Fc domain fusions (See, e.g., Chamow et al., 1996, Trends Biotechnol 14:52-60; Ashkenazi et al., 1997, Curr Opin Immunol 9:195-200; Heidaran et al., 1995, FASEB J. 9:140-5.).

[0211] In one embodiment, a multidomain comprises an antibody domain that binds to a molecule (i.e., target antigen) including, but not limited to, those disclosed herein (see Section 5.3) fused to a fusion partner. Fusion partners include, but are not limited to, peptides, polypeptides, proteins, small molecules, mimetic agents, synthetic drugs, inorganic molecules, and organic molecules. In one embodiment, a fusion partner is a polypeptide comprising at least 5, at least 10, at least 20, at least 30, at least 40, at least 50, at least 60, at least 70, at least 80, at least 90 or at least 100 contiguous amino acid residues, and is heterologous to the amino acid sequence of the antibody domain. In certain embodiments, said fusion partner is a bioactive molecule. The nucleotide sequences encoding a bioactive molecule may be obtained from any information available to those of skill in the art (i.e., from Genbank, the literature, or by routine cloning).

[0212] The fusion does not necessarily need to be direct, but may occur through linker sequences. Such linker molecules are commonly known in the art and described in Denardo et al., 1998, Clin Cancer Res 4:2483; Peterson et al., 1999, Bioconjug Chem 10:553;

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Zimmerman et al., 1999, Nucl Med Biol 26:943; Garnett, 2002, Adv Drug Deliv Rev 53:171. For example, antibody domains may be used to target heterologous polypeptides to particular cell types, either in vitro or in vivo, by fusing or conjugating the heterologous protein to antibodies domains specific for particular cell surface receptors. Antibody domains fused or conjugated to heterologous polypeptides may also be used in in vitro immunoassays and purification methods using methods known in the art. See e.g., International publication No. WO 93/21232; European Patent No. EP 439,095; Naramura et al., 1994, Immunol. Lett. 39:91-99; U.S. Patent No. 5,474,981; Gillies et al., 1992, PNAS 89:1428-1432; and Fell et al., 1991, J. Immunol. 146:2446-2452.

[0213] Methods for fusing or conjugating polypeptides to antibody portions are well known in the art. See, e.g., U.S. Patent Nos. 5,336,603, 5,783,181, 5,622,929, 5,359,046, 5,349,053, 5,447,851, 5,723,125, 5,908,626, 5,844,095, and 5,112,946; European Patent Nos. EP 307,434 and EP 367,166 and EP 394,827; PCT Publication Nos. WO 96/04388, WO 91/06570 WO 96/22024, WO 97/34631, and WO 99/04813; Ashkenazi et al., 1991, Proc. Natl. Acad. Sci. USA 88: 10535-10539; Traunecker et al., 1988, Nature, 331:84-86; Zheng et al., 1995, J. Immunol. 154:5590-5600; and Vil et al., 1992, Proc. Natl. Acad. Sci. USA 89:11337- 11341.

[0214] Multidomain proteins (e.g., an antibody domain fusion protein) can be produced by standard recombinant DNA techniques or by protein synthetic techniques, e.g., by use of a peptide synthesizer. For example, a nucleic acid molecule encoding a multidomain protein (e.g., an antibody domain fusion protein) can be synthesized by conventional techniques including automated DNA synthesizers. Alternatively, PCR amplification of gene fragments can be carried out using anchor primers which give rise to complementary overhangs between two consecutive gene fragments which can subsequently be annealed and reamplified to generate a chimeric gene sequence (see, e.g., Current Protocols in Molecular Biology, Ausubel et al., eds., John Wiley & Sons, 1992). The nucleotide sequence coding for a multidomain protein (e.g., an antibody domain fusion protein) can be inserted into an appropriate expression vector, i.e., a vector that contains the necessary elements for the transcription and translation of the inserted protein-coding sequence. A variety of host-vector systems may be utilized in the present invention to express the protein-coding sequence. These include but are not limited to mammalian cell systems infected with virus (e.g., vaccinia virus, adenovirus, etc.); insect cell systems infected with virus (e.g., baculovirus); microorganisms such as yeast containing yeast vectors; or

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bacteria transformed with bacteriophage, DNA, plasmid DNA, or cosmid DNA. The expression elements of vectors vary in their strengths and specificities. Depending on the host-vector system utilized, any one of a number of suitable transcription and translation elements may be used.

[0215] Additional fusion proteins, e.g., of antibody domains that specifically bind an antigen (e.g., supra), may be generated through the techniques of gene-shuffling, motif-shuffling, exon-shuffling, and/or codon-shuffling (collectively referred to as "DNA shuffling"). DNA shuffling may be employed to alter the activities of antibodies of the invention or fragments thereof (e.g., antibodies or fragments thereof with higher affinities and lower dissociation rates). See, generally, U.S. Patent Nos. 5,605,793; 5,811,238; 5,830,721; 5,834,252; and 5,837,458, and Patten et al., 1997, Curr. Opinion Biotechnol. 8:724-33; Harayama, 1998, Trends Biotechnol. 16(2): 76-82; Hansson, et al., 1999, J. Mol. Biol. 287:265-76; and Lorenzo and Blasco, 1998, Biotechniques 24(2): 308- 313. Antibodies or fragments thereof, or the encoded antibodies or fragments thereof, may be altered by being subjected to random mutagenesis by error-prone PCR, random nucleotide insertion or other methods prior to recombination. One or more portions of a polynucleotide encoding an antibody or antibody fragment, which portions specifically bind to an Antigen may be recombined with one or more components, motifs, sections, parts, domains, fragments, etc. of one or more heterologous molecules.

[0216] Moreover, antibodies or fragments thereof can be fused to marker sequences, such as a peptide to facilitate purification. In certain embodiments, the marker amino acid sequence is a hexa-histidine peptide, such as the tag provided in a pQE vector (QIAGEN, Inc., 9259 Eton Avenue, Chatsworth, CA, 91311), among others, many of which are commercially available. As described in Gentz et al., 1989, Proc. Natl. Acad. Sci. USA 86:821-824, for instance, hexa-histidine provides for convenient purification of the fusion protein. Other peptide tags useful for purification include, but are not limited to, the hemagglutinin "HA" tag, which corresponds to an epitope derived from the influenza hemagglutinin protein (Wilson et al., 1984, Cell 37:767) and the "flag" tag.

[0217] Antibodies and antibody domain fusion proteins include derivatives that are modified (i.e., by the covalent attachment of any type of molecule to an antibody or antibody domain fusion protein) such derivatives are collectively referred to herein as "antibody derivatives". For example, but not by way of limitation, the antibody derivatives include antibodies and antibody domain fusion proteins that have been modified, e.g., by

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glycosylation, acetylation, pegylation, phosphorylation, amidation, derivatization by known protecting/blocking groups, proteolytic cleavage, linkage to a cellular ligand or other protein, etc. Any of numerous chemical modifications may be carried out by known techniques, including, but not limited to, specific chemical cleavage, acetylation, formylation, metabolic synthesis of tunicamycin, etc. Additionally, the derivative may contain one or more non-classical amino acids.

[0218] Antibodies or antibody domain fusion proteins with increased in vivo half-lives can be generated by attaching to said antibodies or antibody domain fusion proteins, polymer molecules such as high molecular weight polyethyleneglycol (PEG). PEG can be attached to said antibodies or antibody domain fusion proteins with or without a multifunctional linker either through site-specific conjugation of the PEG to the N– or C-terminus of said antibodies or antibody fragments or via epsilon-amino groups present on lysine residues. Linear or branched polymer derivatization that results in minimal loss of biological activity will be used. The degree of conjugation will be closely monitored by SDS-PAGE and mass spectrometry to ensure proper conjugation of PEG molecules to the antibodies. Unreacted PEG can be separated from antibody-PEG conjugates by, e.g., size exclusion or ion-exchange chromatography.

[0219] Further, antibodies or antibody domain fusion proteins can be conjugated to albumin in order to make them more stable in vivo or have a longer half life in vivo. The techniques are well known in the art, see e.g., International Publication Nos. WO 93/15199, WO 93/15200, and WO 01/77137; and European Patent No. EP 413, 622. The present invention encompasses the use of antibodies or antibody domain fusion proteins conjugated or fused to one or more moieties, including but not limited to, peptides, polypeptides, proteins, fusion proteins, nucleic acid molecules, small molecules, mimetic agents, synthetic drugs, inorganic molecules, and organic molecules.

[0220] In certain embodiments, antibody domains are conjugated to a diagnostic or detectable agent. Such multidomain proteins can be useful for monitoring or prognosing the development or progression of a cancer as part of a clinical testing procedure, such as determining the efficacy of a particular therapy. Such diagnosis and detection can be accomplished by coupling the antibody to detectable substances including, but not limited to various enzymes, such as but not limited to horseradish peroxidase, alkaline phosphatase, beta-galactosidase, or acetylcholinesterase; prosthetic groups, such as but not limited to streptavidin/biotin and avidin/biotin; fluorescent materials, such as but not limited to,

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umbelliferone, fluorescein, fluorescein isothiocynate, rhodamine, dichlorotriazinylamine fluorescein, dansyl chloride or phycoerythrin; luminescent materials, such as but not limited to, luminol; bioluminescent materials, such as but not limited to, luciferase, luciferin, and aequorin; radioactive materials, such as but not limited to iodine (131I, 125I, 123I, 121I,), carbon (14C), sulfur (35S), tritium (3H), indium (115In, 113In, 112In, 111In,), and technetium (99Tc), thallium (201Ti), gallium (68Ga, 67Ga), palladium (103Pd), molybdenum (99Mo), xenon (133Xe), fluorine (18F), 153Sm, 177Lu, 159Gd, 149Pm, 140La, 175Yb, 166Ho, 90Y, 47Sc, 186Re, 188Re,142 Pr, 105Rh, 97Ru, 68Ge, 57Co, 65Zn, 85Sr, 32P, 153Gd, 169Yb, 51Cr, 54Mn, 75Se, 113Sn, and 117Tin; positron emitting metals using various positron emission tomographies, noradioactive paramagnetic metal ions, and molecules that are radiolabelled or conjugated to specific radioisotopes.

[0221] An antibody or an antibody domain may be conjugated to a therapeutic moiety such as a cytotoxin, e.g., a cytostatic or cytocidal agent, a therapeutic agent or a radioactive metal ion, e.g., alpha-emitters. A cytotoxin or cytotoxic agent includes any agent that is detrimental to cells. Examples include ribonuclease, monomethylauristatin E and F, paclitaxel, cytochalasin B, gramicidin D, ethidium bromide, emetine, mitomycin, etoposide, tenoposide, vincristine, vinblastine, colchicin, doxorubicin, daunorubicin, dihydroxy anthracin dione, mitoxantrone, mithramycin, actinomycin D, 1-dehydrotestosterone, glucocorticoids, procaine, tetracaine, lidocaine, propranolol, puromycin, epirubicin, and cyclophosphamide and analogs or homologs thereof. Therapeutic agents include, but are not limited to, antimetabolites (e.g., methotrexate, 6-mercaptopurine, 6-thioguanine, cytarabine, 5-fluorouracil decarbazine), alkylating agents (e.g., mechlorethamine, thioepa chlorambucil, melphalan, carmustine (BCNU) and lomustine (CCNU), cyclothosphamide, busulfan, dibromomannitol, streptozotocin, mitomycin C, and cisdichlorodiamine platinum (II) (DDP) cisplatin), anthracyclines (e.g., daunorubicin (formerly daunomycin) and doxorubicin), antibiotics (e.g., dactinomycin (formerly actinomycin), bleomycin, mithramycin, and anthramycin (AMC)), and anti-mitotic agents (e.g., vincristine and vinblastine). A more extensive list of therapeutic moieties can be found in PCT publications WO 03/075957.

[0222] Further, an antibody or antibody domain may be conjugated to a therapeutic agent or drug moiety that modifies a given biological response. Therapeutic agents or drug moieties are not to be construed as limited to classical chemical therapeutic agents. For example, the drug moiety may be a protein or polypeptide possessing a desired biological activity. Such proteins may include, for example, a toxin such as abrin, ricin A, Onconase (or

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another cytotoxic RNase), pseudomonas exotoxin, cholera toxin, or diphtheria toxin; a protein such as tumor necrosis factor, α-interferon, β-interferon, nerve growth factor, platelet derived growth factor, tissue plasminogen activator, an apoptotic agent, e.g., TNF-α, TNF-β, AIM I (see, International Publication No. WO 97/33899), AIM II (see, International Publication No. WO 97/34911), Fas Ligand (Takahashi et al., 1994, J. Immunol., 6:1567), and VEGI (see, International Publication No. WO 99/23105), a thrombotic agent or an anti-angiogenic agent, e.g., angiostatin or endostatin; or, a biological response modifier such as, for example, a lymphokine (e.g., interleukin-1 ("IL-1"), interleukin-2 ("IL-2"), interleukin-6 ("IL-6"), granulocyte macrophage colony stimulating factor ("GM-CSF"), and granulocyte colony stimulating factor ("G-CSF")), or a growth factor (e.g., growth hormone ("GH")).

[0223] Moreover, an antibody can be conjugated to therapeutic moieties such as a radioactive materials or macrocyclic chelators useful for conjugating radiometal ions (see above for examples of radioactive materials). In certain embodiments, the macrocyclic chelator is 1,4,7,10-tetraazacyclododecane-N,N',N'',N''-tetraacetic acid (DOTA) which can be attached to the antibody via a linker molecule. Such linker molecules are commonly known in the art and described in Denardo et al., 1998, Clin Cancer Res. 4:2483; Peterson et al., 1999, Bioconjug. Chem. 10:553; and Zimmerman et al., 1999, Nucl. Med. Biol. 26:943.

[0224] Techniques for conjugating therapeutic moieties to antibodies are well known. Moieties can be conjugated to antibodies by any method known in the art, including, but not limited to aldehyde/Schiff linkage, sulphydryl linkage, acid-labile linkage, cis-aconityl linkage, hydrazone linkage, enzymatically degradable linkage (see generally Garnett, 2002, Adv Drug Deliv Rev 53:171). Techniques for conjugating therapeutic moieties to antibodies are well known, see, e.g., Arnon et al., "Monoclonal Antibodies For Immunotargeting Of Drugs In Cancer Therapy", in Monoclonal Antibodies And Cancer Therapy, Reisfeld et al. (eds.), pp. 243-56 (Alan R. Liss, Inc. 1985); Hellstrom et al., "Antibodies For Drug Delivery", in Controlled Drug Delivery (2nd Ed.), Robinson et al. (eds.), pp. 623-53 (Marcel Dekker, Inc. 1987); Thorpe, "Antibody Carriers Of Cytotoxic Agents In Cancer Therapy: A Review", in Monoclonal Antibodies '84: Biological And Clinical Applications, Pinchera et al. (eds.), pp. 475-506 (1985); "Analysis, Results, And Future Prospective Of The Therapeutic Use Of Radiolabeled Antibody In Cancer Therapy", in Monoclonal Antibodies For Cancer Detection And Therapy, Baldwin et al. (eds.), pp. 303-16 (Academic Press 1985), and Thorpe et al., 1982, Immunol. Rev. 62:119.

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[0225] Alternatively, an antibody or antibody domain can be conjugated to a second antibody to form an antibody heteroconjugate as described by Segal in U.S. Patent No. 4,676,980.

5.6. Production Of Multidomain Proteins

[0226] Recombinant expression of a multidomain protein, derivative, analog or fragment thereof, (*e.g.*, an antibody or fusion protein), requires construction of an expression vector containing a polynucleotide that encodes the multidomain protein (e.g., antibody, or fusion protein). Once a polynucleotide encoding a multidomain protein (e.g., antibody, or fusion protein) has been obtained, the vector for the production of the multidomain protein (e.g., antibody, or fusion protein) may be produced by recombinant DNA technology using techniques well known in the art. Thus, methods for preparing a protein by expressing a polynucleotide containing a multidomain protein (e.g., antibody, or fusion protein) encoding nucleotide sequence are described herein. Methods that are well known to those skilled in the art can be used to construct expression vectors containing multidomain protein (e.g., antibody, or fusion protein) coding sequences and appropriate transcriptional and translational control signals. These methods include, for example, in vitro recombinant DNA techniques, synthetic techniques, and in vivo genetic recombination. The invention, thus, provides replicable vectors comprising a nucleotide sequence encoding a multidomain protein of the invention, operably linked to a promoter. Such vectors may include the nucleotide sequence encoding the constant region of the antibody molecule (see, e.g., International Publication No. WO 86/05807; International Publication No. WO 89/01036; and U.S. Patent No. 5,122,464) and the variable domain of the antibody, or a polypeptide for generating an multidomain protein may be cloned into such a vector for expression of the full length antibody chain (e.g. heavy or light chain), or complete multidomain protein comprising a fusion of a non-antibody derived polypeptide and a an antibody domain.

[0227] The expression vector is transferred to a host cell by conventional techniques and the transfected cells are then cultured by conventional techniques to produce a multidomain. Thus, the invention includes host cells containing a polynucleotide encoding a multidomain protein of the invention, operably linked to a heterologous promoter. In specific embodiments for the expression of multidomain proteins comprising double-chained antibodies, vectors encoding both the heavy and light chains may be co-expressed in the host cell for expression of the entire immunoglobulin molecule, as detailed below.

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[0228] A variety of host-expression vector systems may be utilized to express the multidomain proteins of the invention (e.g., antibody or fusion protein molecules) (see, e.g., U.S. Patent No. 5,807,715). Such host-expression systems represent vehicles by which the coding sequences of interest may be produced and subsequently purified, but also represent cells which may, when transformed or transfected with the appropriate nucleotide coding sequences, express an multidomain protein of the invention in situ. These include but are not limited to microorganisms such as bacteria (e.g., E. coli and B. subtilis) transformed with recombinant bacteriophage DNA, plasmid DNA or cosmid DNA expression vectors containing multidomain protein coding sequences; yeast (e.g., Saccharomyces Pichia) transformed with recombinant yeast expression vectors containing multidomain protein coding sequences; insect cell systems infected with recombinant virus expression vectors (e.g., baculovirus) containing multidomain protein coding sequences; plant cell systems infected with recombinant virus expression vectors (e.g., cauliflower mosaic virus, CaMV; tobacco mosaic virus, TMV) or transformed with recombinant plasmid expression vectors (e.g., Ti plasmid) containing multidomain protein coding sequences; or mammalian cell systems (e.g., COS, CHO, BHK, 293, NS0, and 3T3 cells) harboring recombinant expression constructs containing promoters derived from the genome of mammalian cells (e.g., metallothionein promoter) or from mammalian viruses (e.g., the adenovirus late promoter; the vaccinia virus 7.5K promoter). In certain embodiments, bacterial cells such as Escherichia coli, or eukaryotic cells, are used for the expression of a multidomain protein which is a recombinant antibody or fusion protein molecules. For example, mammalian cells such as Chinese hamster ovary cells (CHO), in conjunction with a vector such as the major intermediate early gene promoter element from human cytomegalovirus is an effective expression system for antibodies (Foecking et al., 1986, Gene 45:101; and Cockett et al., 1990, Bio/Technology 8:2). In a specific embodiment, the expression of nucleotide sequences encoding a multidomain protein of the invention (e.g., antibody or fusion protein) is regulated by a constitutive promoter, inducible promoter or tissue specific promoter.

[0229] In bacterial systems, a number of expression vectors may be advantageously selected depending upon the use intended for the multidomain protein (e.g., antibody or fusion protein) being expressed. For example, when a large quantity of such a protein is to be produced, for the generation of pharmaceutical compositions of a multidomain protein, vectors that direct the expression of high levels of fusion protein products that are readily purified may be desirable. Such vectors include, but are not limited to, the E. coli expression

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vector pUR278 (Ruther et al., 1983, EMBO 12:1791), in which the multidomain protein coding sequence may be ligated individually into the vector in frame with the lac Z coding region so that a lac Z-fusion protein is produced; pIN vectors (Inouye & Inouye, 1985, Nucleic Acids Res. 13:3101-3109; Van Heeke & Schuster, 1989, J. Biol. Chem. 24:5503-5509); and the like. pGEX vectors may also be used to express foreign polypeptides as fusion proteins with glutathione 5-transferase (GST). In general, such fusion proteins are soluble and can easily be purified from lysed cells by adsorption and binding to matrix glutathione agarose beads followed by elution in the presence of free glutathione. The pGEX vectors are designed to include thrombin or factor Xa protease cleavage sites so that the cloned target gene product can be released from the GST moiety.

[0230] In an insect system, Autographa californica nuclear polyhedrosis virus (AcNPV) is used as a vector to express foreign genes. The virus grows in Spodoptera frugiperda cells. The multidomain protein (e.g., antibody or fusion protein) coding sequence may be cloned individually into non-essential regions (for example the polyhedrin gene) of the virus and placed under control of an AcNPV promoter (for example the polyhedrin promoter).

[0231] In mammalian host cells, a number of viral-based expression systems may be utilized. In cases where an adenovirus is used as an expression vector, the multidomain protein (e.g., antibody or fusion protein) coding sequence of interest may be ligated to an adenovirus transcription/translation control complex, e.g., the late promoter and tripartite leader sequence. This chimeric gene may then be inserted in the adenovirus genome by in vitro or in vivo recombination. Insertion in a non-essential region of the viral genome (e.g., region El or E3) will result in a recombinant virus that is viable and capable of expressing the multidomain protein (e.g., antibody or fusion protein) in infected hosts (e.g., see Logan & Shenk, 1984, Proc. Natl. Acad. Sci. USA 8 1:355-359). Specific initiation signals may also be required for efficient translation of inserted multidomain protein coding sequences. These signals include the ATG initiation codon and adjacent sequences. Furthermore, the initiation codon must be in phase with the reading frame of the desired coding sequence to ensure translation of the entire insert. These exogenous translational control signals and initiation codons can be of a variety of origins, both natural and synthetic. The efficiency of expression may be enhanced by the inclusion of appropriate transcription enhancer elements, transcription terminators, etc. (see, e.g., Bittner et al., 1987, Methods in Enzymol. 153:516-544).

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[0232] The expression of a multidomain protein (e.g., antibody or fusion protein) may be controlled by any promoter or enhancer element known in the art. Promoters which may be used to control the expression of the gene encoding an multidomain protein (e.g., antibody or fusion protein) include, but are not limited to, the SV40 early promoter region (Bernoist and Chambon, 1981, Nature 290:304-310), the promoter contained in the 3' long terminal repeat of Rous sarcoma virus (Yamamoto, et al., 1980, Cell 22:787-797), the herpes thymidine kinase promoter (Wagner et al., 1981, Proc. Natl. Acad. Sci. U.S.A. 78:1441-1445), the regulatory sequences of the metallothionein gene (Brinster et al., 1982, Nature 296:39-42), the tetracycline (Tet) promoter (Gossen et al., 1995, Proc. Nat. Acad. Sci. USA 89:5547-5551); prokaryotic expression vectors such as the β-lactamase promoter (Villa-Kamaroff et al., 1978, Proc. Natl. Acad. Sci. U.S.A. 75:3727-3731), or the tac promoter (DeBoer et al., 1983, Proc. Natl. Acad. Sci. U.S.A. 80:21-25; see also "Useful proteins from recombinant bacteria" in Scientific American, 1980, 242:74-94); plant expression vectors comprising the nopaline synthetase promoter region (Herrera-Estrella et al., Nature 303:209-213) or the cauliflower mosaic virus 35S RNA promoter (Gardner et al., 1981, Nucl. Acids Res. 9:2871), and the promoter of the photosynthetic enzyme ribulose biphosphate carboxylase (Herrera-Estrella et al., 1984, Nature 310:115-120); promoter elements from yeast or other fungi such as the Gal 4 promoter, the ADC (alcohol dehydrogenase) promoter, PGK (phosphoglycerol kinase) promoter, alkaline phosphatase promoter, and the following animal transcriptional control regions, which exhibit tissue specificity and have been utilized in transgenic animals: elastase I gene control region which is active in pancreatic acinar cells (Swift et al., 1984, Cell 38:639-646; Ornitz et al., 1986, Cold Spring Harbor Symp. Quant. Biol. 50:399-409; MacDonald, 1987, Hepatology 7:425-515); insulin gene control region which is active in pancreatic beta cells (Hanahan, 1985, Nature 315:115-122), immunoglobulin gene control region which is active in lymphoid cells (Grosschedl et al., 1984, Cell 38:647-658; Adames et al., 1985, Nature 318:533-538; Alexander et al., 1987, Mol. Cell. Biol. 7:1436-1444), mouse mammary tumor virus control region which is active in testicular, breast, lymphoid and mast cells (Leder et al., 1986, Cell 45:485-495), albumin gene control region which is active in liver (Pinkert et al., 1987, Genes and Devel. 1:268-276), alpha-fetoprotein gene control region which is active in liver (Krumlauf et al., 1985, Mol. Cell. Biol. 5:1639-1648; Hammer et al., 1987, Science 235:53-58; alpha 1-antitrypsin gene control region which is active in the liver (Kelsey et al., 1987, Genes and Devel. 1:161-171), beta-globin gene control region which is active in myeloid cells (Mogram et al., 1985, Nature 315:338-340; Kollias et al., 1986, Cell 46:89-94; myelin basic protein gene control

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region which is active in oligodendrocyte cells in the brain (Readhead et al., 1987, Cell 48:703-712); myosin light chain-2 gene control region which is active in skeletal muscle (Sani, 1985, Nature 314:283-286); neuronal-specific enolase (NSE) which is active in neuronal cells (Morelli et al., 1999, Gen. Virol. 80:571-83); brain-derived neurotrophic factor (BDNF) gene control region which is active in neuronal cells (Tabuchi et al., 1998, Biochem. Biophysic. Res. Com. 253:818-823); glial fibrillary acidic protein (GFAP) promoter which is active in astrocytes (Gomes et al., 1999, Braz J Med Biol Res 32(5): 619-631; Morelli et al., 1999, Gen. Virol. 80:571-83) and gonadotropic releasing hormone gene control region which is active in the hypothalamus (Mason et al., 1986, Science 234:1372-1378).

[0233] Expression vectors containing inserts of a gene encoding a multidomain protein (e.g., antibody or fusion protein) can be identified by three general approaches: (a) nucleic acid hybridization, (b) presence or absence of "marker" gene functions, and (c) expression of inserted sequences. In the first approach, the presence of a gene encoding a peptide, polypeptide, protein or a fusion protein in an expression vector can be detected by nucleic acid hybridization using probes comprising sequences that are homologous to an inserted gene encoding the peptide, polypeptide, protein or the fusion protein, respectively. In the second approach, the recombinant vector/host system can be identified and selected based upon the presence or absence of certain "marker" gene functions (e.g., thymidine kinase activity, resistance to antibiotics, transformation phenotype, occlusion body formation in baculovirus, etc.) caused by the insertion of a nucleotide sequence encoding a multidomain protein (e.g., antibody or fusion protein) in the vector. For example, if the nucleotide sequence encoding the multidomain protein (e.g., antibody or fusion protein) is inserted within the marker gene sequence of the vector, recombinants containing the gene encoding the multidomain protein (e.g., antibody or fusion protein) insert can be identified by the absence of the marker gene function. In the third approach, recombinant expression vectors can be identified by assaying the gene product (e.g., antibody or fusion protein) expressed by the recombinant. Such assays can be based, for example, on the physical or functional properties of the fusion protein in in vitro assay systems, e.g., binding with anti-bioactive molecule antibody.

[0234] In addition, a host cell strain may be chosen which modulates the expression of the inserted sequences, or modifies and processes the gene product in the specific fashion desired. Expression from certain promoters can be elevated in the presence of certain

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inducers; thus, expression of the genetically engineered fusion protein may be controlled. Furthermore, different host cells have characteristic and specific mechanisms for the translational and post-translational processing and modification (e.g., glycosylation, phosphorylation of proteins). Appropriate cell lines or host systems can be chosen to ensure the desired modification and processing of the foreign protein expressed. For example, expression in a bacterial system will produce an unglycosylated product and expression in yeast will produce a glycosylated product. Eukaryotic host cells that possess the cellular machinery for proper processing of the primary transcript (e.g., glycosylation, and phosphorylation) of the gene product may be used. Such mammalian host cells include, but are not limited to, CHO, VERY, BHK, Hela, COS, MDCK, 293, 3T3, WI38, NS0, and in particular, neuronal cell lines such as, for example, SK-N-AS, SK-N-FI, SK-N-DZ human neuroblastomas (Sugimoto et al., 1984, J. Natl. Cancer Inst. 73: 51-57), SK-N-SH human neuroblastoma (Biochim. Biophys. Acta, 1982, 704: 450-460), Daoy human cerebellar medulloblastoma (He et al., 1992, Cancer Res. 52: 1144-1148) DBTRG-05MG glioblastoma cells (Kruse et al., 1992, In Vitro Cell. Dev. Biol. 28A: 609-614), IMR-32 human neuroblastoma (Cancer Res., 1970, 30: 2110-2118), 1321N1 human astrocytoma (Proc. Natl Acad. Sci. USA, 1977, 74: 4816), MOG-G-CCM human astrocytoma (Br. J. Cancer, 1984, 49: 269), U87MG human glioblastoma-astrocytoma (Acta Pathol. Microbiol. Scand., 1968, 74: 465-486), A172 human glioblastoma (Olopade et al., 1992, Cancer Res. 52: 2523-2529), C6 rat glioma cells (Benda et al., 1968, Science 161: 370-371), Neuro-2a mouse neuroblastoma (Proc. Natl. Acad. Sci. USA, 1970, 65: 129-136), NB41A3 mouse neuroblastoma (Proc. Natl. Acad. Sci. USA, 1962, 48: 1184-1190), SCP sheep choroid plexus (Bolin et al., 1994, J. Virol. Methods 48: 211-221), G355-5, PG-4 Cat normal astrocyte (Haapala et al., 1985, J. Virol. 53: 827-833), Mpf ferret brain (Trowbridge et al., 1982, In Vitro 18: 952-960), and normal cell lines such as, for example, CTX TNA2 rat normal cortex brain (Radany et al., 1992, Proc. Natl. Acad. Sci. USA 89: 6467-6471) such as, for example, CRL7030 and Hs578Bst. Furthermore, different vector/host expression systems may effect processing reactions to different extents.

[0235] For long-term, high-yield production of recombinant proteins, stable expression is often preferred. For example, cell lines which stably express a multidomain protein of the invention (e.g., antibody or fusion protein) may be engineered. Rather than using expression vectors that contain viral origins of replication, host cells can be transformed with DNA controlled by appropriate expression control elements (e.g., promoter,

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enhancer, sequences, transcription terminators, polyadenylation sites, etc.), and a selectable marker. Following the introduction of the foreign DNA, engineered cells may be allowed to grow for 1-2 days in an enriched medium, and then are switched to a selective medium. The selectable marker in the recombinant plasmid confers resistance to the selection and allows cells to stably integrate the plasmid into their chromosomes and grow to form foci that in turn can be cloned and expanded into cell lines. This method may advantageously be used to engineer cell lines that express a multidomain protein that specifically binds to an antigen. Such engineered cell lines may be particularly useful in screening and evaluation of compounds that affect the activity of a multidomain protein (e.g., a polypeptide or a fusion protein) that specifically binds to an antigen.

[0236] A number of selection systems may be used, including but not limited to the herpes simplex virus thymidine kinase (Wigler et al., 1977, Cell 11:223), hypoxanthine-guanine phosphoribosyltransferase (Szybalska & Szybalski, 1962, Proc. Natl. Acad. Sci. USA 48:2026), and adenine phosphoribosyltransferase (Lowy et al., 1980, Cell 22:817) genes can be employed in tk-, hgprt- or aprt- cells, respectively. Also, antimetabolite resistance can be used as the basis of selection for dhfr, which confers resistance to methotrexate (Wigler et al., 1980, Natl. Acad. Sci. USA 77:3567; O'Hare et al., 1981, Proc. Natl. Acad. Sci. USA 78:1527); gpt, which confers resistance to mycophenolic acid (Mulligan & Berg, 1981, Proc. Natl. Acad. Sci. USA 78:2072); neo, which confers resistance to the aminoglycoside G-418 (Colberre-Garapin et al., 1981, J. Mol. Biol. 150:1); and hygro, which confers resistance to hygromycin (Santerre et al., 1984, Gene 30:147) genes.

[0237] Once an multidomain protein (e.g., antibody, or a fusion protein) has been produced by recombinant expression, it may be purified by any method known in the art for purification of a protein, for example, by chromatography (e.g., ion exchange, affinity, particularly by affinity for the specific antigen after Protein A, and sizing column chromatography), centrifugation, differential solubility, or by any other standard technique for the purification of proteins.

[0238] The expression levels of an multidomain protein (e.g., antibody or fusion protein) can be increased by vector amplification (for a review, see Bebbington and Hentschel, The use of vectors based on gene amplification for the expression of cloned genes in mammalian cells in DNA cloning, Vol.3. (Academic Press, New York, 1987)). For example, when a marker in the vector system expressing a multidomain protein (e.g., antibody or fusion protein) is amplifiable, increase in the level of inhibitor present in culture

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of host cell will increase the number of copies of the marker gene. Since the amplified region is associated with the multidomain protein gene, production of the multidomain protein will also increase (Crouse et al., 1983, Mol. Cell. Biol. 3:257).

[0239] The host cell may be co-transfected with two expression vectors of the invention. For example, the first vector encoding a heavy chain derived polypeptide and the second vector encoding a light chain derived polypeptide. The two vectors may contain identical selectable markers, which enable equal expression of heavy and light chain polypeptides. Alternatively, a single vector may be used which encodes, and is capable of expressing, a fusion protein or both heavy and light chain polypeptides. The coding sequences for the fusion protein or heavy and light chains may comprise cDNA or genomic DNA.

5.7. Preparation Of Liquid Formulations Of Multidomain Proteins

[0240] The liquid formulations of multidomain proteins, such as antibodies, can be prepared using any method known in the art. In one embodiment, a liquid preparation can be prepared by a method comprising: purifying the multidomain proteins from conditioned medium (either single lots or pooled lots of medium) and concentrating a fraction of the purified multidomain proteins to a final concentration from about 15 mg/ml, about 20 mg/ml, about 30 mg/ml, about 40 mg/ml, about 50 mg/ml, about 60 mg/ml, about 70 mg/ml, about 80 mg/ml, about 90 mg/ml, about 100 mg/ml, about 110 mg/ml, about 125 mg/ml, about 150 mg/ml, about 200 mg/ml, about 250 mg/ml, or about 300 mg/ml.

[0241] In a specific embodiment, the liquid formulations can be prepared by a method comprising concentrating a fraction containing the purified antibody or a fragment to a final antibody or fragment concentration of from about 15 mg/ml, about 20 mg/ml, about 30 mg/ml, about 40 mg/ml, about 50 mg/ml, about 60 mg/ml, about 70 mg/ml, about 80 mg/ml, about 90 mg/ml, about 100 mg/ml, about 110 mg/ml, about 125 mg/ml, about 150 mg/ml, about 200 mg/ml, about 250 mg/ml, or about 300 mg/ml using a semipermeable membrane with an appropriate molecular weight (MW) cutoff (e.g., 30 kD cutoff for whole antibody molecules and F(ab')2 fragments; and 10 kD cutoff for antibody fragments, such as Fab fragments) and difiltrating the concentrated antibody fraction into the formulation buffer using the same membrane. Conditioned medium containing antibody or a fragment thereof that specifically binds to a target antigen is subjected to CUNO filtration and the filtered antibody is subjected to HS50 cation exchange chromatography. The fraction from the HS50

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cation exchange chromatography is then subjected to rProtein A affinity chromatography followed by low pH treatment. Following low pH treatment, the antibody fraction is subject to super Q 650 anion exchange chromatography and then nanofiltration. The fraction of the antibody obtained after nanofiltration is then subjected to diafiltration to concentrate the antibody fraction into the formulation buffer using the same membrane.

[0242] The formulation buffer can comprise histidine at a concentration ranging from about 1 mM to about 100 mM, about 10 mM to about 50 mM, or about 20 mM to about 30 mM. The formulations may further comprise an amino acid at a concentration of less than 100 mM, less than 50 mM, less than 3.0 mM, less than 2.0 mM, or less than 1.8 mM. The amount of amino acid in the formulation should not cause a significant buffering in order to avoid multidomain protein precipitation at its isoelectric point. The pH of the formulation may range from about 5.0 to about 7.0, or about 5.5 to about 6.5, or about 5.8 to about 6.2, or about 6.0. To obtain an appropriate pH for a particular multidomain protein, it is generally understood that histidine (and glycine, if added) is first dissolved in water to obtain a buffer solution with higher pH than the desired pH and then the pH is brought down to the desired level by adding HCl. This way, the formation of inorganic salts (e.g., formation of NaCl when, for example, histidine hydrochloride is used as histidine and pH is raised to a desired level by adding NaOH) can be avoided.

[0243] The liquid formulations can be prepared as unit dosage forms by preparing a vial containing an aliquot of the liquid formulation for a one-time use. For example, a unit dosage per vial may contain 1 ml, 2 ml, 3 ml, 4 ml, 5 ml, 6 ml, 7 ml, 8 ml, 9 ml, 10 ml, 15 ml, or 20 ml of different concentrations of a multidomain protein ranging from about 15 mg/ml to about 300 mg/ml. If necessary, these preparations can be adjusted to a desired concentration by adding a sterile diluent to each vial. In a specific embodiment, the multidomain protein is an antibody that binds to a target antigen.

[0244] The liquid formulations of the present invention may be sterilized by various sterilization methods, including sterile filtration, radiation, etc. In a specific embodiment, the difiltrated antibody formulation is filter-sterilized with a presterilized 0.2 or 0.22-micron filter.

5.8. Preparation Of Lyophilized Formulations Of Multidomain Proteins

[0245] Lyophilization is a freeze drying process that is often used in the preparation of pharmaceutical products to preserve their biological activity. The liquid composition is

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prepared, then lyophilized to form a dry cake-like product. The process generally involves drying a previously frozen sample in a vacuum to remove the ice, leaving the non- water components intact, in the form of a powdery or cake-like substance. The lyophilized product can be stored for prolonged periods of time, and at elevated temperatures, without loss of biological activity, and can be readily reconstituted into a particle-free solution by the addition of an appropriate diluent. An appropriate diluent can be any liquid which is biologically acceptable and in which the lyophilized powder is completely soluble. Water, particularly sterile, pyrogen-free water, is a preferred diluent, since it does not include salts or other compounds which may affect the stability of the multidomain protein. The advantage of lyophilization is that the water content is reduced to a level that greatly reduce the various molecular events which lead to instability of the product upon long-term storage. The lyophilized product is also more readily able to withstand the physical stresses of shipping. The reconstituted product is preferably substantially particle free, thus it can be administered without prior filtration.

[0246] The following criteria are important in developing stable lyophilized protein products. Protein unfolding during lyophilization should be minimized. Various degradation pathways should be minimized. Residual moisture should be low. A strong and elegant cake structure should be obtained. A reconstitution time 15 should be short, for example, less than 60 minutes, or less then 40 minutes, or less then 20 minutes, or less then 10 minutes, or less then 5 minutes, or less than 2 minutes, or less than 1 minute.

[0247] The protein in the pre-lyophilized formulation has a high concentration of at least 5 mg/ml, or at least 10 mg/ml, or at least 25 mg/ml, or at least 50 mg/ml or greater. The ph of the formulation may range from about 5.0 to about 7.0, or about 5.5 to about 6.5, or about 5.8 to about 6.2, or about 6. Examples of buffers that control the ph in this range include succinate (such as sodium succinate), gluconate, histidine, citrate and other organic acid buffers. Histidine is a preferred buffer for subcutaneous, intramuscular and peritoneal injection. A specific buffer contains about 5-30 mm histidine.

[0248] A surfactant may be added to the protein formulation. exemplary surfactants include nonionic surfactants such as polysorbates (*e.g.* polysorbates 20, 80, such as tween 20, 10 tween 80) or poloxamers (*e.g.* poloxamer 188). The amount of surfactant added is such that it reduces aggregation of the formulated protein and/or minimizes the formation of particulates in the formulation and/or reduces protein adsorption onto the container. The surfactant also reduces the reconstitution time of the lyophilized formulation. For example,

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the surfactant is present in the formulation in an amount from about 0.001% to about 0.5%, or from about 0. 005% to about 0.1 % or from about 0.01% to about 0.05%.

[0249] Lyophilized formulations may optional contain one or more of the following, an excipient, such as saccharides, polyols and sugar alcohols, a bulking agent that provides good lyophilized cake properties, such as serine, glycine, mannitol, and tonicity modifiers such as salts (*e.g.*, NaCl, KCl, $MgCl_2$, $CaCl_2$).

5.9. Administration Of Formulations Of Multidomain Proteins

[0250] The formulated protein drug can be administrated to a subject in an effective amount for treating or preventing a disease condition in the subject. The subject is preferably a mammal such as non-primate (*e.g.*, cows, pigs, horses, cats, dogs, rats etc.) and a primate (*e.g.*, monkey such as a cynomolgous monkey and a human). In a specific embodiment, the subject is a human.

[0251] Various delivery systems are known and can be used to administer the formulated drug. Methods of administering formulations include, but are not limited to, parenteral administration (*e.g.*, intradermal, intramuscular, intraperitoneal, intravenous and subcutaneous), epidural administration, topical administration, pulmonary administration, and mucosal administration (*e.g.*, intranasal and oral routes). In a specific embodiment, liquid formulations, including reconstituted lyophilized formulations, of a therapeutic protein are administered intramuscularly, intravenously, subcutaneously or , intramuscularly. The formulations may be administered by any convenient route, for example by infusion or bolus injection, by absorption through epithelial or mucocutaneous linings (*e.g.*, oral mucosa, rectal and intestinal mucosa, etc.) and may be administered together with other biologically active agents. Administration can be systemic or local. In addition, pulmonary administration can be employed, *e.g.*, by use of an inhaler or nebulizer.

[0252] The formulation of the present invention can be packaged in a hermetically sealed container such as an ampoule or sachette indicating the quantity of multidomain protein. It is contemplated that the formulations of the present invention are in a hermetically sealed container indicating the quantity and concentration of multidomain protein. in certain embodiments, the formulation of the present invention is supplied in a hermetically sealed container at least 15 mg/ml, 20 mg/ml, 30 mg/ml, 40 mg/ml, 50 mg/ml, 60 mg/ml, 70 mg/ml, 80 mg/ml, 90 mg/ml, 100 mg/ml, 150 mg/ml, 200 mg/ml, 250 mg/ml, or 300 mg/ml, in a quantity of about 1 ml, 2 ml, 3 ml, 4 ml, 5 ml, 6 ml, 7 ml, 8 ml, 9 ml, 10 ml, 15 ml, or 20 ml.

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[0253] The amount of the formulations of the present invention which will be effective in the treatment, prevention, management or amelioration of a disease, one or more symptoms thereof, or an undesirable condition associated with the disease, can be determined by standard clinical techniques. For example, the dosage of a drug formulation which will be effective in the treatment, prevention, management or amelioration of a disease can be determined by administering the formulation to an animal model (*e.g.*, a cotton rat or monkey) and measuring the serum titer of the active protein, *e.g.*, the serum titer of the multidomain protein. Accordingly, a dosage of the formulation that results in a serum titer of at least 1 μg/ml, at least 2 μg/ml, at least 5 μg/ml, at least 10 μg/ml, at least 20 μg/ml, at least 25 μg/ml, at least 35 μg/ml, at least 40 μg/ml, at least 50 μg/ml, at least 75 μg/ml, at least 100 μg/ml, at least 125 μg/ml, at least 150 μg/ml, at least 200 μg/ml, at least 250 μg/ml, at least 300 μg/ml, at least 350 μg/ml, at least 400 μg/ml, or at least 450 μg/ml can be administered to a human for the treatment, prevention, management or amelioration of a disease. In addition, *in vitro* assays may optionally be employed to help identify optimal dosage ranges. In specific embodiments, the multidomain protein is an antibody that bind to a target antigen

[0254] The precise dose to be employed in the formulation will also depend on the route of administration, and the seriousness of the disease, and should be decided according to the judgment of the practitioner and each patient's circumstances. Effective doses may be extrapolated from dose-response curves derived from *in vitro* or animal model (*e.g.*, the cotton rat or cynomolgous monkey) test systems.

[0255] For antibodies, proteins, polypeptides, peptides and fusion proteins, the dosage administered to a patient may be about 0.1 mg/kg to 30 mg/kg of the patients body weight. For example, generally, human antibodies have a longer half-life within the human body than antibodies from other species due to the immune response to the foreign polypeptides. Thus, lower dosages of human antibodies and less frequent administration is often possible. Further, the dosage, volume and frequency of administration of liquid formulations, including reconstituted lyophilized formulations, of the present invention may be reduced by increasing the concentration of an antibody or a fragment thereof in the formulations, increasing affinity and/or avidity of the antibody or a fragment thereof, and/or increasing the half-life of the antibody or a fragment thereof.

[0256] Exemplary doses of a small molecule include milligram or microgram amounts of the small molecule per kilogram of subject or sample weight (*e.g.*, about 1 microgram per

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kilogram to about 500 milligrams per kilogram, about 100 micrograms per kilogram to about 5 milligrams per kilogram, or about 1 microgram per kilogram to about 50 micrograms per kilogram).

6. EXAMPLES

[0257] The following examples are presented by way of illustration of the present invention, and is not intended to limit the present invention in any way. In the examples, to show the structural relationships among the antibodies, a naming scheme illustrated in Fig. 23 is used. In the naming scheme, the first 3 characters identify the antigen binding domain: the capital letter designates the target, the lower case letter designates a particular epitope of the target, the number designates the variant of the antibody (for simplicity reasons, number 0 is often omitted). The last 4 characters identify the Fc domain: the first 3 characters identify the source and subclass of the Fc domain, the last lower case letter designates the Fc variant. The example in FIG. 23, Aa1-hG1a, thus identifies the "1" variant of an antibody that binds epitope "a" of target "A" and has variant "a" of a human gamma-1 (hG1) as its Fc domain. Such a naming scheme allows easy determination, *e.g.*, that antibodies Aa-hG1 and Aa1-hG1 are different variants of an antibody that both bind to the same epitope of the same target and have the same Fc domain, or that antibodies Aa-hG1 and Ab-hG1 are different antibodies that bind to different epitopes of the same target and have the same Fc region, and so on.

6.1. EXAMPLE 1: Contribution Of Fab And Fc Domains To Tm Values And Stability

[0258] The Fab and Fc fragments of Ca-hG1 and Ba-hG1 were generated in order to learn more about the properties of the antibody Components. One long-term goal in studies of intact Mabs and their fragments is to understand the relationship between stability and structure. Currently it is known that Ca-hG1 is more stable with respect to aggregation when compared to Ba-hG1. This stability is further confirmed using the battery of analytical stability indicating assays. This stability difference offers an opportunity to compare properties of each antibody and to determine if there are measurable differences that can be exploited to understand the stability of these specific Mabs and more broadly applied to additional antibodies.

[0259] Fab and Fc domains were generated from full Mabs Ca-hG1 and Ba-hG1 using papain. A commercial kit from Pierce (Immunopure Fab Preparation Kit Pierce product # 44885: Immunopure IgG Binding Buffer, Immunopure IgG Elution Buffer,

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Affinitypak Immobilized Protein A Column, Immobilized Papain, Cysteine Monohydrochloride, Phosphate Buffer, and Serum Separators) was used to digest the intact antibodies. Ca-hG1 was successfully digested using the method described in the kit. Ba-hG1 required an alternate chromatography step. For Ba-hG1, both the Fab and Fc bound to the protein A column. Purification of these components required anion exchange chromatography (Hitrap DEAE FF 5 ml –Amersham Product #17-5154-01). In addition to chromatography optimization, enzymology was optimized to achieve the best cleavage of the Mab in a reasonable time.

[0260] Fab and Fc domains were generated from Ca-hG1 using the following steps: A) adding antibody to papain and incubating overnight at 37°C, ~ 10 mg of IgG per digestion; B) separating crude digest from immobilized enzyme; C) applying digest to protein A column; D) eluting the Fab fragment in unretained fraction at pH-8.0; E) eluting the Fc fragment at pH-3.0; and F) dialyzing the fragments into a required buffer.

[0261] Fab and Fc domains were generated from Ba-hG1 using the above procedure with the following modification: Using double enzyme to Mab ratio, increasing agitation, increasing incubation time to 24 hrs, omitting protein A column, buffering exchange digested solution into equilibration buffer for DEAE column (Start Buffer: 10 mM NaCl, 10 mM Tris pH-7.8, Elution Buffer: 100 mM NaCl, 10 mM Tris pH-7.8). The Fab portion of the antibody was in the unretained fraction which was eluted during sample loading. The Fc fragment was eluted with the 100 mM NaCl buffer. Table 1 summarizes the Fab and Fc fragments obtained by the procedures.

Table 1. Fab And Fc Obtained

Fragment	Ca-hG1	Ba-hG1
Fab	Purified	No Recovery
Fc	Purified	Fc +Fab Mix

[0262] Differential Scanning Calorimetry (DSC) was used to examine the melting curve of the full length monoclonal antibody (Mab) Ca-hG1 (FIG. 1, Top). Deconvolution of the thermogram of the full length Mab reveals that at least three separate Tm values (Tm1 = 69°C, Tm2 = 83°C And Tm3 = 87°C) make up the curve (FIG. 2). Fab and Fc domain fragments were generated from Ca-hG1 and the purified fragments were analyzed individually by DSC (FIG. 1, bottom). The results show that individual Tm values in a full antibody may be assigned to individual domains with the largest peak generated by the Fab domain (FIG. 1 bottom, also see FIG. 10 bottom). Analysis of the peaks generated by the Fc

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domain indicate that the Tm of the C_H2 region is represented by the first peak in the Fc DSC profile and the Tm of the C_H3 region is represented by the second peak (FIG. 1 bottom, also see FIG. 10 bottom).

[0263] The reversibility of melting was examined at two different temperatures for the full length Ca-hG1 Mab (FIGS. 3 and 4), The Fab domain (FIGS. 5 and 6) and the Fc domain (FIGS. 7 and 8). The results show that instability of the full antibody is a result of the instability of the Fab domain.

[0264] The DSC profiles of an unrelated full length Mab, Ba-hG1, were also measured and compared to Ca-hG1 (FIG. 9). To determine which domain contributes the most to the differences in the Tm profile, The DSC profiles of the Fab and Fc domains of Ba-hG1 were determined individually. In FIG. 10, the top panel shows the DSC profile for the intact Ba-hG1 antibody and the bottom panel shows the profiles for the Fc and Fab domains. As was seen for Ca-hG1, the largest peak is generated by the melting of the Fab domain. As expected, the Fc region generated two smaller peaks which correspond to those seen for the identical Fc region isolated from Ca-hG1 (compare FIG. 1 and 10, bottom panels). Deconvolution of the full antibody DSC profile indicates that at least three separate Tm values (Tm1 = 71°C, Tm2 = 82°C And Tm3 = 93°C) make up the curve of full length Ba-hG1 (FIG. 11). The reversibility of melting was examined for the full length Ba-hG1 Mab (FIGS. 12 and 13), The Fab domain (FIGS. 14 and 15) and the Fc domain (FIG. 16). The results also indicate that instability of the full antibody is a result of the instability of the Fab domain.

[0265] A comparison of the DSC profiles of Ba-hG1 and Ca-hG1 shows that the Fab domain contributes the most to the difference between the profiles for the two different Mab molecules (compare FIG. 1, bottom panel and FIG. 9, bottom panel). The results show that Ba-hG1 is less stable than Ca-hG1 because the Fab domain of Ba-hG1 is less stable than the Fab domain of Ca-hG1. Thus, the stability of an antibody may be predicted by evaluating the stability of the Fab domain.

6.2. EXAMPLE 2: Examination Of The Contribution Of The Variable Domain To Tm And pI Values

[0266] Fab fragments from 6 individual antibodies, several of which recognize the same epitope (Ca-hG1, Ca1-hG1 and Ca1-hG1a) were isolated. The Tm and pI for each was determined. The Fab fragments from Ca-hG1 and Ca1-hG1 differ by only about 13 amino acids, while Ca1-hG1 and Ca1-hG1a differ by only 3 amino acids. These three highly related

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molecules show only small differences in their pI and Tm values. In contrast, the completely unrelated molecules, Aa-hG1, Ba-hG1 and Da-hG1, show very different profiles (FIG. 17).

[0267] To examine the contribution of the Fab region to Tm and pI values in the context of a full length antibody, 18 individual Fab clones isolated from a single phage display library were converted into full length IgG1 and purified from transient transfections. These molecules differ only in their variable regions. The subsequent analysis of these clones demonstrate that they have a wide range of characteristics. For example, they exhibit dissociation constants (Kd) between a high of about 330 nM to a low of just 22 nM (data not shown). The Tm values of the Fab fragments, determined by DSC analysis of the intact antibodies, range from a low of just about 70°C to a high of about 90°C (FIGS. 18B and 18C). pI values of the intact antibodies also showed a wide range with the antibodies having pI values from 7.8 – 9.0 (FIGS. 18A and 18C).

[0268] FIG. 19 shows Tm and pI values of an additional panel of antibodies that bind to a variety of different epitopes present on a single protein as well as the previously analyzed Ca1-hG1 and two chimeric antibodies (Ha-hG1, Ia-hG1) generated by combining the heavy and light chains from two different antibodies. These antibodies also have a common Fc domain and vary only in their Fab domains. As was seen above, the different Fab domains result in a wide range of both pI and Tm values. In contrast, FIG. 20 shows the Tm and pI values of a panel of antibodies which differ by only a few amino acids in the hinge domain. These hinge variants, which have identical Fab domains, vary little in either their pI or Tm. Note that for the hinge variants for which a pI was determined, the amino acid changes made did not alter the net charge based on amino acid sequence.

[0269] FIG. 21 shows the viscosities of a 100 mg/mL solution of Ca-hG1, Ca1-hG1, Ba-hG1 and Da-hG1 as a function of temperature. It can be seen that the antibody with the lowest pI, Da-hG1, had the highest viscosity under the conditions measured. Also shown is the viscosity of Ba-hG1 as a function of temperature at increasing concentrations (100, 126, 138 and 150 mg/mL). The higher the concentration the higher the viscosity of the antibody solution. Accordingly, for the formulation of high concentration liquid formulations it is generally desirable to use an antibody with a lower inherent viscosity. These studies indicate that the pI of an antibody provides a measure indicative of the viscosity of the antibody in solution.

[0270] FIG. 22A shows the aggregation rates of the Ba-hG1, Ca-hG1, Ca1-hG1 and Da-hG1 antibodies at ~40°C as a function of the Tm of the Fab. It can be seen that the

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aggregation rate increases for antibodies having a lower Fab Tm. As shown in Table 2 this trend is also consistent for these molecules when stored at room temperature (25°C) and 5°C. These results indicate that increased Fab Tm values correlate with reduced aggregation rates over a wide temperature range. Two of these antibodies, Ba-hG1 and Ca-hG1, were chosen for further analysis.

[0271] The Fab and Fc fragments of Ba-hG1 and Ca-hG1 were isolated and the stability at 40°C of each fragment was examined. FIG 22B shows the aggregation profiles of the Fab and Fc fragments of Ba-hG1 and Ca-hG1 over time at 40°C. The ratio of the aggregation rates of both the Fab fragments and the full length Mabs are shown in Table 2. The ratio for the Fab fragments (Ba-hG1/Ca-hG1) is about 2.8 which is similar to ratio of the aggregation rates for the intact antibodies, about 2.4 (see Table 2). The aggregation rate of the Fc region is similar to that seen for the Ba-hG1 Fab fragment. Together these data indicate that the Fab domain plays a significant role in the formation of aggregates in the intact antibodies and that the aggregation rate of the intact antibody is influenced by the Tm of the Fab domain. Furthermore, these data also indicate that an increase in the Tm of the Fab region reduced the tendency for an antibody to aggregate over time and results in a more stable molecule. Accordingly, rapid screening by heating a cooling cycles using DSC can be used as a measure for the propensity of and antibody to form aggregate upon storage.

Table 2. Aggregation Rates

Aggregation Rate (% aggregate/month)				
MAb	**20°C**	**5°C**	**40°C**	**Ratio**
Ba-hG1	0.19	0.06	Fab of Ba-hG1 to Fab of Ca-hG1	2.8
Da-hG1	0.25	0.04	Mab of Ba-hG1 to Mab of Ca-hG1	2.4
Ca-hG1	0.08	0.01		
Ca1-hG1	0.06	0.02		

[0272] These results show that antibodies with various preferred characteristics can be screened using relevant in vitro and *in vivo* studies to determine the most desirable combination of characteristics. For example, for targeting a particular target, *e.g.*, target "E", a panel of antibodies that bind different antigens of the target, have different Tm values, and

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different pI values may be screened to obtain one or more that have desired combinations of these characteristics.

6.3. EXAMPLE 3: Examination Of The Contribution Of The Fc Hinge Region To Tm And pI Values

[0273] A number of different mutations were generated in the hinge region of the antibody Fa6-hG1. The Tm of the Fab domain of the parental antibody and each hinge mutant was determined by DSC analysis of the intact antibodies (FIG. 20). In addition, the pI values of the parent and several of the mutants were determined (FIG. 20). Note that for the hinge variants for which a pI was determined, the amino acid changes made did not alter the net charge based on amino acid sequence and as expected has little effect on the pI. In addition, the Tm values for these closely related molecules are nearly identical indicating that the sequence of hinge has little influence on the Tm of the Fab.

6.4. EXAMPLE 4: Engineering The Fc Domain To Alter The pI

[0274] A series of amino acid residue substitutions were generated in the Fc domain (human IgG1) of an anti-IL9 antibody to raise or lower the isoelectric point (pI). The substitutions were selected to have minimal impact on effector functions such as antibody-dependent cell-mediated cytotoxicity (ADCC) and complement-dependent cytotoxicity (CDC). The substitutions were also chosen to prevent disruption of the binding sites for protein A (a protein used for antibody purification) and FcRn (a receptor that mediates IgG homeostasis). Using the crystal structure of the human Fc as a guide, residues in the following regions: 339-375 and 390-414 (using the EU numbering scheme as described in Kabat et al., 1991, NIH Publication 91-3242, National Technical Information Service, Springfield, VA) were selected for substitution. Within these regions, prolines were excluded as possible sites for substitution because of the likelihood that prolines are necessary to maintain the protein fold. Ribbon diagrams of the human Fc CH2-CH3 regions are shown in Figures 24 and 25. The red indicates a region where mutations may affect C1q, FcγR, FcRn, and protein A binding, the blue indicates a region where substitutions may affect FcγR and FcRn binding, and the green indicates a region where substitutions may affect FcRn and protein A binding. The yellow region is where the two CH3 domains pack against each other. The location of the residues selected for substitution are indicated in pink and are space filled.

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[0275] The pI of a protein is defined as the pH at which the protein carries no net charge. At a pH below the protein's pI, the protein carries a net positive charge and at a pH above the protein's pI the protein carries a net negative charge. The acidic amino acids aspartic acid (D) and glutamic acid (E) are deprotonated at or near physiological pH and carry a negative charge. The basic amino acids lysine (K) and arginine (R) are protonated at or near physiological pH and carry a positive charge. At each amino acid residue of a protein, there are two possible changes that can be made: charged residues can be changed to uncharged residues or residues with the opposite charge and uncharged residues can be changed to residues with either a positive or negative charge. The maximum change in charge that can occur is where an amino acid is substituted with another amino acid of opposite charge. Replacing a charged residue with an uncharged residue serves only to remove charge, not add opposite charge and is less effective than replacing a charged residue with one of opposite charge. Substitutions of D and E with either K or R, or vice versa, are likely to have the greatest impact on pI. When choosing what residue should substitute for a given residue in the wild type sequence, the MHC type II immunogenicity of the new residue was checked using the website: http://www.syfpeithi.de/scripts/MHCServer.dll/home.htm. It was discovered that introducing a polar uncharged residue for a charged residue was less likely to be immunogenic than introducing a nonpolar residue for a charged residue.

[0276] Five sites were initially chosen for substitution, K340, E345, R355, Q362, and D401 (Figure 24). Site-directed mutagenesis was performed on the anti-IL9 antibody using a Stratagene QuikChange II XL kit. The modified antibodies were produced in 293H cells and purified using protein A. Isoelectric focusing gels (IEF) were run to determine the pI changes. The IEF gels are shown Figures 26 and 27 and the pI values and net changes are summarized in Table 3. The trend for pI changes was as expected. The wild type produced in 293H cells was used as a basis for comparison in Figures 26 and 27. The pI of wild type produced in NSO cells was found to be nearly identical to that seen for antibody produced in 293H cells (Figure 27, compare lanes 1 and 2). K340E had a lower pI than K340Q and both of these were lower than the pI of the wild type. The same pattern was observed for R355E and R355Q. E345K had a higher pI than E345Q and both of these mutants had a higher pI than wild type. This same pattern was also observed for D401K and D401N. Replacement of the residue Q362, which does not carry a charge, with E lowered the pI and replacement of the residue Q362 with K increased the pI. The largest magnitude change that lowered the pI was -0.62, R355E, and the largest magnitude change that increased the pI was 0.47, E345K.

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[0277] After analyzing that data on the single substitutions, combinatorial substitutions were made. As expected, combinatorial substitutions had a greater impact on pI than single mutations alone (Figure 27 and Table 3). The K340E R355E double substitutions showed a larger decrease in charge than the R355E Q362E double substitutions (-1.03 and –0.82, respectively). This decrease resulted from the switching in charge of two residues while in the R355E Q362E double substitution only the residue R355 was switched to its opposite charge. Both the E345K D401N and E345K D401K double substitution gave a greater magnitude increase in pI than any of the single mutations (0.68 and 0.62, respectively), although switching the charge of both residues didn't result in a greater increase in the pI. Their pIs fall very close to each other and are probably within the experimental error of the gel (note the smearing of the band in Figure 27). The K340E R355E Q362E and K340Q R355E Q362E triple substitutions followed the expected pattern and had the largest pI decreases of any of the substitutions. The E345K Q362K D401K and E345K Q362K D401N triple substitutions ran off the gel shown in Figure 27 which suggested that their pIs were largely increased.

[0278] Several additional sites for substitution, G341, Q342, R344, E356, M358, T359, N361, L365, N390, L398, and K409, were also chosen (Figure 25). The pI could not be determined for the M358K substitution because the proteins were too faint to make a clear determination. The change in pI for the remaining substitutions followed the same trends as was seen for the first set of single substitutions (Figure 28 and Table 3). These data demonstrate that targeted substitutions within the Fc domain are useful for engineering the pI of an antibody. In addition, these data indicate that targeted substitutions will prove useful for engineering the pI of other therapeutic molecules such as Fc fusion proteins.

[0279] Differential Scanning Calorimetry (DSC) was used to examine the melting curves of the single and triple substitutions to examine the effect of each substitution on the Tm of the substituted antibodies. The E345Q, E345K, R355Q, R335E, Q362E and Q362K substitutions have similar Tm profiles as wild type (Figure 30, left panel), while the K340Q, K340E and D401K substitutions resulted in altered Tm profiles (Figure 30, right panel). The triple substitutions, which both contain a substitution at position D401, show a similar alteration in Tm profiles as the single substitution D401K (compare Figure 30, left panel and Figure 31). These results indicate that substitutions may be selected to both engineer the pI and the Tm of protein domains such as, for example, the Fc domain.

Table 3. Isoelectric points of single, double, and triple mutants.

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Name	pI	pI Change from WT	Charge Change from WT
Wild Type	8.15	0	0
K340Q	7.88	-0.27	-1
K340E	7.57	-0.58	-2
E345Q	8.37	0.22	1
E345K	8.62	0.47	2
R355Q	7.79	-0.36	-1
R355E	7.53	-0.62	-2
Q362E	7.83	-0.32	-1
Q362K	8.36	0.21	1
D401N	8.34	0.19	1
D401K	8.49	0.34	2
K340E R355E	7.12	-1.03	-4
R355E Q362E	7.33	-0.82	-3
E345K D401N	8.83	0.68	3
E345K D401K	8.77	0.62	4
K340E R355E Q362E	6.80	-1.35	-5
K340Q R355E Q362E	6.99	-1.16	-4
E345K Q362K D401K	ND[¥]	ND[¥]	5
E345K Q362K D401N	ND[¥]	ND[¥]	4
Q342E	7.88	-0.27	-1
Q342K	8.32	0.17	1
R344Q	7.90	-0.25	-1
R344E	7.66	-0.49	-2
E356Q	8.31	0.16	1
E356K	8.59	0.44	2
L365E[a]	8.20	0.05	-1
L365K[a]	8.22	0.07	1
L398E	7.92	-0.23	-1
L398K	8.31	0.16	1
K409Q[a]	7.93	-0.22	-1
K409E[a]	7.77	-0.38	-2
G341D	7.97	-0.18	-1
G341K	8.45	0.3	+1
M358E	7.95	-0.2	-1
M358K	ND[‡]	ND[‡]	+1
T359E	7.94	-0.21	-1
T359K	8.45	0.3	+1
N361D	7.90	-0.25	-1
N361K	8.44	0.29	+1
N390D	7.90	-0.25	-1
N390K	8.39	0.24	+1
E345KQ362K	8.73	0.58	+3

[a]this position is a buried residue

ND[¥] indicates that the value could not be determined using the present IEF gel method likely equal to or more than 9.0

ND[‡] indicates that the value could not be determined because the proteins did not run clearly on the gel or was too faint

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6.5. EXAMPLE 5: pI and Tm Analysis For Candidate Selection

[0280] Two variants of an antibody, designated Fa-hG1, were generated for consideration as clinical candidates. For ease of administration high concentration liquid formulations are desired. The first variant, designated Fa-hG1b, was generated by making several substitutions in the Fc region of the molecule, one of which (L235E) reduces the charge by 1.0 and is expected to modestly reduced the pI (see Example 4 above). The second variant, designated Fa-hG4a, was generated by replacing the human IgG1 Fc region with a human IgG4 Fc region and engineering several substitutions including L235E. Based on amino acid sequence analysis Fa-hG4a will have a charge change of -4 compared to the wild type antibody. The three antibodies were analyzed to determine their Tm and pI values.

[0281] The DSC profiles of each antibody are shown overlaid in Figure 32. As described above, the Tm of the largest peak is used as the Tm of the Fab domain. The Tm of the Fab domain of the parental antibody was seen to be 70.4°C and the Tm of the Fa-hG4a and Fa-hG1b variants was 70.4°C and 70.9°C, respectively. These data demonstrate that the alterations of the Fc region did not change the major Tm peak of the Fab region. However, the DSC profile of Fa-hG4a dropped off dramatically above ~71°C indicating that this antibody may have precipitated due to instability introduced by the addition of the variant IgG4 Fc region.

[0282] Isoelectric focusing gels (IEF) were run to determine the pI of each antibody. The wild type antibody had a pI of ~8.35 (position of the major protein peak in Figure 33). The Fa-hG1b variant showed a modest reduction to ~8.18 while the pI of Fa-hG4a was significantly reduced to ~7.13 (Figure 33). The reduction in pI seen for the Fa-hG1b variant is in agreement with the change in pI seen for similar substitutions (see Table 3). The Fa-hG4a variant had a net pI change of -1.22 and a total charge change of -4 which is also in agreement with the change in pI seen for similar substitutions (see Table 3).

[0283] For selection of a clinical candidate, both the Tm and the pI of the antibody are taken into account. In this case, although the Tm of the Fab domain for each of the variants differed by less then 0.5°C, the DSC profile of the Fa-hG4a antibody indicated that this variant may be subject to some additional instability. Analysis of the pI revealed that the Fa-hG4a variant had a relatively low pI (~7.13). Accordingly, based on the correlation of low pI with increased viscosity and the potential instability revealed by DSC analysis of the Fa-hG4a variant, the Fa-hG1b variant was selected as a clinical candidate.

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6.6. Methods

[0284] *Isoelectric Focusing Gel Electrophoresis*: Isoelectric points were determined using a Pharmacia Biotech Multiphor 2 electrophoresis system with a multi temp 3 refrigerated bath recirculation unit and an EPS 3501 XL power supply. Pre-cast ampholine gels (Amersham Biosciences, pI range 2.5-10 or pI range 3.5-9.5) were loaded with 5-8 μg of protein. Protein samples were dialyzed in 10 mM Histidine pH-6 before loading on the gel as required. Broad range pI marker standards (Amersham, pI range 3-10, 8 μL) were used to determine relative pI for the Mabs. Electrophoresis was performed at 1500 V, 50 mA for 105 minutes. The gel was fixed using a Sigma fixing solution (5x) diluted with purified water to 1x. Staining was performed overnight at room temperature using Simply Blue stain (Invitrogen). Destaining was carried out with a solution that consisted of 25% ethanol, 8% acetic acid and 67% purified water. Isoelectric points were determined using a Bio-Rad's GS-800 calibrated densitometer relative to calibration curves of the standards.

[0285] *Differential Scanning Calorimetry*: Thermal melting temperatures (Tm) were measured with a VP-DSC (MicroCal, LLC) using a scan rate of 1.0°C/min and a temperature range of 25 –120°C. A filter period of 8 seconds was used along with a 5-15 minute pre-scan thermostating. Samples were prepared by dialysis into 10 mM Histidine-HCl, pH 6 using Pierce dialysis cups (3.5 kD). Average Mab concentrations were 50 μg/mL to 790 μg/mL as determined by A280. Melting temperatures were determined following manufacturer procedures using Origin software supplied with the system. Briefly, multiple baselines were run with buffer in both the sample and reference cell to establish thermal equilibrium. After the baseline was subtracted from the sample thermogram, the data were concentration normalized and fitted using the deconvolution function.

[0286] *Viscosity determination*: Viscosity of mAB solutions were performed using a ViscoLab 4000 Viscometer System (Cambridge Applied Systems) equipped with a ViscoLab Piston (SN:7497, 0.3055", 1-20 cP) and S6S Reference Standard (Koehler Instrument Company, Inc.). The viscometer was connected to a water bath and the system equilibrated to 20°C. Piston was checked using S6S viscosity reference standard (8.530 cP @ 20.00°C). Check piston was also checked using RODI H2O (1.00 cP @ 20.0°C). The piston was cleaned and rinsed thoroughly with soap and water between measurements of each different solution type. The system was then cooled to ≤ 2°C. When the system temperature was at or below 2°C, sample was loaded into the chamber and the piston was lowered into the sample.

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After sample was equilibrated to the temperature of the chamber, measurement was initiated. The temperature was increased at 1°C increments every 7-10 minutes to a final temperature of ≥ 25°C. The temperature was adjusted on the water bath but the recorded temperature was what was displayed on the viscometer. The viscosity result was recorded immediately prior to increasing the temperature. The piston remained in motion during measurements to minimize the need for re-equilibration.

[0287] *Site Directed Mutagenesis*: mutagenesis was performed according to the manufacturer's instructions using a Stratagene QuikChange II XL kit and the primers listed in Table 4.

Table 4. Primers used for site directed mutagenesis

Primer	Sequence‡	SEQ ID NO.
K340Q-F	CCATCTCCAAAGCCCAGGGGCAGCCCCGAGAACC	1
K340Q-R	GGTTCTCGGGGCTGCCCCTGGGCTTTGGAGATGG	2
K340E-F	CCATCTCCAAAGCCGAGGGGCAGCCCCGAGAACC	3
K340E-R	GGTTCTCGGGGCTGCCCCTCGGCTTTGGAGATGG	4
E345Q-F	GCCAAAGGGCAGCCCCGACAGCCACAGGTGTACACCC	5
E345Q-R	GGGTGTACACCTGTGGCTGTCGGGGCTGCCCTTTGGC	6
E345K-F	GCCAAAGGGCAGCCCCGAAAGCCACAGGTGTACACCC	7
E345K-R	GGGTGTACACCTGTGGCTTTCGGGGCTGCCCTTTGGC	8
R355Q-F	CCCTGCCCCCATCCCAGGAGGAGATGACCAAGAACC	9
R355Q-R	GGTTCTTGGTCATCTCCTCCTGGGATGGGGGCAGGG	10
R355E-F	CCCTGCCCCCATCCGAGGAGGAGATGACCAAGAACC	11
R355E-R	GGTTCTTGGTCATCTCCTCCTCGGATGGGGGCAGGG	12
Q362E-F	GGAGATGACCAAGAACGAGGTCAGCCTGACCTGCC	13
Q362E-R	CCAGGCAGGTCAGGCTGACCTCGTTCTTGGTCATCTCC	14
Q362K-F	GGAGATGACCAAGAACAAGGTCAGCCTGACCTGCC	15
Q362K-R	CCAGGCAGGTCAGGCTGACCTTGTTCTTGGTCATCTCC	16
D401N-F	CGCCTCCCGTGCTGGACTCCAACGGCTCCTTCTTCC	17
D401N-R	GGAAGAAGGAGCCGTTGGAGTCCAGCACGGGAGGCG	18
D401K-F	CGCCTCCCGTGCTGGACTCCAAGGGCTCCTTCTTCC	19
D401K-R	GGAAGAAGGAGCCCTTGGAGTCCAGCACGGGAGGCG	20
L365E-for	GACCAAGAACCAGGTCAGCGAGACCTGCCTGGTCAAAGGC	21
L365E-rev	GCCTTTGACCAGGCAGGTCTCGCTGACCTGGTTCTTGGTC	22
L365K-for	GACCAAGAACCAGGTCAGCAAGACCTGCCTGGTCAAAGGC	23
L365K-rev	GCCTTTGACCAGGCAGGTCTTGCTGACCTGGTTCTTGGTC	24
K409Q-for	GCTCCTTCTTCCTCTATAGCCAGCTCACCGTGGACAAGAGC	25
K409Q-rev	GCTCTTGTCCACGGTGAGCTGGCTATAGAGGAAGAAGGAGC	26
K409E-for	GCTCCTTCTTCCTCTATAGCGAGCTCACCGTGGACAAGAGC	27
K409E-rev	GCTCTTGTCCACGGTGAGCTCGCTATAGAGGAAGAAGGAGC	28
Q342E-for	CCATCTCCAAAGCCAAAGGGGAGCCCCGAGAACCACAGGTG	29
Q342E-rev	CACCTGTGGTTCTCGGGGCTCCCCTTTGGCTTTGGAGATGG	30
Q342K-for	CCATCTCCAAAGCCAAAGGGAAGCCCCGAGAACCACAGGTG	31
Q342K-rev	CACCTGTGGTTCTCGGGGCTTCCCTTTGGCTTTGGAGATGG	32
R344Q-for	CTCCAAAGCCAAAGGGCAGCCCCAGGAACCACAGGTGTACACCC	33
R344Q-rev	GGGTGTACACCTGTGGTTCCTGGGGCTGCCCTTTGGCTTTGGAG	34
R344E-for	CTCCAAAGCCAAAGGGCAGCCCGAGGAACCACAGGTGTACACCC	35
R344E-rev	GGGTGTACACCTGTGGTTCCTCGGGCTGCCCTTTGGCTTTGGAG	36
E356Q-for	CCCTGCCCCCATCCCGGCAGGAGATGACCAAGAACCAGG	37
E356Q-rev	CCTGGTTCTTGGTCATCTCCTGCCGGGATGGGGGCAGGG	38

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E356K-for	CCCTGCCCCCATCCCGGAAGGAGATGACCAAGAACCAGG	39
E356K-rev	CCTGGTTCTTGGTCATCTCCTTCCGGGATGGGGGCAGGG	40
L398E-for	CAAGACCACGCCTCCCGTGGAGGACTCCGACGGCTCCTTCTTCC	41
L398E-rev	GGAAGAAGGAGCCGTCGGAGTCCTCCACGGGAGGCGTGGTCTTG	42
L398K-for	CAAGACCACGCCTCCCGTGAAGGACTCCGACGGCTCCTTCTTCC	43
L398K-rev	GGAAGAAGGAGCCGTCGGAGTCCTTCACGGGAGGCGTGGTCTTG	44
G341D-F	CCATCTCCAAAGCCAAAGACCAGCCCCGAGAACCACAGG	45
G341D-R	CCTGTGGTTCTCGGGGCTGGTCTTTGGCTTTGGAGATGG	46
G341K-F	CCATCTCCAAAGCCAAAAAGCAGCCCCGAGAACCACAGG	47
G341K-R	CCTGTGGTTCTCGGGGCTGCTTTTTGGCTTTGGAGATGG	48
M358E-F	CCCCCATCCCGGGAGGAGGAAACCAAGAACCAGGTCAGCC	49
M358E-R	GGCTGACCTGGTTCTTGGTTTCCTCCTCCCGGGATGGGGG	50
M358K-F	CCCCCATCCCGGGAGGAGAAGACCAAGAACCAGGTCAGCC	51
M358K-R	GGCTGACCTGGTTCTTGGTCTTCTCCTCCCGGGATGGGGG	52
T359E-F	CCATCCCGGGAGGAGATGGAGAAGAACCAGGTCAGCC	53
T359E-R	GGCTGACCTGGTTCTTCTCCATCTCCTCCCGGGATGG	54
T359K-F	CCATCCCGGGAGGAGATGAAGAAGAACCAGGTCAGCC	55
T359K-R	GGCTGACCTGGTTCTTCTTCATCTCCTCCCGGGATGG	56
N361D-F	CCCGGGAGGAGATGACCAAGGACCAGGTCAGCCTGACCTGC	57
N361D-R	GCAGGTCAGGCTGACCTGGTCCTTGGTCATCTCCTCCCGGG	58
N361K-F	CCCGGGAGGAGATGACCAAGAAGCAGGTCAGCCTGACCTGC	59
N361K-R	GCAGGTCAGGCTGACCTGCTTCTTGGTCATCTCCTCCCGGG	60
N390D-F	GCAATGGGCAGCCGGAGAACGACTACAAGACCACGCCTCCCG	61
N390D-R	CGGGAGGCGTGGTCTTGTAGTCGTTCTCCGGCTGCCCATTGC	62
N390K-F	GCAATGGGCAGCCGGAGAACAAGTACAAGACCACGCCTCCCG	63
N390K-R	CGGGAGGCGTGGTCTTGTACTTGTTCTCCGGCTGCCCATTGC	64

‡ Underlined indicates location of mutation

[0288] *Expression and Purification of Mutated anti-IL9 Antibodies*: 293H cells were grown in Dulbecco's Modified Eagle Medium (DMEM) liquid (4.5 g/L D-glucose), with L-glutamine, and pyridoxine HCl, but no sodium pyruvate, plus 1% nonessential amino acids plus 10% fetal bovine serum. Transfections were performed by mixing 20μg of each of the heavy and light chain vectors per T175 flask (two flasks were used per mutant) with 1.5 ml of Opti-MEM I. This mixture was then combined with 1.5 ml of Opti-MEM I containing 70 μl of Lipofectamine 2000 and left to sit at room temperature for ½ hour. Three mls of this mixture was added to a T175 containing 27 mls of DMEM plus 1% nonessential amino acids plus 5% ultra low bovine IgG fetal bovine serum. Three harvests were performed spaced three days apart. The harvested media was then spun at 1000 rpm and filtered through a 0.2 μm filter. Next, the antibodies were purified using protein A and were concentrated to between 0.1 and 1 mg/ml. Samples were dialyzed into 10 mM Histidine pH 6 and protein concentration adjusted to approximately 1 mg/ml.

[0289] *Stability of Intact Antibodies*: Intact antibodies were concentrated to 100 mg/ml in 10 mM Histidine pH 6. Samples were incubated at three temperatures 2-8°C, 23-27°C, and 38-42°C and analyzed by SEC at predetermined time points. Samples were diluted to 10 mg/ml and 250 µg was injected onto the SEC column (see, SEC Analysis).

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[0290] *Stability of Fab and Fc Fragments*: Fab and Fc fragments were isolated using papain digestion followed by column chromatography (also see, Example 1). The antibodies studied all had the same Fc region. Sample purity was analyzed and confirmed by SDS-PAGE and SEC. Fab and Fc fragments in 10 mM Histidine pH 6 were concentrated to 50 mg/ml. The concentrated material was incubated at 38-42°C and sampled to monitor aggregate. The sample was diluted to 2 mg/ml and 70 µg was injected onto the SEC column (see, Size Exclusion Chromatography (SEC) Analysis).

[0291] *Size Exclusion Chromatography (SEC) Analysis:* SEC analysis was conducted on an Agilent 1100 High Performance Liquid Chromatography (HPLC) System with a flow rate of 1 mL/min. A TOSOH BIOSEP TSK G3000SW_{XL} column (7.8 mm x 30 cm) with guard column was used for the analysis. The mobile phase consisted of 100 mM Sodium Phosphate Dibasic Anhydrous, 100 mM Sodium Sulfate, and 0.05 % Sodium Azide pH 6.8.

7. REFERENCES CITED

[0292] All references cited herein are incorporated herein by reference in their entirety and for all purposes to the same extent as if each individual publication or patent or patent application was specifically and individually indicated to be incorporated by reference in its entirety for all purposes. In addition, United States provisional Patent Application Nos. 60/696,113 filed July 1, 2005 and 60/788,692 filed April 4, 2006 are incorporated by reference in their entirety for all purposes.

[0293] Many modifications and variations of the present invention can be made without departing from its spirit and scope, as will be apparent to those skilled in the art. The specific embodiments described herein are offered by way of example only, and the invention is to be limited only by the terms of the appended claims along with the full scope of equivalents to which such claims are entitled.

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CLAIMS

1. A method of generating a multidomain protein comprising the steps of:
   a. determining the pI and/or Tm for each of a plurality of protein domains having a certain predetermined binding specificity;
   b. selecting one or more protein domains based on its pI and/or Tm; and
   c. constructing a multidomain protein using one or more domain selected in step (b) and one or more other domains.

2. The method of claim 1, wherein each of the selected protein domains has a Tm of at least 50°C, and a pI of at least 6.5 or a Tm of at least 50°C, and a pI of less than 6.5.

3. The method of claim 1 or 2, wherein the multidomain protein is an antibody and where the predetermined binding specificity is specificity for binding a target.

4. The method of claim 3, wherein the plurality of protein domains are antigen binding domains.

5. The method of claim 4, wherein at least some of the antigen binding domains bind different epitopes of the target.

6. The method of claim 4, wherein the antigen binding domains are obtained by screening an expression library with the target.

7. The method of claim 4, wherein the antigen binding domains are obtained by digesting a plurality of monoclonal antibodies.

8. The method of any one of claims 4 to 7, wherein each selected antigen binding domain is combined with an antibody constant region domain to generate the multidomain protein.

9. The method of claim 8, further comprising prior to step (c) the steps of:
   i. determining the pI and/or Tm for each of a plurality of antibody constant region domains; and
   ii. selecting an antibody constant region domain based on its pI and/or Tm.

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10. The method of claim 3, wherein the plurality of protein domains are antibody constant region domains and where the predetermined binding specificity is specificity for binding an Fc ligand.

11. The method of claim 10 , wherein each selected constant region domains is combined with an antigen binding domain to generate the multidomain protein.

12. A method of selecting a multidomain protein comprising the steps of:
    a. determining for each of a plurality of multidomain proteins having a certain predetermined binding specificity the pI and/or Tm of one or more domains within the multidomain protein ; and
    b. selecting one or more multidomain proteins based on the pI and/or Tm of the one or more domains.

13. The method of claim 12, wherein the multidomain protein is an antibody and where the predetermined binding specificity is specificity for binding a target.

14. The method of claim 13, wherein the one or more domains are antigen binding domains.

15. The method of claim 14, wherein at least some of the antigen binding domains binds different epitopes of the target.

16. The method of claim 14 or 15, wherein the plurality of multidomain proteins is obtained by screening an expression library with the target.

17. The method of claim 14, 15 or 16, wherein the antigen binding domains of the selected multidomain proteins have a Tm of at least 50°C, and a pI of at least 6.5 or a Tm of at least 50°C, and a pI of less than 6.5.

18. The method of claim 13, wherein the one or more protein domains are Fc domains.

19. The method of claim 18, wherein the antibody constant region domains of the selected multidomain proteins have a Tm of at least 50°C, and a pI of at least 6.5 or a Tm of at least 50°C, and a pI of less than 6.5.

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20. The method of claim 1 or 12, wherein the pI and/or Tm are determined under one or more different conditions selected from the group consisting of different pH values, different temperatures, different shear stresses, and different freeze/thaw cycles.

21. A method of generating one or more antibodies targeting a predetermined antigen comprising the steps of:
    a. identifying a plurality of antigen binding domains exhibiting a binding affinity for the antigen above a predetermined threshold level;
    b. determining the Tm and pI values for each identified antigen binding domain;
    c. selecting one or more antigen binding domains based on the determined Tm and pI values; and
    d. constructing an antibody comprising an antigen binding domain selected in step (c) and a constant region domain.

22. The method of claim 21, wherein each of the selected antigen binding domains has a Tm of at least 50°C, and a pI of at least 6.5 or a Tm of at least 50°C, and a pI of less than 6.5.

23. The method of claim 21 or 22, wherein the plurality of antigen binding domains are obtained by screening an expression library with the target.

24. The method of claim 21 or 22, wherein the plurality of antigen binding domains are obtained by digesting a plurality of monoclonal antibodies, wherein the monoclonal antibodies bind the target.

25. The method of claim 22, 23 or 24, wherein at least some of the antigen binding domains bind different epitopes of the target.

26. The method of claim 21, further comprising prior to said step (d) the steps of:
    i. determining the pI and/or Tm for each of a plurality of antibody constant region domains; and
    ii. selecting an antibody constant region domain based on its pI and/or Tm.

27. The method of claim 26, wherein each of the selected antibody constant region domains has a Tm of at least 50°C, and a pI of at least 6.5 or a Tm of at least 50°C, and a pI of less than 6.5.

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28. A method of engineering an antibody to improve one or more therapeutic and/or formulation characteristics without significantly reducing one or more biological activities selected from the group consisting of serum half-life, complement fixation, Fc receptor binding and antigen-dependent cellular cytotoxicity of the antibody, comprising substituting and/or inserting one or more amino acids in the antibody, wherein the amino acid substitutions and/or insertions are such that they improve one or more therapeutic and/or formulation characteristics of the antibody.

29. The method of claim 28, wherein said one or more formulation characteristics of are selected from the group consisting of stability, solubility and viscosity.

30. The method of claim 28, wherein said one or more therapeutic characteristics of are selected from the group consisting of non-specific toxicity and biodistribution.

31. The method of claim 29 or 30, wherein stability can be determined by characterizing the Tm and non-specific toxicity, biodistribution, solubility and viscosity can be determined by characterizing the pI.

32. The method of claim 31, wherein the Tm of the engineered antibody is increased.

33. The method of claim 31, wherein the pI of the engineered antibody is increased.

34. The method of claim 31, wherein the pI of the engineered antibody is decreased.

35. The method of claim 28, wherein said amino acid substitutions are such that they further improve one or more biological activities selected from the group consisting of serum half-life, complement fixation, Fc receptor binding and antigen-dependent cellular cytotoxicity of the antibody.

36. A method of evaluating long term stability of a multidomain protein in a solution comprising the steps of:

a. providing a solution of a multidomain protein, wherein the multidomain protein comprises a domain, the unfolding of which leads to aggregation of the multidomain protein;
b. heating the solution of the multidomain protein to a temperature of at least 50°C;
c. determining if the domain denatures; and

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d. classifying the multidomain protein as having long term stability in the solution if the domain in the multidomain protein is determined to not denature in step (c).

37. The method of claim 37, further comprising determining if the domain refolds upon cooling to a temperature of less then 50°C in step (c) and classifying the multidomain protein as having long term stability in said solution if the domain in the multidomain protein is determined to refold in step (c).

38. The method of claim 36 or 37, wherein the multidomain protein is an antibody.

39. The method of claim 38, wherein the domain is an antigen binding domain.

40. The method of claim 38, wherein the domain is a constant region domain.

41. The method of any one of claims 36-40, wherein the steps (b) and (c) are carried out by generating a thermal denaturation curve.

42. The method of claim 41, wherein said thermal denaturation curve is generated using differential scanning calorimetry.

43. A method of identifying in a multidomain protein one or more domains, the unfolding of which causes aggregation of the multidomain protein in a solution comprising the steps of:

a. denaturing the one or more domains by heating the solution to a temperature of at least 50°C;
b. determining if one or more of the domains refold upon cooling to a temperature of less then 50°C; and
c. identifying one or more domains that do not refold upon cooling in step (b), thereby identifying the domain or domains the unfolding of which causes aggregation of the multidomain protein in solution.

44. The method of claim 43, wherein the multidomain protein is an antibody.

45. The method of claim 43 or 44, wherein the domain is an antigen binding domain.

46. The method of claim 43 or 44, wherein the domain is a constant region domain.

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47. The method of any one of claims 43-46, wherein steps (a) and (b) are carried out by generating a thermal denaturation/renaturation curve.

48. The method of claim 47, wherein said thermal denaturation/renaturation curve is generated using differential scanning calorimetry.

49. A method of engineering a multidomain protein to have improved long term stability, wherein the multidomain protein comprises a domain the unfolding of which causes aggregation of the multidomain protein in a solution, the method comprising:
    a. modifying the domain by substituting one or more amino acid residues in the domain to generated a modified domain;
    b. heating a solution of a multidomain protein comprising the modified domain to a temperature of at least 50°C;
    c. determining if the modified domain in the multidomain protein denatures in step (b); and
    d. classifying the multidomain protein containing the modified domain as having improved long term stability if the modified domain is determined to not denature in step (c).

50. The method of claim 49, further comprising determining if the modified domain refolds upon cooling to a temperature of less then 50°C in step (c) and classifying the multidomain protein as having long term stability in solution if the modified domain is determined to refold in step (c).

51. The method of claim 49 or 50, wherein the multidomain protein is an antibody.

52. The method of claim 49 or 50, wherein the domain is an antigen binding domain.

53. The method of claim 49 or 50, wherein the domain is a constant region domain.

54. The method of any one of claims 50-53, wherein steps (b) and (c) are carried out by generating a thermal denaturation curve.

55. The method of claim 54, wherein the thermal denaturation curve is generated using differential scanning calorimetry.

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56. A method of engineering a multidomain protein to have improved solubility and/or lower viscosity comprising the steps of:
    a. modifying a domain of the multidomain protein by substituting and/or inserting one or more amino acid residues in the domain to generated a modified domain;
    b. determining the pI of the modified domain or determining the pI of the multidomain protein containing the modified domain; and
    c. classifying the multidomain protein containing the modified domain as having improved solubility and/or viscosity if the modified domain or multidomain protein containing the modified domain is determined to have a higher pI in step (b).

57. A multidomain protein produced by the method of claim 56.

58. A method of engineering a multidomain protein to have reduced non-specific toxicity comprising the steps of:
    a. modifying a domain of the multidomain protein by substituting and/or inserting one or more amino acid residues in the domain to generated a modified domain;
    b. determining the pI of the modified domain or determining the pI of the multidomain protein containing the modified domain; and
    c. classifying the multidomain protein containing the modified domain as having reduced non-specific toxicity if the modified domain or the multidomain protein containing the modified domain is determined to have a lower pI in step (b).

59. A multidomain protein produced by the method of claim 58.

60. A method of engineering a multidomain protein to have reduced liver toxicity comprising the steps of:
    a. modifying a domain of the multidomain protein by substituting and/or inserting one or more amino acid residues in the domain to generated a modified domain;
    b. determining the pI of the modified domain or determining the pI of the multidomain protein containing the modified domain; and

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c. classifying the multidomain protein containing the modified domain as having reduced non-specific toxicity if the modified domain or the multidomain protein containing the modified domain is determined to have a lower pI in step (b).

61. A multidomain protein produced by the method of claim 60.

62. A method of engineering a multidomain protein to have a specific biodistribution comprising the steps of:

a. modifying a domain of the multidomain protein by substituting and/or inserting one or more amino acid residues in the domain to generated a modified domain;

b. determining the pI of the modified domain or determining the pI of the multidomain protein containing the modified domain; and

c. classifying said protein containing the modified domain as having reduced intracellular localization if the modified domain or the multidomain protein containing the modified domain is determined to have a lower pI in step (b) or as having increased intracellular and/or extravascular localization if the modified domain or the multidomain protein containing the modified domain is determined to have a higher pI in step (b).

63. A multidomain protein produced by the method of claim 62.

64. The method of claim 56, 58, 60 or 61, wherein the multidomain protein is an antibody.

65. The method of claim 56, 58, 60 or 62, wherein the domain is an antigen binding domain.

66. The method of claim 56, 58, 60 or 62, wherein the domain is a constant region domain.

67. The method of claims 56, 58, 60, 61, 64, 65 or 66 wherein step (b) is carried out by isoelectric focusing.

68. The method of claim 66, wherein said modification comprises a replacement at one or more amino acid residues selected from the group consisting of K338, A339, K340,

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G341, Q342, R344, E345, R355, E356, E357, M358, T359, K360, N361, Q362, L365, T366, K370, N390, Y391, K392, T393, T394, V397, L398, D399, S400, D401, F405, K409, L410, D413 and K414 as numbered by the EU index as set forth in Kabat.

69. The method of claim 68, wherein the amino acid replacement is selected from the group consisting of K338 to any uncharged residue, K338D; K338E; A339D; A339E; A339K; A339R; K340 to any uncharged residue; K340D; K340E; G314D; G314E; G314K; G314R; Q342D; Q342E; Q342K; Q342R; R344 to any uncharged residue; R344D; R344E; E345 to any uncharged residue; E345K; E345R; R355 to any uncharged residue; R355D; R355E; E356 to any uncharged residue; E356K; E356R; E357 to any uncharged residue; E357K; E357R; M358D; M358E; M358K; M358R; T359D; T359E; T359K; T359R; K360 to any uncharged residue; K360D; K360E; N361D; N361E; N361K; N361R; Q362D; Q362E; Q362K; Q362R; L365D; L365E; L365K; L365R; T366D; T366E; T366K; T366R; K370 to any uncharged residue; K370D; K370E; N390D; N390E; N390K; N390R; Y391D; Y391E; Y391K; Y391R; K392 to any uncharged residue; K392D; K392E; T393D; T393E; T393K; T393R; T394D; T394E; T394K; T394R; V397D; V397E; V397K; V397R; L398D; L398E; L398K; L398R; D399 to any uncharged residue; D399K; D399R; S400D; S400E; S400K; S400R; D401 to any uncharged residue; D401K; D401R; F405D; F405E; F405K; F405R; K409 to any uncharged residue; K409D; K409E; L410D; L410E; L410K; L410R; D413 to any uncharged residue; D413K; D413R; K414 to any uncharged residue; K414D; and K414E as numbered by the EU index as set forth in Kabat

70. A multidomain protein produced by the method of claim 64, 65, 66, 67, 68 or 69.

71. An engineered multidomain protein comprising an Fc domain, wherein the Fc domain has been modified to raise or lower the pI.

72. The engineered multidomain protein of claim 71, wherein said modification comprises a replacement at one or more amino acid residues selected from the group consisting of K338, A339, K340, G341, Q342, R344, E345, R355, E356, E357, M358, T359, K360, N361, Q362, L365, T366, K370, N390, Y391, K392, T393,

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T394, V397, L398, D399, S400, D401, F405, K409, L410, D413 and K414 as numbered by the EU index as set forth in Kabat.

73. The engineered multidomain protein of claim 73, wherein the amino acid replacement is selected from the group consisting of K338 to any uncharged residue; K338D; K338E; A339D; A339E; A339K; A339R; K340 to any uncharged residue; K340D; K340E; G314D; G314E; G314K; G314R; Q342D; Q342E; Q342K; Q342R; R344 to any uncharged residue; R344D; R344E; E345 to any uncharged residue; E345K; E345R; R355 to any uncharged residue; R355D; R355E; E356 to any uncharged residue; E356K; E356R; E357 to any uncharged residue; E357K; E357R; M358D; M358E; M358K; M358R; T359D; T359E; T359K; T359R; K360 to any uncharged residue; K360D; K360E; N361D; N361E; N361K; N361R; Q362D; Q362E; Q362K; Q362R; L365D; L365E; L365K; L365R; T366D; T366E; T366K; T366R; K370 to any uncharged residue; K370D; K370E; N390D; N390E; N390K; N390R; Y391D; Y391E; Y391K; Y391R; K392 to any uncharged residue; K392D; K392E; T393D; T393E; T393K; T393R; T394D; T394E; T394K; T394R; V397D; V397E; V397K; V397R; L398D; L398E; L398K; L398R; D399 to any uncharged residue; D399K; D399R; S400D; S400E; S400K; S400R; D401 to any uncharged residue; D401K; D401R; F405D; F405E; F405K; F405R; K409 to any uncharged residue; K409D; K409E; L410D; L410E; L410K; L410R; D413 to any uncharged residue; D413K; D413R; K414 to any uncharged residue; K414D; and K414E as numbered by the EU index as set forth in Kabat.

74. The engineered multidomain protein of claim 71, wherein said pI has been lowered.

75. The engineered multidomain protein of claim 74, wherein said modification comprises a replacement at one or more amino acid residues selected from the group consisting of A339, G341, Q342, E345, E356, E357, M358, T359, N361, Q362, L365, T366, N390, Y391, T393, T394, V397, L398, D399, S400, D401, F405, L410 and D413 as numbered by the EU index as set forth in Kabat.

76. The engineered multidomain protein of claim 75, wherein the amino acid replacement is selected from the group consisting of A339K; A339R; G314K; G314R; Q342K; Q342R; E345 to any uncharged residue; E345K; E345R; E356 to any uncharged residue; E356K; E356R; E357 to any uncharged residue; E357K; E357R; M358K;

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M358R; T359K; T359R; N361K; N361R; Q362K; Q362R; L365K; L365R; T366K; T366R; N390K; N390R; Y391K; Y391R; T393K; T393R; T394K; T394R; V397K; V397R; L398K; L398R; D399 to any uncharged residue; D399K; D399R; S400K; S400R; D401 to any uncharged residue; D401K; D401R; F405K; F405R; L410K; L410R; D413 to any uncharged residue; D413K; and D413R as numbered by the EU index as set forth in Kabat

77. The engineered multidomain protein of claim 71, wherein said pI has been raised.

78. The engineered multidomain protein of claim 77, wherein said modification comprises a replacement at one or more amino acid residues selected from the group consisting of K338, A339, K340, G341, Q342, R344, R355, M358, T359, K360, N361, Q362, L365, T366, K370, N390, Y391, K392, T393, T394, V397, L398, S400, F405, K409, L410, and K414 as numbered by the EU index as set forth in Kabat.

79. The engineered multidomain protein of claim 78, wherein said modification comprises a replacement at one or more amino acid residues selected from the group consisting of K338 to any uncharged residue; K338D; K338E; A339D; A339E; K340 to any uncharged residue; K340D; K340E; G314D; G314E; Q342D; Q342E; R344 to any uncharged residue; R344D; R344E; R355 to any uncharged residue; R355D; R355E; M358D; M358E; T359D; T359E; K360 to any uncharged residue; K360D; K360E; N361D; N361E; Q362D; Q362E; L365D; L365E; T366D; K370 to any uncharged residue; K370D; K370E; N390D; N390E; Y391D; Y391E; K392 to any uncharged residue; K392D; K392E; T393D; T393E; T394D; T394E; V397D; V397E; L398D; L398E; S400D; S400E; F405D; F405E; K409 to any uncharged residue; K409D; K409E; L410D; L410E; K414 to any uncharged residue; K414D; and K414E as numbered by the EU index as set forth in Kabat.

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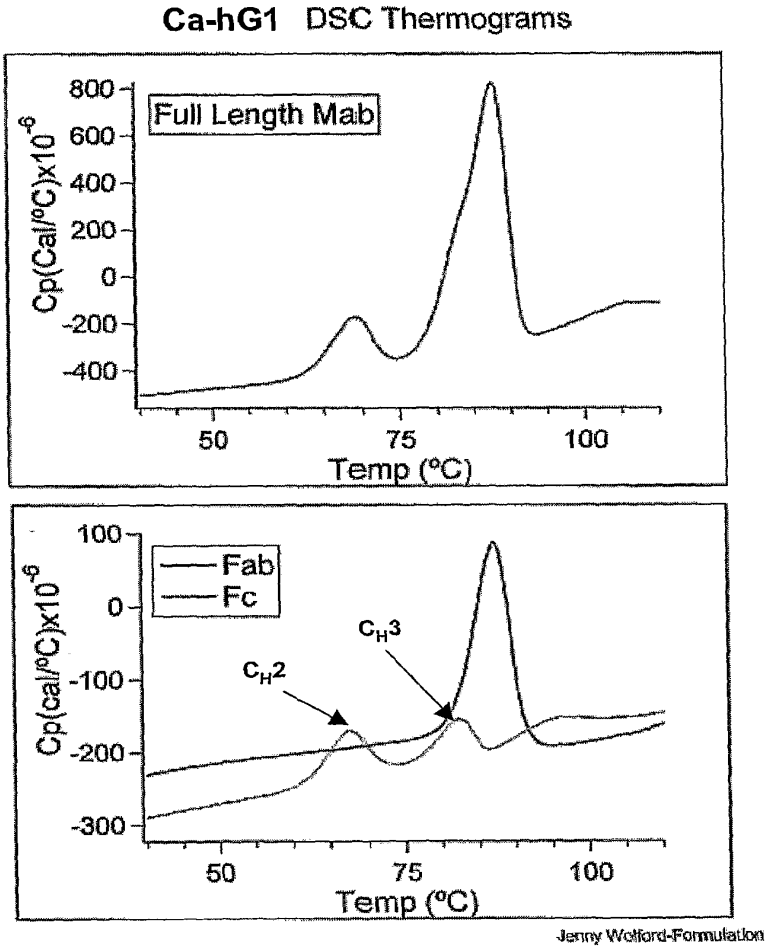

Ca-hG1 DSC Thermograms
Full Length Mab
Cp(Cal/°C)x10⁻⁶
800
600
400
200
0
-200
-400
50
75
100
Temp (°C)
Fab
Fc
C_H2
C_H3
Cp(cal/°C)x10⁻⁶
100
0
-100
-200
-300
50
75
100
Temp (°C)
Jenny Wolford-Formulation

Fig. 1

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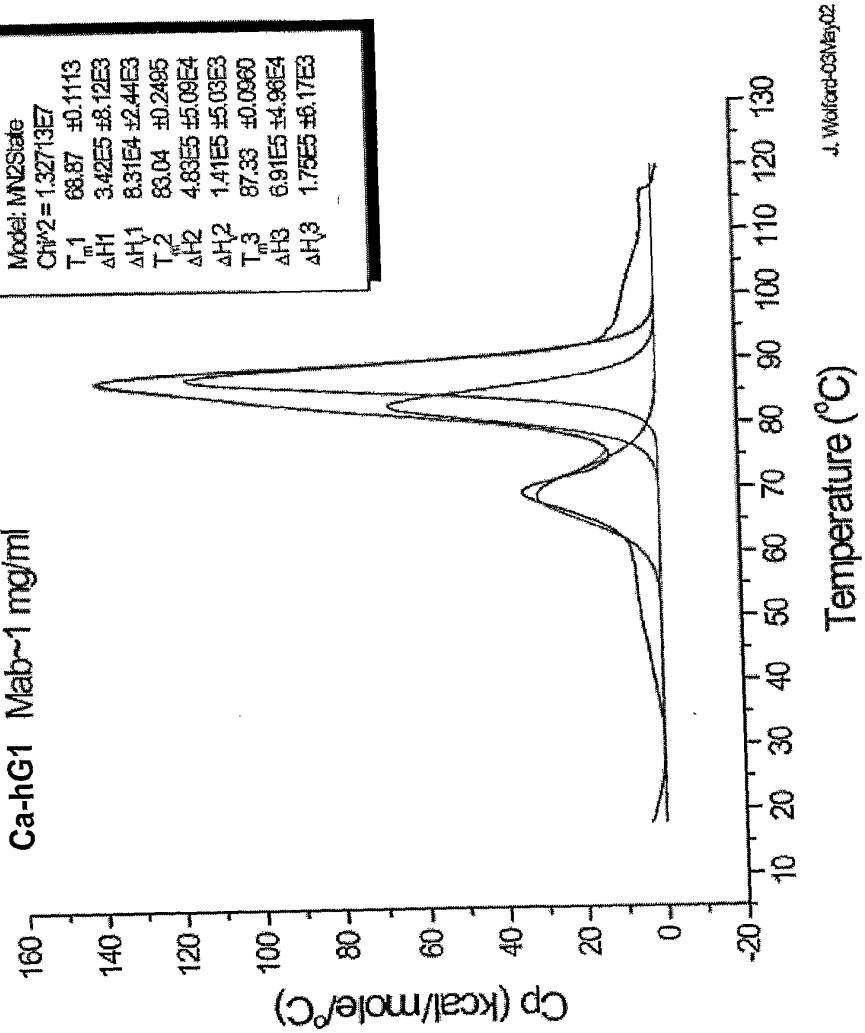


Fig. 2

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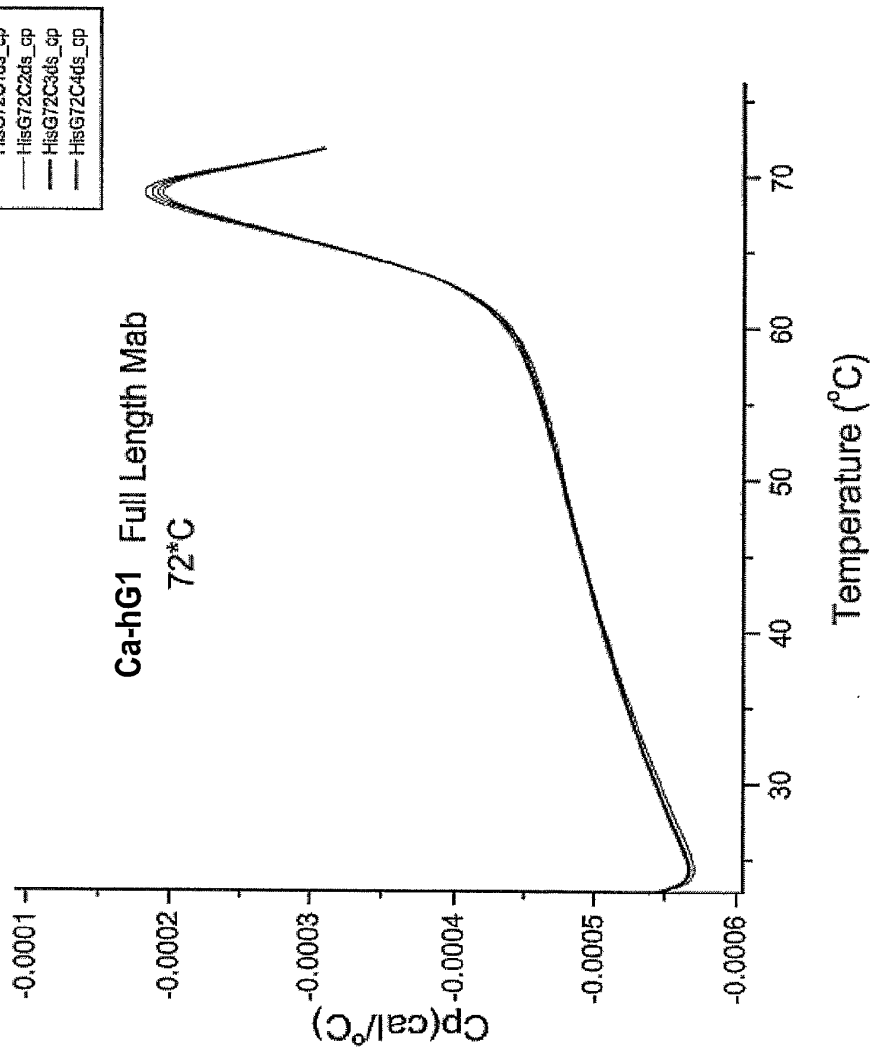


Fig. 3

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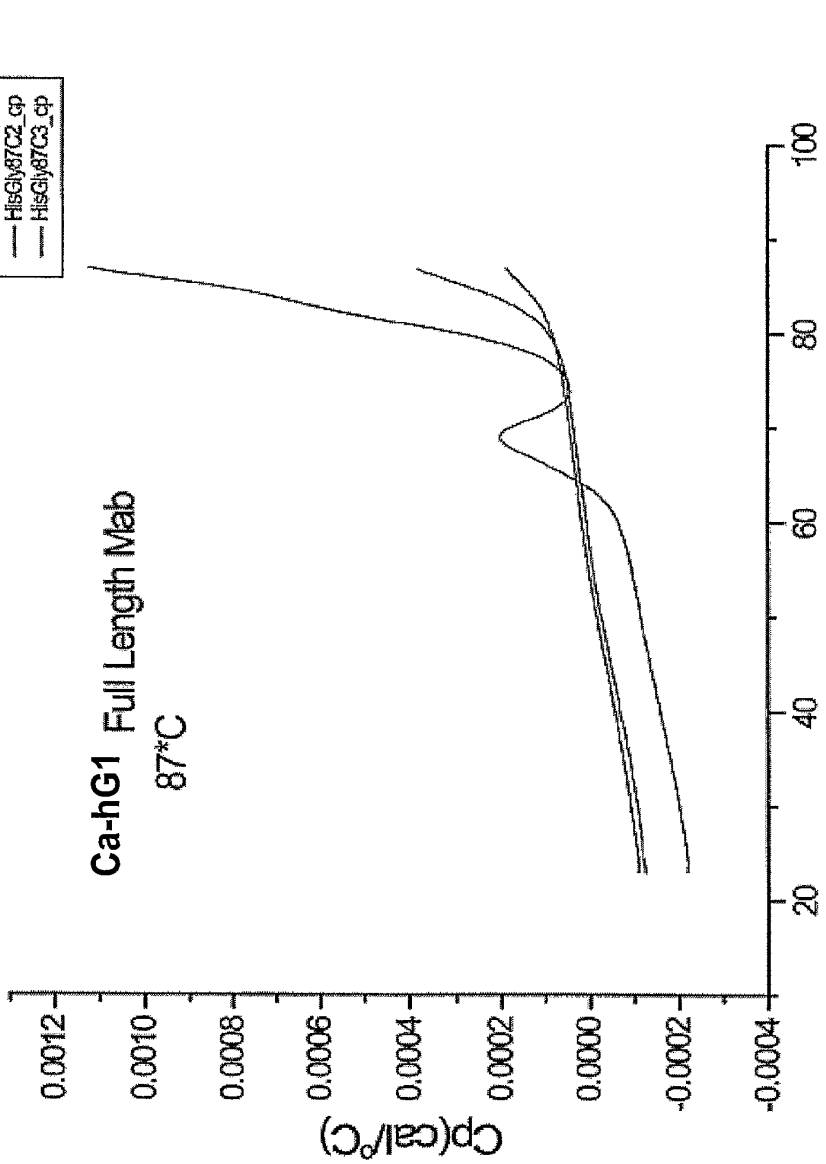


Fig. 4

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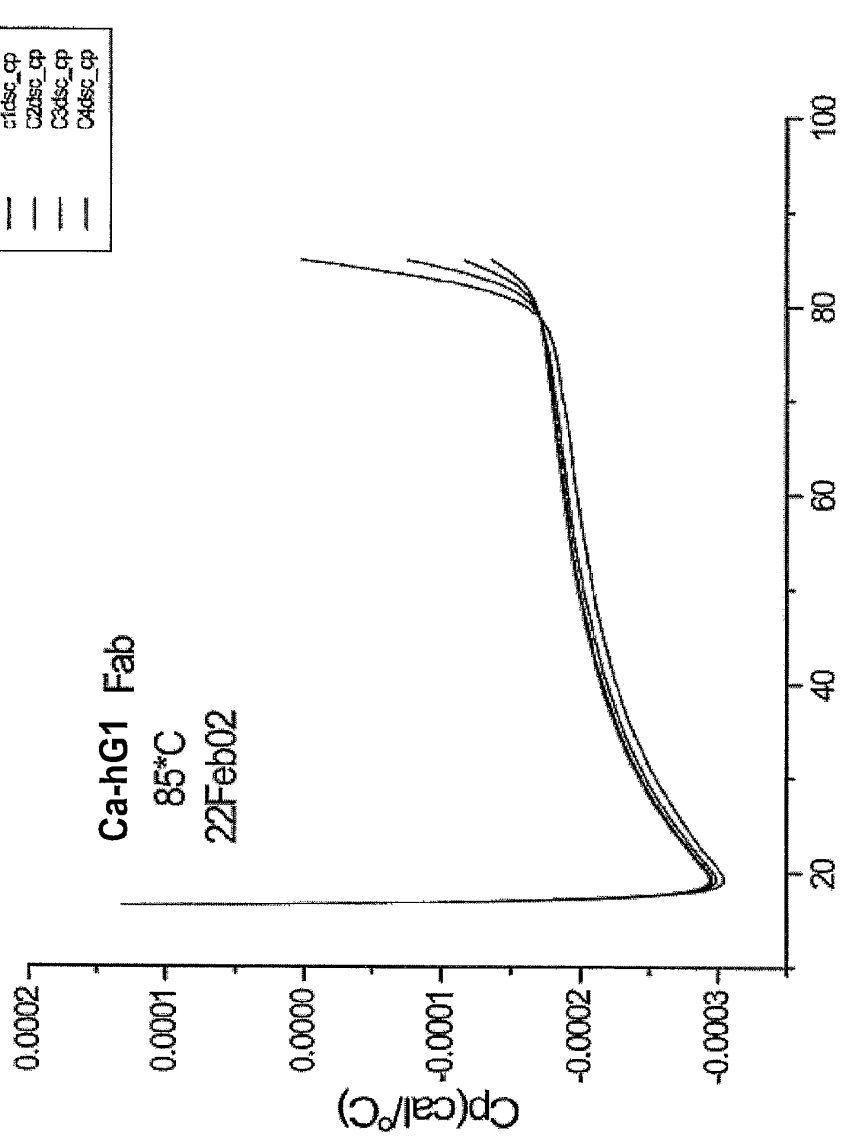


Fig. 5

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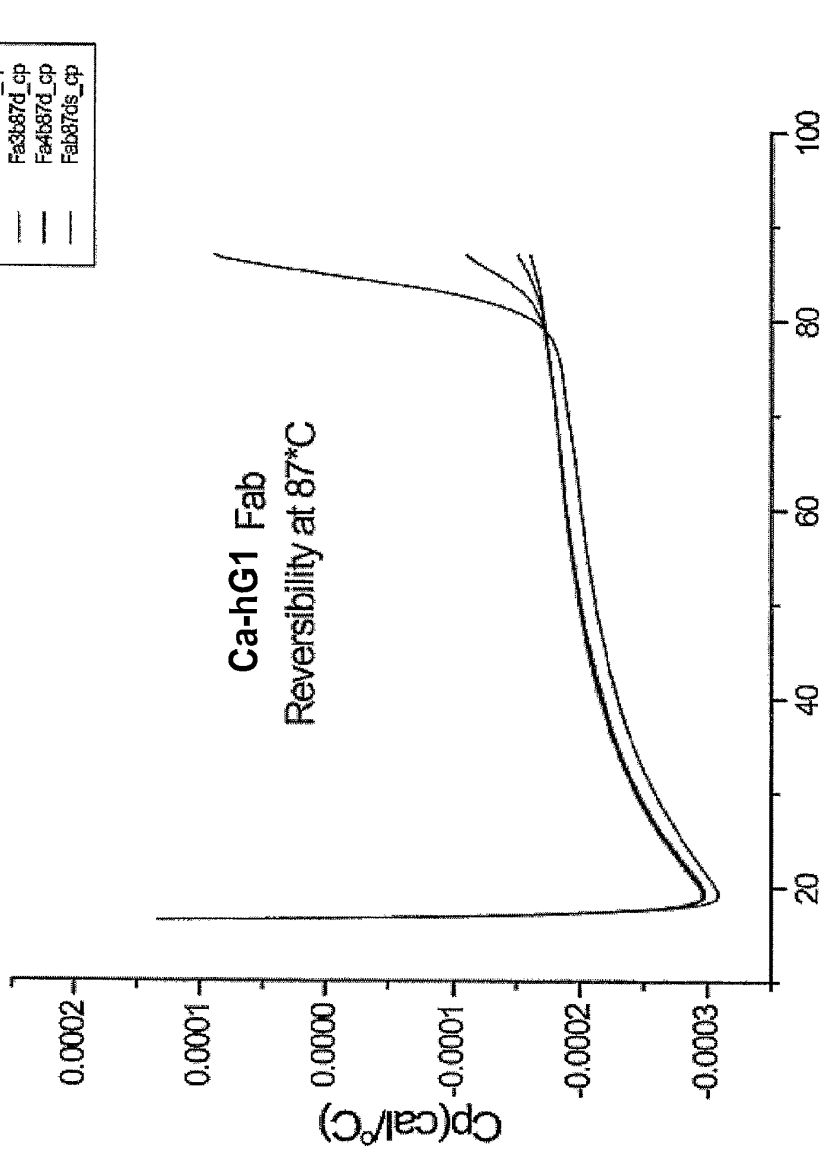


Fig. 6

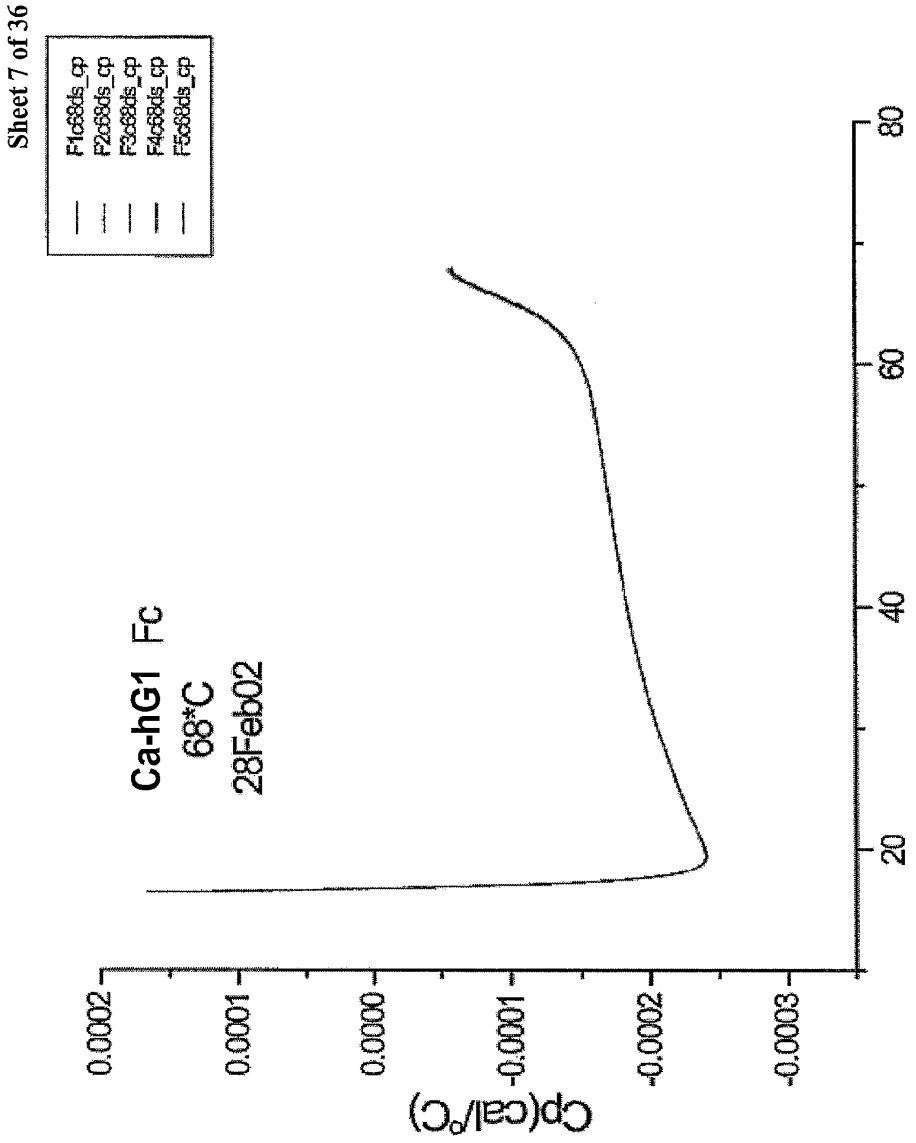

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F2c68ds_cp
F3c68ds_cp
F4c68ds_cp
F5c68ds_cp
Ca-hG1 Fc
68*C
28Feb02
Cp(cal/°C)
0.0002
0.0001
0.0000
-0.0001
-0.0002
-0.0003
20
40
60
80
Temperature (°C)

Fig. 7

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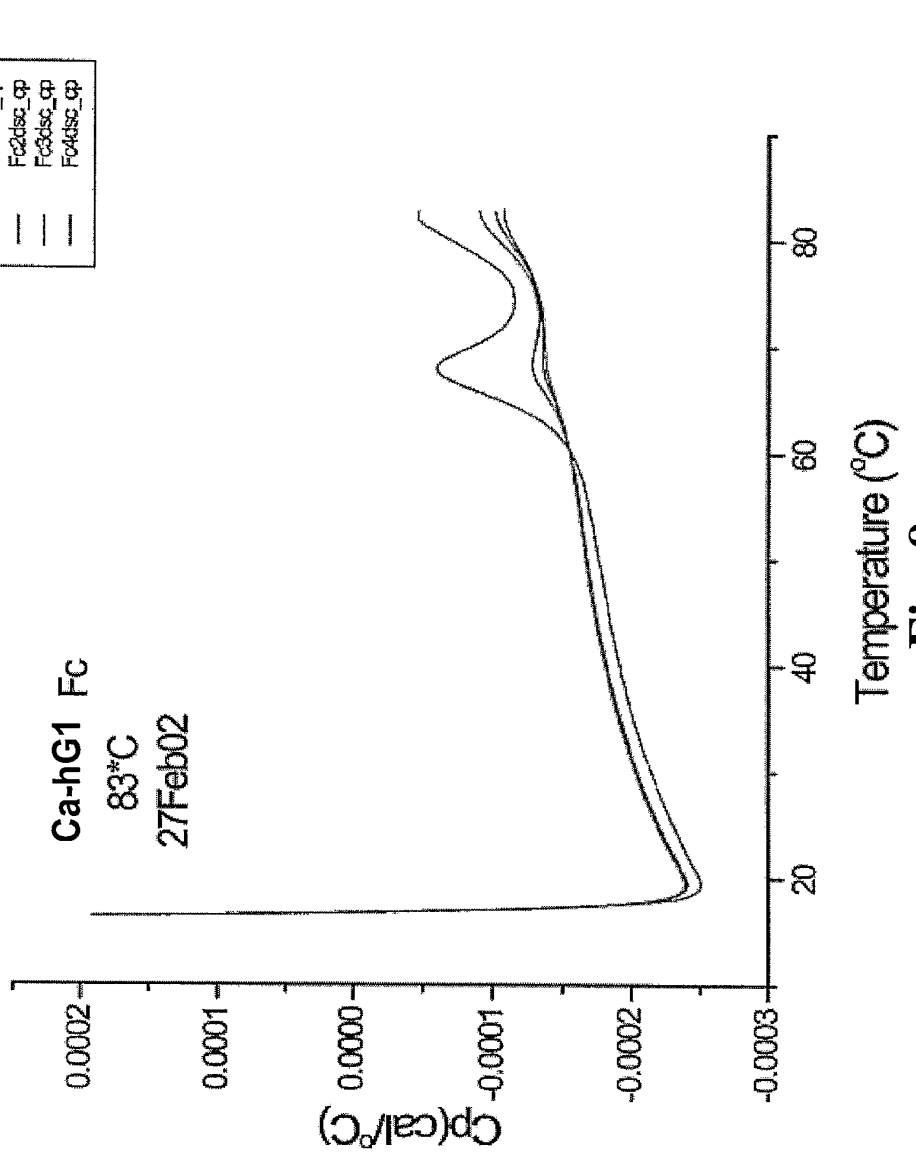


Fig. 8

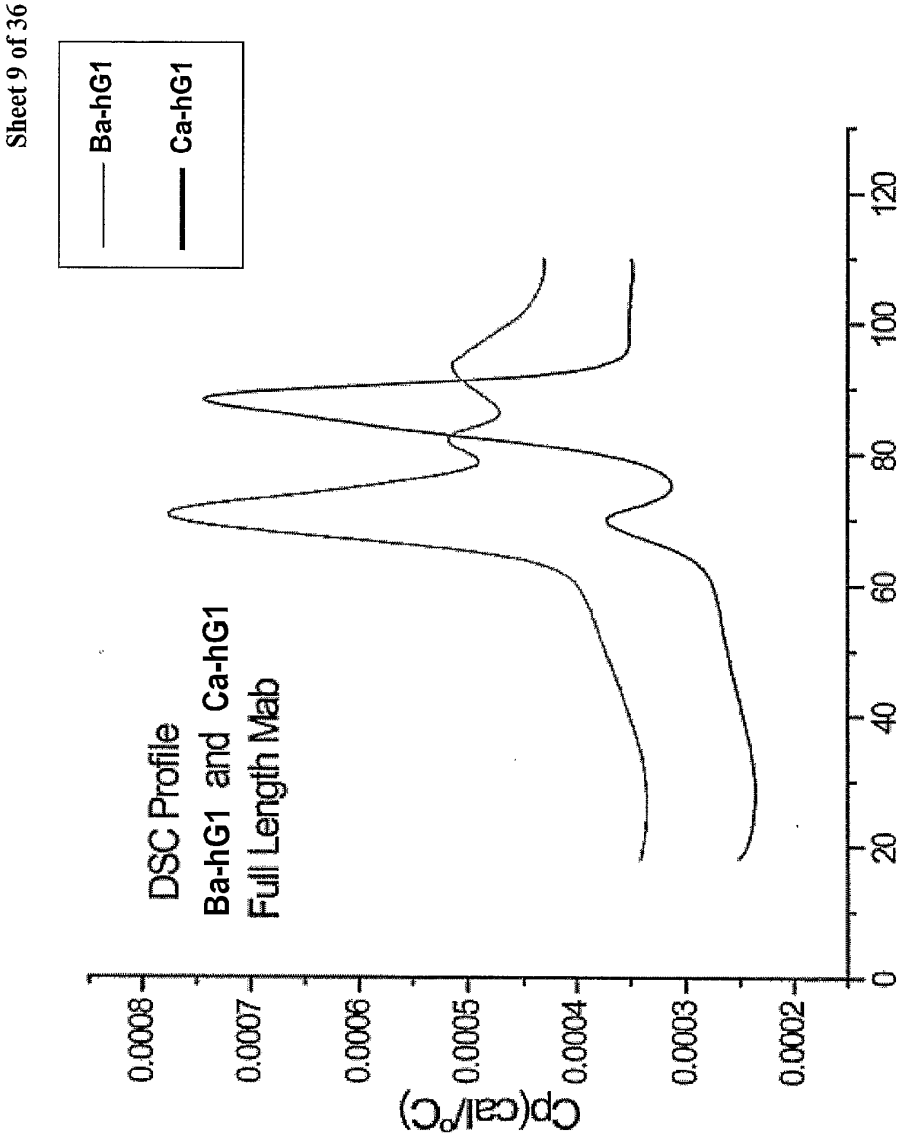

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Ba-hG1
Ca-hG1
DSC Profile
Ba-hG1 and Ca-hG1
Full Length Mab
Cp(cal/°C)
0.0008
0.0007
0.0006
0.0005
0.0004
0.0003
0.0002
0
20
40
60
80
100
120
Temperature (°C)

Fig. 9

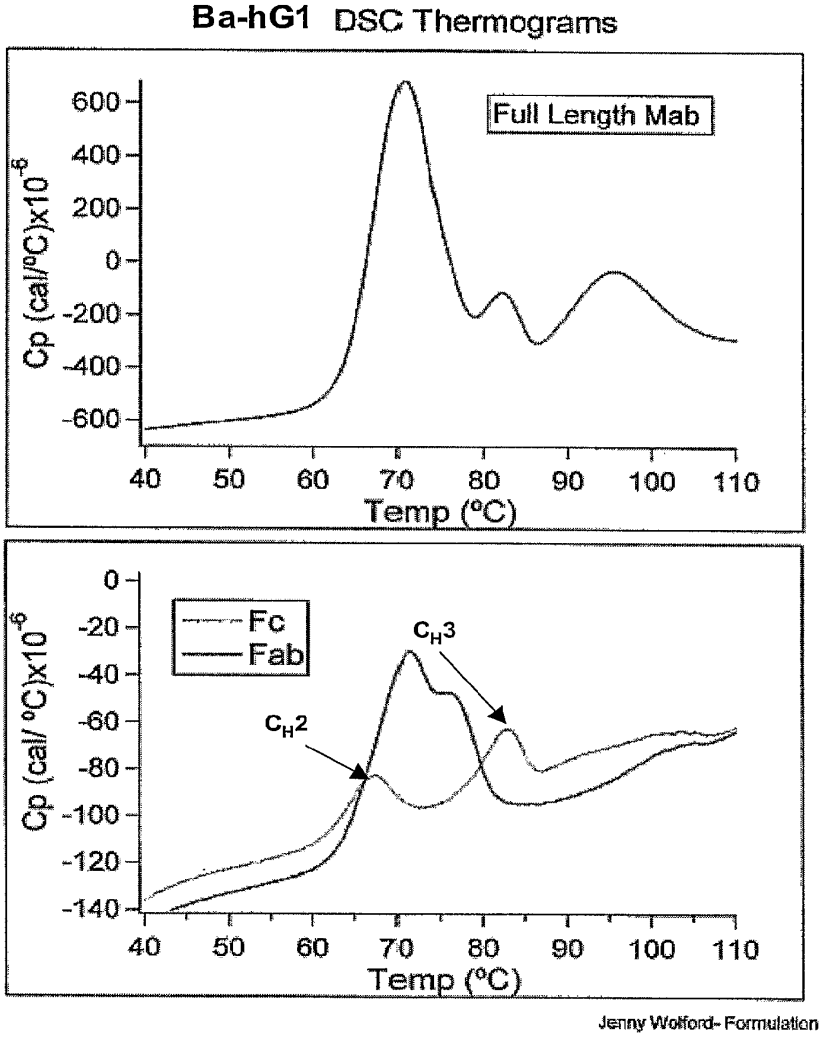

Ba-hG1 DSC Thermograms
Full Length Mab
Cp (cal/°C)x10-6
600
400
200
0
-200
-400
-600
40
50
60
70
80
90
100
110
Temp (°C)
Fc
Fab
CH3
CH2
Cp (cal/ °C)x10-6
0
-20
-40
-60
-80
-100
-120
-140
Temp (°C)
Jenny Wolford- Formulation

Fig. 10

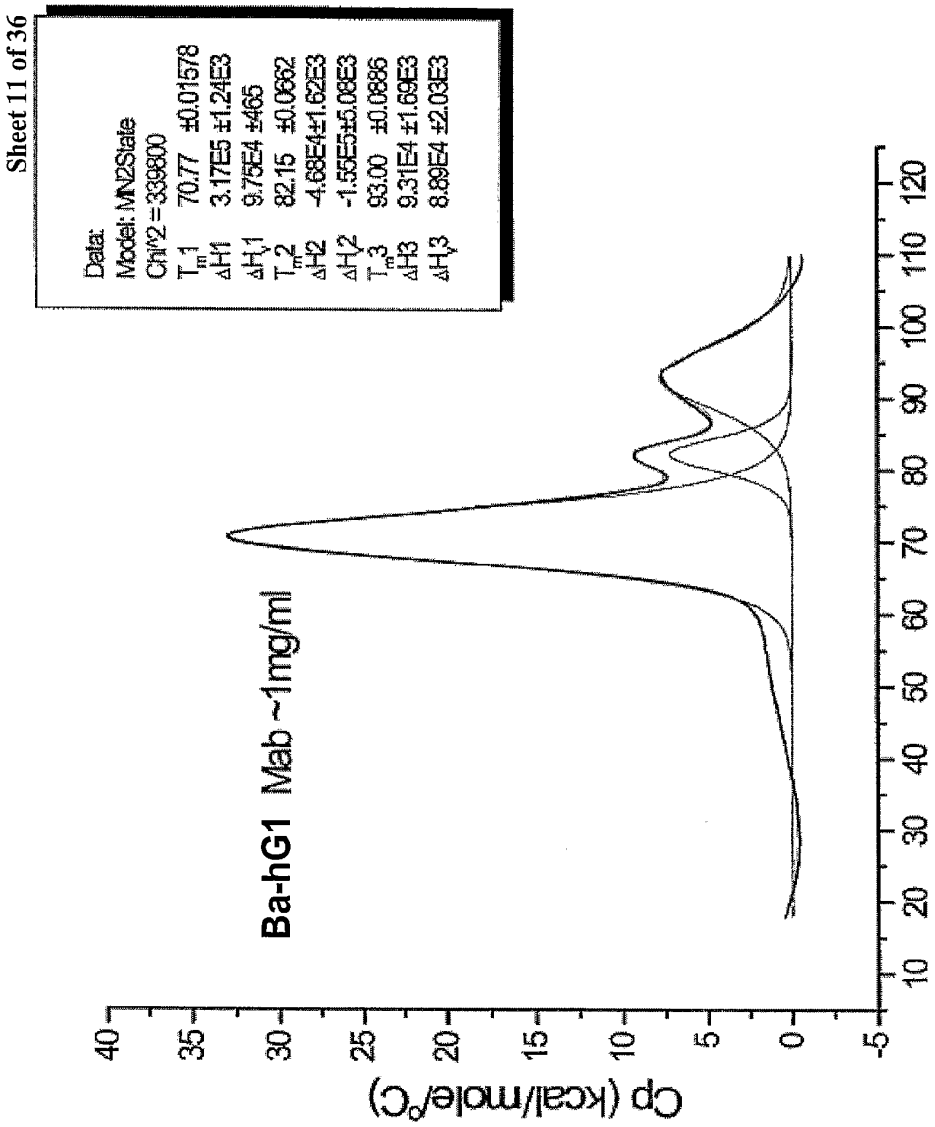

Sheet 11 of 36
Data:
Model: MN2State
Chi^2 = 339800
Tm1 70.77 ±0.01578
ΔH1 3.17E5 ±1.24E3
ΔHv1 9.75E4 ±465
Tm2 82.15 ±0.0662
ΔH2 -4.68E4±1.62E3
ΔHv2 -1.55E5±5.08E3
Tm3 93.00 ±0.0886
ΔH3 9.31E4 ±1.69E3
ΔHv3 8.89E4 ±2.03E3
Ba-hG1 Mab ~1mg/ml
Cp (kcal/mole/°C)
Temperature (°C)
40
35
30
25
20
15
10
5
0
-5
10
20
30
40
50
60
70
80
90
100
110
120

Fig. 11

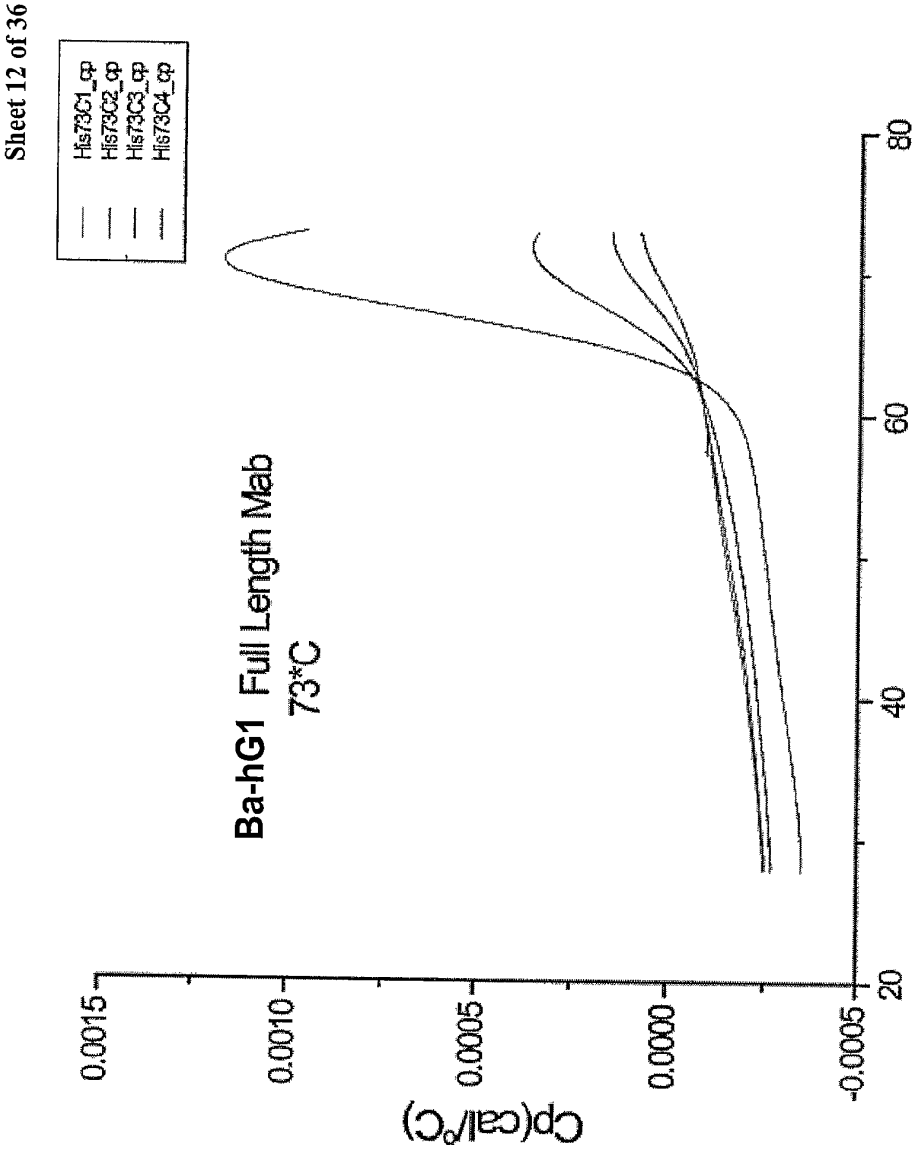

Sheet 12 of 36
His73C1_cp
His73C2_cp
His73C3_cp
His73C4_cp
Ba-hG1 Full Length Mab
73*C
Cp(cal/°C)
0.0015
0.0010
0.0005
0.0000
-0.0005
20
40
60
80
Temperature (°C)

Fig. 12

Sheet 13 of 36

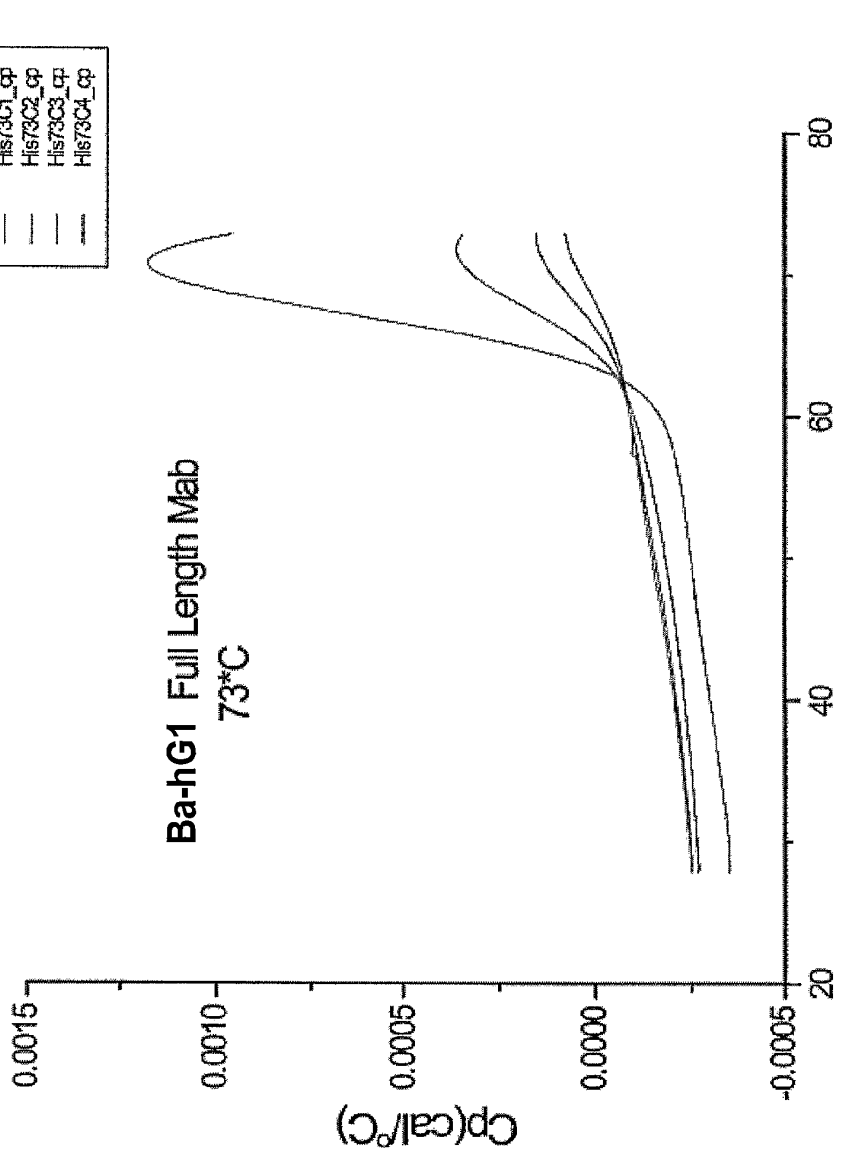


Fig. 13

Sheet 14 of 36

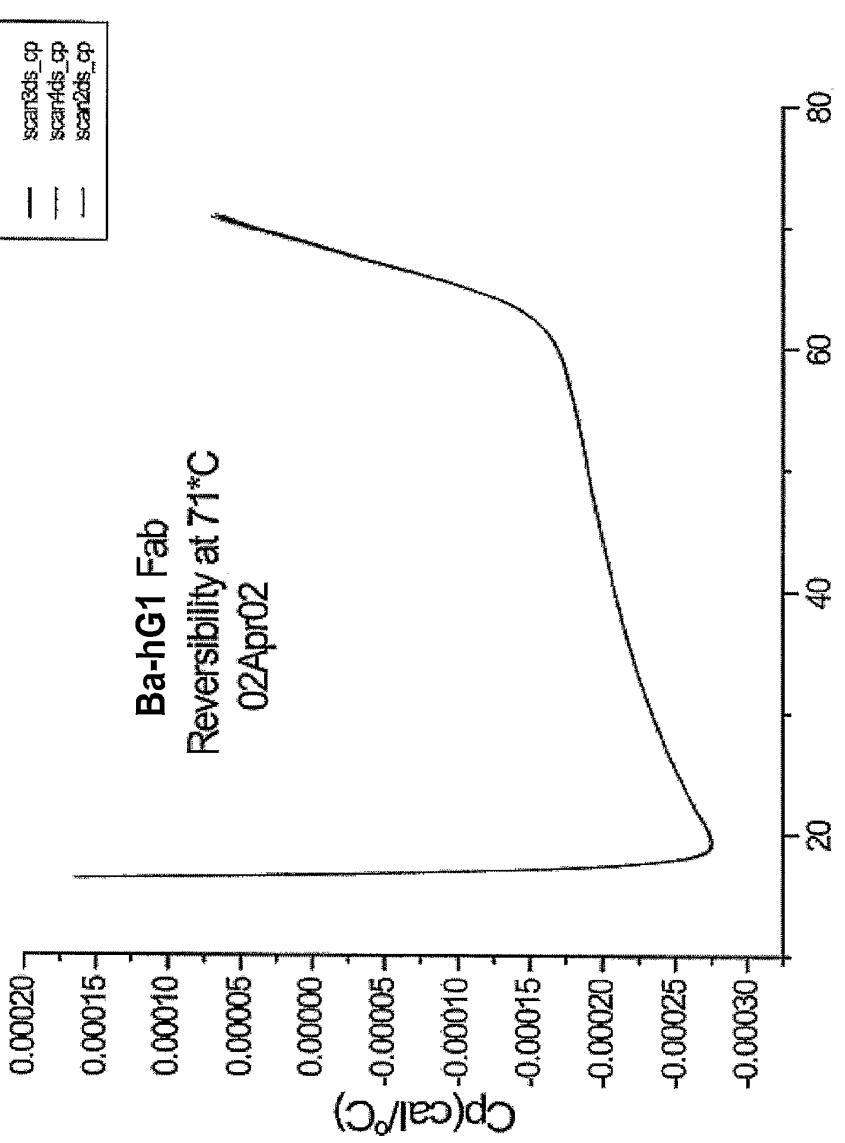


Fig. 14

Sheet 15 of 36

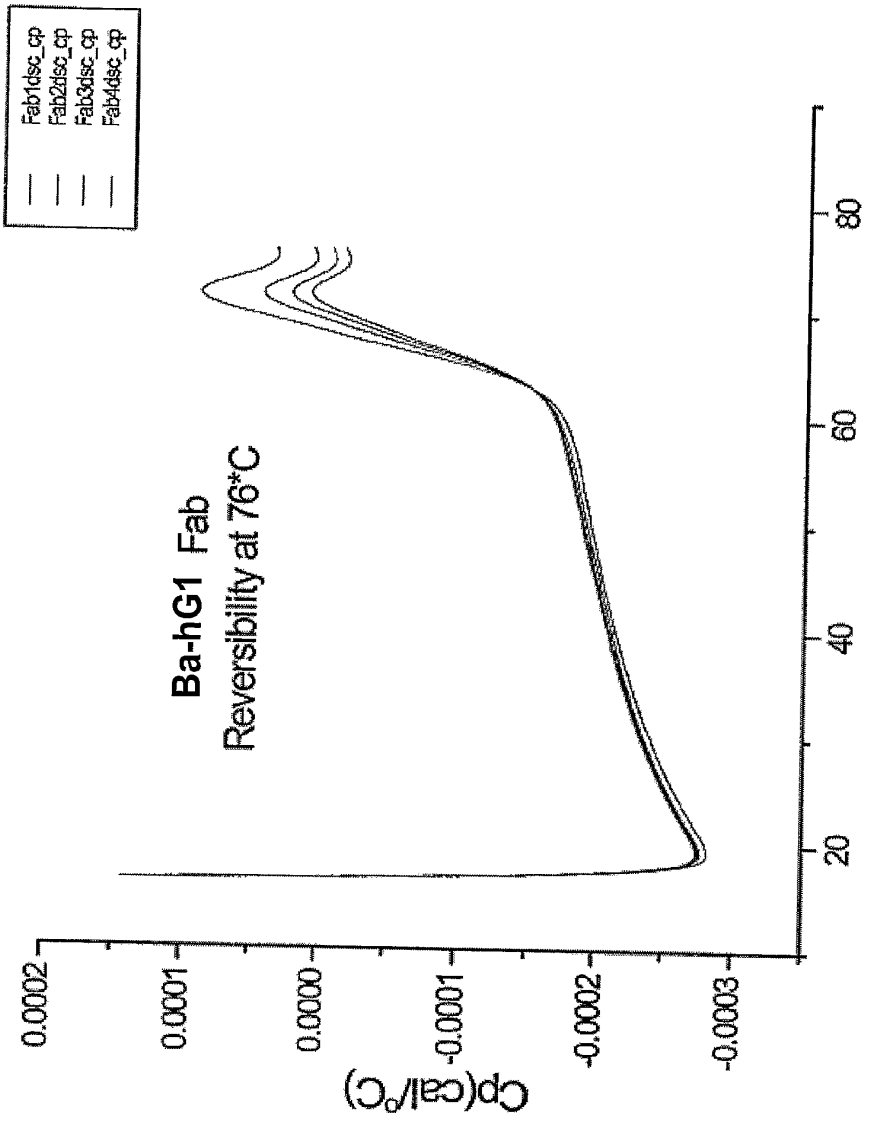


Fig. 15

Sheet 16 of 36

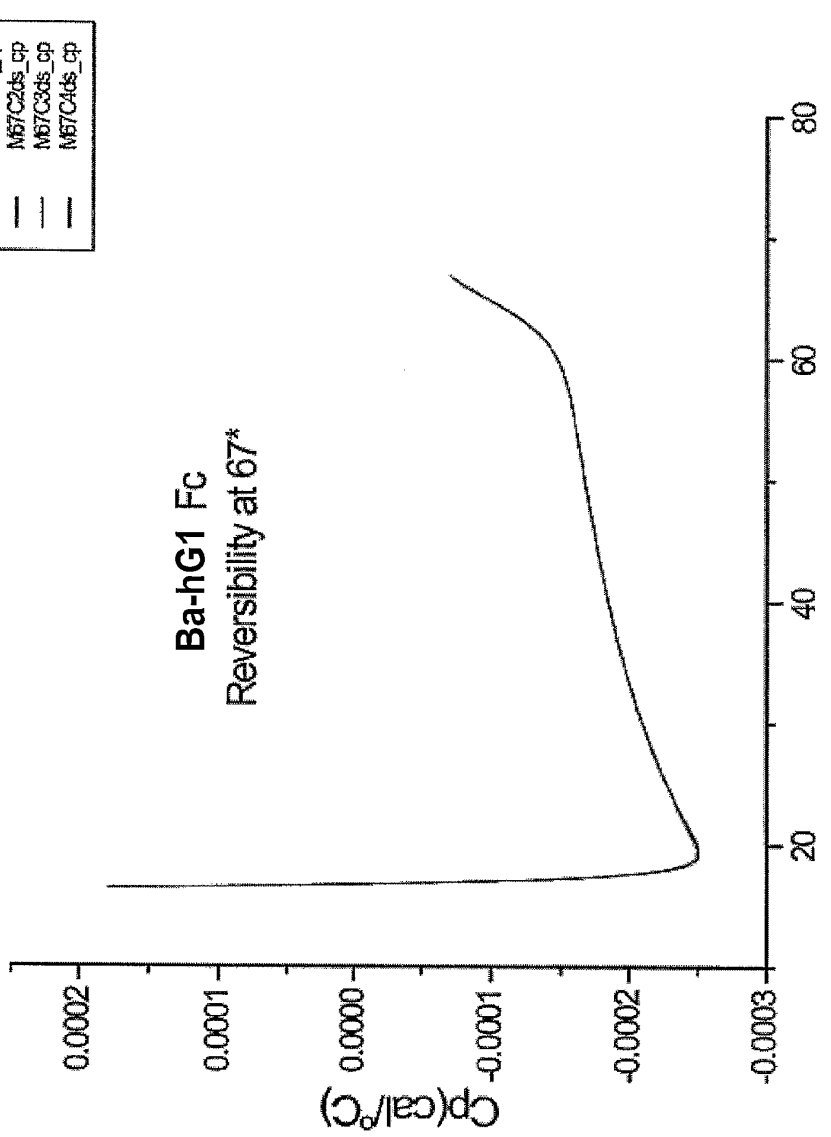


Fig. 16

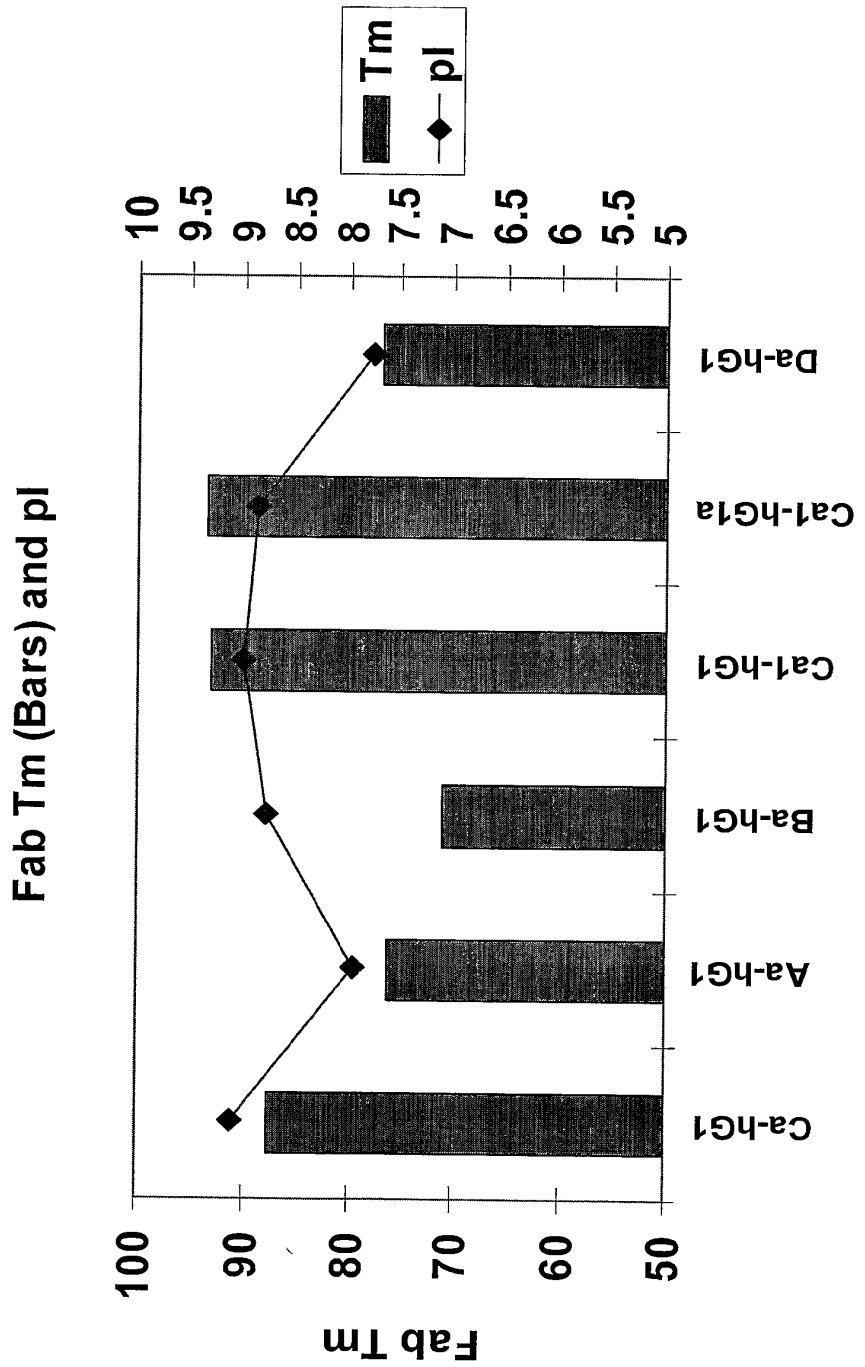

Fab Tm (Bars) and pI
Fab Tm
Tm
pI
100
90
80
70
60
50
10
9.5
9
8.5
8
7.5
7
6.5
6
5.5
5
Ca-hG1
Aa-hG1
Ba-hG1
Ca1-hG1
Ca1-hG1a
Da-hG1

Fig. 17

Sheet 18 of 36

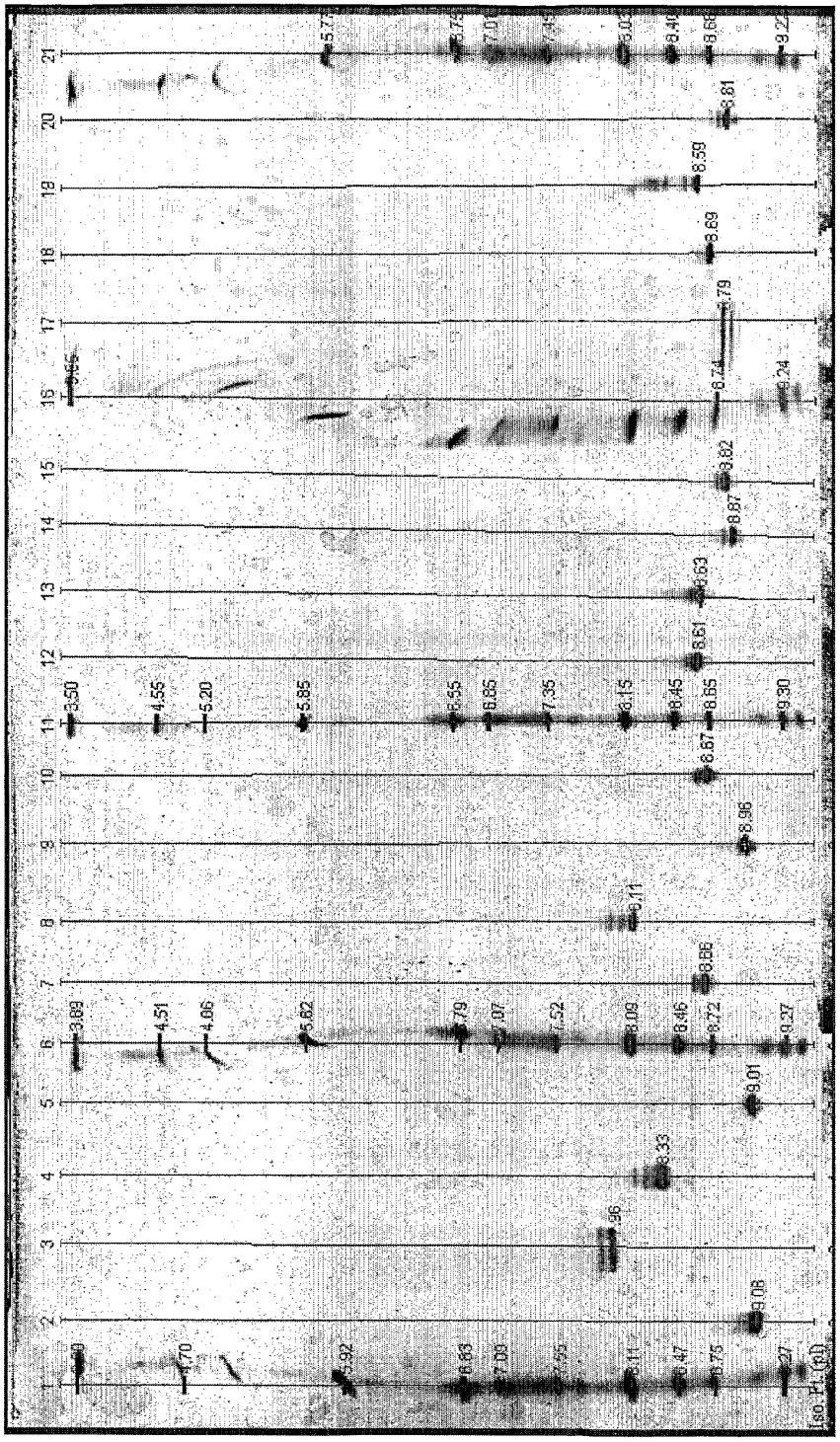


Fig. 18A

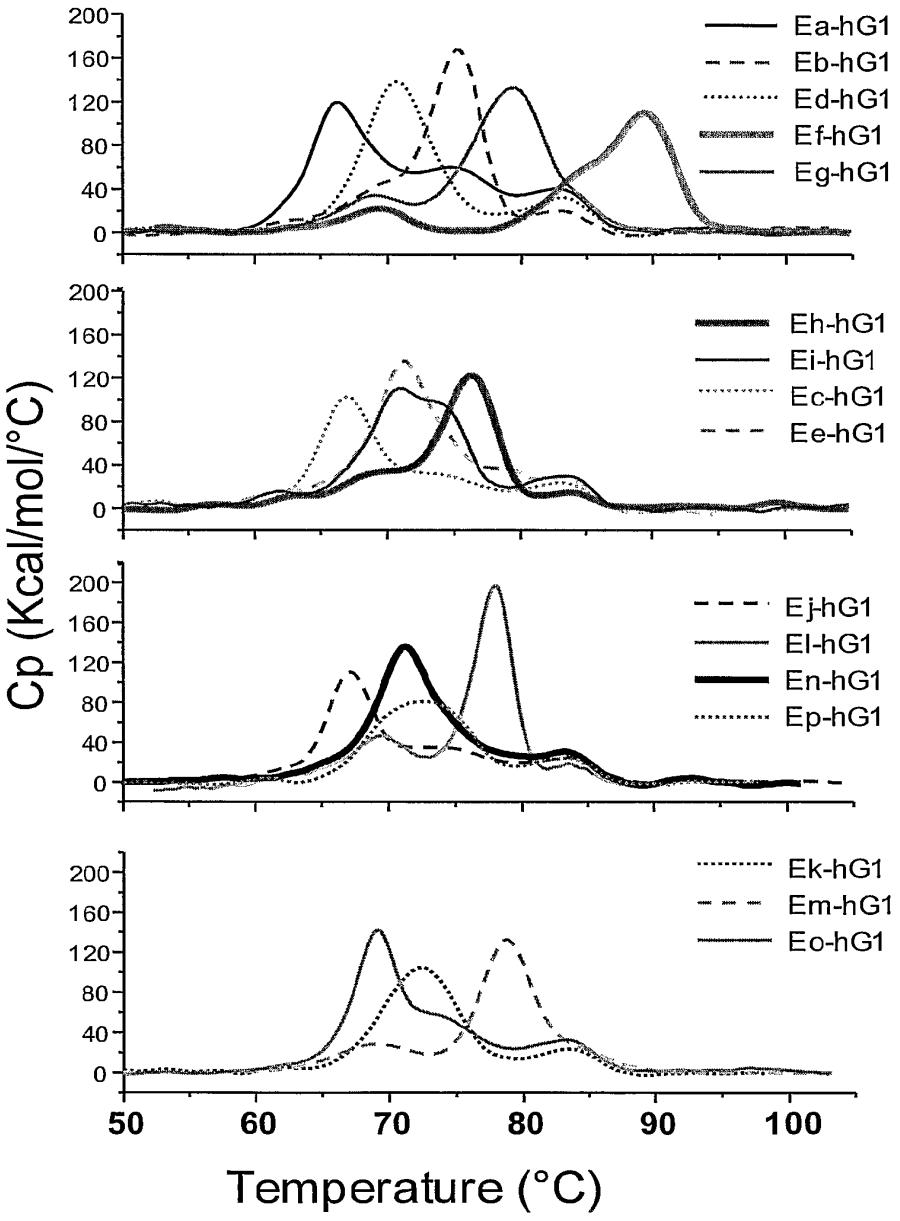

Cp (Kcal/mol/°C)
Temperature (°C)
Ea-hG1
Eb-hG1
Ed-hG1
Ef-hG1
Eg-hG1
Eh-hG1
Ei-hG1
Ec-hG1
Ee-hG1
Ej-hG1
El-hG1
En-hG1
Ep-hG1
Ek-hG1
Em-hG1
Eo-hG1

Fig. 18B

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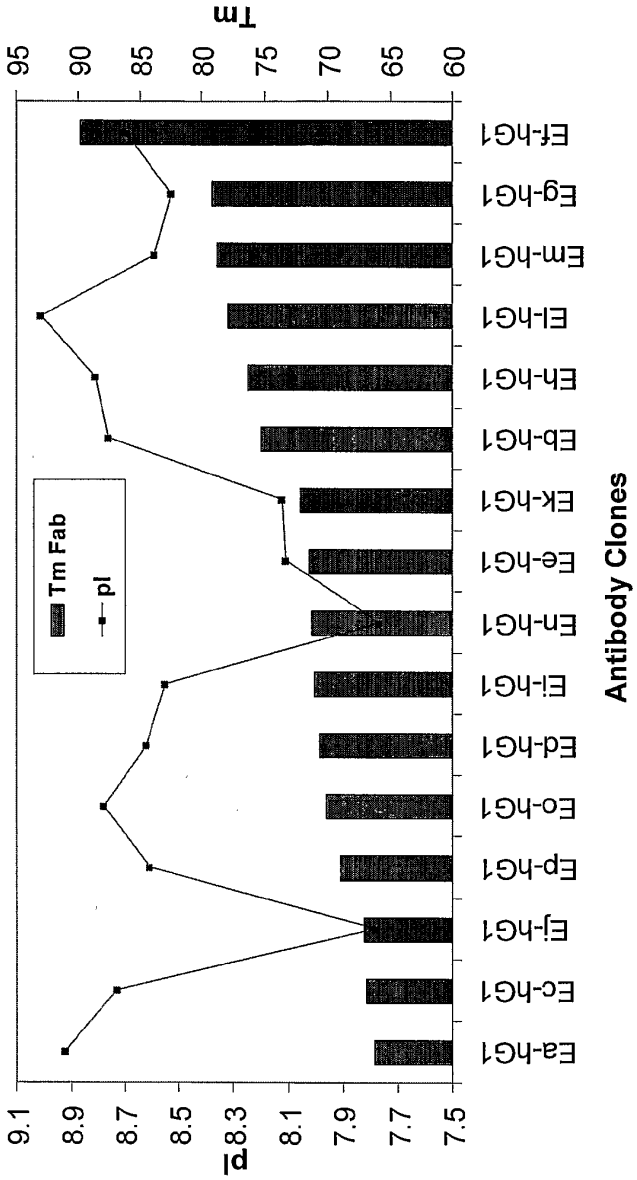


Fig. 18C

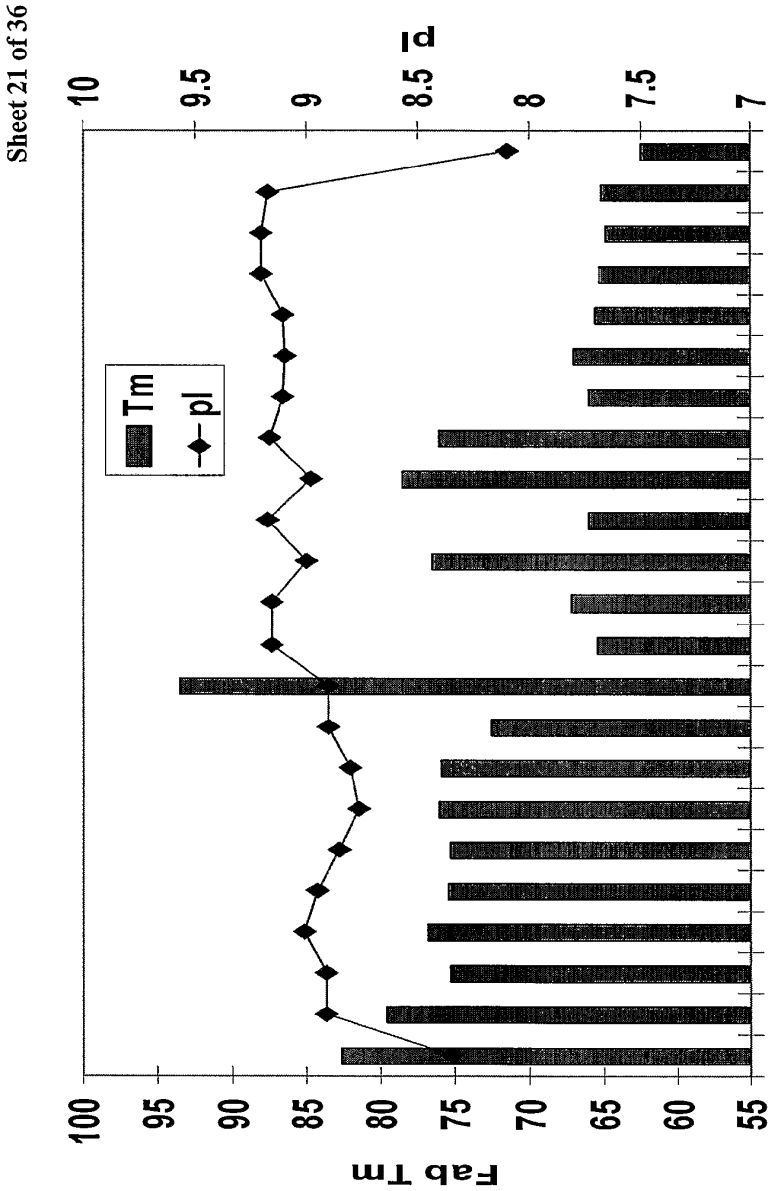

Fab Tm
100
95
90
85
80
75
70
65
60
55
pI
10
9.5
9
8.5
8
7.5
7
Tm
pI
Fc1-hG1
Fb2-hG1
Fb1-hG1
Ga-hG1
Fb2-hG1
Fa11-hG1
Fa12-hG1
Fa13-hG1
Fa14-hG1
Ca1-hG1a
Fa5-hG1
Fa10-hG1
Fb-hG1
Fa4-hG1
Ha-hG1
Ia-hG1
Fa7-hG1
Fa8-hG1
Fa9-hG1
Fa1-hG1
Fa2-hG1
Fa3-hG1
Fa-hG1

Fig. 19

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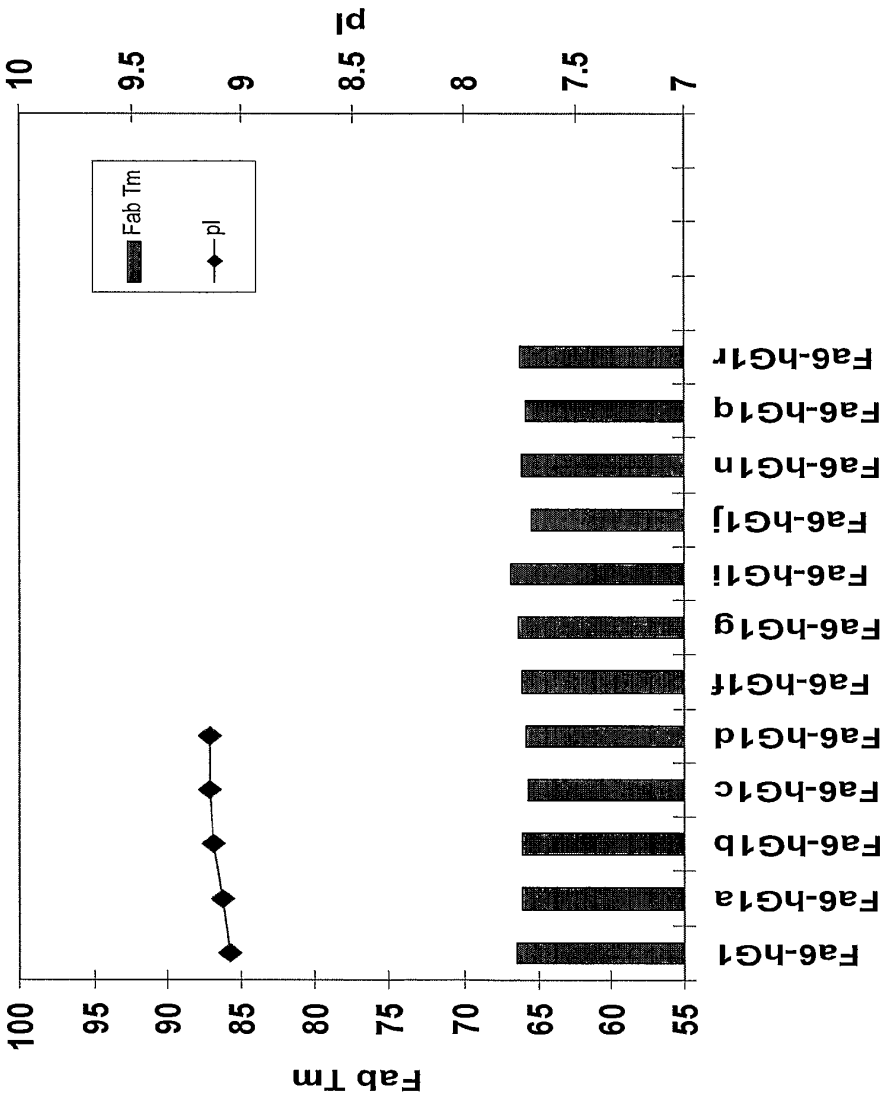


Fig. 20

Sheet 23 of 36

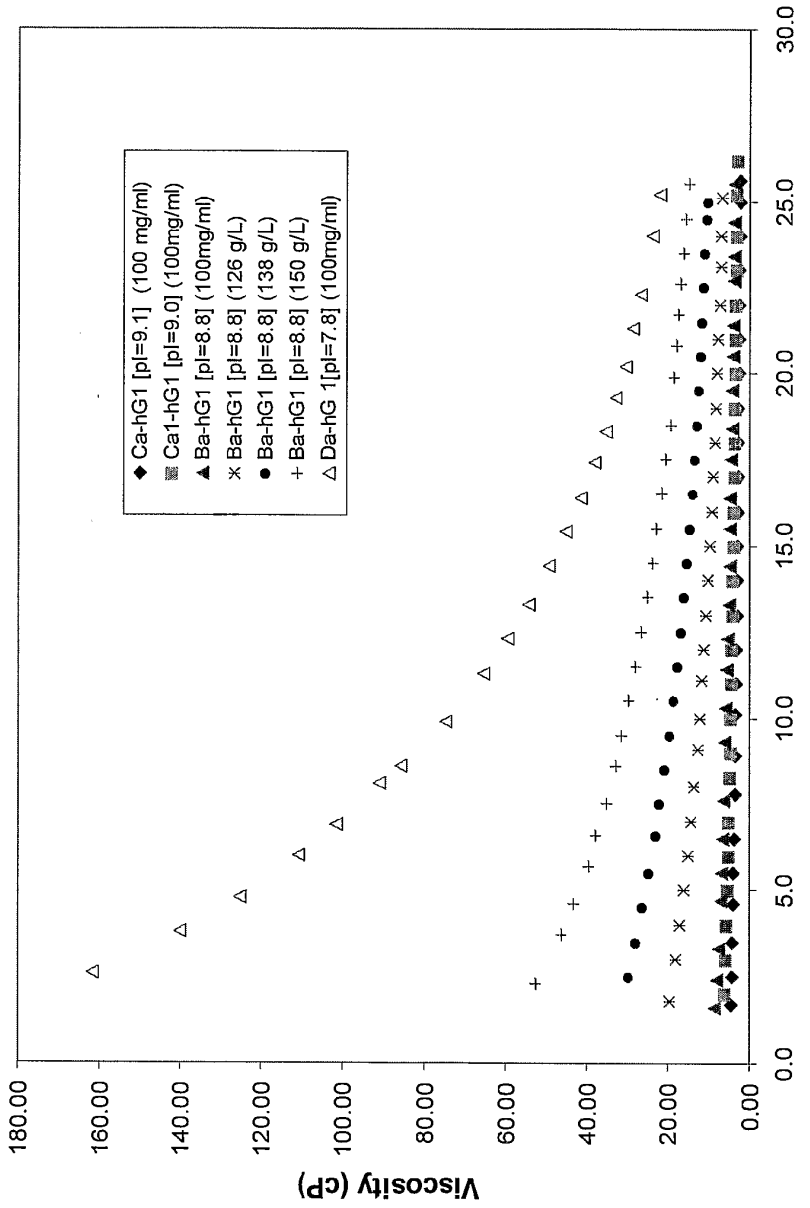


Fig. 21

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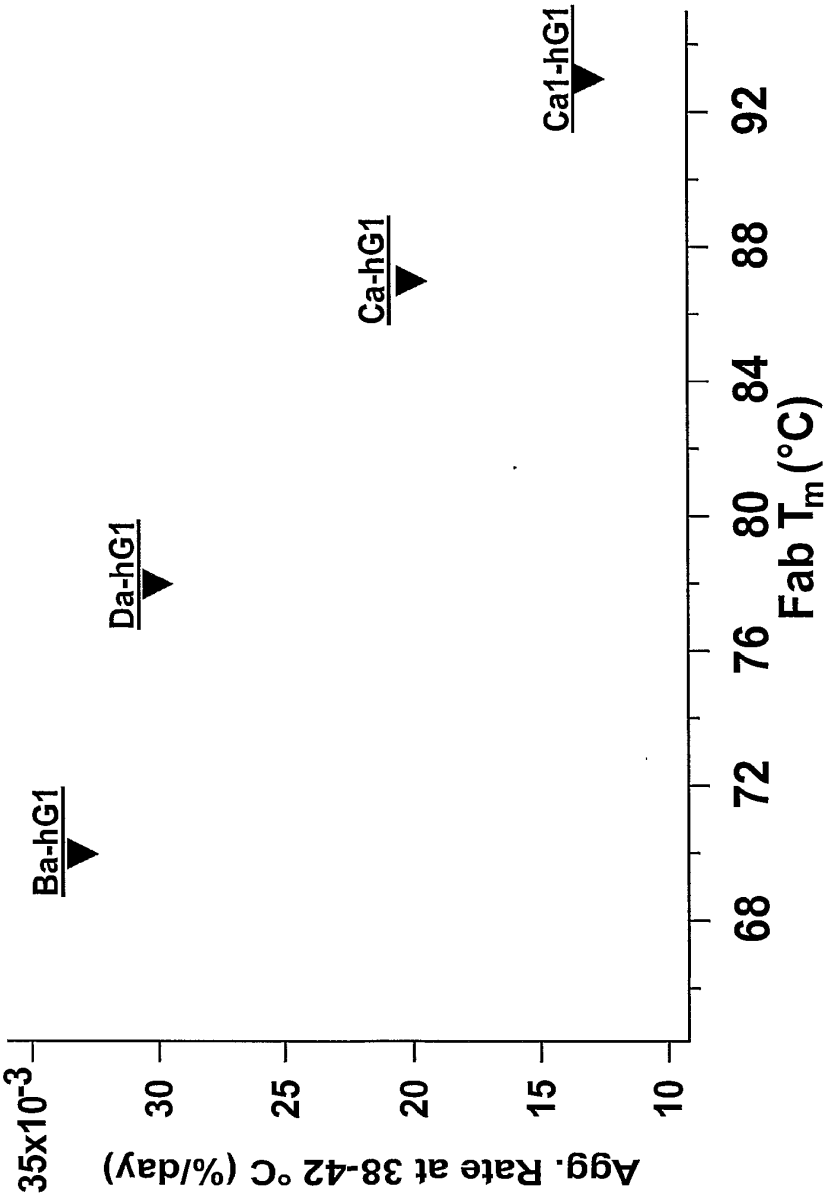


Fig. 22A

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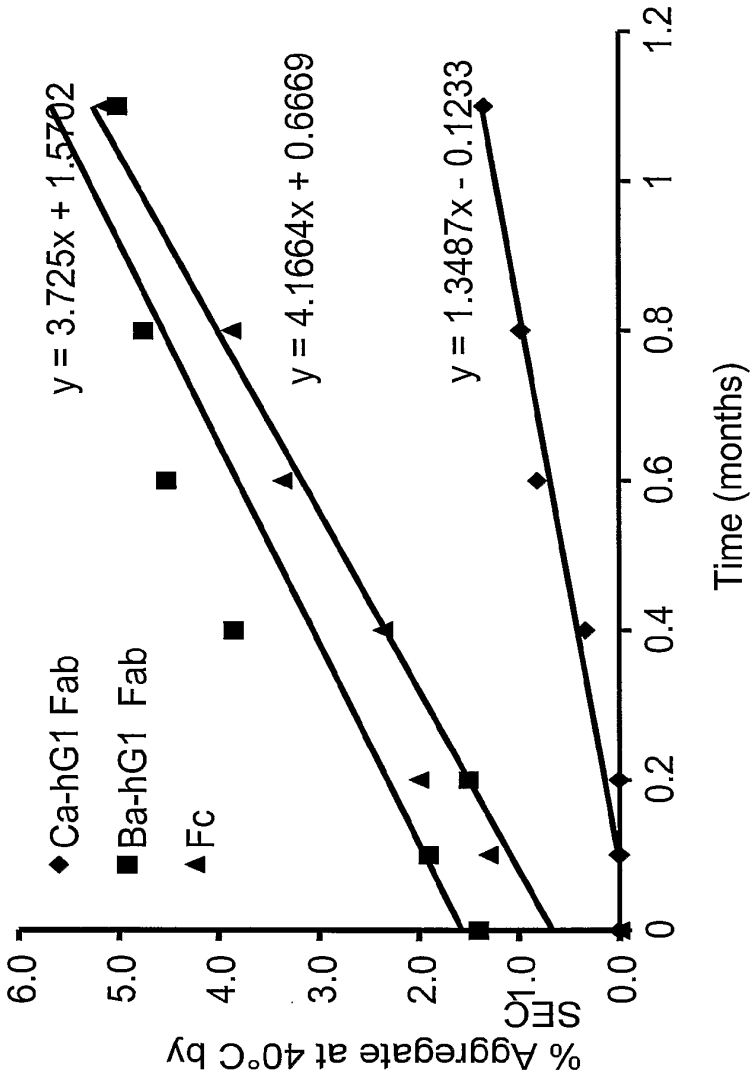


Fig. 22B

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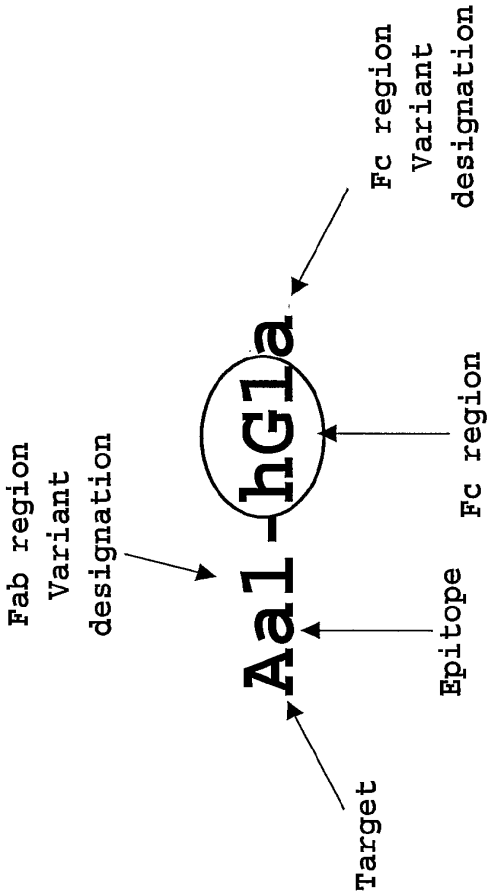


Fig. 23

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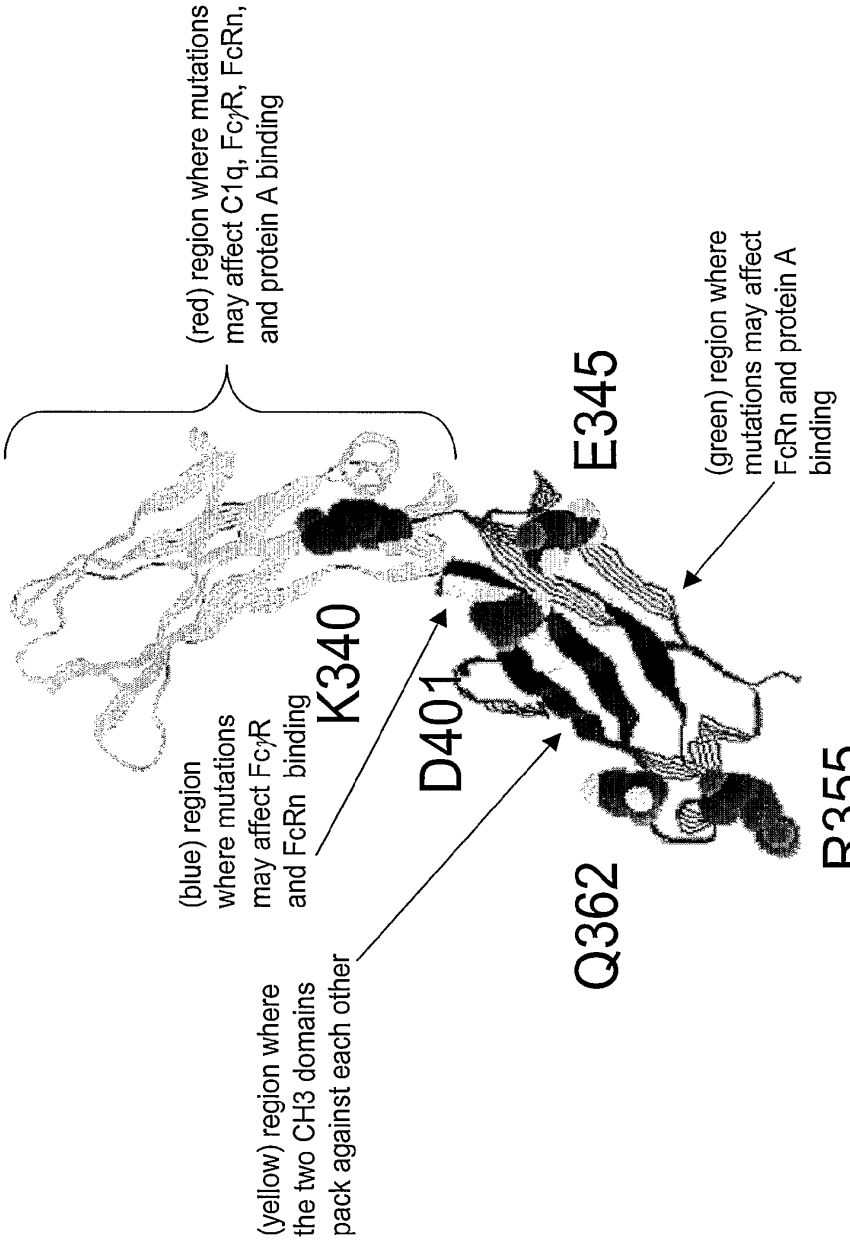


Fig. 24

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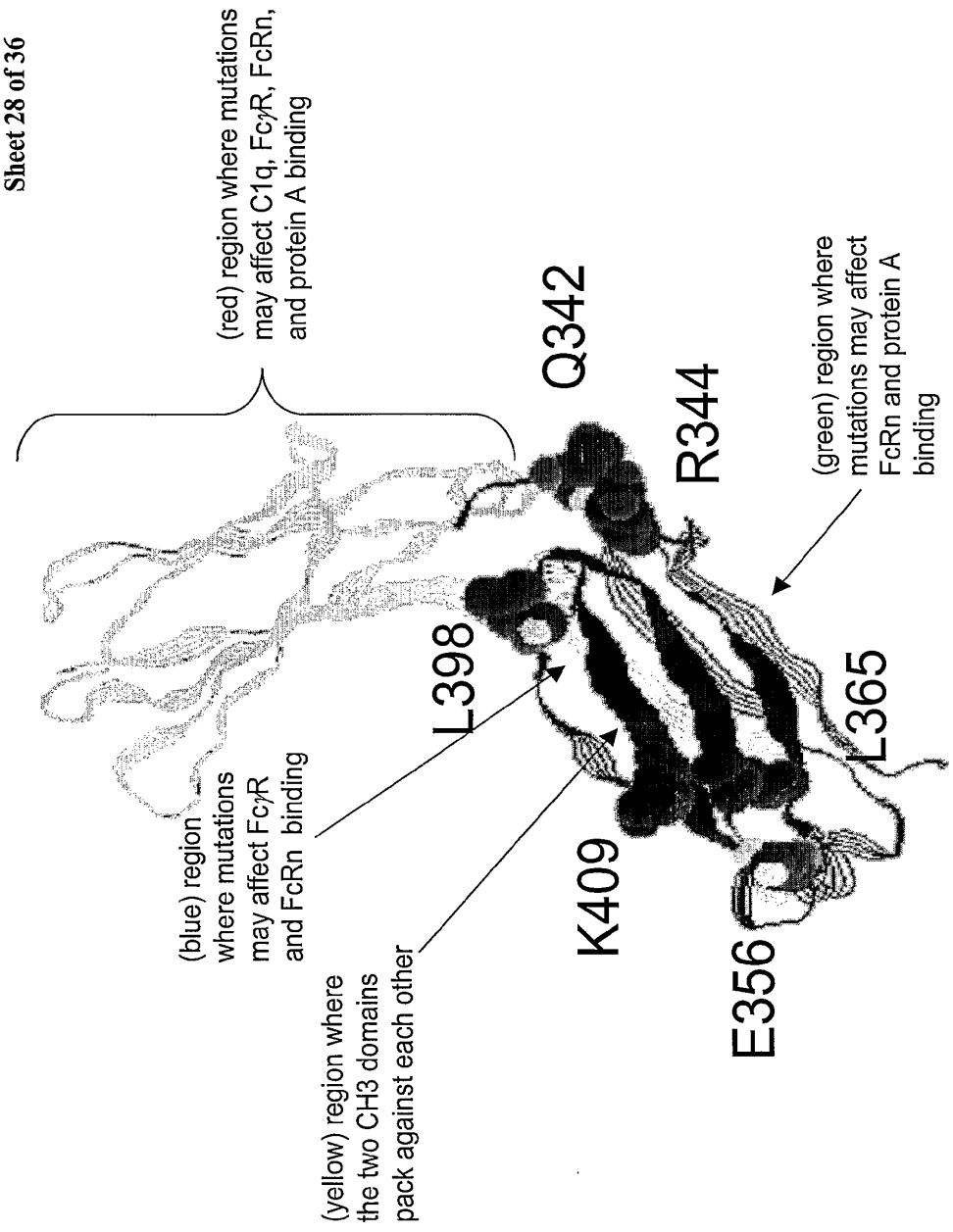


Fig. 25

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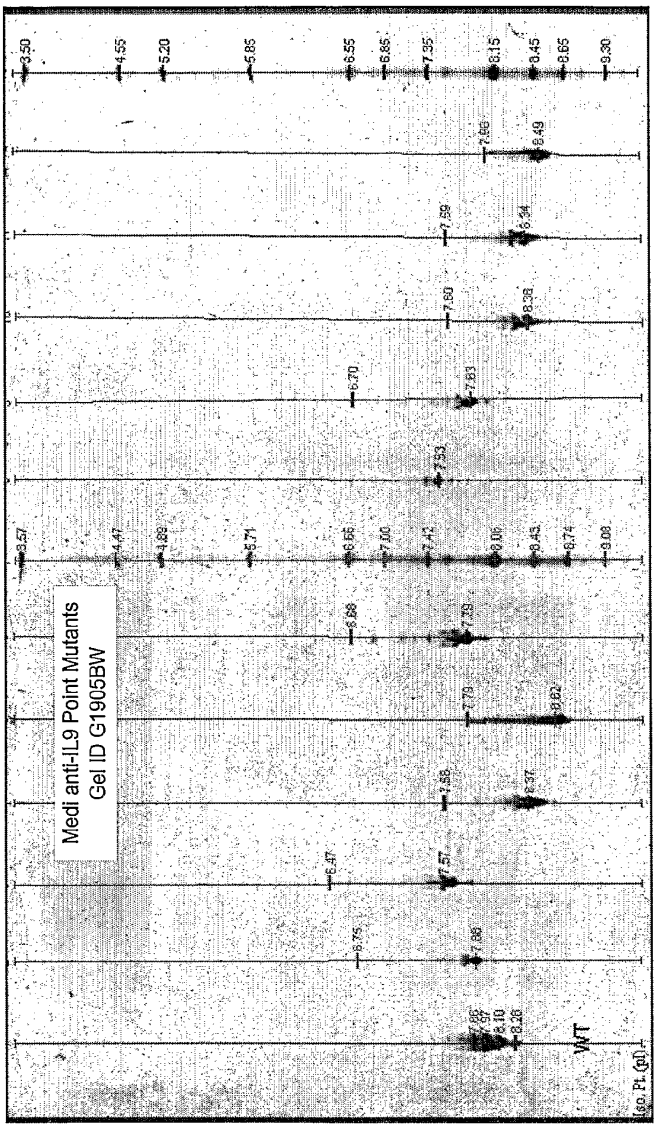


Fig. 26

Sheet 30 of 36

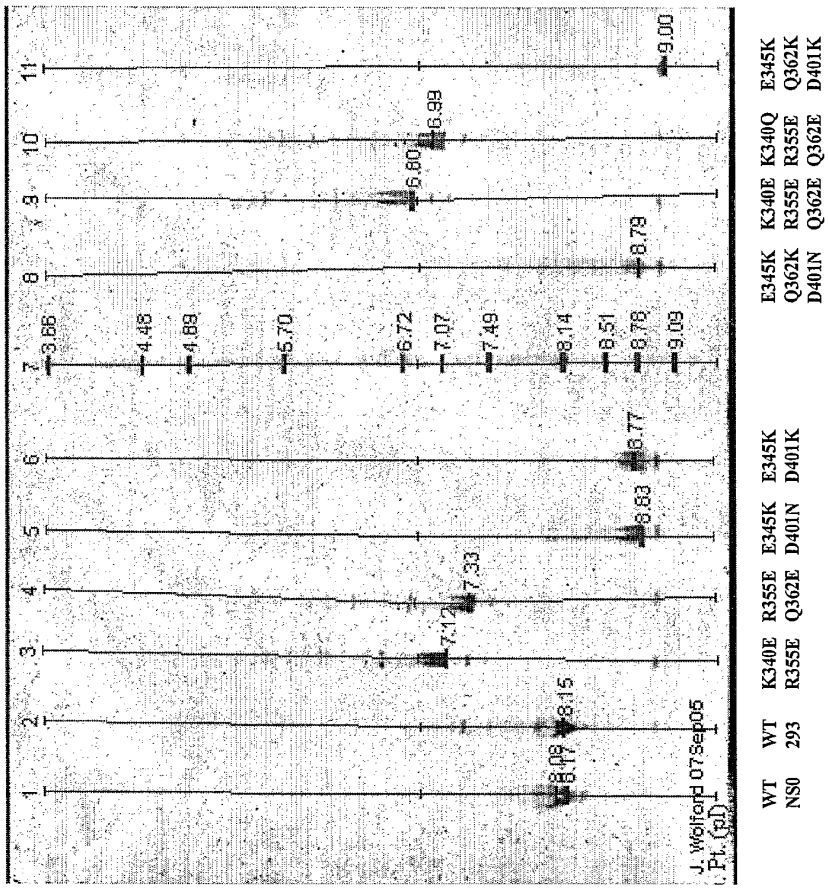


Fig. 27

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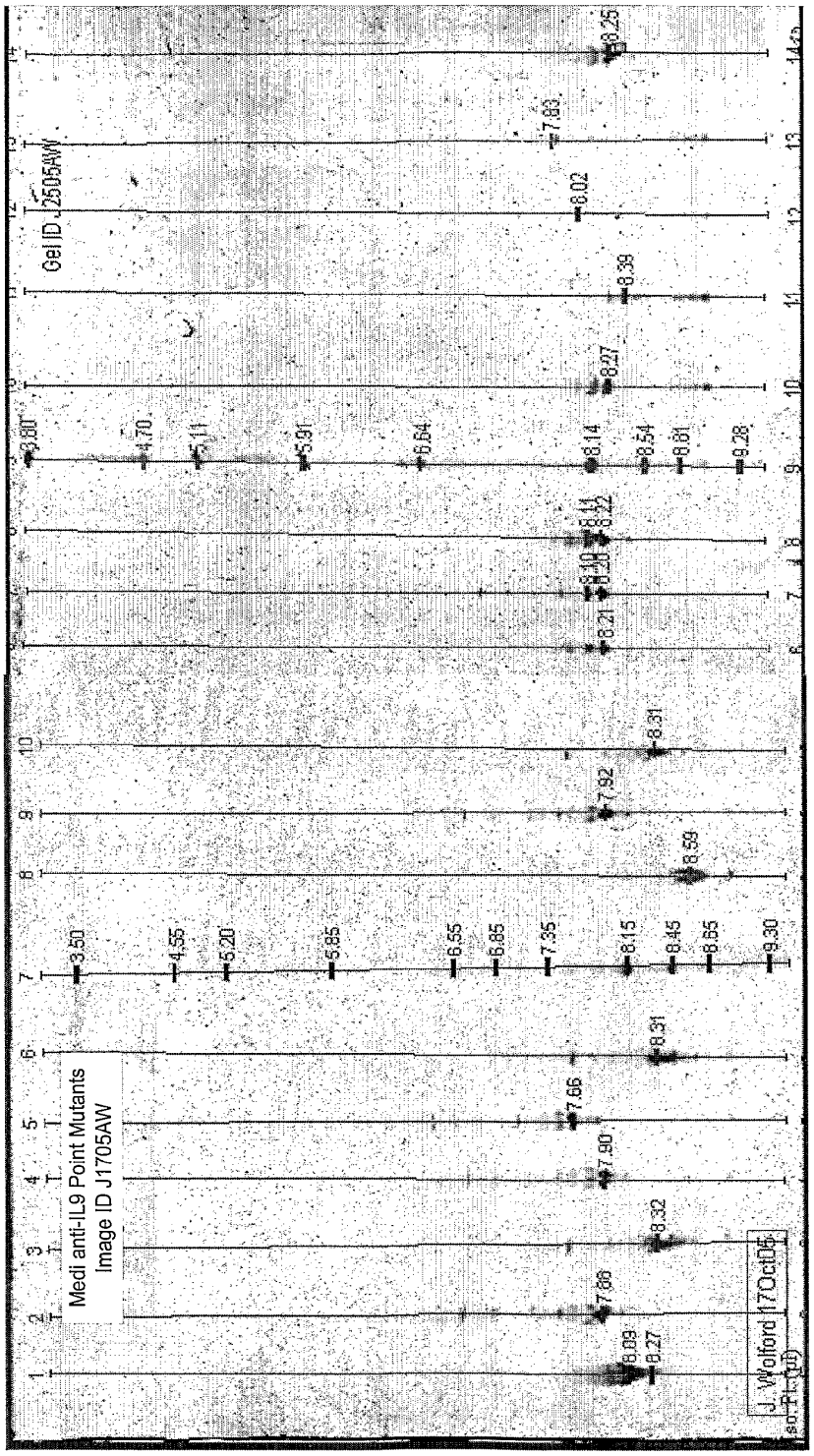


Fig. 28

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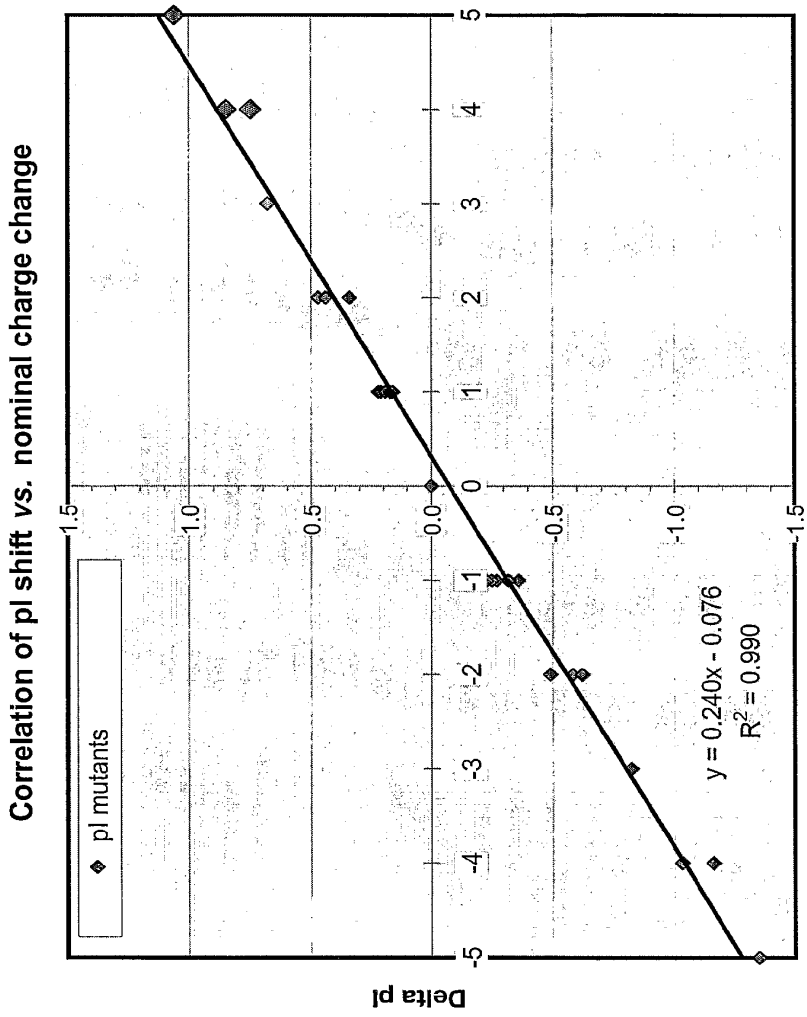


Fig. 29

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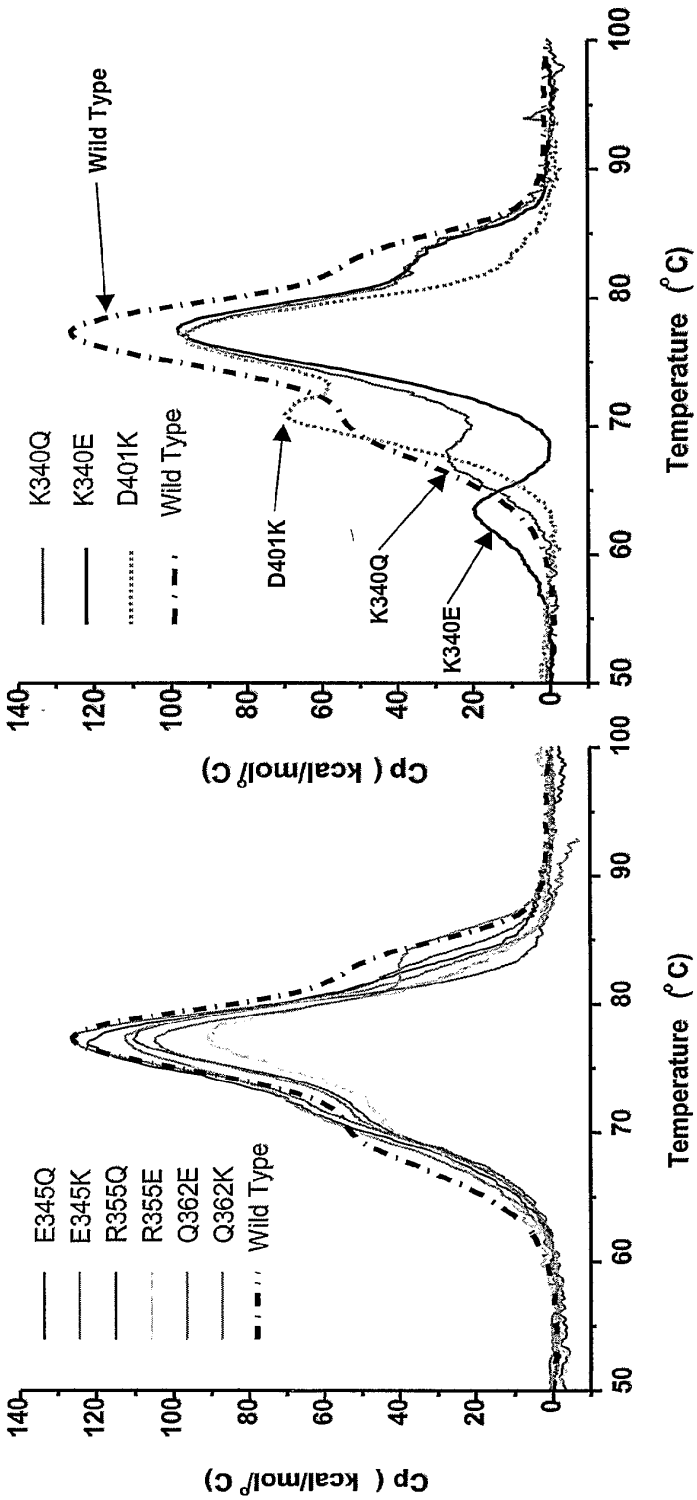


Fig. 30

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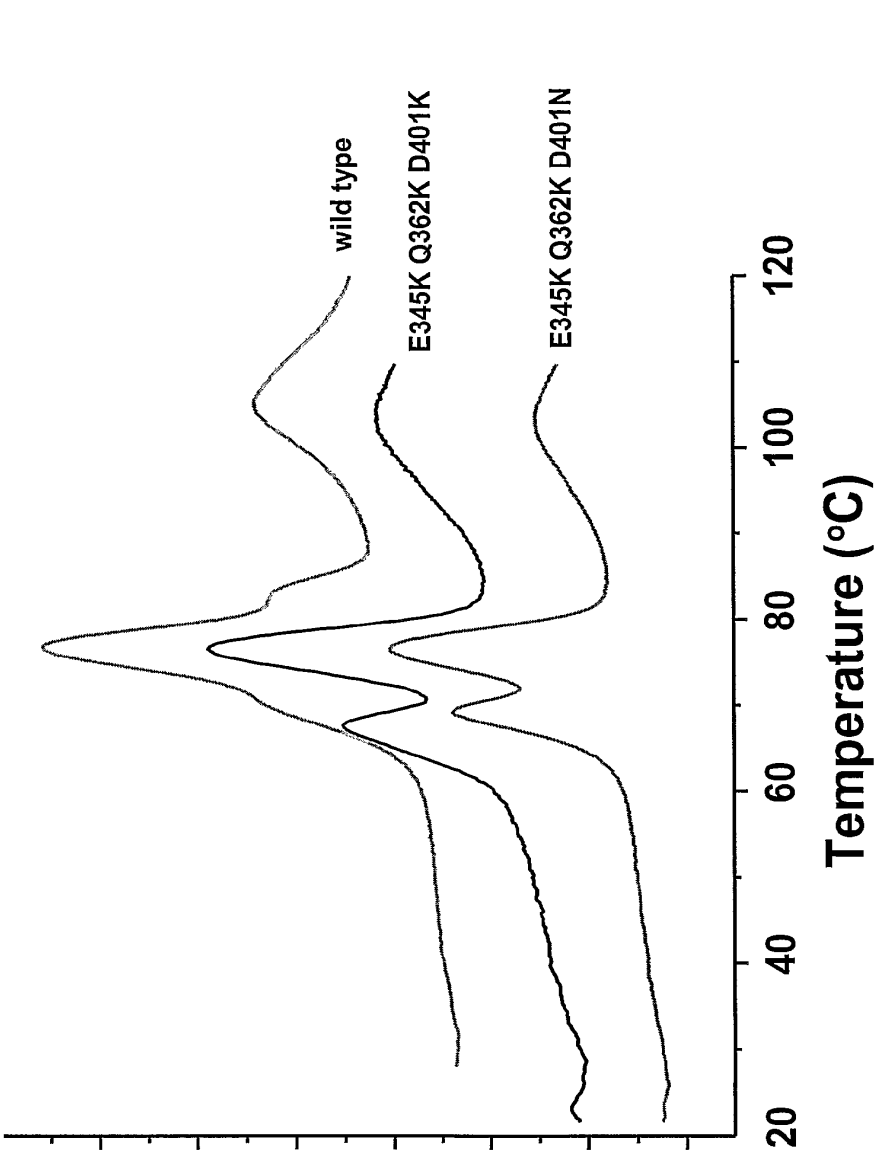


Fig. 31

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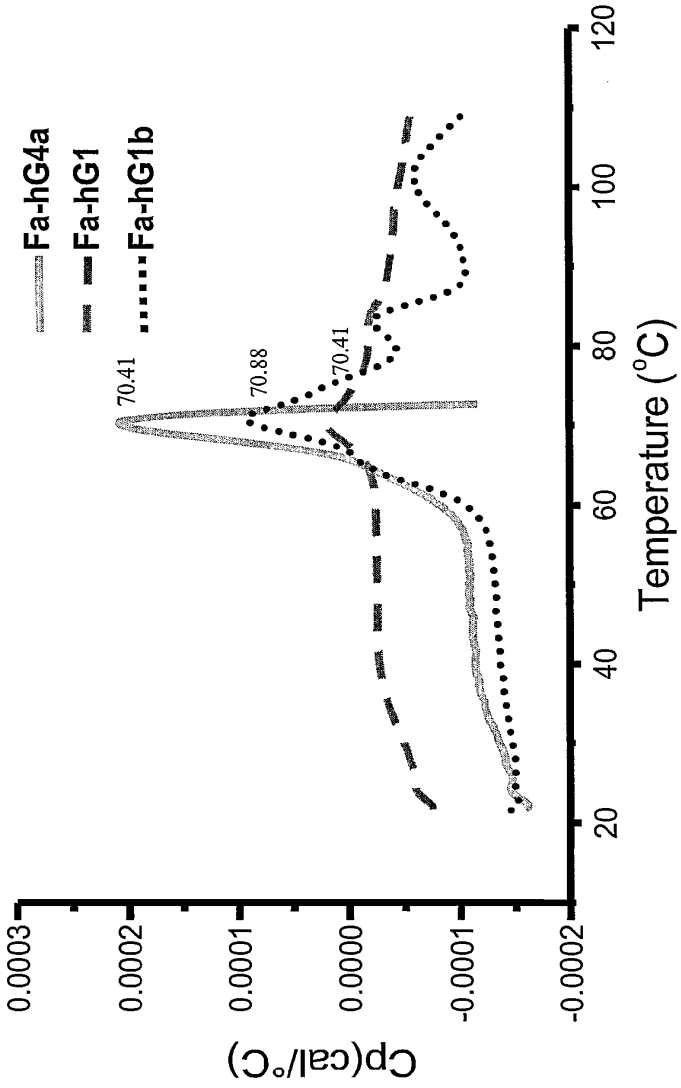


Fig. 32

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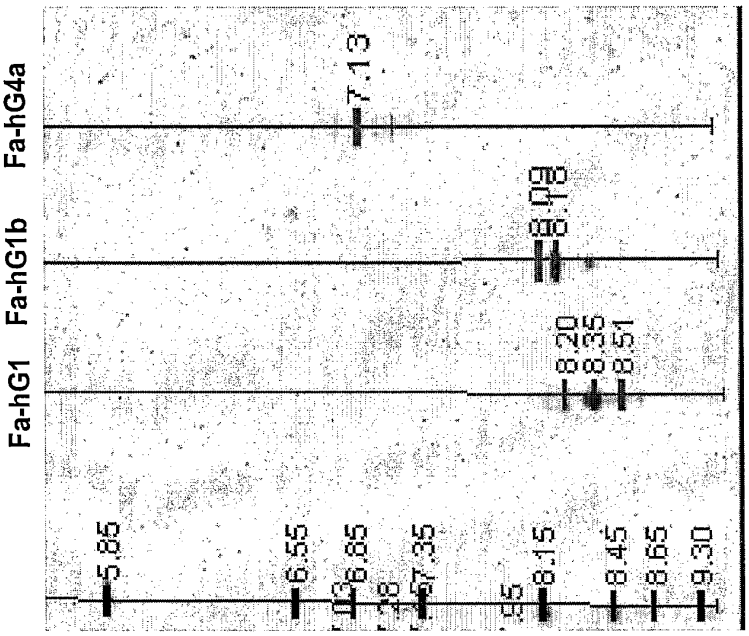


Fig. 33

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Page 856

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