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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
11/127,438	05/11/2005	Yi Wang	ALXN-P02-102	5259

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EXAMINER	
GAMBEL, PHILLIP	
ART UNIT	PAPER NUMBER
1644	

NOTIFICATION DATE	DELIVERY MODE
05/02/2011	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
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Office Action Summary	Application No.	Applicant(s)	
	11/127,438	WANG, YI	
	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 *17 December 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) *15-29,31-34 and 38-57* is/are pending in the application.

4a) Of the above claim(s) *31-34 and 38-45* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *15-29 and 46-57* 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 *-9/16/2010*.
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 12/17/2010, has been entered.

Claims 15, 18, 22 have been amended.

Claims 46-57 have been added.

Claims 30 and 35-37 have been canceled.
Claims 1-14 have been canceled previously.

Claims 15-29, 31-34 and 38-57 are pending.

Claims 15-29 and 46-57 are under consideration as they read on the elected invention and species of anti-C5 antibodies.

Claims 31-34 and 38-45 have been withdrawn from consideration as being directed to a non-elected invention. See 37 C.F.R. 1.142(b) and M.P.E.P. 821.03.

2. The text of those sections of Title 35 USC not included in this Action can be found in a prior Office Action.

Upon reconsideration of applicant's arguments, filed 12/17/2010, particularly as it applies to the teachings of Krause, including its disclosure of anti-C5 antibodies as a C5a receptor-inactive therapeutic agent;
New Grounds of Rejection under 35 U.S.C. 103(a) obviousness have been set forth herein for clarity.

While applicant relies upon the disclosure of paragraphs [0206]-[0207] of Krause et al. to stand for the prior art anti-C5 antibodies to be C5a receptor-inactive therapeutic agents,
the following is noted.

In contrast to applicant's assertions,
paragraph [0207] of Krause describes anti-C5 antibodies such as eculizumab or pexelizumab, which are the same anti-C5 antibodies recited in instant claim 49 and encompassed by anti-C5 antibodies that inhibit the conversion of C5 into C5a and C5b.

Eculizumab is the humanized version of the anti-C5 antibody, 5G1.1

Pexelizumab is the humanized single chain version of the anti-C5 antibody, 5G1.1.

[0206] Still other embodiments of the invention are directed to combinations in which at least one C5a receptor-inactive therapeutic agent is:

[0207] an anti-C5 monoclonal antibody (such as eculizumab or pexelizumab);

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While Krause defines a C5a receptor-inactive therapeutic agent as an agent that does not satisfy the criteria set forth in paragraph [0035] for a C5a antagonist (see paragraph [0036]) and that a C5a receptor-inactive therapeutic agent can be "an active agent" (see paragraph [0037]).

[0035] A "C5a antagonist" or "C5a receptor antagonist" is any compound that exhibits C5a antagonist activity within the a C5a receptor-mediated chemotaxis, radioligand binding assay, or calcium mobilization assay as provided herein. In other words, in a calcium mobilization assay, a compound is a C5a antagonist if incubation of cells with 1 uM of C5a antagonist results in at least a 2-fold increase in the fluorescence response relative to that measured in the presence of C5a alone. In a chemotaxis assay, a compound is a C5a antagonist if it displays an affinity constant or IC.sub.50 of 1 uM or less. Preferably, a C5a antagonist displays an IC.sub.50 of less than 500 nM, 200 nM, 100 nM, 50 nM, 25 nM, 10 nM or 5 nM (in a chemotaxis and/or calcium mobilization assay) in a standard C5a receptor-mediated chemotaxis assay, radioligand binding assay, or calcium mobilization assay. In certain embodiments, C5a antagonists provided herein inhibit activation and/or activity of a primate C5a receptor, such as human C5a receptor, which may be a cloned, recombinantly expressed receptor or a naturally expressed receptor. For treating non-human animals of any particular species, a compound exhibiting high affinity for the C5a receptor of that particular species is preferred.

[0036] As used herein, "therapeutic agent" refers to a compound which has been shown to exhibit clinical efficacy in reducing the symptoms of one or more of arthritis (preferably rheumatoid arthritis) or another autoimmune disorder, asthma, cardio- or cerebrovascular disease, psoriasis, reperfusion injury, burns, or traumatic CNS or spinal cord injury. A "C5a receptor-inactive therapeutic agent" is such an agent that does not satisfy the criteria (above) for a C5a antagonist.

[0037] As used herein, "active agent" refers to either or both of the C5a antagonist and the C5a receptor-inactive therapeutic agent. This term is intended to encompass all salt, ester and prodrug forms of C5a antagonists and C5a receptor-inactive therapeutic agents, even where the prodrug is not active itself but is converted to the active form after administration to the patient.

All three pathways of complement activation (the classical, mannan-binding lectin and alternative pathway) lead to formation of C5 convertase, which cleave C5 into C5a and C5b.

C5a is a potent anaphylatoxin that mediates leukocyte chemotaxis, increases vascular permeability, alters smooth muscle tone and induces secondary inflammatory mediators.

C5a is a key regulator of inflammation, including attracting and activation circulating cells expressing C5aR, particularly monocytes, macrophages and neutrophils.

Given that C5 is common all pathways of complement activation, blockade at this point stops the progression of the cascade regardless of the stimuli, In addition, prevention of C5 cleavage effectively blocks the generation of the potent proinflammatory molecules C5a and the cell lytic terminal complement complex (TCC).

Note, too, that C5 blockade preserves the critical immunoprotective and immunoregulatory function s of upstream components that culminate in C3b-mediated opsonization and immune complex clearance.

The prior teachings of the anti-C5 antibody 5G1.1 or its recombinant forms (eculizumab or pexelizumab) served these purposes.

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That Krause may classify the anti-C5 recombinant antibodies eculizumab or pexelizumab as C5a receptors inactive therapeutic agents does not detract for their potent anti-inflammatory activities at the time the invention was made to the ordinary artisan.

This Office Action will be in response to applicant's arguments, filed 12/17/2010.

The rejections of record can be found in previous Office Action, mailed 08/17/2010.

3. Priority.

The effective filing date of the instant claims 15-29 and 46-57 is deemed to be the filing date of instant priority application USSN 11/127,438, i.e. 05/11/2005.

The previous priority applications do not support sufficient written description for the instant claims, including limitations such as "aerosol composition … suitable for treating a pulmonary condition in a subject", "biopharmaceutical package … " and "pulmonary drug delivery kit …" as well as various limitations of the dependent claims (e.g., "jet air / ultrasonic / shockwave nebulizer".

Applicant should compare the priority applications with the instant claims for differences in the description of the "compositions / kits / packages", "antibody specificities" and "pulmonary conditions" described.

Further, the description of "eculizumab or pexelizumab" as well as "the mutated Fc portions" in the priority documents is not readily apparent.

For example, USSNs 60/469,189 and 60/408,571 are limited to describing the treatment of asthma and not other "pulmonary conditions" in a subject, as currently claimed.
For example, the provisional applications are limited to treating "chronic obstructive pulmonary diseases" such as "asthma" but not generically to "pulmonary conditions", as currently claimed.

As noted previously, "kits" and "packages" do not appear to be described prior to the instant application.

If applicant desires priority prior to 05/11/2005, 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, first paragraph.

Obviousness is not the standard for the addition new limitations to the disclosure as filed.

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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).

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).

4. Applicant's arguments in conjunction with the Wang declaration under 37 C.F.R. § 1.131 filed 12/17/2010 have been fully considered but are not found convincing essentially for the reasons of record.

Applicant's arguments that the Wang WO2004/022096 claims priority to the same U.S. provisional applications USSN 60/408,571 and 60/469,189 as the instant application.

Given applicant's arguments concerning the priority of the instant application to the provisional applications, that is, an effective filing date of 09/06/2002,
applicant submits the withdrawal of the prior art rejection.

In contrast to applicant's / declarant's assertions,
the Wang 131 declaration does not provide for the generic anti-C5 antibodies that inhibit the conversion of C5 into C5a and C5b, as currently claimed.

While the anti-C5 antibody BB5.1 described in the Wang 131 declaration may or may not inhibit the conversion of C5 into C5a and C5b,
there is no disclosure that the generic properties of anti-C5 antibodies that inhibit the conversion of C5 into C5a and C5b in the context of the claimed invention was described in a manner that provides for conception, diligence and reduction to practice prior to the claimed invention in a manner that obviates the prior art teachings.

Even if the anti-C5 antibody BB5.1 described in the Wang 131 declaration did inhibit the conversion of C5 into C5a and C5b,
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). See MPEP 2163.05(b).

While applicant relies upon the provisional application USSN 60/408,571 to provide written description for "treating a pulmonary condition" generically,
this provisional document describes asthma, bronchitis and emphysema as chronic obstructive pulmonary diseases and does not describe pulmonary diseases or conditions generically as currently claimed in the instant application.

For example, pulmonary or respiratory diseases encompass a variety of diseases or conditions not described in the provisional application USSN 60/408,571 or the Wang 131 Declaration.

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For example, pulmonary or respiratory diseases encompass respiratory tract infections (e.g., resulting in pneumonia), respiratory tumors (e.g., small cell lung cancer), and pulmonary vascular diseases (e.g., pulmonary embolism, pulmonary arterial hypertension, pulmonary hemorrhage).

In contrast to applicant's assertions and the reliance upon MPEP 2163 (II)(A)(2), applicant's reliance for the disclosure of "administered via ... aerosol" in priority applications USSN 60/469,189 and 60/408,571 does not provide sufficient written description for "something more than the composition itself – namely: a delivery device such as an inhaler or a nebulizer", unless such limitations are specifically described.

In contrast to applicant's assertions, obviousness is not the standard for the addition new limitations to the disclosure as filed.

Essentially, applicant is admitting to adding "something more" to the original disclosure.

To satisfy the written description requirement, the disclosure of the earlier filed application must describe the later claimed invention "in sufficient detail that one skilled in the art can clearly conclude that the inventor invented the claimed invention as of the filing date sought".

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.

To provide a written description of the invention, the specification must include a written description of each and every element of the claimed subject matter.

See Lockwood v. American Airlines Inc., 41 USPQ2d 1961 (Fed. Cir. 1977).

See Ariad Pharmaceuticals Inc. v. Eli Lilly & Co., 94 USPQ2d 1161 (Fed. Cir. 2010)

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).

In contrast to applicant's assertions, the instant claims are not entitled to an effective filing date of 09/06/2002, based upon the disclosure of priority application USSN 60/408,571.

In turn and for the reasons herein /above, applicant's arguments in conjunction with the Wang declaration under 37 C.F.R. § 1.131 filed 12/17/2010 do not obviate the prior art teachings based upon Wang (WO2004/022096) and Krause et al. (US 2004/0014782).

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5. Claims 15-17 and 46-50 are rejected under 35 U.S.C. § 102(b) as being anticipated by Wang et al. (WO 2004/022096) (1449; BB) (see entire document).

Applicant's arguments filed 12/17/2010 have been fully considered but are not found convincing essentially for the reasons of record.

Applicant's submits that the Wang WO2004/022096 claims priority to the same U.S. provisional applications USSN 60/408,571 and 60/469,189 as the instant application.

Given applicant's arguments concerning the priority of the instant application to the provisional applications, that is, an effective filing date of 09/06/2002,
applicant submits withdrawal of the prior art rejection.

Applicant's arguments have not been found persuasive for the reason set forth above in Section 3 on Priority.

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).

Wang et al. teach formulations, including aerosol (e.g., pages 20-21, overlapping paragraph and Summary of the Invention) comprising anti-C5 antibodies, including anti-C5 5G1.1 antibodies and recombinant forms thereof (e.g., see pages 14-17) that are useful for the treatment of asthma, including combination therapy (e.g., see Summary of the Invention and Detailed Description) (see entire document, including claims).

A species will anticipate a claim to a genus. See MPEP 2131.02.

6. Claims 15-18, 22, 30, 46-50, 52, 53 and 55-57 are rejected under 35 U.S.C. § 102(b)(e) as being anticipated by Krause et al. (US 2004/0014782) (see entire document).

Applicant's arguments in conjunction with the Wang declaration under 37 C.F.R. § 1.131 filed 12/17/2010 have been fully considered but are not found convincing essentially for the reasons of record.

Applicant argues that the inventor had conceived of the invention by 12/20/2001 or earlier, as indicated by the experimental plans evaluating the efficacy of the anti-C5 antibody BB5.1 using an asthma mouse model, which is also demonstrated in Examples 1-3 of provisional application USSN 60/408,571, filed 09/06/2002.

Applicant argues that Krause et al. does not include anti-C5 antibodies in the teachings of C5a antagonists and does not include anti-C5 antibodies in the asthma-related methods and kits.

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Applicant's arguments have not been found persuasive in view of the rebuttals set forth above in Section 2 concerning the teachings of Krause, Section 3 concerning Priority and Section 4 concerning reliance upon the Wang declaration under 37 C.F.R. § 1.131.

Krause et al. teach the use of C5a antagonists, including anti-C5 antibodies (e.g., see paragraphs [0207] and [0277]) in the treat respiratory diseases lung disorders, including ARDS and asthma (e.g., see paragraphs [0039], [0204] [0227, [0274]), including inhaled compositions, nebulizers or other devices that may be provided in a kit for the treatment of asthma (e.g., see paragraphs [0273]—[0275], [0279]-[0281], [0288]-[[0303]) as well as combinations for the treatment of lung disorders (e.g., see paragraphs [0200], [0225]-[0235]) and dosages consistent with the broad range recited in claim 31 (e.g., see paragraphs [0263]-[0300]) (see entire document).

Given that there may be ambiguity over the effective priority date of the instant claims, this rejection is made under 35 U.S.C. 102(b)(e), as it would apply to the priority of the instant claims if applicant can provide appropriate written support and enablement for the instant or possibly amended claims. See Section 5 above concerning priority of the instant claims.

7. This is a New Grounds of Rejection.

Claims 15-29 and 46-57 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Krause et al. (US 2004/0014782) in view of Evans et al. (U.S. Patent No. 6,355,245) (1449; #AB), Fung et al. (U.S. Patent No. 6,956,107), Fung et al. (U.S. Patent No. 6,998,468), West et al. (U.S. Patent No. 7,071,299), Babington (U.S. Patent No. 4,228,795) (892; of record) and Lobb et al. (U.S. Patent No. 5,871,734) (1449; #AA) and Winter et al. (U.S. Patent No. 5,648,260).

Applicant's arguments in conjunction with the Wang declaration under 37 C.F.R. § 1.131 filed 12/17/2010 have been fully considered but are not found convincing essentially for the reasons of record.

Applicant argues that the C5a antagonists disclosed by Krause do not include anti-C5 antibodies and the reference does not disclose methods of kits including anti-C5 antibodies for use in treating respiratory disorders.

In contrast to applicant's narrow reading of Krause et al.,
Krause et al. is clearly drawn to C5a antagonists and compositions / kits comprising said C5a antagonists and their use to treat a variety of inflammatory or autoimmune diseases / conditions (e.g., Background, Summary of the Invention and Detailed Description of the Invention, including Terminology in paragraphs [0034]-[0039]).

While applicant relies upon the disclosure of paragraphs [0206]-[0207] of Krause et al. to stand for the prior art anti-C5 antibodies to be C5a receptor-inactive therapeutic agents,
the following is noted.

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In contrast to applicant's assertions,
paragraph [0207] of Krause describes anti-C5 antibodies such as eculizumab or pexelizumab, which are the same anti-C5 antibodies recited in instant claim 49 and encompassed by anti-C5 antibodies that inhibit the conversion of C5 into C5a and C5b.

Eculizumab is the humanized version of the anti-C5 antibody, 5G1.1

Pexelizumab is the humanized single chain version of the anti-C5 antibody, 5G1.1.

[0206] Still other embodiments of the invention are directed to combinations in which at least one C5a receptor-inactive therapeutic agent is:

[0207] an anti-C5 monoclonal antibody (such as eculizumab or pexelizumab);

While Krause defines a C5a receptor-inactive therapeutic agent as an agent that does not satisfy the criteria set forth in paragraph [0035] for a C5a antagonist (see paragraph [0036]) and that a C5a receptor-inactive therapeutic agent can be "an active agent" (see paragraph [0037]).

[0035] A "C5a antagonist" or "C5a receptor antagonist" is any compound that exhibits C5a antagonist activity within the a C5a receptor-mediated chemotaxis, radioligand binding assay, or calcium mobilization assay as provided herein. In other words, in a calcium mobilization assay, a compound is a C5a antagonist if incubation of cells with 1 uM of C5a antagonist results in at least a 2-fold increase in the fluorescence response relative to that measured in the presence of C5a alone. In a chemotaxis assay, a compound is a C5a antagonist if it displays an affinity constant or IC.sub.50 of 1 uM or less. Preferably, a C5a antagonist displays an IC.sub.50 of less than 500 nM, 200 nM, 100 nM, 50 nM, 25 nM, 10 nM or 5 nM (in a chemotaxis and/or calcium mobilization assay) in a standard C5a receptor-mediated chemotaxis assay, radioligand binding assay, or calcium mobilization assay. In certain embodiments, C5a antagonists provided herein inhibit activation and/or activity of a primate C5a receptor, such as human C5a receptor, which may be a cloned, recombinantly expressed receptor or a naturally expressed receptor. For treating non-human animals of any particular species, a compound exhibiting high affinity for the C5a receptor of that particular species is preferred.

[0036] As used herein, "therapeutic agent" refers to a compound which has been shown to exhibit clinical efficacy in reducing the symptoms of one or more of arthritis (preferably rheumatoid arthritis) or another autoimmune disorder, asthma, cardio- or cerebrovascular disease, psoriasis, reperfusion injury, burns, or traumatic CNS or spinal cord injury. A "C5a receptor-inactive therapeutic agent" is such an agent that does not satisfy the criteria (above) for a C5a antagonist.

[0037] As used herein, "active agent" refers to either or both of the C5a antagonist and the C5a receptor-inactive therapeutic agent. This term is intended to encompass all salt, ester and prodrug forms of C5a antagonists and C5a receptor-inactive therapeutic agents, even where the prodrug is not active itself but is converted to the active form after administration to the patient.

All three pathways of complement activation (the classical, mannan-binding lectin and alternative pathway) lead to formation of C5 convertase, which cleave C5 into C5a and C5b.

C5a is a potent anaphylatoxin that mediates leukocyte chemotaxis, increases vascular permeability, alters smooth muscle tone and induces secondary inflammatory mediators.

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C5a is a key regulator of inflammation, including attracting and activation circulating cells expressing C5aR, particularly monocytes, macrophages and neutrophils.

Given that C5 is common all pathways of complement activation, blockade at this point stops the progression of the cascade regardless of the stimuli, In addition, prevention of C5 cleavage effectively blocks the generation of the potent proinflammatory molecules C5a and the cell lytic terminal complement complex (TCC).

Note, too, that C5 blockade preserves the critical immunoprotective and immunoregulatory function s of upstream components that culminate in C3b-mediated opsonization and immune complex clearance.

The prior teachings of the anti-C5 antibody 5G1.1 or its recombinant forms (eculizumab or pexelizumab) served these purposes.

That Krause may classify the anti-C5 recombinant antibodies eculizumab or pexelizumab as C5a receptors inactive therapeutic agents does not detract for their potent anti-inflammatory activities nor their role as C5 antagonists at the time the invention was made to the ordinary artisan.

In addition, applicant's arguments have not been found persuasive in view of the rebuttals set forth above in Section 2 concerning the teachings of Krause, Section 3 concerning Priority and Section 4 concerning reliance upon the Wang declaration under 37 C.F.R. § 1.131 with respect to the status of Krause as a proper prior art reference under 103(a) based upon 102(e).

Evans et al. has been added to provide the teachings of anti-C5 antibodies, including the 5G1.1. specificity, in the treatment of inflammatory diseases, including the specificities and advantages discussed herein above (e.g., see entire document, including Summary of the Invention; Background Physiology and Pathology, particularly as it reads on The Complement System; Description of the Preferred Embodiments; Favored Embodiments; and Examples)

The following references have been added to provide further evidence of targeting C5-mediated inflammation in the context of treating asthma at the time the invention was made.

Although Fung et al. (U.S. Patent No. 6,956,107) was focused on Factor D inhibitors, Fung et al. teach the role of C5a anaphylatoxin in complement-mediated inflammation (e.g., see Background of the Invention), including the inhibition of C5a anaphylatoxin (e.g., see column 9, lines 39-41) in the context of severe asthma (e.g., see column 9, lines 62-63) as well as appropriate pharmaceutical formulations that can be administered by a variety of routes, including intranasal and intratracheal (e.g., see column 9, lines 32-38).

Although Fung et al. (U.S. Patent No. 6,998,468) was focused on complement Ca2 inhibitors, Fung et al. teach the role of C5a anaphylatoxin in complement-mediated inflammation and the inhibition of the complement and lectin complement pathways including C5 convertases and C5 activation (e.g., see Background of the Invention and Applications of the Anti-C2a Molecules).

In response to applicant's amended claims, which recite "mutated Fc portion … which does not activate complement",
Winter et al. teach that it was well known in the art at the time the invention was made to alter effector function in therapeutic antibodies of interest, including reducing the antibody for an effector molecule such as Fc receptor or a complement component, but does not altered the binding affinity of such antibodies (See entire document, including Background of the Invention, Summary of the Invention; also see modifications on columns 4-10).

Given the teaching of antagonistic anti-C5 antibodies, it would have been obvious to the ordinary artisan to modify such antagonistic anti-C5 antibodies such that they themselves do not activate complement as well as inhibiting C5-mediated interactions and activities.

Note that Krause et al. does teach anti-C5 antibodies such as eculizumab or pexelizumab (see paragraph [0207].

The following is reiterated for applicant's convenience.

Krause et al. teach the use of C5a antagonists, including anti-C5 antibodies (e.g., see paragraphs [0207] and [0277]) in the treat respiratory diseases lung disorders, including ARDS and asthma (e.g., see paragraphs [0039], [0204] [0227, [0274]), including compositions and pharmaceutical kits for the treatment of asthma (e.g., see paragraphs [0273]—[0275], [0279]-[0281], [0288]-[[0303]) and instructions (e.g., see claim 29, paragraphs 263, [0273], [0278], [0297]) as well as combinations for the treatment of lung disorders (e.g., see paragraphs [0200], [0225]-[0235]) and dosages consistent with the broad range recited in claim 31 (e.g., see paragraphs [0263]-[0300]) (see entire document).

Krause et al. differs from the claimed compositions / packages and kits by not describing the nature of the well known inhalers at the time the invention was made.

West et al. teach compositions comprising complement inhibitors of complement activation for therapy including administration via inhalation, mucosal membrane, pulmonary routes, intranasal delivery with aid of dry-powder dispensers, liquid aerosol generators or nebulizers as well as the provision of such compositions of complement inhibitors in the kit form, with can comprise written information or indication and usage of the pharmaceutical composition (e.g., see Therapeutic Uses of Complement C1s Inhibitors Peptides and Polypeptides on columns 31-35) (see entire document).

Babington teaches nebulizers which can be used to aerosolize medication for nasal inhalation (e.g., see Figure 4 and columns 6-8), which is suitable for use with viscous or sticky substances (e.g., see column 8, lines 34-37) and can use a jet of air to disperse the medicament (e.g., see column 4, lines 35-39 and claims 18, 19) or ultrasonic nebulizers in the art (e.g., see column 1, lines 23-34 and claim 19) (see entire document).

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In addition to the teachings above Lobb et al. teach that aqueous antibody solutions can be delivered to airways using a nebulizer (e.g., see column 6, lines 36-41 and column 12, lines 37-52) as well as the use of antibodies for the treatment of asthma (see entire document, including Summary of the Invention). Note, too, that Lobb et al. also teach the well known applicability of combination therapy, including combination having a therapeutic effect on airway responsiveness (e.g., see column 8, paragraphs 4-5).

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to employ the nebulizers taught by West et al. and Babington to administer the anti-C5a antibodies via the aerosol / nebulizer means taught by Krause et al. in the treatment of certain respiratory / lung disorders / diseases such as asthma One would have been motivated with a reasonable expectation of success to administer the antibodies directly to the respiratory mucosa, which is often the first line of encounter of an immune system with pathogenic organisms and by the teachings of the prior art as a known and effective means to target the respiratory system in the treatment of certain disorders/diseases.

With respect to the limitation of comprising "instructions for the use of the composition", the following is noted. Note, however, that C5 antagonists as well as anti-C5 antibodies are taught herein for the treatment of pulmonary or lung disorders / diseases and that Krause et al. and West et al. both teach the applicability of "instructions".

The printed matter on the label or package insert does not lend patentable weight as a limitation of the claimed invention because the recited intended use does not physically or chemically change the nature of the agent within the container and the artisan can still use the agent for other purposes. The intended use of a product, in this case an anti-C5 antibody, does not materially change the product as the product can still be used for other purposes, such as assaying C5 binding or immunopurification of C5, which are routinely practiced in the art. The recited "limitations" only further limit the intended use method printed on the label or package insert and do not change the physical and/or chemical properties of the components of the kit.

Also, see In re Haller, 73 USPQ 403 (CCPA 1947), In re Venezia, 189 USPQ 149 (CCPA 1976) In re Ngai, 70 USPQ2d 1862 (Fed. Cir. 2004), In re Gulack, 217 USPQ 401, 404 (Fed. Cir. 1983) and MPEP 2112.01
Where the only difference between a prior art product and a claimed product is printed matter that is not functionally related to the product, the content of the printed matter will not distinguish the claimed product from the prior art. In re Ngai, 70 USPQ2d 1862, 1864 (Fed. Cir. 2004).
Since providing C5 antagonists as well as anti-C5 antibodies to ameliorate various pulmonary conditions / diseases such as asthma would have been predictable at the time of the invention, there would have been reasonable expectation of successful development of providing said C5 antagonists alone or in combination with other agents to treat said conditions/diseases in composition or kit form for convenience and economy. The prior art had recognized the advantages of C5 antagonists such as anti-C5 antibodies in the treatment of pulmonary diseases/ disorders and pharmaceutical kits as a standard and convenient means of providing pharmaceutical agents to the ordinary artisan.

"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.").

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Given that the prior art goal was to inhibit complement activation in order to treat pulmonary diseases/conditions, incorporating known inhibitors such as anti-C5 antibodies into pharmaceutical compositions . kits would have been routine to the ordinary artisan at the time the invention was made and therefore obvious in designing therapeutic products regimens to treat pulmonary diseases / conditions.

From the teachings of the references, a person of ordinary skill in the art would have a reasonable expectation of success at the time the invention was made. 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.

8. No claim is allowed.

9. 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
April 11, 2011

Samsung Bioepis Exhibit No. 1002
Page 8881

Notice of References Cited	Application/Control No. 11/127,438	Applicant(s)/Patent Under Reexamination WANG, YI	
	Examiner PHILLIP GAMBEL	Art Unit 1644	Page 1 of 1

U.S. PATENT DOCUMENTS

*		Document Number Country Code-Number-Kind Code	Date MM-YYYY	Name	Classification
*	A	US-6,956,107	10-2005	Fung et al.	530/387.1
*	B	US-6,998,468	02-2006	Fung et al.	530/388.25
	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	Classification
	N					
	O					
	P					
	Q					
	R					
	S					
	T					

NON-PATENT DOCUMENTS

*		Include as applicable: Author, Title Date, Publisher, Edition or Volume, Pertinent Pages)
	U	
	V	
	W	
	X	

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

Search Notes	Application/Control No.	Applicant(s)/Patent Under Reexamination
	11127438	WANG, YI
	Examiner	**Art Unit**
	F. Pierre VanderVegt	1644

SEARCHED			
Class	**Subclass**	**Date**	**Examiner**

SEARCH NOTES		
Search Notes	**Date**	**Examiner**
PALM Inventor, 10/655,861, 60/408,571, 60/469,189 EAST, STN Medline Embase scisearch	8/26/08	
search strategy ATTACHED	8/28/08	PV
PALM related / priority USSNs	08/12/2010	PG
WEST / DIALOG	08/12/2010	PG
PALM related / priority USSNs	03/02/2011	PG
WEST	03/02/2011	PG
DIALOG 03/16/2011 and 03/28/2011	03/28/2011	PG

INTERFERENCE SEARCH			
Class	**Subclass**	**Date**	**Examiner**

	/Phillip Gambel/ Primary Examiner.Art Unit 1644

PTO/SB/08a (07-09)
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INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Use as many sheets as necessary)

Sheet 1 of 2

Complete if Known	
Application Number	11/127,438
Filing Date	May 11, 2005
First Named Inventor	Yi Wang
Art Unit	1644
Examiner Name	Phillip Gambel
Attorney Docket Number	ALXN-P02-102

U.S. PATENT DOCUMENTS

Examiner Initials*	Cite No.[1]	Document Number Number-Kind Code[2] (if known)	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear

FOREIGN PATENT DOCUMENTS

Examiner Initials*	Cite No.[1]	Foreign Patent Document Country Code[3]-Number[4]-Kind Code[5] (if known)	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages Or Relevant Figures Appear	T[6]
	BD	CA 2 189 015	11-09-1995	Alexion Pharmaceuticals, Inc.		
	BE	CA 2 198 706	03-28-1996	Alexion Pharmaceuticals, Inc.		

Examiner Signature	/Phillip Gambel/	Date Considered	03/07/2011

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25381235_1

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /P.G./

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INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Use as many sheets as necessary)

Sheet 2 of 2

Complete if Known	
Application Number	11/127,438
Filing Date	May 11, 2005
First Named Inventor	Yi Wang
Art Unit	1644
Examiner Name	Phillip Gambel
Attorney Docket Number	ALXN-P02-102

NON PATENT LITERATURE DOCUMENTS

Examiner Initials*	Cite No.[1]	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, page(s), volume-issue number(s), publisher, city and/or country where published.	T[2]

Examiner Signature	/Phillip Gambel/	Date Considered	03/07/2011

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[1]Applicant's unique citation designation number (optional). [2]Applicant is to place a check mark here if English language Translation is attached.

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 begin 5,73,155,399
       16mar11 07:32:42 User208760 Session D3252.2
            $0.00    0.115 DialUnits File410
     $0.00  Estimated cost File410
     $0.03  TELNET
     $0.03  Estimated cost this search
     $0.66  Estimated total session cost   0.273 DialUnits

SYSTEM:OS  - DIALOG OneSearch
  File   5:Biosis Previews(R) 1926-2011/Mar W1
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thesaurus.
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      Set  Items  Description
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? s (c5 or c5a or anti(W)c5?) and (asthma)
           41299  C5
           14978  C5A
         2495697  ANTI
          420721  C5?
            1051  ANTI(W)C5?
          393083  ASTHMA
      S1     662  (C5 OR C5A OR ANTI(W)C5?) AND (ASTHMA)
? s (c5 or c5a or anti(W)c5?)(20n)(antibod? or inhibit? or suppress? or block? or
antagon? or prevent?) and (asthma)
Processing
Processing
           41299  C5
           14978  C5A
         2495697  ANTI
          420721  C5?
            1051  ANTI(W)C5?
         2804105  ANTIBOD?
         6375204  INHIBIT?
         1384256  SUPPRESS?
         2013322  BLOCK?
         1674147  ANTAGON?
         3907597  PREVENT?
           10454  ((C5 OR C5A) OR ANTI(W)C5?)(20N)(((((ANTIBOD? OR
                  INHIBIT?) OR SUPPRESS?) OR BLOCK?) OR ANTAGON?) OR
                  PREVENT?)
          393083  ASTHMA
      S2     234  (C5 OR C5A OR ANTI(W)C5?)(20N)(ANTIBOD? OR INHIBIT? OR
                  SUPPRESS? OR BLOCK? OR ANTAGON? OR PREVENT?) AND (ASTHMA)
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      S3     154  RD S2  (unique items)
? s s3 and py<2004
Processing
Processing
Processing
           154  S3
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      S4      57  S3 AND PY<2004
? rd s4
      S5      57  RD S4  (unique items)
? t s5/3/all

 5/3/1     (Item 1 from file: 5)
DIALOG(R)File   5:Biosis Previews(R)
(c) 2011 The Thomson Corporation. All rts. reserv.

17678937   BIOSIS NO.: 200400059694
Inhibition of complement activation decreases airway inflammation and
  hyperresponsiveness.
AUTHOR: Taube Christian; Rha Yeong-Ho; Takeda Katsuyuki; Park Jung-Won;
  Joetham Anthony; Balhorn Annette; Dakhama Azzeddine; Giclas Patricia C;
  Holers V Michael; Gelfand Erwin W (Reprint)
AUTHOR ADDRESS: National Jewish Medical and Research Center, 1400 Jackson
  Street, Denver, CO, 80206, USA**USA
AUTHOR E-MAIL ADDRESS: gelfande@njc.org
JOURNAL: American Journal of Respiratory and Critical Care Medicine  168 (
11): p1333-1341 December 1, 2003 2003
MEDIUM: print
ISSN: 1073-449X _(ISSN print)
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English


 5/3/2     (Item 2 from file: 5)
DIALOG(R)File   5:Biosis Previews(R)
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17312537   BIOSIS NO.: 200300267070
Proteoglycans are potent modulators of the biological responses of
  eosinophils to chemokines.
AUTHOR: Culley Fiona J (Reprint); Fadlon Emma J; Kirchem Antje; Williams
  Timothy J; Jose Peter J; Pease James E
AUTHOR ADDRESS: Respiratory Medicine, Imperial College London, Norfolk
  Place, St Mary's Campus, London, W2 1PG, UK**UK
AUTHOR E-MAIL ADDRESS: f.culley@imperial.ac.uk
JOURNAL: European Journal of Immunology  33 (5): p1302-1310 May 2003
2003
MEDIUM: print
ISSN: 0014-2980 _(ISSN print)
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English


 5/3/3     (Item 3 from file: 5)
DIALOG(R)File   5:Biosis Previews(R)
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17248537   BIOSIS NO.: 200300207256
F(ab)'2-mediated neutralization of C3a and C5a anaphylatoxins: A novel
  effector function of immunoglobulins.
AUTHOR: Basta Milan (Reprint); Van Goor Fredric; Luccioli Stefano; Billings
  Eric M; Vortmeyer Alexander O; Baranyi Lajos; Szebeni Janos; Alving Carl
  R; Carroll Michael C; Berkower Ira; Stojilkovic Stanko S; Metcalfe Dean D
AUTHOR ADDRESS: Neuronal Excitability Section, National Institute for
  Neurological Disorders and Stroke, National Institutes of Health,
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Page 8887

Bethesda, MD, USA**USA
AUTHOR E-MAIL ADDRESS: mb29r@nih.gov
JOURNAL: Nature Medicine 9 (4): p431-438 April 2003 2003
MEDIUM: print
ISSN: 1078-8956 _(ISSN print)
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

5/3/4 (Item 4 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)
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17015827 BIOSIS NO.: 200200609338
Contribution of anaphylatoxin C5a to allergic late airway responses after repeated antigen exposure
AUTHOR: Abe Masayoshi (Reprint); Shibata Kazuhiko; Akatsu Hiroyasu; Shimizu Naomi; Katsuragi Takeshi (Reprint); Okada Hidechika
AUTHOR ADDRESS: Department of Pharmacology, Fukuoka University, Fukuoka, 814-0180, Japan**Japan
JOURNAL: International Immunopharmacology 2 (9): p1369 August, 2002 2002
MEDIUM: print
CONFERENCE/MEETING: XIX International Complement Workshop Palermo, Italy September 22-26, 2002; 20020922
ISSN: 1567-5769
DOCUMENT TYPE: Meeting; Meeting Abstract
RECORD TYPE: Citation
LANGUAGE: English

5/3/5 (Item 5 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)
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16311521 BIOSIS NO.: 200100483360
Anaphylatoxins and infectious and non-infectious inflammatory diseases
AUTHOR: Koehl Joerg (Reprint)
AUTHOR ADDRESS: Institute of Medical Microbiology, Medical School Hannover, Carl-Neubergstrasse 1, 30625, Hannover, Germany**Germany
JOURNAL: Molecular Immunology 38 (2-3): p175-187 August, 2001 2001
MEDIUM: print
ISSN: 0161-5890
DOCUMENT TYPE: Article; Literature Review
RECORD TYPE: Abstract
LANGUAGE: English

5/3/6 (Item 6 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)
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16148495 BIOSIS NO.: 200100320334
Involvement of A3 receptors in the potentiation by adenosine of the inhibitory effect of theophylline on human eosinophil degranulation: Possible novel mechanism of the anti-inflammatory action of theophylline
AUTHOR: Ezeamuzie Charles I (Reprint)
AUTHOR ADDRESS: Department of Pharmacology and Toxicology, Faculty of Medicine, Kuwait University, Safat, 13110, Kuwait**Kuwait
JOURNAL: Biochemical Pharmacology 61 (12): p1551-1559 15 June, 2001

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Page 8888

2001
MEDIUM: print
ISSN: 0006-2952
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

5/3/7 (Item 7 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)
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16119661 BIOSIS NO.: 200100291500
Complement-dependent immune complex-induced bronchial inflammation and hyperreactivity
AUTHOR: Lukacs Nicholas W (Reprint); Glovsky M Michael; Ward Peter A
AUTHOR ADDRESS: Dept. of Pathology, Univ. of Michigan Medical School, 1301 Catherine, Ann Arbor, MI, 48109-0602, USA**USA
JOURNAL: American Journal of Physiology 280 (3 Part 1): pL512-L518 March, 2001 2001
MEDIUM: print
ISSN: 0002-9513
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

5/3/8 (Item 8 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)
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15978973 BIOSIS NO.: 200100150812
Studies on the effects of adenosine A3 receptor stimulation on human eosinophils isolated from non-asthmatic or asthmatic donors
AUTHOR: Reeves J J (Reprint); Harris C A; Hayes B P; Butchers P R; Sheehan M J
AUTHOR ADDRESS: Receptor Pharmacology Unit, GlaxoWellcome Medicines Research Centre, Gunnels Wood Road, Stevenage, Hertfordshire, SG1 2NY, UK **UK
JOURNAL: Inflammation Research 49 (12): p666-672 December, 2000 2000
MEDIUM: print
ISSN: 1023-3830
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

5/3/9 (Item 9 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)
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15921732 BIOSIS NO.: 200100093571
Identification of complement factor 5 as a susceptibility locus for experimental allergic asthma
AUTHOR: Karp Christopher L; Grupe Andrew; Schadt Eric; Ewart Susan L; Keane-Moore Michelle; Cuomo Peter J; Kohl Jorg; Wahl Larry; Kuperman Douglas; Germer Soren; Aud Dee; Peltz Gary; Wills-Karp Marsha (Reprint)
AUTHOR ADDRESS: Department of Environmental Health Sciences, Johns Hopkins University School of Hygiene and Public Health, Baltimore, 615 N. Wolfe St., Baltimore, MD, 21205, USA**USA
JOURNAL: Nature Immunology 1 (3): p221-226 September, 2000 2000

Samsung Bioepis Exhibit No. 1002
Page 8889

MEDIUM: print
ISSN: 1529-2908
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

5/3/10 (Item 10 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)
(c) 2011 The Thomson Corporation. All rts. reserv.

15033207 BIOSIS NO.: 199900292867
Effect of zafirlukast on cough reflex sensitivity in asthmatics
AUTHOR: Dicpinigaitis Peter V (Reprint); Dobkin Jay B
AUTHOR ADDRESS: Albert Einstein Hospital, 1825 Eastchester Road, Bronx, NY, 10461, USA**USA
JOURNAL: Journal of Asthma 36 (3): p265-270 May, 1999 1999
MEDIUM: print
ISSN: 0277-0903
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

5/3/11 (Item 11 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)
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15023674 BIOSIS NO.: 199900283334
Adenosine A3 receptors on human eosinophils mediate inhibition of degranulation and superoxide anion release
AUTHOR: Ezeamuzie Charles I (Reprint); Philips Elizabeth
AUTHOR ADDRESS: Department of Pharmacology and Toxicology, Faculty of Medicine, Kuwait University, Safat, Kuwait**Kuwait
JOURNAL: British Journal of Pharmacology 127 (1): p188-194 May, 1999 1999
MEDIUM: print
ISSN: 0007-1188
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

5/3/12 (Item 12 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)
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14872644 BIOSIS NO.: 199900132304
Budesonide (BDS) inhibits eosinophil (Eos) chemotaxis through epithelial monolayers and intercellular adhesion molecule (ICAM)-1 expression in C5a-activated bronchial epithelial cells (HBECs)
AUTHOR: Gonzalez R (Reprint); Silvestri M; Cordone A; Morelli M C; Rossi G A
AUTHOR ADDRESS: Pulm Div-Gaslini Inst., Univ. Genoa, Genoa, Italy**Italy
JOURNAL: European Respiratory Journal 12 (SUPPL. 28): p421S Sept., 1998 1998
MEDIUM: print
CONFERENCE/MEETING: European Respiratory Society Annual Congress Geneva, Switzerland September 19-23, 1998; 19980919
SPONSOR: The European Respiratory Society
ISSN: 0903-1936

Samsung Bioepis Exhibit No. 1002
Page 8890

DOCUMENT TYPE: Meeting; Meeting Abstract
RECORD TYPE: Citation
LANGUAGE: English

5/3/13 (Item 13 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)
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14796287 BIOSIS NO.: 199900055947
LFA-1 expression by blood eosinophils is increased in atopic asthmatic children and is involved in eosinophil locomotion
AUTHOR: Lantero S (Reprint); Alessandri G; Spallarossa D; Scarso L; Rossi G A
AUTHOR ADDRESS: Pulmonary Division, G. Gaslini Institute, Largo G, Gaslini 5, 16147 Genoa, Italy**Italy
JOURNAL: European Respiratory Journal 12 (5): p1094-1098 Nov., 1998 1998
MEDIUM: print
ISSN: 0903-1936
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

5/3/14 (Item 14 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)
(c) 2011 The Thomson Corporation. All rts. reserv.

14568578 BIOSIS NO.: 199800362825
Human circulating eosinophils secrete macrophage migration inhibitory factor (MIF): Potential role in asthma
AUTHOR: Rossi Adriano G; Haslett Christopher; Hirani Nikhil; Greening Andrew P; Rahman Irfan; Metz Christine N; Bucala Richard; Donnelly Seamas C (Reprint)
AUTHOR ADDRESS: Respir. Med. Unit, Rayne Lab., Univ. Edinburgh, Med. Sch., Teviot Place, Edinburgh EH8 9AG, UK**UK
JOURNAL: Journal of Clinical Investigation 101 (12): p2869-2874 June 15, 1998 1998
MEDIUM: print
ISSN: 0021-9738
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

5/3/15 (Item 15 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)
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14366033 BIOSIS NO.: 199800160280
Effects of some anti-asthma drugs of human eosinophil superoxide anions release and degranulation
AUTHOR: Ezeamuzie Charles I (Reprint); Al-Hage Mary
AUTHOR ADDRESS: Dep. Pharmacol. Toxicol., Fac. Med., Kuwait Univ., PO Box 24923, Safat 13110, Kuwait**Kuwait
JOURNAL: International Archives of Allergy and Immunology 115 (2): p 162-168 Feb., 1998 ***1998***
MEDIUM: print
ISSN: 1018-2438
DOCUMENT TYPE: Article

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Page 8891

RECORD TYPE: Abstract
LANGUAGE: English

5/3/16 (Item 16 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)
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14304341 BIOSIS NO.: 199800098588
Differential effects of salbutamol and salmeterol on human eosinophil responses
AUTHOR: Ezeamuzie Charles I (Reprint); Al-Hage Mary
AUTHOR ADDRESS: Dep. Pharmacol. Toxicol., Fac. Med., Kuwait Univ., P.O. Box 24923, Safat 13110, Kuwait**Kuwait
JOURNAL: Journal of Pharmacology and Experimental Therapeutics 284 (1): p 25-31 Jan., 1998 ***1998***
MEDIUM: print
ISSN: 0022-3565
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

5/3/17 (Item 17 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)
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13908242 BIOSIS NO.: 199799542302
Identification of neutrophil chemotactic factors in bronchoalveolar lavage fluid of asthmatic patients
AUTHOR: Teran L M; Campos M G; Begishvilli B T; Schroeder J-M; Djukanovic R ; Shute J K; Church M K; Holgate S T (Reprint); Davies D E
AUTHOR ADDRESS: Univ. Med., Level D, Centre Block, Southampton Gen. Hosp., Southampton S016 6YD, UK**UK
JOURNAL: Clinical and Experimental Allergy 27 (4): p396-405 1997 1997
ISSN: 0954-7894
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

5/3/18 (Item 18 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)
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13551361 BIOSIS NO.: 199699185421
Human eotaxin represents a potent activator of the respiratory burst of human eosinophils
AUTHOR: Elsner Joern (Reprint); Hoechstetter Renate; Kimmig Daniela; Kapp Alexander
AUTHOR ADDRESS: Hannover Med. Sch., Dep. Dermatol., Ricklinger Str. 5, D-3049 Hannover, Germany**Germany
JOURNAL: European Journal of Immunology 26 (8): p1919-1925 1996 1996
ISSN: 0014-2980
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

5/3/19 (Item 19 from file: 5)

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DIALOG(R)File 5:Biosis Previews(R)
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13005856 BIOSIS NO.: 199598473689
PDE isoenzymes as targets for anti-asthma drugs
AUTHOR: Schudt C (Reprint); Tenor H; Hatzelmann A
AUTHOR ADDRESS: Dep. Biochemistry, Byk Gulden, Byk-Gulden-Str. 2, 78467 Konstanz, Germany**Germany
JOURNAL: European Respiratory Journal 8 (7): p1179-1183 1995 1995
ISSN: 0903-1936
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

5/3/20 (Item 20 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)
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12950360 BIOSIS NO.: 199598418193
Elevated intracellular cyclic AMP inhibits chemotaxis in human eosinophils
AUTHOR: Kaneko Takeshi; Alvarez Robert; Ueki Iris F; Nadel Jay A (Reprint)
AUTHOR ADDRESS: Cardiovasc. Res. Inst., Box 0130, Univ. Calif. San Francisco, San Francisco, CA 94143-0130, USA**USA
JOURNAL: Cellular Signalling 7 (5): p527-534 1995 1995
ISSN: 0898-6568
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

5/3/21 (Item 21 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)
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12475460 BIOSIS NO.: 199497496745
Effect of in vivo desensitization to leukotriene B-4 on eosinophil infiltration in response to C5a in guinea-pig skin
AUTHOR: Pettipher E R (Reprint); Salter E D; Showell H J
AUTHOR ADDRESS: Dep. Immunology Infectious Diseases, Central Res. Div., Pfizer Inc., Groton, CT 06340, USA**USA
JOURNAL: British Journal of Pharmacology 113 (1): p117-120 1994 1994
ISSN: 0007-1188
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

5/3/22 (Item 22 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)
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11833093 BIOSIS NO.: 199395135359
Inhibition of cytokine-primed eosinophil chemotaxis by nedocromil sodium
AUTHOR: Warringa Ruud A J; Mengelers Hein J J; Maikoe Tjander; Bruijnzeel P L B; Koenderman L (Reprint)
AUTHOR ADDRESS: Dep. Pulm. Dis., Univ. Hosp. Utrecht, P.O. Box 85500, 3500 GA Utrecht, Netherlands Antilles**Netherlands Antilles
JOURNAL: Journal of Allergy and Clinical Immunology 91 (3): p802-809 1993
ISSN: 0091-6749

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DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

5/3/23 (Item 23 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)
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11210584 BIOSIS NO.: 199293053475
COMPLEMENT FRAGMENTS IN PATIENTS WITH BRONCHIAL ASTHMA
AUTHOR: ONODERA H (Reprint); OKAMOTO M; TAKEMURA S; DOI T; KASAMATSU Y; YANAGIDA K; FUKUDA W; TANAKA M; DEGUCHI M; ET AL
AUTHOR ADDRESS: DIV PULMONARY DISEASE, YOSANOUMI KYOTO PREFECTURAL HOSPITAL, KYOTO, JAPAN**JAPAN
JOURNAL: Japanese Journal of Allergology 40 (10): p1272-1281 1991
ISSN: 0021-4884
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: JAPANESE

5/3/24 (Item 24 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)
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08191223 BIOSIS NO.: 198682037610
INHIBITION OF IMMUNOLOGICAL AND NON-IMMUNOLOGICAL HISTAMINE RELEASE FROM HUMAN BASOPHILS AND LUNG MAST CELLS BY FORMOTEROL
AUTHOR: SUBRAMANIAN N (Reprint)
AUTHOR ADDRESS: PHARMACEUTICALS RES DIV, CIBA-GEIGY LTD, POSTFACH, CH-4002 BASEL, SWITZ**SWITZERLAND
JOURNAL: Arzneimittel-Forschung 36 (3): p502-505 1986
ISSN: 0004-4172
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: ENGLISH

5/3/25 (Item 25 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)
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06583748 BIOSIS NO.: 198274000171
DIGESTION OF THE 5TH COMPONENT OF COMPLEMENT C-5 BY EOSINOPHIL LYSOSOMAL ENZYMES PRODUCTION OF EOSINOPHIL SPECIFIC CHEMO TACTIC ACTIVITY
AUTHOR: OGAWA H (Reprint); KUNKEL S L; FANTONE J C; WARD P A
AUTHOR ADDRESS: DEP PATHOL, UNIV MICHIGAN MED SCH, ANN ARBOR, MICHIGAN 48109, USA**USA
JOURNAL: Virchows Archiv B Cell Pathology Including Molecular Pathology 38 (2): p149-158 1981
ISSN: 0340-6075
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: ENGLISH

5/3/26 (Item 1 from file: 73)
DIALOG(R)File 73:EMBASE
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0079809422 EMBASE/Medline No: 2003165428
F(ab)' SUB 2-mediated neutralization of C3a and C5a anaphylatoxins: A novel effector function of immunoglobulins
Basta M.; Van Goor F.; Luccioli S.; Billings E.M.; Vortmeyer A.O.; Baranyi L.; Szebeni J.; Alving C.R.; Carroll M.C.; Berkower I.; Stojilkovic S.S.; Metcalfe D.D.
Neuronal Excitability Section, Natl. Inst. Neurol. Disord./Stroke, Bethesda, MD, United States
AUTHOR EMAIL: mb29r@nih.gov
CORRESP. AUTHOR/AFFIL: Basta M.: Neuronal Excitability Section, Natl. Inst. Neurol. Disord./Stroke, Bethesda, MD, United States
CORRESP. AUTHOR EMAIL: mb29r@nih.gov

Nature Medicine (Nat. Med.) (United States) April 1, 2003, 9/4 (431-438)
CODEN: NAMEF ISSN: 1078-8956
DOI: 10.1038/nm836
DOCUMENT TYPE: Journal; Article RECORD TYPE: Abstract
LANGUAGE: English SUMMARY LANGUAGE: English
NUMBER OF REFERENCES: 38

5/3/27 (Item 2 from file: 73)
DIALOG(R)File 73:EMBASE
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0079523963 EMBASE/Medline No: 2003230236
The complement system as a therapeutic target in autoimmunity
Holers V.M.
Dept. of Medicine and Immunology, Health Science Center, University of Colorado, Denver, CO 80262, United States; Dept. of Medicine and Immunology, Health Science Center, University of Colorado, 4200 E. Ninth Ave., Denver, CO 80262, United States
AUTHOR EMAIL: michael.holers@uchsc.edu
CORRESP. AUTHOR/AFFIL: Holers V.M.: Dept. of Medicine and Immunology, Health Science Center, University of Colorado, 4200 E. Ninth Ave., Denver, CO 80262, United States
CORRESP. AUTHOR EMAIL: michael.holers@uchsc.edu

Clinical Immunology (Clin. Immunol.) (United States) June 1, 2003, 107/3 (140-151)
CODEN: CLIIF ISSN: 1521-6616
DOI: 10.1016/S1521-6616(03)00034-2
DOCUMENT TYPE: Journal; Review RECORD TYPE: Citation
LANGUAGE: English
NUMBER OF REFERENCES: 161

5/3/28 (Item 3 from file: 73)
DIALOG(R)File 73:EMBASE
(c) 2011 Elsevier B.V. All rts. reserv.

0079223518 EMBASE/Medline No: 2002387438
Classical and alternative pathways of mast cell activation
Stassen M.; Hultner L.; Schmitt E.
Institut fur Immunologie, Hochhaus am Augustusplatz, D-55101 Mainz, Germany
CORRESP. AUTHOR/AFFIL: Schmitt E.: Institut fur Immunologie, Hochhaus am Augustusplatz, D-55101 Mainz, Germany
CORRESP. AUTHOR EMAIL: eschmitt@mail.uni-mainz.de

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Page 8895

Critical Reviews in Immunology (Crit. Rev. Immunol.) (United States)
November 13, 2002, 22/2 (115-140)
CODEN: CCRID ISSN: 1040-8401
DOCUMENT TYPE: Journal; Review RECORD TYPE: Abstract
LANGUAGE: English SUMMARY LANGUAGE: English
NUMBER OF REFERENCES: 264

5/3/29 (Item 4 from file: 73)
DIALOG(R)File 73:EMBASE
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0078928240 EMBASE/Medline No: 2002091926
Differential mediator release from basophils of allergic and non-allergic asthmatic patients after stimulation with anti-IgE and C5a
Abrahamsen O.; Haas H.; Schreiber J.; Schlaak M.
Medizinische Klnik Borstel, Parkallee 35, D-23845 Borstel, Germany
CORRESP. AUTHOR/AFFIL: Abrahamsen O.: Medizinische Klnik Borstel, Parkallee 35, D-23845 Borstel, Germany
CORRESP. AUTHOR EMAIL: hhaas@fz-borstel.de

Clinical and Experimental Allergy (Clin. Exp. Allergy) (United Kingdom)
December 1, 2001, 31/3 (368-378)
CODEN: CLEAE ISSN: 0954-7894
DOI: 10.1046/j.1365-2222.2001.00965.x
DOCUMENT TYPE: Journal; Article RECORD TYPE: Abstract
LANGUAGE: English SUMMARY LANGUAGE: English
NUMBER OF REFERENCES: 44

5/3/30 (Item 5 from file: 73)
DIALOG(R)File 73:EMBASE
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0078755074 EMBASE/Medline No: 2001361431
Contribution of anaphylatoxin C5a to late airway responses after repeated exposure of antigen to allergic rats
Abe M.; Shibata K.; Akatsu H.; Shimizu N.; Sakata N.; Katsuragi T.; Okada H.
Department of Pharmacology, School of Medicine, Fukuoka University, Fukuoka 814-0180, Japan
CORRESP. AUTHOR/AFFIL: Abe M.: Department of Pharmacology, School of Medicine, Fukuoka University, Fukuoka 814-0180, Japan
CORRESP. AUTHOR EMAIL: abemasa@fukuoka-u.ac.jp

Journal of Immunology (J. Immunol.) (United States) October 15, 2001, 167/8 (4651-4660)
CODEN: JOIMA ISSN: 0022-1767
DOCUMENT TYPE: Journal; Article RECORD TYPE: Abstract
LANGUAGE: English SUMMARY LANGUAGE: English
NUMBER OF REFERENCES: 37

5/3/31 (Item 6 from file: 73)
DIALOG(R)File 73:EMBASE
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0078584430 EMBASE/Medline No: 2001190709
Involvement of A SUB 3 receptors in the potentiation by adenosine of the inhibitory effect of theophylline on human eosinophil degranulation: Possible novel mechanism of the anti-inflammatory action of theophylline

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Ezeamuzie C.I.
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CORRESP. AUTHOR EMAIL: ezeamuzie@hsc.edu.kw

Biochemical Pharmacology (Biochem. Pharmacol.) (United States) June 15, 2001, 61/12 (1551-1559)
CODEN: BCPCA ISSN: 0006-2952
PUBLISHER ITEM IDENTIFIER: S000629520100613X
DOI: 10.1016/S0006-2952(01)00613-X
DOCUMENT TYPE: Journal; Article RECORD TYPE: Abstract
LANGUAGE: English SUMMARY LANGUAGE: English
NUMBER OF REFERENCES: 44

5/3/32 (Item 7 from file: 73)
DIALOG(R)File 73:EMBASE
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0078431604 EMBASE/Medline No: 2001037439
Studies on the effects of adenosine A SUB 3 receptor stimulation on human eosinophils isolated from non-asthmatic or asthmatic donors
Reeves J.J.; Harris C.A.; Hayes B.P.; Butchers P.R.; Sheehan M.J.
Receptor Pharmacology Unit, GlaxoWellcome Medicines Research Centre, Gunnels Wood Road, Stevenage, Hertfordshire SG1 2NY, United Kingdom
CORRESP. AUTHOR/AFFIL: Reeves J.J.: Receptor Pharmacology Unit, GlaxoWellcome Medicines Res. Ctr., Gunnels Wood Road, Stevenage, Hertfordshire SG1 2NY, United Kingdom

Inflammation Research (Inflamm. Res.) (Switzerland) December 1, 2000, 49/12 (666-672)
CODEN: INREF ISSN: 1023-3830
DOI: 10.1007/s000110050644
DOCUMENT TYPE: Journal; Article RECORD TYPE: Abstract
LANGUAGE: English SUMMARY LANGUAGE: English
NUMBER OF REFERENCES: 29

5/3/33 (Item 8 from file: 73)
DIALOG(R)File 73:EMBASE
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0077674791 EMBASE/Medline No: 1999160983
Adenosine A SUB 3 receptors on human eosinophils mediate inhibition of degranulation and superoxide anion release
Ezeamuzie C.I.; Philips E.
Dept. of Pharmacol. and Toxicology, Faculty of Medicine, Kuwait University, P.O. Box 24923, Safat, Kuwait
AUTHOR EMAIL: ezeamuzie@hsc.kuniv.edu.kw
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CORRESP. AUTHOR EMAIL: ezeamuzie@hsc.kuniv.edu.kw

British Journal of Pharmacology (Br. J. Pharmacol.) (United Kingdom) May 19, 1999, 127/1 (188-194)
CODEN: BJPCB ISSN: 0007-1188
DOCUMENT TYPE: Journal; Article RECORD TYPE: Abstract

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LANGUAGE: English SUMMARY LANGUAGE: English
NUMBER OF REFERENCES: 37

5/3/34 (Item 9 from file: 73)
DIALOG(R)File 73:EMBASE
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0077408734 EMBASE/Medline No: 1998319152
Eosinophil degranulation in the presence of lung fibroblasts
Takafuji S.; Shoji S.; Ito K.; Yamamoto K.; Nakagawa T.
Dept. of Med. and Physical Therapy, Faculty of Medicine, University of Tokyo; Department of Internal Medicine, Toyoko Hospital, St. Marianna Univ. Sch. of Medicine, Kawasaki-City, Japan; Department of Internal Medicine, Toyoko Hospital, St. Marianna Univ. Sch. of Medicine, 3-435 Kosugi, Kawasaki-City, Kanagawa 211-0063, Japan
AUTHOR EMAIL: takafu@po.iijnet.or.jp
CORRESP. AUTHOR/AFFIL: Takafuji S.: Department of Internal Medicine, Toyoko Hospital, St. Marianna Univ. School Medicine, 3-435 Kosugi, Kawasaki-City, Kanagawa 211-0063, Japan
CORRESP. AUTHOR EMAIL: takafu@po.iijnet.or.jp

International Archives of Allergy and Immunology (Int. Arch. Allergy Immunol.) (Switzerland) September 1, 1998, 117/SUPPL. 1 (52-54)
CODEN: IAAIE ISSN: 1018-2438
DOCUMENT TYPE: Journal; Conference Paper RECORD TYPE: Abstract
LANGUAGE: English SUMMARY LANGUAGE: English
NUMBER OF REFERENCES: 7

5/3/35 (Item 10 from file: 73)
DIALOG(R)File 73:EMBASE
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0077402613 EMBASE/Medline No: 1998313031
Triple role of platelet-activating factor in eosinophil migration across monolayers of lung epithelial cells: Eosinophil chemoattractant and priming agent and epithelial cell activator
Liu L.; Zuurbier A.E.M.; Mul F.P.J.; Verhoeven A.J.; Lutter R.; Knol E.F.; Roos D.
Ctrl. Lab. Netherlands Red Cross B., Lab. of Exp. and Clinical Immunology, University of Amsterdam, Amsterdam, Netherlands
AUTHOR EMAIL: d; roos@clb.nl
CORRESP. AUTHOR/AFFIL: Roos D.: Central Laboratory, Netherlands Red Cross, Blood Transfusion Service, Plesmanlaan 125, 1066 CX Amsterdam, Netherlands

Journal of Immunology (J. Immunol.) (United States) September 15, 1998, 161/6 (3064-3070)
CODEN: JOIMA ISSN: 0022-1767
DOCUMENT TYPE: Journal; Article RECORD TYPE: Abstract
LANGUAGE: English SUMMARY LANGUAGE: English
NUMBER OF REFERENCES: 54

5/3/36 (Item 11 from file: 73)
DIALOG(R)File 73:EMBASE
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0077208165 EMBASE/Medline No: 1998116870
The effect of salmeterol on human eosinophils is both stimulus- and

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response-dependent
  Ezeamuzie C.I.; Al-Hage M.; Nwankwoala R.N.P.
  Dept. of Pharmacol./Toxicol., Faculty of Medicine, Kuwait University, P.O. Box 24923, Safat, 13110, Kuwait
  CORRESP. AUTHOR/AFFIL: Ezeamuzie C.I.: Dept. of Pharmacol./Toxicol., Faculty of Medicine, Kuwait University, P.O. Box 24923, Safat, 13110, Kuwait

  International Journal of Immunopharmacology (Int. J. Immunopharmacol.) (United Kingdom) December 1, 1997, 19/8 (421-430)
  CODEN: IJIMD ISSN: 0192-0561
  PUBLISHER ITEM IDENTIFIER: S0192056197000994
  DOI: 10.1016/S0192-0561(97)00099-4
  DOCUMENT TYPE: Journal; Article RECORD TYPE: Abstract
  LANGUAGE: English SUMMARY LANGUAGE: English
  NUMBER OF REFERENCES: 33

 5/3/37 (Item 12 from file: 73)
DIALOG(R)File 73:EMBASE
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0077125113 EMBASE/Medline No: 1998033540
  Effects of some anti-asthma drugs on human eosinophil superoxide anions release and degranulation
  Ezeamuzie C.I.; Al-Hage M.
  Dept. of Pharmacology and Toxicology, Faculty of Medicine, Kuwait University, Safat, Kuwait; Dept. of Pharmacology and Toxicology, Faculty of Medicine, Kuwait University, PO Box 24923, Safat 13110, Kuwait
  CORRESP. AUTHOR/AFFIL: Ezeamuzie C.I.: Department Pharmacology Toxicology, Faculty of Medicine, Kuwait University, PO Box 24923, Safat 13110, Kuwait

  International Archives of Allergy and Immunology (Int. Arch. Allergy Immunol.) (Switzerland) February 1, 1998, 115/2 (162-168)
  CODEN: IAAIE ISSN: 1018-2438
  DOCUMENT TYPE: Journal; Article RECORD TYPE: Abstract
  LANGUAGE: English SUMMARY LANGUAGE: English
  NUMBER OF REFERENCES: 27

 5/3/38 (Item 13 from file: 73)
DIALOG(R)File 73:EMBASE
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0076905205 EMBASE/Medline No: 1997198322
  Eosinophil cationic protein in allergic disease (part one)
  Proteina cationica del eosinofilo en enfermedades alergicas (Primera parte)
  Miralles Lopez J.C.; Negro J.M.; Hernandez J.; Caravaca F.; Sarrio F.
  Plaza Juan XXIII, no. 3, 30008 Murcia, Spain
  CORRESP. AUTHOR/AFFIL: Mirales Lopez J.C.: Plaza Juan XXIII, no. 3, 30008 Murcia, Spain

  Revista Espanola de Alergologia e Inmunologia Clinica (REV. ESP. ALERGOL. INMUNOL. CLIN.) (Spain) December 1, 1996, 11/2 (77-84)
  CODEN: REACE ISSN: 0214-1477
  DOCUMENT TYPE: Journal; Review RECORD TYPE: Abstract
  LANGUAGE: Spanish SUMMARY LANGUAGE: English; Spanish
  NUMBER OF REFERENCES: 47

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5/3/39 (Item 14 from file: 73)
DIALOG(R)File 73:EMBASE
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0074972758 EMBASE/Medline No: 1992124431
Complement activation by house dust: Reduced reactivity of serum complement in patients with bronchial asthma
Castro F.F.M.; Schmitz-Schumann M.; Rother U.; Kirschfink M.
Institute of Immunology, University of Heidelberg, Im Neuenheimer Feld 305, D-W-6900 Heidelberg, Germany
CORRESP. AUTHOR/AFFIL: Kirschfink M.: Institute of Immunology, University of Heidelberg, Im Neuenheimer Feld 305, D-W-6900 Heidelberg, Germany

International Archives of Allergy and Applied Immunology (INT. ARCH. ALLERGY APPL. IMMUNOL.) (Switzerland) December 1, 1991, 96/4 (305-310)
CODEN: IAAAA ISSN: 0020-5915
DOCUMENT TYPE: Journal; Article RECORD TYPE: Abstract
LANGUAGE: English SUMMARY LANGUAGE: English

5/3/40 (Item 15 from file: 73)
DIALOG(R)File 73:EMBASE
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0074963760 EMBASE/Medline No: 1992115433
In vivo priming of platelet-activating factor-induced eosinophil chemotaxis in allergic asthmatic individuals
Warringa R.A.J.; Mengelers H.J.J.; Kuijper P.H.M.; Raaijmakers J.A.M.; Bruijnzeel P.L.B.; Koenderman L.
Pulmonary Diseases Department, University Hospital Utrecht, PO Box 85500, 3500 GA Utrecht, Netherlands
CORRESP. AUTHOR/AFFIL: Koenderman L.: Pulmonary Diseases Department, University Hospital Utrecht, PO Box 85500, 3500 GA Utrecht, Netherlands

Blood (BLOOD) (United States) April 15, 1992, 79/7 (1836-1841)
CODEN: BLOOA ISSN: 0006-4971
DOCUMENT TYPE: Journal; Article RECORD TYPE: Abstract
LANGUAGE: English SUMMARY LANGUAGE: English

5/3/41 (Item 16 from file: 73)
DIALOG(R)File 73:EMBASE
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0072279433 EMBASE/Medline No: 1982022051
Digestion of the fifth component of complement by eosinophil lysosomal enzymes. Production of eosinophil specific chemotactic activity
Ogawa H.; Kunkel S.L.; Fantone J.C.; Ward P.A.
Dept. Pathol., Univ. Michigan Med. Sch., Ann Arbor, MI 48109, United States:
CORRESP. AUTHOR/AFFIL: Dept. Pathol., Univ. Michigan Med. Sch., Ann Arbor, MI 48109, United States

Virchows Archiv Abteilung B Cell Pathology (VIRCHOWS ARCH. ABT. B CELL PATHOL.) (Germany) December 1, 1981, 38/2 (149-157)
CODEN: VAAZA
DOCUMENT TYPE: Journal; Article RECORD TYPE: Abstract
LANGUAGE: English

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5/3/42 (Item 17 from file: 73)
DIALOG(R)File 73:EMBASE
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0071514916 EMBASE/Medline No: 1979248367
Late immune reactions in the allergen induced bronchial asthma
ZUR PATHOGENESE VERZOGERTER IMMUNREAKTIONEN BEIM ASTHMA BRONCHIALE
Dorsch W.; Baur X.; Becker Th.
Inst. Poliklin. Arbeitsmed., Klin. Grosshadern, Germany:
CORRESP. AUTHOR/AFFIL: Inst. Poliklin. Arbeitsmed., Klin. Grosshadern, Germany

Atemwegs- und Lungenkrankheiten (ATEMWEGS- LUNGENKR.) (Germany)
December 17, 1979, 5/4 (294-297)
CODEN: ATLUD ISSN: 0341-3055
DOCUMENT TYPE: Journal RECORD TYPE: Abstract
LANGUAGE: German SUMMARY LANGUAGE: English

5/3/43 (Item 18 from file: 73)
DIALOG(R)File 73:EMBASE
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0067846920 EMBASE/Medline No: 9730868
A CD18/ICAM-1-dependent pathway mediates eosinophil adhesion to human bronchial epithelial cells.
Burke-Gaffney A.; Hellewell P.G.
Department of Applied Pharmacology, Imperial College School of Medicine at the National Heart and Lung Institute, London, United Kingdom.
CORRESP. AUTHOR/AFFIL: Burke-Gaffney A.: Department of Applied Pharmacology, Imperial College School of Medicine at the National Heart and Lung Institute, London, United Kingdom.
CORRESP. AUTHOR EMAIL: a.burke-gaffney@ic.ac.uk

American journal of respiratory cell and molecular biology (Am. J. Respir. Cell Mol. Biol.) (United States) September 1, 1998, 19/3 (408-418)
ISSN: 1044-1549
DOCUMENT TYPE: Journal; Article RECORD TYPE: Abstract
FILE SEGMENT: Medline
LANGUAGE: English

5/3/44 (Item 1 from file: 155)
DIALOG(R)File 155:MEDLINE(R)
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14836962 PMID: 11719302
Effect of wortmannin on human eosinophil responses in vitro and on bronchial inflammation and airway hyperresponsiveness in Guinea pigs in vivo.
Ezeamuzie C I; Sukumaran J; Philips E
Department of Pharmacology and Toxicology, Faculty of Medicine, Kuwait University, Safat, Kuwait. ezeamuzie@hsc.kuniv.edu.kw
American journal of respiratory and critical care medicine (United States) Nov 1 2001, 164 (9) p1633-9, ISSN 1073-449X--Print 1073-449X --Linking Journal Code: 9421642
Publishing Model Print
Document type: Evaluation Studies; In Vitro; Journal Article; Research Support, Non-U.S. Gov't
Languages: ENGLISH

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Main Citation Owner: NLM
Record type: MEDLINE; Completed

5/3/45 (Item 2 from file: 155)
DIALOG(R)File 155:MEDLINE(R)
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13404955 PMID: 9860239
Eosinophil leukocyte degranulation in response to serum-opsonized beads: C5a and platelet-activating factor enhance ECP release, with roles for protein kinases A and C.
Egesten A; Malm J
Department of Medicine, Lund University, University Hospital MAS, Malmo, Sweden.
Allergy (DENMARK) Nov 1998, 53 (11) p1066-73, ISSN 0105-4538 --Print 0105-4538--Linking Journal Code: 7804028
Publishing Model Print
Document type: Journal Article; Research Support, Non-U.S. Gov't
Languages: ENGLISH
Main Citation Owner: NLM
Record type: MEDLINE; Completed

5/3/46 (Item 3 from file: 155)
DIALOG(R)File 155:MEDLINE(R)
(c) format only 2011 Dialog. All rts. reserv.

12495041 PMID: 8947334
Allergic bronchial asthma: eosinophil chemotaxis and antihistaminic drug modulation.
Ventura M T; Casale G; Cenci L; Tursi A
Department of Allergology and Clinical Immunology, University of Bari, Italy.
Allergy (DENMARK) Nov 1996, 51 (11) p777-81, ISSN 0105-4538--Print 0105-4538--Linking Journal Code: 7804028
Publishing Model Print
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: MEDLINE; Completed

5/3/47 (Item 4 from file: 155)
DIALOG(R)File 155:MEDLINE(R)
(c) format only 2011 Dialog. All rts. reserv.

08766625 PMID: 3608241
Airway responses in vitro following C5a des Arg-induced hyper-responsiveness in vivo in rabbits.
Armour C L; Black J L; Vincenc K S; Johnson P R; Ward H; Berend N
Clinical and experimental pharmacology & physiology (ENGLAND) Jan 1987, 14 (1) p7-14, ISSN 0305-1870--Print 0305-1870--Linking Journal Code: 0425076
Publishing Model Print
Document type: Comparative Study; In Vitro; Journal Article; Research Support, Non-U.S. Gov't
Languages: ENGLISH
Main Citation Owner: NLM
Record type: MEDLINE; Completed

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Page 8902

5/3/48 (Item 5 from file: 155)
DIALOG(R)File 155:MEDLINE(R)
(c) format only 2011 Dialog. All rts. reserv.

08204591 PMID: 2415448
[Cellular and humoral bases of allergic reactions].
Zellulare und humorale Grundlagen allergischer Reaktionen.
Kownatzki E
Immunitat und Infektion (GERMANY, WEST) Sep 1985, 13 (5) p165-70, ISSN 0340-1162--Print 0340-1162--Linking Journal Code: 7505519
Publishing Model Print
Document type: English Abstract; Journal Article
Languages: GERMAN
Main Citation Owner: NLM
Record type: MEDLINE; Completed

5/3/49 (Item 6 from file: 155)
DIALOG(R)File 155:MEDLINE(R)
(c) format only 2011 Dialog. All rts. reserv.

07002752 PMID: 6459046
Immune complex injury of the lung. Symposium held at the 74th annual meeting of the American Thoracic Society, Las Vegas, Nevada, May 1979.
Daniele R P; Henson P M; Fantone J C; Ward P A; Dreisin R B
American review of respiratory disease (UNITED STATES) Dec 1981, 124 (6) p738-55, ISSN 0003-0805--Print 0003-0805--Linking Journal Code: 0370523
Contract/Grant No.: AI-09651; AI; NIAID NIH HHS United States; HL-21565; HL; NHLBI NIH HHS United States; HL-23877; HL; NHLBI NIH HHS United States; +
Publishing Model Print
Document type: Journal Article; Research Support, Non-U.S. Gov't; Research Support, U.S. Gov't, P.H.S.; Review
Languages: ENGLISH
Main Citation Owner: NLM
Record type: MEDLINE; Completed

5/3/50 (Item 1 from file: 399)
DIALOG(R)File 399:CA SEARCH(R)
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139307760 CA: 139(20)307760a PATENT
Preparation of new aryl imidazoles and related compounds as C5a receptor modulators
INVENTOR(AUTHOR): Luke, George P.; Maynard, George; Mitchell, Scott; Thurkauf, Andrew; Xie, Linghong; Zhang, Luyan; Zhang, Suoming; Zhao, He; Chenard, Bertrand L.; Gao, Yang; Han, Bingsong; He, Xiao Shu
LOCATION: USA
ASSIGNEE: Neurogen Corporation
PATENT: PCT International ; WO 200382829 A1 DATE: 20031009
APPLICATION: WO 2003US9938 (20030328) *US PV369112 (20020329) *US PV392145 (20020626)
PAGES: 356 pp. CODEN: PIXXD2 LANGUAGE: English
PATENT CLASSIFICATIONS:
CLASS: C07D-233/54A; A61K-031/4164B
DESIGNATED COUNTRIES: AE; AG; AL; AM; AT; AU; AZ; BA; BB; BG; BR; BY; BZ; CA; CH; CN; CO; CR; CU; CZ; DE; DK; DM; DZ; EC; EE; ES; FI; GB; GD; GE; GH; GM; HR; HU; ID; IL; IN; IS; JP; KE; KG; KP; KR; KZ; LC; LK; LR; LS; LT; LU;

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Page 8903

LV; MA; MD; MG; MK; MN; MW; MX; MZ; NO; NZ; OM; PH; PL; PT; RO; RU; SC; SD;
SE; SG; SK; SL; TJ; TM; TN; TR; TT; TZ; UA; UG; US; UZ; VC; VN; YU; ZA; ZM;
ZW; AM; AZ; BY; KG; KZ; MD; RU; TJ; TM DESIGNATED REGIONAL: GH; GM; KE; LS
; MW; MZ; SD; SL; SZ; TZ; UG; ZM; ZW; AT; BE; BG; CH; CY; CZ; DE; DK; EE;
ES; FI; FR; GB; GR; HU; IE; IT; LU; MC; NL; PT; RO; SE; SI; SK; TR; BF; BJ;
CF; CG; CI; CM; GA; GN; GQ; GW; ML; MR; NE; SN; TD; TG

5/3/51 (Item 2 from file: 399)
DIALOG(R)File 399:CA SEARCH(R)
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139307693 CA: 139(20)307693f PATENT
Preparation of substituted tetrahydroisoquinolines as C5a receptor modulators
INVENTOR(AUTHOR): Mitchell, Scott; Ohliger, Robert; Zhang, Luyan; Zhao, He; Currie, Kevin; Lee, Kyungae
LOCATION: USA
ASSIGNEE: Neurogen Corporation
PATENT: PCT International ; WO 200382828 A1 DATE: 20031009
APPLICATION: WO 2003US9046 (20030325) *US PV368199 (20020328)
PAGES: 104 pp. CODEN: PIXXD2 LANGUAGE: English
PATENT CLASSIFICATIONS:
CLASS: C07D-217/04A; A61K-031/47B
DESIGNATED COUNTRIES: AE; AG; AL; AM; AT; AU; AZ; BA; BB; BG; BR; BY; BZ;
CA; CH; CN; CO; CR; CU; CZ; DE; DK; DM; DZ; EC; EE; ES; FI; GB; GD; GE; GH;
GM; HR; HU; ID; IL; IN; IS; JP; KE; KG; KP; KR; KZ; LC; LK; LR; LS; LT; LU;
LV; MA; MD; MG; MK; MN; MW; MX; MZ; NO; NZ; OM; PH; PL; PT; RO; RU; SC; SD;
SE; SG; SK; SL; TJ; TM; TN; TR; TT; TZ; UA; UG; US; UZ; VC; VN; YU; ZA; ZM;
ZW; AM; AZ; BY; KG; KZ; MD; RU; TJ; TM DESIGNATED REGIONAL: GH; GM; KE; LS
; MW; MZ; SD; SL; SZ; TZ; UG; ZM; ZW; AT; BE; BG; CH; CY; CZ; DE; DK; EE;
ES; FI; FR; GB; GR; HU; IE; IT; LU; MC; NL; PT; RO; SE; SI; SK; TR; BF; BJ;
CF; CG; CI; CM; GA; GN; GQ; GW; ML; MR; NE; SN; TD; TG

5/3/52 (Item 3 from file: 399)
DIALOG(R)File 399:CA SEARCH(R)
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139307607 CA: 139(20)307607f PATENT
Preparation of substituted biaryl amides as C5a receptor modulators
INVENTOR(AUTHOR): Gao, Yang; Hutchison, Alan; Peterson, John; Pringle, Wallace; Thurkauf, Andrew; Yoon, Taeyoung; Zhao, He
LOCATION: USA
ASSIGNEE: Neurogen Corporation
PATENT: PCT International ; WO 200382826 A1 DATE: 20031009
APPLICATION: WO 2003US9045 (20030325) *US PV368462 (20020328) *US PV372150 (20021204)
PAGES: 144 pp. CODEN: PIXXD2 LANGUAGE: English
PATENT CLASSIFICATIONS:
CLASS: C07D-215/00A; C07D-233/02B; C07D-235/02B; C07D-317/44B; C07D-405/00B; C07D-409/00B; A61K-031/38B; A61K-031/40B; A61K-031/415B
DESIGNATED COUNTRIES: AE; AG; AL; AM; AT; AU; AZ; BA; BB; BG; BR; BY; BZ;
CA; CH; CN; CO; CR; CU; CZ; DE; DK; DM; DZ; EC; EE; ES; FI; GB; GD; GE; GH;
GM; HR; HU; ID; IL; IN; IS; JP; KE; KG; KP; KR; KZ; LC; LK; LR; LS; LT; LU;
LV; MA; MD; MG; MK; MN; MW; MX; MZ; NO; NZ; OM; PH; PL; PT; RO; RU; SC; SD;
SE; SG; SK; SL; TJ; TM; TN; TR; TT; TZ; UA; UG; US; UZ; VC; VN; YU; ZA; ZM;
ZW; AM; AZ; BY; KG; KZ; MD; RU; TJ; TM DESIGNATED REGIONAL: GH; GM; KE; LS
; MW; MZ; SD; SL; SZ; TZ; UG; ZM; ZW; AT; BE; BG; CH; CY; CZ; DE; DK; EE;
ES; FI; FR; GB; GR; HU; IE; IT; LU; MC; NL; PT; RO; SE; SI; SK; TR; BF; BJ;
CF; CG; CI; CM; GA; GN; GQ; GW; ML; MR; NE; SN; TD; TG

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5/3/53 (Item 4 from file: 399)
DIALOG(R)File 399:CA SEARCH(R)
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139286343 CA: 139(19)286343z PATENT
Combination therapy using a C5a antagonist and a C5a receptor-inactive therapeutic agent for the treatment of conditions with pathogenic inflammatory components
INVENTOR(AUTHOR): Krause, James
LOCATION: USA
ASSIGNEE: Neurogen Corporation
PATENT: PCT International ; WO 200384524 A1 DATE: 20031016
APPLICATION: WO 2003US9424 (20030327) *US PV368925 (20020329)
PAGES: 221 pp. CODEN: PIXXD2 LANGUAGE: English
PATENT CLASSIFICATIONS:
CLASS: A61K-031/19A; A61K-031/415B; A61K-031/445B
DESIGNATED COUNTRIES: AE; AG; AL; AM; AT; AU; AZ; BA; BB; BG; BR; BY; BZ; CA; CH; CN; CO; CR; CU; CZ; DE; DK; DM; DZ; EC; EE; ES; FI; GB; GD; GE; GH; GM; HR; HU; ID; IL; IN; IS; JP; KE; KG; KP; KR; KZ; LC; LK; LR; LS; LT; LU; LV; MA; MD; MG; MK; MN; MW; MX; MZ; NI; NO; NZ; OM; PH; PL; PT; RO; RU; SC; SD; SE; SG; SK; SL; TJ; TM; TN; TR; TT; TZ; UA; UG; US; UZ; VC; VN; YU; ZA; ZM; ZW; AM; AZ; BY; KG; KZ; MD; RU; TJ; TM DESIGNATED REGIONAL: GH; GM; KE; LS; MW; MZ; SD; SL; SZ; TZ; UG; ZM; ZW; AT; BE; BG; CH; CY; CZ; DE; DK; EE; ES; FI; FR; GB; GR; HU; IE; IT; LU; MC; NL; PT; RO; SE; SI; SK; TR; BF; BJ; CF; CG; CI; CM; GA; GN; GQ; GW; ML; MR; NE; SN; TD; TG

5/3/54 (Item 5 from file: 399)
DIALOG(R)File 399:CA SEARCH(R)
(c) 2011 American Chemical Society. All rts. reserv.

138331692 CA: 138(22)331692e PATENT
Cyclic peptides and peptidomimetic compounds as G protein-coupled receptor antagonists, and therapeutic use
INVENTOR(AUTHOR): Taylor, Steve; Shiels, Ian Alexander
LOCATION: Australia
ASSIGNEE: University of Queensland
PATENT: PCT International ; WO 200333528 A1 DATE: 20030424
APPLICATION: WO 2002AU1427 (20021017) *AU 20018334 (20011017)
PAGES: 97 pp. CODEN: PIXXD2 LANGUAGE: English
PATENT CLASSIFICATIONS:
CLASS: C07K-007/56A; A61K-038/08B; A61P-011/00B; A61P-009/10B; A61P-017/00B; A61P-037/00B
DESIGNATED COUNTRIES: AE; AG; AL; AM; AT; AU; AZ; BA; BB; BG; BR; BY; BZ; CA; CH; CN; CO; CR; CU; CZ; DE; DK; DM; DZ; EC; EE; ES; FI; GB; GD; GE; GH; GM; HR; HU; ID; IL; IN; IS; JP; KE; KG; KP; KR; KZ; LC; LK; LR; LS; LT; LU; LV; MA; MD; MG; MK; MN; MW; MX; MZ; NO; NZ; OM; PH; PL; PT; RO; RU; SD; SE; SG; SI; SK; SL; TJ; TM; TN; TR; TT; TZ; UA; UG; US; UZ; VN; YU; ZA; ZM; ZW; AM; AZ; BY; KG; KZ; MD; RU; TJ; TM DESIGNATED REGIONAL: GH; GM; KE; LS; MW; MZ; SD; SL; SZ; TZ; UG; ZM; ZW; AT; BE; BG; CH; CY; CZ; DE; DK; EE; ES; FI; FR; GB; GR; IE; IT; LU; MC; NL; PT; SE; SK; TR; BF; BJ; CF; CG; CI; CM; GA; GN; GQ; GW; ML; MR; NE; SN; TD; TG

5/3/55 (Item 6 from file: 399)
DIALOG(R)File 399:CA SEARCH(R)
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136068714 CA: 136(5)68714t PATENT

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Peptide and polypeptide inhibitors of complement C1s
INVENTOR(AUTHOR): West, Robert R.; Sheppard, Paul O.; Fox, Brian A.
LOCATION: USA
ASSIGNEE: Zymogenetics, Inc.
PATENT: PCT International ; WO 200198365 A2 DATE: 20011227
APPLICATION: WO 2001US19405 (20010618) *US PV212998 (20000621)
PAGES: 99 pp. CODEN: PIXXD2 LANGUAGE: English
PATENT CLASSIFICATIONS:
CLASS: C07K-700/A
DESIGNATED COUNTRIES: AE; AG; AL; AM; AT; AU; AZ; BA; BB; BG; BR; BY; BZ; CA; CH; CN; CO; CR; CU; CZ; DE; DK; DM; DZ; EC; EE; ES; FI; GB; GD; GE; GH; GM; HR; HU; ID; IL; IN; IS; JP; KE; KG; KP; KR; KZ; LC; LK; LR; LS; LT; LU; LV; MA; MD; MG; MK; MN; MW; MX; MZ; NO; NZ; PL; PT; RO; RU; SD; SE; SG; SI; SK; SL; TJ; TM; TR; TT; TZ; UA; UG; UZ; VN; YU; ZA; ZW; AM; AZ; BY; KG; KZ; MD; RU; TJ; TM DESIGNATED REGIONAL: GH; GM; KE; LS; MW; MZ; SD; SL; SZ; TZ ; UG; ZW; AT; BE; CH; CY; DE; DK; ES; FI; FR; GB; GR; IE; IT; LU; MC; NL; PT; SE; TR; BF; BJ; CF; CG; CI; CM; GA; GN; GW; ML; MR; NE; SN; TD; TG

5/3/56 (Item 7 from file: 399)
DIALOG(R)File 399:CA SEARCH(R)
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129314955 CA: 129(24)314955q PATENT
Inhibition of B-1 cell mediated immune conditions
INVENTOR(AUTHOR): Askenase, Philip W.; Tsuji, Ryohei; Paliwal, Vipin; Kawikova, Ivana
LOCATION: USA
ASSIGNEE: Yale University
PATENT: PCT International ; WO 9846255 A1 DATE: 19981022
APPLICATION: WO 98US7535 (19980417) *US 45234 (19970417)
PAGES: 66 pp. CODEN: PIXXD2 LANGUAGE: English
PATENT CLASSIFICATIONS:
CLASS: A61K-038/20A; A61K-039/395B; G01N-033/53B
DESIGNATED COUNTRIES: AU; CA; JP; US DESIGNATED REGIONAL: AT; BE; CH; CY ; DE; DK; ES; FI; FR; GB; GR; IE; IT; LU; MC; NL; PT; SE

5/3/57 (Item 8 from file: 399)
DIALOG(R)File 399:CA SEARCH(R)
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129157717 CA: 129(13)157717u PATENT
Human c5a-like receptor
INVENTOR(AUTHOR): Coleman, Roger; Bandman, Olga
LOCATION: USA
ASSIGNEE: Incyte Pharmaceuticals, Inc.
PATENT: PCT International ; WO 9833908 A1 DATE: 19980806
APPLICATION: WO 98US1182 (19980120) *US 791974 (19970131)
PAGES: 60 pp. CODEN: PIXXD2 LANGUAGE: English
PATENT CLASSIFICATIONS:
CLASS: C12N-015/12A; C07K-014/705B; C12Q-001/68B; C12N-005/10B; A61K-038/17B; C07K-016/28B; C07K-014/72B
DESIGNATED COUNTRIES: AT; AU; BR; CA; CH; CN; DE; DK; ES; FI; GB; IL; JP; KR; MX; NO; NZ; RU; SE; SG; US; AM; AZ; BY; KG; KZ; MD; RU; TJ; TM
DESIGNATED REGIONAL: GH; GM; KE; LS; MW; SD; SZ; UG; ZW; AT; BE; CH; DE; DK; ES; FI; FR; GB; GR; IE; IT; LU; MC; NL; PT; SE; BF; BJ; CF; CG; CI; CM; GA; GN; ML; MR; NE; SN; TD; TG
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Set Items Description

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S1        662   (C5 OR C5A OR ANTI(W)C5?) AND (ASTHMA)
S2        234   (C5 OR C5A OR ANTI(W)C5?)(20N)(ANTIBOD? OR INHIBIT? OR SUP-
                PRESS? OR BLOCK? OR ANTAGON? OR PREVENT?) AND (ASTHMA)
S3        154   RD S2  (unique items)
S4         57   S3 AND PY<2004
S5         57   RD S4  (unique items)
? t s7/1,3,4,7,9,15,26,27,28,30,37,46
>>>Format 46 is not valid in file 5
>>>Format 46 is not valid in file 73
>>>Format 46 is not valid in file 155
>>>Format 46 is not valid in file 399
? t s5/7/1,3,4,7,9,15,26,27,28,30,37,46

 5/7/1     (Item 1 from file: 5)
DIALOG(R)File   5:Biosis Previews(R)
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17678937   BIOSIS NO.: 200400059694
Inhibition of complement activation decreases airway inflammation and
  hyperresponsiveness.
AUTHOR: Taube Christian; Rha Yeong-Ho; Takeda Katsuyuki; Park Jung-Won;
  Joetham Anthony; Balhorn Annette; Dakhama Azzeddine; Giclas Patricia C;
  Holers V Michael; Gelfand Erwin W (Reprint)
AUTHOR ADDRESS: National Jewish Medical and Research Center, 1400 Jackson
  Street, Denver, CO, 80206, USA**USA
AUTHOR E-MAIL ADDRESS: gelfande@njc.org
JOURNAL: American Journal of Respiratory and Critical Care Medicine  168 (
11): p1333-1341 December 1, 2003 2003
MEDIUM: print
ISSN: 1073-449X _(ISSN print)
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: Studies in murine models have suggested the involvement of the
  complement anaphylatoxins (C3a and C5a) in the development of
  allergic   ***asthma***  . We investigated the effects of   ***inhibiting***
  complement activation after sensitization but before allergen challenge
  on the development of allergic airway inflammation and airway
  hyperresponsiveness. To prevent complement activation, we used a
  recombinant soluble form of the mouse membrane complement inhibitor
  complement receptor-related gene y (Crry) fused to the IgG1 hinge, CH2
  and CH3 domains (Crry-Ig), which has decay-accelerating activity for both
  the classic and alternative pathways of complement as well as cofactor
  activity for factor I-mediated cleavage of C3b and C4b. C57BL/6 mice were
  sensitized (Days 1 and 14) and challenged (Days 24-26) with ovalbumin.
  Crry-Ig was administered after allergen sensitization either as an
  intraperitoneal injection or by nebulization before allergen challenge.
  Crry-Ig significantly prevented the development of airway
  hyperresponsiveness, decreased airway and lung eosinophilia as well as
  the numbers of lung lymphocytes, decreased levels of interleukin (IL)-4,
  IL-5, and IL-13 in bronchoalveolar lavage fluid and decreased serum
  ovalbumin-specific IgE and IgG1. These results suggest that prevention of
  complement activation may have a therapeutic role in the treatment of
  allergic airway inflammation and   ***asthma***   in sensitized individuals.


 5/7/3     (Item 3 from file: 5)
DIALOG(R)File   5:Biosis Previews(R)
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17248537 BIOSIS NO.: 200300207256
F(ab)'2-mediated neutralization of C3a and C5a anaphylatoxins: A novel effector function of immunoglobulins.
AUTHOR: Basta Milan (Reprint); Van Goor Fredric; Luccioli Stefano; Billings Eric M; Vortmeyer Alexander O; Baranyi Lajos; Szebeni Janos; Alving Carl R; Carroll Michael C; Berkower Ira; Stojilkovic Stanko S; Metcalfe Dean D
AUTHOR ADDRESS: Neuronal Excitability Section, National Institute for Neurological Disorders and Stroke, National Institutes of Health, Bethesda, MD, USA**USA
AUTHOR E-MAIL ADDRESS: mb29r@nih.gov
JOURNAL: Nature Medicine 9 (4): p431-438 April 2003 2003
MEDIUM: print
ISSN: 1078-8956 _(ISSN print)
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: High-dose intravenous immunoglobulin (IVIG) prevents immune damage by scavenging complement fragments C3b and C4b. We tested the hypothesis that exogenous immunoglobulin molecules also bind anaphylatoxins C3a and C5a, thereby neutralizing their pro-inflammatory effects. Single-cell calcium measurements in HMC-1 human mast cells showed that a rise in intracellular calcium caused by C3a and C5a was inhibited in a concentration-dependent manner by IVIG, F(ab)'2-IVIG and irrelevant human monoclonal ***antibody*** . C3a- and C5a-induced thromboxane (TXB2) generation and histamine release from HMC-1 cells and whole-blood basophils were also suppressed by exogenous immunoglobulins. In a mouse model of ***asthma*** , immunoglobulin treatment reduced cellular migration to the lung. Lethal C5a-mediated circulatory collapse in pigs was prevented by pretreatment with F(ab)'2-IVIG. Molecular modeling, surface plasmon resonance (SPR) and western blot analyses suggested a physical association between anaphylatoxins and the constant region of F(ab)'2. This binding could interfere with the role of C3a and C5a in inflammation.

5/7/4 (Item 4 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)
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17015827 BIOSIS NO.: 200200609338
Contribution of anaphylatoxin C5a to allergic late airway responses after repeated antigen exposure
AUTHOR: Abe Masayoshi (Reprint); Shibata Kazuhiko; Akatsu Hiroyasu; Shimizu Naomi; Katsuragi Takeshi (Reprint); Okada Hidechika
AUTHOR ADDRESS: Department of Pharmacology, Fukuoka University, Fukuoka, 814-0180, Japan**Japan
JOURNAL: International Immunopharmacology 2 (9): p1369 August, 2002 2002
MEDIUM: print
CONFERENCE/MEETING: XIX International Complement Workshop Palermo, Italy September 22-26, 2002; 20020922
ISSN: 1567-5769
DOCUMENT TYPE: Meeting; Meeting Abstract
RECORD TYPE: Citation
LANGUAGE: English

5/7/7 (Item 7 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

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Page 8908

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16119661 BIOSIS NO.: 200100291500
Complement-dependent immune complex-induced bronchial inflammation and hyperreactivity
AUTHOR: Lukacs Nicholas W (Reprint); Glovsky M Michael; Ward Peter A
AUTHOR ADDRESS: Dept. of Pathology, Univ. of Michigan Medical School, 1301 Catherine, Ann Arbor, MI, 48109-0602, USA**USA
JOURNAL: American Journal of Physiology 280 (3 Part 1): pL512-L518 March, 2001 2001
MEDIUM: print
ISSN: 0002-9513
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: Bronchoconstriction responses in the airway are caused by multiple insults and are the hallmark symptom in ***asthma*** . In an acute lung injury model in mice, IgG immune complex deposition elicited severe airway hyperreactivity that peaked by 1 h, was maintained at 4 h, and was resolved by 24 h. The depletion of complement with cobra venom factor (CVF) markedly reduced the hyperreactive airway responses, suggesting that complement played an important role in the response. Blockade of C5a with specific antisera also significantly reduced airway hyperreactivity in this acute lung model. Complement depletion by CVF treatment significantly reduced tumor necrosis factor and histamine levels in bronchoalveolar lavage fluids, correlating with reductions in airway hyperreactivity. To further examine the role of specific complement requirement, we initiated the immune complex response in C5-sufficient and C5-deficient congenic animals. The airway hyperreactivity response was partially reduced in the C5-deficient mice. Complement depletion with CVF attenuated airway hyperreactivity in the C5-sufficient mice but had a lesser effect on the airway hyperreactive response and histamine release in bronchoalveolar lavage fluids in C5-deficient mice. These data indicate that acute lung injury in mice after deposition of IgG immune complexes induced airway hyperreactivity that is C5 and C5a dependent.

5/7/9 (Item 9 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)
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15921732 BIOSIS NO.: 200100093571
Identification of complement factor 5 as a susceptibility locus for experimental allergic asthma
AUTHOR: Karp Christopher L; Grupe Andrew; Schadt Eric; Ewart Susan L; Keane-Moore Michelle; Cuomo Peter J; Kohl Jorg; Wahl Larry; Kuperman Douglas; Germer Soren; Aud Dee; Peltz Gary; Wills-Karp Marsha (Reprint)
AUTHOR ADDRESS: Department of Environmental Health Sciences, Johns Hopkins University School of Hygiene and Public Health, Baltimore, 615 N. Wolfe St., Baltimore, MD, 21205, USA**USA
JOURNAL: Nature Immunology 1 (3): p221-226 September, 2000 2000
MEDIUM: print
ISSN: 1529-2908
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: The prevalence and severity of allergic asthma continue to rise, lending urgency to the search for environmental triggers and

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Page 8909

genetic substrates. Using microarray analysis of pulmonary gene expression and single nucleotide polymorphism-based genotyping, combined with quantitative trait locus analysis, we identified the gene encoding complement factor 5 (C5) as a susceptibility locus for allergen-induced airway hyperresponsiveness in a murine model of ***asthma*** . A deletion in the coding sequence of C5 leads to C5-deficiency and susceptibility. Interleukin 12 (IL-12) is able to ***prevent*** or reverse experimental allergic ***asthma*** . ***Blockade*** of the C5a receptor rendered human monocytes unable to produce IL-12, mimicking blunted IL-12 production by macrophages from C5-deficient mice and providing a mechanism for the regulation of susceptibility to ***asthma*** by C5. The role of complement in modulating susceptibility to asthma highlights the importance of immunoregulatory events at the interface of innate and adaptive immunity in disease pathogenesis.

5/7/15 (Item 15 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)
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14366033 BIOSIS NO.: 199800160280
Effects of some anti-asthma drugs of human eosinophil superoxide anions release and degranulation
AUTHOR: Ezeamuzie Charles I (Reprint); Al-Hage Mary
AUTHOR ADDRESS: Dep. Pharmacol. Toxicol., Fac. Med., Kuwait Univ., PO Box 24923, Safat 13110, Kuwait**Kuwait
JOURNAL: International Archives of Allergy and Immunology 115 (2): p 162-168 Feb., 1998 ***1998***
MEDIUM: print
ISSN: 1018-2438
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: Background: Eosinophil infiltration of bronchial tissues and subsequent release of inflammatory mediators by them are the hallmarks of bronchial asthma but it has not yet been clarified whether anti-***asthma*** drugs affect these cells directly. In this study, we investigated the direct effects of 8 clinically used anti-asthma drugs (salbutamol, salmeterol, theophylline, denbufylline, disodium cromoglycate (DSCG), azelastine, ketotifen and dexamethasone) on superoxide anions (O2-) and eosinophil peroxidase (EPO) release from human blood eosinophils in vitro. Methods: Highly purified eosinophils were stimulated for O2release with platelet-activating factor (PAF) or interleukin-5 (IL-5), while for EPO release complement fragment (C5a) or N-formyl-methionyl-leucyl-phenylalanine (FMLP) was employed. Generated products were assayed by standard techniques. Results: All the drugs, except ketotifen and dexamethasone, inhibited PAF-induced O2- release in a dose-dependent manner. The IC50 values were 0.7, 5.8, 330, 3,500, 4,200 and 6,250 nM for DSCG, denbufylline, salmeterol, azelastine, salbutamol and theophylline, respectively. On IL-5-induced release, the effects were similar except that salbutamol completely failed to inhibit the release induced by this stimulus. In contrast, EPO release was generally poorly ***inhibited*** , especially when the release was induced by ***C5a*** . Only theophylline and azelastine (both at 10-4 M or more) were able to ***inhibit*** EPO release by both ***C5a*** and FMLP. Salbutamol and, to a lesser extent, salmeterol inhibited FMLP-, but not C5a -induced EPO release, while all the other drugs tested were inactive. Conclusions: The results show that some of the anti-asthma drugs, but not all, do exert direct effects on human blood eosinophils but these effects may be stimulus-dependent and by far more pronounced against O2-

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release than against degranulation.

5/7/26 (Item 1 from file: 73)
DIALOG(R)File 73:EMBASE
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0079809422 EMBASE/Medline No: 2003165428
F(ab)' SUB 2-mediated neutralization of C3a and C5a anaphylatoxins: A novel effector function of immunoglobulins
Basta M.; Van Goor F.; Luccioli S.; Billings E.M.; Vortmeyer A.O.; Baranyi L.; Szebeni J.; Alving C.R.; Carroll M.C.; Berkower I.; Stojilkovic S.S.; Metcalfe D.D.
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CORRESP. AUTHOR EMAIL: mb29r@nih.gov

Nature Medicine (Nat. Med.) (United States) April 1, 2003, 9/4 (431-438)
CODEN: NAMEF ISSN: 1078-8956
DOI: 10.1038/nm836
DOCUMENT TYPE: Journal; Article RECORD TYPE: Abstract
LANGUAGE: English SUMMARY LANGUAGE: English
NUMBER OF REFERENCES: 38

High-dose intravenous immunoglobulin (IVIG) prevents immune damage by scavenging complement fragments C3b and C4b. We tested the hypothesis that exogenous immunoglobulin molecules also bind anaphylatoxins C3a and CSa, thereby neutralizing their pro-inflammatory effects. Single-cell calcium measurements in HMC-1 human mast cells showed that a rise in intracellular calcium caused by C3a and CSa was inhibited in a concentration-dependent manner by IVIG, F(ab)'2-IVIG and irrelevant human monoclonal ***antibody*** . C3a- and ***C5a*** -induced thromboxane (TXB SUB 2) generation and histamine release from HMC-1 cells and whole-blood basophils were also ***suppressed*** by exogenous immunoglobulins. In a mouse model of asthma, immunoglobulin treatment reduced cellular migration to the lung. Lethal CSa-mediated circulatory collapse in pigs was prevented by pretreatment with F(ab)' SUB 2-IVIG. Molecular modeling, surface plasmon resonance (SPR) and western blot analyses suggested a physical association between anaphylatoxins and the constant region of F(ab)' SUB 2. This binding could interfere with the role of C3a and CSa in inflammation.

5/7/27 (Item 2 from file: 73)
DIALOG(R)File 73:EMBASE
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0079523963 EMBASE/Medline No: 2003230236
The complement system as a therapeutic target in autoimmunity
Holers V.M.
Dept. of Medicine and Immunology, Health Science Center, University of Colorado, Denver, CO 80262, United States; Dept. of Medicine and Immunology, Health Science Center, University of Colorado, 4200 E. Ninth Ave., Denver, CO 80262, United States
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CORRESP. AUTHOR/AFFIL: Holers V.M.: Dept. of Medicine and Immunology, Health Science Center, University of Colorado, 4200 E. Ninth Ave., Denver, CO 80262, United States

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Page 8911

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Clinical Immunology (Clin. Immunol.) (United States) June 1, 2003, 107/3 (140-151)
CODEN: CLIIF ISSN: 1521-6616
DOI: 10.1016/S1521-6616(03)00034-2
DOCUMENT TYPE: Journal; Review RECORD TYPE: Citation
LANGUAGE: English
NUMBER OF REFERENCES: 161

5/7/28 (Item 3 from file: 73)
DIALOG(R)File 73:EMBASE
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0079223518 EMBASE/Medline No: 2002387438
Classical and alternative pathways of mast cell activation
Stassen M.; Hultner L.; Schmitt E.
Institut fur Immunologie, Hochhaus am Augustusplatz, D-55101 Mainz, Germany
CORRESP. AUTHOR/AFFIL: Schmitt E.: Institut fur Immunologie, Hochhaus am Augustusplatz, D-55101 Mainz, Germany
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Critical Reviews in Immunology (Crit. Rev. Immunol.) (United States) November 13, 2002, 22/2 (115-140)
CODEN: CCRID ISSN: 1040-8401
DOCUMENT TYPE: Journal; Review RECORD TYPE: Abstract
LANGUAGE: English SUMMARY LANGUAGE: English
NUMBER OF REFERENCES: 264

It has long since been recognized that mast cells are critical effectors of anaphylactic reactions, and the existence of these potentially hazardous cells has solely been justified due to their beneficial role in some infections with extracellular parasites. A novel understanding of mast cells as sentinels of the immune system has been made possible by taking advantage of mast cell-deficient mice in order to study the roles of mast cells in vivo and by detailed analyses of mast cell activation in vitro. Collectively, these experiments have revealed a variety of IgE-independent stimuli, which lead to the activation of mast cells as crucial initiators of an inflammatory response. Besides their effector function, a variety of studies reviewed herein point towards important regulatory roles for mast cells, especially regarding their interaction with other cell types.

5/7/30 (Item 5 from file: 73)
DIALOG(R)File 73:EMBASE
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0078755074 EMBASE/Medline No: 2001361431
Contribution of anaphylatoxin C5a to late airway responses after repeated exposure of antigen to allergic rats
Abe M.; Shibata K.; Akatsu H.; Shimizu N.; Sakata N.; Katsuragi T.; Okada H.
Department of Pharmacology, School of Medicine, Fukuoka University, Fukuoka 814-0180, Japan
CORRESP. AUTHOR/AFFIL: Abe M.: Department of Pharmacology, School of Medicine, Fukuoka University, Fukuoka 814-0180, Japan
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Journal of Immunology (J. Immunol.) (United States) October 15, 2001,

Samsung Bioepis Exhibit No. 1002
Page 8912

167/8 (4651-4660)
CODEN: JOIMA ISSN: 0022-1767
DOCUMENT TYPE: Journal; Article RECORD TYPE: Abstract
LANGUAGE: English SUMMARY LANGUAGE: English
NUMBER OF REFERENCES: 37

We attempted to elucidate the contribution of complement to allergic ***asthma*** . Rat sensitized to OVA received repeated intratracheal exposures to OVA for up to 3 consecutive days, and pulmonary resistance was then estimated for up to 6 h after the last exposure. Whereas the immediate airway response (IAR) in terms of R SUB L tended to decrease in proportion to the number of OVA exposures, late airway response (LAR) became prominent only after three. Although premedication with two kinds of complement inhibitors, soluble complement receptor type 1 (sCR1) or nafamostat mesylate, resulted in inhibition of the IAR after either a single or a double exposure, the LAR was ***inhibited*** after the triple. Premedication with a C5a receptor antagonist (C5aRA) before every exposure to OVA also ***inhibited*** the LAR after three. Repeated OVA exposure resulted in eosinophil and neutrophil infiltration into the bronchial submucosa which was suppressed by premedication with sCR1 or C5aRA. Up-regulation of C5aR mRNA was shown in lungs after triple OVA exposure, but almost no up-regulation of C3aR. Pretreatment with sCR1 or C5aRA suppressed the up-regulation of C5aR expression as well as cytokine messages in the lungs. The ***suppression*** of LAR by pretreatment with sCR1 was reversed by intratracheal instillation of rat C5a desArg the action of which was ***inhibited*** by C5aRA. In contrast, rat C3a desArg or cytokine-induced neutrophil chemoattractant-1 induced cellular infiltration into the bronchial submucosa by costimulation with OVA, but these had no influence on the LAR. These differences might be explained by the fact that costimulation with OVA and C5a synergistically potentiated IAR, whereas that with OVA and either C3a or cytokine-induced neutrophil chemoattractant-1 did not. C5a generated by Ag-Ab complexes helps in the production of cytokines and contributes to the LAR after repeated exposure to Ag.

5/7/37 (Item 12 from file: 73)
DIALOG(R)File 73:EMBASE
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0077125113 EMBASE/Medline No: 1998033540
Effects of some anti-asthma drugs on human eosinophil superoxide anions release and degranulation
Ezeamuzie C.I.; Al-Hage M.
Dept. of Pharmacology and Toxicology, Faculty of Medicine, Kuwait University, Safat, Kuwait; Dept. of Pharmacology and Toxicology, Faculty of Medicine, Kuwait University, PO Box 24923, Safat 13110, Kuwait
CORRESP. AUTHOR/AFFIL: Ezeamuzie C.I.: Department Pharmacology Toxicology, Faculty of Medicine, Kuwait University, PO Box 24923, Safat 13110, Kuwait

International Archives of Allergy and Immunology (Int. Arch. Allergy Immunol.) (Switzerland) February 1, 1998, 115/2 (162-168)
CODEN: IAAIE ISSN: 1018-2438
DOCUMENT TYPE: Journal; Article RECORD TYPE: Abstract
LANGUAGE: English SUMMARY LANGUAGE: English
NUMBER OF REFERENCES: 27

Background: Eosinophil infiltration of bronchial tissues and subsequent release of inflammatory mediators by them are the hallmarks of bronchial asthma but it has not yet been clarified whether anti-asthma

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Page 8913

drugs affect these cells directly. In this study, we investigate the direct effects of 8 clinically used anti-asthma drugs [salbutamol, salmeterol, theophylline, denbufylline, disodium cromoglycate (DSCG), azelastine, ketotifen and dexamethasone] on superoxide anions (O SUB 2 SUP -) and eosinophil peroxidase (EPO) release from human blood eosinophils in vitro. Methods: Highly purified eosinophils were stimulated for O SUB 2 SUP - release with platelet-activating factor (PAF) or interleukin-5 (IL-5), while for EPO release complement fragment (C5a) or N-formyl-methionyl-leucyl-phenylalanine (FMLP) was employed. Generated products were assayed by standard techniques. Results: All the drugs, except ketotifen and dexamethasone, inhibited PAF-induced O SUB 2 SUP - release in a dose-dependent manner. The IC SUB 50 values were 0.7, 5.8, 330, 3500, 4200 and 6250 nM for DSCG, denbufylline, salmeterol, azelastine, salbutamol and theophylline, respectively. On IL-5-induced release, the effects were similar except that salbutamol completely failed to inhibit the release induced by this stimulus. In contrast, EPO release was generally poorly inhibited, especially when the release was induced by ***C5a*** . Only theophylline and azelastine (both at 10 SUP -4 M or more) were able to ***inhibit*** EPO release by both ***C5a*** and FMLP. Salbutamol and, to a lesser extent, salmeterol inhibited FMLP-, but not C5a-induced EPO release, while all the other drugs tested were inactive. Conclusions: The results show that some of the anti- ***asthma*** drugs, but not all, do exert direct effects on human blood eosinophils but these effects may be stimulus-dependent and by far more pronounced against O SUB 2 SUP - release than against degranulation.

5/7/46 (Item 3 from file: 155)
DIALOG(R)File 155:MEDLINE(R)
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12495041 PMID: 8947334
Allergic bronchial asthma: eosinophil chemotaxis and antihistaminic drug modulation.
Ventura M T; Casale G; Cenci L; Tursi A
Department of Allergology and Clinical Immunology, University of Bari, Italy.
Allergy (DENMARK) Nov 1996, 51 (11) p777-81, ISSN 0105-4538--Print 0105-4538--Linking Journal Code: 7804028
Publishing Model Print
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: MEDLINE; Completed
This paper investigated the chemotactic capacity of blood eosinophils (EOS) in response to C5a and formyl-leucyl-phenylalanine (FMLP) in 15 Parietaria-pollen-allergic patients with mild asthma during the Parietaria pollen season. Data showed that EOS chemotaxis toward C5a was significantly reduced during the peak pollen count, compared with the values obtained in normal subjects. On the other hand, FMLP could induce EOS chemotactic activity only in Parietaria-allergic patients, the highest value being registered during the height of the Parietaria season. In vitro cimetidine modulation of chemotactic function in comparison with C5a led to a recovery of the impaired results obtained in the presence of high histamine levels. Moreover, diphenhydramine preincubation of EOS induced a reduction of the enhanced chemotactic activity obtained with low concentrations. The data suggest that different serum histamine levels give rise to an impaired immune-phlogistic response in allergic patients and that histamine-receptor antagonists may modulate this effect.
Record Date Created: 19970303
Record Date Completed: 19970303

Samsung Bioepis Exhibit No. 1002
Page 8914

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PLEASE ENTER A COMMAND OR BE LOGGED OFF IN 5 MINUTES
? ds

Set     Items   Description
S1        662   (C5 OR C5A OR ANTI(W)C5?) AND (ASTHMA)
S2        234   (C5 OR C5A OR ANTI(W)C5?)(20N)(ANTIBOD? OR INHIBIT? OR SUP-
             PRESS? OR BLOCK? OR ANTAGON? OR PREVENT?) AND (ASTHMA)
S3        154   RD S2  (unique items)
S4         57   S3 AND PY<2004
S5         57   RD S4  (unique items)
? ds

Set     Items   Description
S1        662   (C5 OR C5A OR ANTI(W)C5?) AND (ASTHMA)
S2        234   (C5 OR C5A OR ANTI(W)C5?)(20N)(ANTIBOD? OR INHIBIT? OR SUP-
             PRESS? OR BLOCK? OR ANTAGON? OR PREVENT?) AND (ASTHMA)
S3        154   RD S2  (unique items)
S4         57   S3 AND PY<2004
S5         57   RD S4  (unique items)
? s (5g1? or pexelizumab or eculizumab) and asthma
             206  5G1?
             410  PEXELIZUMAB
             902  ECULIZUMAB
          393083  ASTHMA
      S6      52  (5G1? OR PEXELIZUMAB OR ECULIZUMAB) AND ASTHMA
? rd s6
      S7      50  RD S6  (unique items)
? t s7/3/all

 7/3/1     (Item 1 from file: 5)
DIALOG(R)File   5:Biosis Previews(R)
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0021222022   BIOSIS NO.: 200900563459
The effect of C5 inhibition by eculizumab on allergen-induced
  asthmatic responses in patients
AUTHOR: Gail Gauvreau (Reprint); Louis-Philippe Boulet; Beth Severino; Rick
  Watson; Tao Peng; George Obminski; Philippe Prince; Francine Deschesnes;
  Tara Strinich; Killian K J; Joanne Cote; Paul O'Byrne; Yi Wang
AUTHOR ADDRESS: McMaster Univ, Fac Hlth Sci, Dept Med, Hamilton, ON L8N
  3Z5, Canada**Canada
JOURNAL: Molecular Immunology  46 (14, Sp. Iss. SI): p2837-2838 SEP 2009
2009
ITEM IDENTIFIER: doi:10.1016/j.molimm.2009.05.240
CONFERENCE/MEETING: 12th European Meeting on Complement in Human Disease
Visegrad, HUNGARY  September 05 -08, 2009; 20090905
ISSN: 0161-5890
DOCUMENT TYPE: Meeting; Meeting Abstract
RECORD TYPE: Citation
LANGUAGE: English


 7/3/2     (Item 2 from file: 5)
DIALOG(R)File   5:Biosis Previews(R)
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0021046584   BIOSIS NO.: 200900388021
The effect of C5 inhibition by eculizumab on allergen-induced
  asthmatic responses
AUTHOR: Gauvreau G (Reprint); Boulet L; Severino B; Watson R; Peng T;
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Page 8915

Obminski G; Prince P; Deschesnes F; Strinich T; Killian K; Cote J; Wang Y ; O'Byrne P
AUTHOR ADDRESS: McMaster Univ, Fac Hlth Sci, Dept Med, Hamilton, ON L8N 3Z5, Canada**Canada
JOURNAL: Allergy (Oxford) 64 (Suppl. 90): p16 2009 2009
CONFERENCE/MEETING: 28th Congress of the European-Academy-of-Allergy-and-Clinical-Immunology Warsaw, POLAND June 06 -10, 2009; 20090606
SPONSOR: European Acad Allergy & Clin Immunol
ISSN: 0105-4538
DOCUMENT TYPE: Meeting; Meeting Abstract
RECORD TYPE: Citation
LANGUAGE: English

7/3/3 (Item 1 from file: 73)
DIALOG(R)File 73:EMBASE
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0084483911 EMBASE/Medline No: 2011085999
Immunogenicity of protein therapeutics: The key causes, consequences and challenges
Baker M.P.; Reynolds H.M.; Lumicisi B.; Bryson C.J.
Antitope Ltd, Babraham Research Campus, Babraham, Cambridge, United Kingdom
AUTHOR EMAIL: matthew.baker@antitope.co.uk
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Self/Nonself - Immune Recognition and Signaling (Self Nonself - Immune Recogn. Signal.) (United States) October 1, 2010, 1/4 (314-322)
ISSN: 1938-2030 eISSN: 1938-2049
DOI: 10.4161/self.1.4.13904
URL: http://www.landesbioscience.com/journals/selfnonself/Baker-SELF1-4.pdf
DOCUMENT TYPE: Journal; Review RECORD TYPE: Abstract
LANGUAGE: English SUMMARY LANGUAGE: English
NUMBER OF REFERENCES: 92

7/3/4 (Item 2 from file: 73)
DIALOG(R)File 73:EMBASE
(c) 2011 Elsevier B.V. All rts. reserv.

0084464563 EMBASE/Medline No: 2011073119
Advances in the assessment and control of the effector functions of therapeutic antibodies
Jiang X.-R.; Song A.; Bergelson S.; Arroll T.; Parekh B.; May K.; Chung S.; Strouse R.; Mire-Sluis A.; Schenerman M.
Analytical Biochemist, MedImmune, Gaithersburg, MD 20878, United States
AUTHOR EMAIL: jiangx@medimmune.com
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Nature Reviews Drug Discovery (Nat. Rev. Drug Discov.) (United Kingdom) February 1, 2011, 10/2 (101-110)
CODEN: NRDDA ISSN: 1474-1776 eISSN: 1474-1784
PUBLISHER ITEM IDENTIFIER: NRD3365
DOI: 10.1038/nrd3365

DOCUMENT TYPE: Journal; Review RECORD TYPE: Abstract
LANGUAGE: English SUMMARY LANGUAGE: English
NUMBER OF REFERENCES: 63

7/3/5 (Item 3 from file: 73)
DIALOG(R)File 73:EMBASE
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0084458154 EMBASE/Medline No: 2011066412
Current and novel therapeutics in the treatment of systemic lupus erythematosus
Yildirim-Toruner C.; Diamond B.
Department of Pediatrics, Columbia University Medical Center, Morgan Stanley Children's Hospital of New York Presbyterian, New York, NY, United States; Center for Autoimmune and Musculoskeletal Disease, Feinstein Institute for Medical Research, Manhasset, NY, United States
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Journal of Allergy and Clinical Immunology (J. Allergy Clin. Immunol.) (United States) February 1, 2011, 127/2 (303-312)
CODEN: JACIB ISSN: 0091-6749
PUBLISHER ITEM IDENTIFIER: S0091674910030472
DOI: 10.1016/j.jaci.2010.12.1087
DOCUMENT TYPE: Journal; Review RECORD TYPE: Abstract
LANGUAGE: English SUMMARY LANGUAGE: English
NUMBER OF REFERENCES: 85

7/3/6 (Item 4 from file: 73)
DIALOG(R)File 73:EMBASE
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0084453720 EMBASE/Medline No: 2011053656
The complement system
ISSUE TITLE: Innate Immunity
Sarma J.V.; Ward P.A.
Department of Pathology, University of Michigan Medical School, Box 5602, 1301 Catherine Rd., Ann Arbor, MI 48109-5602, United States
AUTHOR EMAIL: pward@umich.edu
CORRESP. AUTHOR/AFFIL: Ward P. A.: Department of Pathology, University of Michigan Medical School, Box 5602, 1301 Catherine Rd., Ann Arbor, MI 48109-5602, United States
CORRESP. AUTHOR EMAIL: pward@umich.edu

Cell and Tissue Research (Cell Tissue Res.) (Germany) January 1, 2011 , 343/1 (227-235)
CODEN: CTSRC ISSN: 0302-766X
DOI: 10.1007/s00441-010-1034-0
DOCUMENT TYPE: Journal; Review RECORD TYPE: Abstract
LANGUAGE: English SUMMARY LANGUAGE: English
NUMBER OF REFERENCES: 61

7/3/7 (Item 5 from file: 73)
DIALOG(R)File 73:EMBASE
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0084439880 EMBASE/Medline No: 2011058712
Immune system - part III the delicate balance of the immune system between tolerance and autoimmunity
de Souza A.W.S.; Mesquita Jr. D.; Araujo J.A.P.; Catelan T.T.T.; Cruvinel W.M.; Andrade L.E.C.; da Silva N.P.
Universidade Federal de Sao Paulo - UNIFESP
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Revista Brasileira de Reumatologia (Rev. Bras. Reumatol.) (Brazil)
November 1, 2010, 50/6 (665-694)
CODEN: RBREB ISSN: 0482-5004
URL: http://www.scielo.br/pdf/rbr/v50n6/en v50n6a07.pdf
DOCUMENT TYPE: Journal; Review RECORD TYPE: Abstract
LANGUAGE: English SUMMARY LANGUAGE: English
NUMBER OF REFERENCES: 91

7/3/8 (Item 6 from file: 73)
DIALOG(R)File 73:EMBASE
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0084384102 EMBASE/Medline No: 2010702950
What is IgG4? A review of the biology of a unique immunoglobulin subtype
Nirula A.; Glaser S.M.; Kalled S.L.; Taylora F.R.
Biogen Idec, 5200 Research Place, San Diego, CA 92130, United States
AUTHOR EMAIL: ajay.nirula@biogenidec.com
CORRESP. AUTHOR/AFFIL: Nirula A.: Biogen Idec, 5200 Research Place, San Diego, CA 92130, United States
CORRESP. AUTHOR EMAIL: ajay.nirula@biogenidec.com

Current Opinion in Rheumatology (Curr. Opin. Rheumatol.) (United States) January 1, 2011, 23/1 (119-124)
CODEN: CORHE ISSN: 1040-8711
PUBLISHER ITEM IDENTIFIER: 00002281201101000000021
DOI: 10.1097/BOR.0b013e3283412fd4
DOCUMENT TYPE: Journal; Article RECORD TYPE: Abstract
LANGUAGE: English SUMMARY LANGUAGE: English
NUMBER OF REFERENCES: 41

7/3/9 (Item 7 from file: 73)
DIALOG(R)File 73:EMBASE
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0084351225 EMBASE/Medline No: 2010659318
Metrics for antibody therapeutics development
Reichert J.M.
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AUTHOR EMAIL: janice.reichert@tufts.edu
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mAbs (mAbs) (United States) November 1, 2010, 2/6 (695-700)
ISSN: 1942-0862
DOI: 10.4161/mabs.2.6.13603
URL:

Samsung Bioepis Exhibit No. 1002
Page 8918

http://www.landesbioscience.com/journals/mabs/article/EditorsCornerArticle-MABS2-6.pdf
DOCUMENT TYPE: Journal; Review RECORD TYPE: Abstract
LANGUAGE: English SUMMARY LANGUAGE: English
NUMBER OF REFERENCES: 14

7/3/10 (Item 8 from file: 73)
DIALOG(R)File 73:EMBASE
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0084291751 EMBASE/Medline No: 2010609313
Monoclonal antibodies used as prophylactic, therapeutic and diagnostic agents
Chakhtoura M.; Abdelnoor A.M.
Department of Microbiology and Immunology, Faculty of Medicine, American University of Beirut, 0236-Riad el-Solh, Beirut 11972020, Lebanon
AUTHOR EMAIL: aanoor@aub.edu.lb
CORRESP. AUTHOR/AFFIL: Abdelnoor A. M.: Department of Microbiology and Immunology, Faculty of Medicine, American University of Beirut, 0236-Riad el-Solh, Beirut 11972020, Lebanon
CORRESP. AUTHOR EMAIL: aanoor@aub.edu.lb

Immunopharmacology and Immunotoxicology (Immunopharmacol. Immunotoxicol.) (United States) December 1, 2010, 32/4 (533-542)
CODEN: IITOE ISSN: 0892-3973 eISSN: 1532-2513
DOI: 10.3109/08923971003646597
DOCUMENT TYPE: Journal; Review RECORD TYPE: Abstract
LANGUAGE: English SUMMARY LANGUAGE: English
NUMBER OF REFERENCES: 68

7/3/11 (Item 9 from file: 73)
DIALOG(R)File 73:EMBASE
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0084276235 EMBASE/Medline No: 2010604135
Biological therapy in pediatrics
Les biotherapies en pediatrie
Belot A.; Cochat P.
Service de nephrologie et rhumatologie pediatrique, Hopital Femme-Mere-Enfant, Hospices civils de Lyon, universite de Lyon, 69677 Bron cedex, France
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Archives de Pediatrie (Arch. Pediatr.) (France) November 1, 2010, 17/11 (1573-1582)
CODEN: APEDE ISSN: 0929-693X
PUBLISHER ITEM IDENTIFIER: S0929693X10003623
DOI: 10.1016/j.arcped.2010.08.026
DOCUMENT TYPE: Journal; Short Survey RECORD TYPE: Abstract
LANGUAGE: French SUMMARY LANGUAGE: French; English
NUMBER OF REFERENCES: 47

7/3/12 (Item 10 from file: 73)
DIALOG(R)File 73:EMBASE

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0084206230 EMBASE/Medline No: 2010552937
Therapeutic complement inhibition: New developments
Emlen W.; Li W.; Kirschfink M.
Taligen Therapeutics, Cambridge, MA, United States
AUTHOR EMAIL: kirschfink@uni-hd.de
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Seminars in Thrombosis and Hemostasis (Semin. Thromb. Hemost.) (United States) October 18, 2010, 36/6 (660-668)
CODEN: STHMB ISSN: 0094-6176 eISSN: 1098-9064
DOI: 10.1055/s-0030-1262888
DOCUMENT TYPE: Journal; Review RECORD TYPE: Abstract
LANGUAGE: English SUMMARY LANGUAGE: English
NUMBER OF REFERENCES: 46

7/3/13 (Item 11 from file: 73)
DIALOG(R)File 73:EMBASE
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0084015243 EMBASE/Medline No: 2010360911
An augmented passive immune therapy to treat fulminant bacterial infections
Rajam G.; Sampson J.; Carlone G.M.; Ades E.W.
Division of Bacterial Diseases, Centers for Disease Control and Prevention, Building 18, MS G-05, 1600, Clifton Road, Atlanta, GA 30333, United States
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Recent Patents on Anti-Infective Drug Discovery (Recent Pat. Anti-Infect. Drug Discov.) (United Kingdom) August 11, 2010, 5/2 (157-167)
ISSN: 1574-891X
DOI: 10.2174/157489110791233496
DOCUMENT TYPE: Journal; Article RECORD TYPE: Abstract
LANGUAGE: English SUMMARY LANGUAGE: English
NUMBER OF REFERENCES: 136

7/3/14 (Item 12 from file: 73)
DIALOG(R)File 73:EMBASE
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0083957510 EMBASE/Medline No: 2010382591
Clinical pharmacokinetics of therapeutic monoclonal antibodies
Keizer R.J.; Huitema A.D.R.; Schellens J.H.M.; Beijnen J.H.
Department of Pharmacy and Pharmacology, Netherlands Cancer Institute, Slotervaart Hospital, Amsterdam, Netherlands
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Page 8920

Clinical Pharmacokinetics (Clin. Pharmacokinet.) (New Zealand) July 21, 2010, 49/8 (493-507)
CODEN: CPKND ISSN: 0312-5963 eISSN: 1179-1926
DOI: 10.2165/11531280-000000000-00000
DOCUMENT TYPE: Journal; Review RECORD TYPE: Abstract
LANGUAGE: English SUMMARY LANGUAGE: English
NUMBER OF REFERENCES: 128

7/3/15 (Item 13 from file: 73)
DIALOG(R)File 73:EMBASE
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0083762384 EMBASE/Medline No: 2010247700
Therapeutic antibodies for autoimmunity and inflammation
Chan A.C.; Carter P.J.
Department of Immunology, Genentech, Inc., 1 DNA Way, South San Francisco, CA 94080, United States
AUTHOR EMAIL: acc@gene.com; pjc@gene.com
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Nature Reviews Immunology (Nat. Rev. Immunol.) (United Kingdom) May 1, 2010, 10/5 (301-316)
CODEN: NRIAB ISSN: 1474-1733
PUBLISHER ITEM IDENTIFIER: NRI2761
DOI: 10.1038/nri2761
DOCUMENT TYPE: Journal; Review RECORD TYPE: Abstract
LANGUAGE: English SUMMARY LANGUAGE: English
NUMBER OF REFERENCES: 165

7/3/16 (Item 14 from file: 73)
DIALOG(R)File 73:EMBASE
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0083687982 EMBASE/Medline No: 2010207381
The safety and side effects of monoclonal antibodies
Hansel T.T.; Kropshofer H.; Singer T.; Mitchell J.A.; George A.J.T.
Imperial Clinical Respiratory Research Unit (ICRRU), Mint Wing First Floor, St Mary's Hospital, Paddington, London W2 1NY, United Kingdom; National Heart and Lung Institute, Imperial College, Dovehouse Street, London SW3 6LY, United Kingdom
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Nature Reviews Drug Discovery (Nat. Rev. Drug Discov.) (United Kingdom) April 1, 2010, 9/4 (325-338)
CODEN: NRDDA ISSN: 1474-1776 eISSN: 1474-1784
PUBLISHER ITEM IDENTIFIER: NRD3003
DOI: 10.1038/nrd3003
DOCUMENT TYPE: Journal; Review RECORD TYPE: Abstract
LANGUAGE: English SUMMARY LANGUAGE: English
NUMBER OF REFERENCES: 211

7/3/17 (Item 15 from file: 73)

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DIALOG(R)File 73:EMBASE
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0083687734 EMBASE/Medline No: 2010185840
Applying physiological and biochemical concepts to optimize biological drug development
Lowe P.J.
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Clinical Pharmacology and Therapeutics (Clin. Pharmacol. Ther.) (United Kingdom) April 1, 2010, 87/4 (492-496)
CODEN: CLPTA ISSN: 0009-9236 eISSN: 1532-6535
PUBLISHER ITEM IDENTIFIER: CLPT2009302
DOI: 10.1038/clpt.2009.302
DOCUMENT TYPE: Journal; Review RECORD TYPE: Abstract
LANGUAGE: English SUMMARY LANGUAGE: English
NUMBER OF REFERENCES: 31

7/3/18 (Item 16 from file: 73)
DIALOG(R)File 73:EMBASE
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0083529442 EMBASE/Medline No: 2010029624
What's new in internal medicine?
Quoi de neuf en medecine interne ?
Bletry O.; Sene T.; Kahn J.-E.; Ackermann F.; Charles P.; Leport J.; Piette A.-M.
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Annales de Dermatologie et de Venereologie (Ann. Dermatol. Venereol.) (France) December 1, 2009, 136/SUPPL. 7 (S417-S425)
CODEN: ADVED ISSN: 0151-9638
PUBLISHER ITEM IDENTIFIER: S0151963809733836
DOI: 10.1016/S0151-9638(09)73383-6
DOCUMENT TYPE: Journal; Article RECORD TYPE: Abstract
LANGUAGE: French SUMMARY LANGUAGE: French; English
NUMBER OF REFERENCES: 32

7/3/19 (Item 17 from file: 73)
DIALOG(R)File 73:EMBASE
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0083518062 EMBASE/Medline No: 2010039402
Therapeutic potential of complement modulation
Wagner E.; Frank M.M.
Centre de Recherche en Rhumatologie et Immunologie, Centre Hospitalier Universitaire de Quebec, Department de Microbiologie-Infectiologie et Immunologie, QC, Canada
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Page 8922

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Nature Reviews Drug Discovery (Nat. Rev. Drug Discov.) (United Kingdom)
January 1, 2010, 9/1 (43-56)
CODEN: NRDDA ISSN: 1474-1776 eISSN: 1474-1784
PUBLISHER ITEM IDENTIFIER: NRD3011
DOI: 10.1038/nrd3011
DOCUMENT TYPE: Journal; Review RECORD TYPE: Abstract
LANGUAGE: English SUMMARY LANGUAGE: English
NUMBER OF REFERENCES: 122

7/3/20 (Item 18 from file: 73)
DIALOG(R)File 73:EMBASE
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0083391404 EMBASE/Medline No: 2009610652
Complement activation and disease: Protective effects of hyperbilirubinaemia
Basiglio C.L.; Arriaga S.M.; Pelusa F.; Almara A.M.; Kapitulnik J.; Mottino A.D.
Institute of Experimental Physiology (CONICET), National University of Rosario, S2002LRL-Rosario, Argentina
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Clinical Science (Clin. Sci.) (United Kingdom) January 7, 2010, 118/2 (99-113)
CODEN: CSCIA ISSN: 0143-5221
DOI: 10.1042/CS20080540
URL: http://www.clinsci.org/cs/118/0099/1180099.pdf
DOCUMENT TYPE: Journal; Review RECORD TYPE: Abstract
LANGUAGE: English SUMMARY LANGUAGE: English
NUMBER OF REFERENCES: 119

7/3/21 (Item 19 from file: 73)
DIALOG(R)File 73:EMBASE
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0083383823 EMBASE/Medline No: 2009630604
Americas antibody congress: September 21-23, 2009, Washington, D.C.
Lacy S.E.; Bond C.J.; Reichert J.M.; Benjamin D.; Gerber H.-P.; Dimitrov D.
Abbott, Worcester, MA, United States
AUTHOR EMAIL: janice.reichert@tufts.edu
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mAbs (mAbs) (United States) November 1, 2009, 1/6 (523-530)
ISSN: 1942-0862
URL: http://www.landesbioscience.com/journals/mabs/article/LacyMABS1-6.pdf
DOCUMENT TYPE: Journal; Conference Paper RECORD TYPE: Abstract
LANGUAGE: English SUMMARY LANGUAGE: English

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7/3/22 (Item 20 from file: 73)
DIALOG(R)File 73:EMBASE
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0083313524 EMBASE/Medline No: 2009549388
Therapeutic antibodies: Successes, limitations and hopes for the future
Chames P.; Van Regenmortel M.; Weiss E.; Baty D.
Laboratoire d'Ingenierie des Systemes Macromole culaires, CNRS, GDR2352, 31 chemin Joseph Aiguier, F-13402 Marseille Cedex 20, France
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CORRESP. AUTHOR EMAIL: pchames@ibsm.cnrs-mrs.fr

British Journal of Pharmacology (Br. J. Pharmacol.) (United Kingdom) May 1, 2009, 157/2 (220-233)
CODEN: BJPCB ISSN: 0007-1188 eISSN: 1476-5381
DOI: 10.1111/j.1476-5381.2009.00190.x
DOCUMENT TYPE: Journal; Review RECORD TYPE: Abstract
LANGUAGE: English SUMMARY LANGUAGE: English
NUMBER OF REFERENCES: 87

7/3/23 (Item 21 from file: 73)
DIALOG(R)File 73:EMBASE
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0083255836 EMBASE/Medline No: 2009489473
Bioanalytical methods for the quantification of therapeutic monoclonal antibodies and their application in clinical pharmacokinetic studies
Damen C.W.N.; Schellens J.H.M.; Beijnen J.H.
Department of Pharmacy and Pharmacology, Slotervaart Hospital, Netherlands Cancer Institute, Louwesweg 6, 1066 EC Amsterdam, Netherlands
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Human Antibodies (Hum. Antibodies) (Netherlands) October 22, 2009, 18/3 (47-73)
CODEN: HUANF ISSN: 1093-2607
DOI: 10.3233/HAB-2009-0206
DOCUMENT TYPE: Journal; Review RECORD TYPE: Abstract
LANGUAGE: English SUMMARY LANGUAGE: English
NUMBER OF REFERENCES: 208

7/3/24 (Item 22 from file: 73)
DIALOG(R)File 73:EMBASE
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0083238681 EMBASE/Medline No: 2009389340
Fundamentals of antibody-related therapy and diagnostics
Albrecht H.; Rodosevich J.A.; Babich M.
University of California Davis Medical Center, Sacramento, CA, United States
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Page 8924

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Drugs of Today (Drugs Today) (Spain) March 1, 2009, 45/3 (199-211)
CODEN: MDACA ISSN: 1699-4019
DOI: 101358/dot20094531341343
DOCUMENT TYPE: Journal; Review RECORD TYPE: Abstract
LANGUAGE: English SUMMARY LANGUAGE: English
NUMBER OF REFERENCES: 48

7/3/25 (Item 23 from file: 73)
DIALOG(R)File 73:EMBASE
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0083202456 EMBASE/Medline No: 2009382723
Probabilities of success for antibody therapeutics
Reichert J.M.
Tufts Center for the Study of Drug Development, Boston, MA, United States ; 75 Kneeland Street, Boston, MA 02111, United States
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mAbs (mAbs) (United States) July 1, 2009, 1/4 (387-389)
ISSN: 1942-0862
URL: http://www.landesbioscience.com/journals/mabs/article/EditorsCornerMABS1-4.pdf
DOCUMENT TYPE: Journal; Editorial RECORD TYPE: Citation
LANGUAGE: English
NUMBER OF REFERENCES: 6

7/3/26 (Item 24 from file: 73)
DIALOG(R)File 73:EMBASE
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0083170501 EMBASE/Medline No: 2009389290
Editorial: The monoclonal antibodies in therapeutics
Editorial: Les anticorps monoclonaux en therapeutique
Scheen A.J.; Moutschen M.
Universite de Liege; Service de Diabetologie, Nutrition et Maladies Metaboliques, Unite de Pharmacologie Clinique, CHU de Liege; Service de Diabetologie, Nutrition et Maladies Metaboliques, 4000 Liege, Belgium
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Revue Medicale de Liege (Rev. Med. Liege) (Belgium) May 1, 2009, 64/5-6 (233-236)
CODEN: RMLIA ISSN: 0035-3663
URL: http://www.rmlg.ulg.ac.be/aboel.php?num id=1883$langue=FR
DOCUMENT TYPE: Journal; Editorial RECORD TYPE: Citation
LANGUAGE: French
NUMBER OF REFERENCES: 14

7/3/27 (Item 25 from file: 73)
DIALOG(R)File 73:EMBASE
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0083163067 EMBASE/Medline No: 2009406555
New drug therapies and their effect on the skin
Neue Therapeutika und ihre Auswirkungen auf die Haut
Treudler R.
Department of Dermatology, Venerology Allergology, Universitatsklinikum Leipzig A.o.R., Germany; Klinik fur Dermatologie, Venerologie und Allergologie, Universitatsklinikum Leipzig A.o.R., R. Philipp-Rosenthal-Strafie 23, D-04103 Leipzig, Germany
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JDDG - Journal of the German Society of Dermatology (JDDG J. German Soc. Dermatol.) (United Kingdom) July 1, 2009, 7/7 (623-636)
CODEN: JJDDA ISSN: 1610-0379 eISSN: 1610-0387
DOI: 10.1111/j.1610-0387.2009.07139.x
DOCUMENT TYPE: Journal; Review RECORD TYPE: Abstract
LANGUAGE: German; English SUMMARY LANGUAGE: English; German
NUMBER OF REFERENCES: 13

7/3/28 (Item 26 from file: 73)
DIALOG(R)File 73:EMBASE
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0082989962 EMBASE/Medline No: 2009228067
Antibodies for therapeutic uses and the evolution of biotechniques
Nieri P.; Donadio E.; Rossi S.; Adinolfi B.; Podesta A.
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Current Medicinal Chemistry (Curr. Med. Chem.) (Netherlands) May 27, 2009, 16/6 (753-779)
CODEN: CMCHE ISSN: 0929-8673
DOI: 10.2174/092986709787458380
URL: http://www.ingentaconnect.com/content/ben/cmc/2009/00000016/00000006/art00008
DOCUMENT TYPE: Journal; Review RECORD TYPE: Abstract
LANGUAGE: English SUMMARY LANGUAGE: English
NUMBER OF REFERENCES: 311

7/3/29 (Item 27 from file: 73)
DIALOG(R)File 73:EMBASE
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0082969929 EMBASE/Medline No: 2009212481
What is biotherapy? The monoclonal antibody case
Qu'est-ce qu'une biotherapie ? L'exemple des anticorps monoclonaux
Teillaud J.-L.
INSERM, U872, Centre de recherche des Cordeliers, Universite Pierre et Marie Curie-Paris 6, F-75006 Paris, France
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Presse Medicale (Presse Med.) (France) May 1, 2009, 38/5 (825-831)
CODEN: PRMEE ISSN: 0755-4982
PUBLISHER ITEM IDENTIFIER: S0755498209000803
DOI: 10.1016/j.lpm.2008.12.025
DOCUMENT TYPE: Journal; Short Survey RECORD TYPE: Abstract
LANGUAGE: French SUMMARY LANGUAGE: French; English
NUMBER OF REFERENCES: 17

7/3/30 (Item 28 from file: 73)
DIALOG(R)File 73:EMBASE
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0082967205 EMBASE/Medline No: 2009212480
Biotherapy of auto-immune diseases : past, present and future perspectives
Les biotherapies immunomodulatrices du futur : quelles perspectives ?
Arnaud L.; Haroche J.; Piette J.-C.; Amoura Z.
Service de medecine interne 2, Centre de reference des maladies auto-immunes et systemiques rares, Hopital Pitie-Salpetriere, F-75013 Paris Cedex 13, France
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Presse Medicale (Presse Med.) (France) May 1, 2009, 38/5 (749-760)
CODEN: PRMEE ISSN: 0755-4982
PUBLISHER ITEM IDENTIFIER: S0755498209000608
DOI: 10.1016/j.lpm.2008.12.023
DOCUMENT TYPE: Journal; Short Survey RECORD TYPE: Abstract
LANGUAGE: French SUMMARY LANGUAGE: French; English
NUMBER OF REFERENCES: 82

7/3/31 (Item 29 from file: 73)
DIALOG(R)File 73:EMBASE
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0082875595 EMBASE/Medline No: 2009091132
Good practices of administration of the monoclonal antibodies
Bonnes pratiques d'administration des anticorps monoclonaux
Dupont C.; Madelaine-Chambrin I.; Faure P.
Service de Pharmacie, Hopital Saint-Louis, AP-HP, 1 avenue Claude Vellefaux, 75475 Paris Cedex 10
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Journal de Pharmacie Clinique (J. Pharm. Clin.) (France) October 1, 2008, 27/4 (205-209)
CODEN: JPCLD ISSN: 0291-1981
DOI: 10.1684/jpc.2008.0102
DOCUMENT TYPE: Journal; Article RECORD TYPE: Abstract

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Page 8927

LANGUAGE: French SUMMARY LANGUAGE: English; French
NUMBER OF REFERENCES: 8

7/3/32 (Item 30 from file: 73)
DIALOG(R)File 73:EMBASE
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0082864457 EMBASE/Medline No: 2009092623
Development and production of commercial therapeutic monoclonal antibodies in mammalian cell expression systems: An overview of the current upstream technologies
Chartrain M.; Chu L.
Department of Bioprocess R and D, Merck Research Laboratories, P.O. Box 2000, Rahway, NJ 07065, United States
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Current Pharmaceutical Biotechnology (Curr. Pharm. Biotechnol.) (Netherlands) December 1, 2008, 9/6 (447-467)
CODEN: CPBUB ISSN: 1389-2010 eISSN: 1873-4316
DOI: 10.2174/138920108786786367
URL: http://www.ingentaconnect.com/search/download?pub=infobike%3a%2f%2fben%2fcpb%2f2008%2f00000009%2f00000006%2fart00005&mimetype=application%2fpdf&exitTargetId=1235764188183
DOCUMENT TYPE: Journal; Review RECORD TYPE: Abstract
LANGUAGE: English SUMMARY LANGUAGE: English
NUMBER OF REFERENCES: 197

7/3/33 (Item 31 from file: 73)
DIALOG(R)File 73:EMBASE
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0082627791 EMBASE/Medline No: 2008371430
An integrated science-based approach to drug development
Parren P.W.; van de Winkel J.G.
Genmab, Yalelaan 60, P.O. Box 85199, 3508 AD Utrecht, Netherlands
AUTHOR EMAIL: p.parren@genmab.com; j.vandewinkel@genmab.com
CORRESP. AUTHOR/AFFIL: Parren P.W.: Genmab, Yalelaan 60, P.O. Box 85199, 3508 AD Utrecht, Netherlands
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Current Opinion in Immunology (Curr. Opin. Immunol.) (United Kingdom) August 1, 2008, 20/4 (426-430)
CODEN: COPIE ISSN: 0952-7915
PUBLISHER ITEM IDENTIFIER: S0952791508001118
DOI: 10.1016/j.coi.2008.06.006
DOCUMENT TYPE: Journal; Editorial RECORD TYPE: Citation
LANGUAGE: English
NUMBER OF REFERENCES: 13

7/3/34 (Item 32 from file: 73)
DIALOG(R)File 73:EMBASE
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0082532345 EMBASE/Medline No: 2008337552

Samsung Bioepis Exhibit No. 1002
Page 8928

The spectrum of complement alternative pathway-mediated diseases
Holers V.M.
Department of Medicine and Immunology, University of Colorado Denver School of Medicine, Aurora, CO, United States; Department of Medicine and Immunology, Division of Rheumatology, University of Colorado Denver School of Medicine, P.O. Box 6511, Aurora, CO 80045, United States
AUTHOR EMAIL: michael.holers@uchsc.edu
CORRESP. AUTHOR/AFFIL: Holers V. M.: Department of Medicine and Immunology, Division of Rheumatology, University of Colorado Denver School of Medicine, P.O. Box 6511, Aurora, CO 80045, United States
CORRESP. AUTHOR EMAIL: michael.holers@uchsc.edu

Immunological Reviews (Immunol. Rev.) (United Kingdom) June 1, 2008, 223/1 (300-316)
CODEN: IMRED ISSN: 0105-2896 eISSN: 1600-065X
DOI: 10.1111/j.1600-065X.2008.00641.x
DOCUMENT TYPE: Journal; Review RECORD TYPE: Abstract
LANGUAGE: English SUMMARY LANGUAGE: English
NUMBER OF REFERENCES: 136

7/3/35 (Item 33 from file: 73)
DIALOG(R)File 73:EMBASE
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0082137801 EMBASE/Medline No: 2007551026
Complement-targeted therapeutics
Ricklin D.; Lambris J.D.
Department of Pathology and Laboratory Medicine, School of Medicine, University of Pennsylvania, 422 Curie Blvd., Philadelphia, PA 19104, United States
AUTHOR EMAIL: lambris@mail.med.upenn.edu
CORRESP. AUTHOR/AFFIL: Lambris J.D.: Department of Pathology and Laboratory Medicine, School of Medicine, University of Pennsylvania, 422 Curie Blvd., Philadelphia, PA 19104, United States
CORRESP. AUTHOR EMAIL: lambris@mail.med.upenn.edu

Nature Biotechnology (Nat. Biotechnol.) (United States) November 1, 2007, 25/11 (1265-1275)
CODEN: NABIF ISSN: 1087-0156 eISSN: 1546-1696
PUBLISHER ITEM IDENTIFIER: NBT1342
DOI: 10.1038/nbt1342
DOCUMENT TYPE: Journal; Review RECORD TYPE: Abstract
LANGUAGE: English SUMMARY LANGUAGE: English
NUMBER OF REFERENCES: 103

7/3/36 (Item 34 from file: 73)
DIALOG(R)File 73:EMBASE
(c) 2011 Elsevier B.V. All rts. reserv.

0082114304 EMBASE/Medline No: 2007527498
Immunostimulatory antibodies: Challenging the drug testing paradigm
ISSUE TITLE: Fourteenth International Workshop on In Vitro Toxicology
Bhogal N.; Combes R.
Fund for the Replacement of Animals in Medical Experiments, 96-98 North Sherwood Street, Nottingham, NG1 4EE, United Kingdom
AUTHOR EMAIL: nirmala@frame.org.uk
CORRESP. AUTHOR/AFFIL: Bhogal N.: Fund for the Replacement of Animals in Medical Experiments, 96-98 North Sherwood Street, Nottingham, NG1 4EE, United Kingdom

Samsung Bioepis Exhibit No. 1002
Page 8929

CORRESP. AUTHOR EMAIL: nirmala@frame.org.uk

Toxicology in Vitro (Toxicol. Vitro) (United Kingdom) October 1, 2007
, 21/7 (1227-1232)
CODEN: TIVIE ISSN: 0887-2333
PUBLISHER ITEM IDENTIFIER: S0887233307000574
DOI: 10.1016/j.tiv.2007.02.010
DOCUMENT TYPE: Journal; Article RECORD TYPE: Abstract
LANGUAGE: English SUMMARY LANGUAGE: English
NUMBER OF REFERENCES: 19

7/3/37 (Item 35 from file: 73)
DIALOG(R)File 73:EMBASE
(c) 2011 Elsevier B.V. All rts. reserv.

0082079406 EMBASE/Medline No: 2007513970
Considerations for the sensible use of rodent models of inflammatory disease in predicting efficacy of new biological therapeutics in the clinic
ISSUE TITLE: Prediction of Therapeutic and Drug Delivery Outcomes Using Animal Models
Arnett H.A.; Viney J.L.
Amgen, Inc. Department of Inflammation, Seattle, WA 98119, United States
AUTHOR EMAIL: vineyj@amgen.com
CORRESP. AUTHOR/AFFIL: Viney J.L.: Amgen, Inc. Department of Inflammation, Seattle, WA 98119, United States
CORRESP. AUTHOR EMAIL: vineyj@amgen.com

Advanced Drug Delivery Reviews (Adv. Drug Deliv. Rev.) (Netherlands)
September 30, 2007, 59/11 (1084-1092)
CODEN: ADDRE ISSN: 0169-409X
PUBLISHER ITEM IDENTIFIER: S0169409X07001743
DOI: 10.1016/j.addr.2007.06.013
DOCUMENT TYPE: Journal; Review RECORD TYPE: Abstract
LANGUAGE: English SUMMARY LANGUAGE: English
NUMBER OF REFERENCES: 104

7/3/38 (Item 36 from file: 73)
DIALOG(R)File 73:EMBASE
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0082070115 EMBASE/Medline No: 2007504675
Function, structure and therapeutic potential of complement C5a receptors
Monk P.N.; Scola A.-M.; Madala P.; Fairlie D.P.
Academic Neurology Unit, School of Medicine and Biomedical Science, University of Sheffield, Sheffield, United Kingdom; Academic Neurology Unit, School of Medicine and Biomedical Science, University of Sheffield, Beech Hill Road, Sheffield S10 2RX, United Kingdom
AUTHOR EMAIL: p.monk@shef.ac.uk
CORRESP. AUTHOR/AFFIL: Monk P.N.: Academic Neurology Unit, School of Medicine and Biomedical Science, University of Sheffield, Beech Hill Road, Sheffield S10 2RX, United Kingdom
CORRESP. AUTHOR EMAIL: p.monk@shef.ac.uk

British Journal of Pharmacology (Br. J. Pharmacol.) (United Kingdom)
October 1, 2007, 152/4 (429-448)
CODEN: BJPCB ISSN: 0007-1188 eISSN: 1476-5381
PUBLISHER ITEM IDENTIFIER: 0707332
DOI: 10.1038/sj.bjp.0707332
DOCUMENT TYPE: Journal; Review RECORD TYPE: Abstract

Samsung Bioepis Exhibit No. 1002
Page 8930

LANGUAGE: English SUMMARY LANGUAGE: English
NUMBER OF REFERENCES: 259

7/3/39 (Item 37 from file: 73)
DIALOG(R)File 73:EMBASE
(c) 2011 Elsevier B.V. All rts. reserv.

0082039278 EMBASE/Medline No: 2007473697
American Chemical Society - 234th National meeting - Targeting inflammation
Dalziel C.; Veryard C.
Thomson Scientific, 77 Hatton Garden, London, EC1N 8JS, United Kingdom
AUTHOR EMAIL: christopher.dalziel@thomson.com; claire.veryard@thomson.com
CORRESP. AUTHOR/AFFIL: Dalziel C.: Thomson Scientific, 77 Hatton Garden, London, EC1N 8JS, United Kingdom
CORRESP. AUTHOR EMAIL: christopher.dalziel@thomson.com

IDrugs (IDrugs) (United Kingdom) October 1, 2007, 10/10 (674-675)
CODEN: IDRUF ISSN: 1369-7056
DOCUMENT TYPE: Journal; Conference Paper RECORD TYPE: Citation
LANGUAGE: English

7/3/40 (Item 38 from file: 73)
DIALOG(R)File 73:EMBASE
(c) 2011 Elsevier B.V. All rts. reserv.

0082024534 EMBASE/Medline No: 2007458937
Monoclonal antibodies in Pediatrics: Use in prevention and treatment
Martin-Mateos M.A.
Department of Pediatrics, Sant Joan de Deu Hospital - Clinic Hospital, University of Barcelona, Spain; Section Immunology-Allergy, Hospital Sant Joan de Deu, Pg. Sant Joan de Deu, 2, 08950 Esplugues (Barcelona), Spain
AUTHOR EMAIL: martinmateos@hsjdbcn.org
CORRESP. AUTHOR/AFFIL: Martin-Mateos M.A.: Section Immunology-Allergy, Hospital Sant Joan de Deu, Pg. Sant Joan de Deu, 2, 08950 Esplugues (Barcelona), Spain
CORRESP. AUTHOR EMAIL: martinmateos@hsjdbcn.org

Allergologia et Immunopathologia (Allergol. Immunopathol.) (Spain)
July 1, 2007, 35/4 (145-150)
CODEN: AGIMB ISSN: 0301-0546 eISSN: 1578-1267
DOI: 10.1157/13108225
URL: http://external.doyma.es/prepdf/water.asp?pident articulo=13108225&pident usuario=797308&pident revista=105&fichero=105v35n04a13108225pdf001.pdf&ty=49&accion=L&origen=doyma&web=www.doyma.es&lan=es
DOCUMENT TYPE: Journal; Review RECORD TYPE: Abstract
LANGUAGE: English SUMMARY LANGUAGE: English
NUMBER OF REFERENCES: 16

7/3/41 (Item 39 from file: 73)
DIALOG(R)File 73:EMBASE
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0081633412 EMBASE/Medline No: 2007066844
Eculizumab : ***5G1*** .1, h5G1.1, long-acting anti-C5 monoclonal antibody ***5G1*** -1, long-acting anti-C5 monoclonal antibody ***5G1*** .1

Samsung Bioepis Exhibit No. 1002
Page 8931

Drugs in R and D (Drugs R D) (New Zealand) March 16, 2007, 8/1 (61-68)
CODEN: DRDDF ISSN: 1174-5886
DOI: 10.2165/00126839-200708010-00006
URL:
http://drugsrd.adisonline.com/pt/re/rdd/pdfhandler.00126839-200708010-00006.pdf;jsessionid=F2Lp8pZfXmXhPxvXBJfnLVHwnsnmrbLncVlh8mGpQW82WCXkYhD3!1416047858!-949856144!8091!-1
DOCUMENT TYPE: Journal; Article RECORD TYPE: Abstract
LANGUAGE: English SUMMARY LANGUAGE: English
NUMBER OF REFERENCES: 23

7/3/42 (Item 40 from file: 73)
DIALOG(R)File 73:EMBASE
(c) 2011 Elsevier B.V. All rts. reserv.

0081552153 EMBASE/Medline No: 2006615808
Drug evaluation: The C5a receptor antagonist PMX-53
Kohl J.
Cincinnati Children's Hospital Research Foundation, Division of Molecular Immunology, Cincinnati, OH 45229, United States
AUTHOR EMAIL: Joerg.Koehl@chmcc.org
CORRESP. AUTHOR/AFFIL: Kohl J.: Cincinnati Children's Hospital Research Foundation, Division of Molecular Immunology, Cincinnati, OH 45229, United States
CORRESP. AUTHOR EMAIL: Joerg.Koehl@chmcc.org

Current Opinion in Molecular Therapeutics (Curr. Opin. Mol. Ther.) (United Kingdom) December 1, 2006, 8/6 (529-538)
CODEN: CUOTF ISSN: 1464-8431
DOCUMENT TYPE: Journal; Review RECORD TYPE: Abstract
LANGUAGE: English SUMMARY LANGUAGE: English
NUMBER OF REFERENCES: 110

7/3/43 (Item 41 from file: 73)
DIALOG(R)File 73:EMBASE
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0081539106 EMBASE/Medline No: 2006602707
Gateways to clinical trials
Bayes M.; Rabasseda X.; Prous J.R.
Prous Science, S.A., P.O. Box 540, 08080 Barcelona, Spain
AUTHOR EMAIL: mbayes@prous.com
CORRESP. AUTHOR/AFFIL: Bayes M.: Prous Science, S.A., P.O. Box 540, 08080 Barcelona, Spain
CORRESP. AUTHOR EMAIL: mbayes@prous.com

Methods and Findings in Experimental and Clinical Pharmacology (Methods Find. Exp. Clin. Pharmacol.) (Spain) October 1, 2006, 28/8 (533-591)
CODEN: MFEPD ISSN: 0379-0355
DOCUMENT TYPE: Journal; Article RECORD TYPE: Abstract
LANGUAGE: English SUMMARY LANGUAGE: English
NUMBER OF REFERENCES: 335

7/3/44 (Item 42 from file: 73)
DIALOG(R)File 73:EMBASE
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0081531730 EMBASE/Medline No: 2006595313

Samsung Bioepis Exhibit No. 1002
Page 8932

Monoclonal antibodies: Targeted therapy
Gupta N.; Srivastava A.
Intas Biotechnology/Oncology, Plot No. 423/P/A/GIDC, S. Bavla Hwy., Moraiya, Tal: Sanand, Ahmedabad-382 210, India
AUTHOR EMAIL: neera; gupta@intaspharma.com
CORRESP. AUTHOR/AFFIL: Gupta N.: Intas Biotechnology/Oncology, Plot No. 423/P/A/GIDC, S. Bavla Hwy., Moraiya, Tal: Sanand, Ahmedabad-382 210, India
CORRESP. AUTHOR EMAIL: neera; gupta@intaspharma.com

Indian Journal of Pharmacology (Indian J. Pharmacol.) (India) November 1, 2006, 38/6 (390-396)
CODEN: INJPD ISSN: 0253-7613
DOCUMENT TYPE: Journal; Review RECORD TYPE: Abstract
LANGUAGE: English SUMMARY LANGUAGE: English
NUMBER OF REFERENCES: 33

7/3/45 (Item 43 from file: 73)
DIALOG(R)File 73:EMBASE
(c) 2011 Elsevier B.V. All rts. reserv.

0081326448 EMBASE/Medline No: 2006388890
Gateways to clinical trials: July/August 2006
Bayes M.; Rabasseda X.; Prous J.R.
Prous Science, S.A., P.O. Box 540, 08080 Barcelona, Spain
AUTHOR EMAIL: mbayes@prous.com
CORRESP. AUTHOR/AFFIL: Bayes M.: Prous Science, S.A., P.O. Box 540, 08080 Barcelona, Spain
CORRESP. AUTHOR EMAIL: mbayes@prous.com

Methods and Findings in Experimental and Clinical Pharmacology (Methods Find. Exp. Clin. Pharmacol.) (Spain) July 1, 2006, 28/6 (379-412)
CODEN: MFEPD ISSN: 0379-0355
DOCUMENT TYPE: Journal; Review RECORD TYPE: Abstract
LANGUAGE: English SUMMARY LANGUAGE: English
NUMBER OF REFERENCES: 192

7/3/46 (Item 44 from file: 73)
DIALOG(R)File 73:EMBASE
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0081229443 EMBASE/Medline No: 2006291613
Complement factor 5a as a therapeutic target
Woodruff T.M.; Proctor L.M.; Strachan A.J.; Taylor S.M.
Promics Ltd., 35 Miles Platting Road, Brisbane, QLD 4113, Australia
AUTHOR EMAIL: trent.woodruff@promics.com
CORRESP. AUTHOR/AFFIL: Woodruff T.M.: Promics Ltd., 35 Miles Platting Road, Brisbane, QLD 4113, Australia
CORRESP. AUTHOR EMAIL: trent.woodruff@promics.com

Drugs of the Future (Drugs Future) (Spain) April 1, 2006, 31/4 (325-334)
CODEN: DRFUD ISSN: 0377-8282
DOI: 10.1358/dof.2006.031.04.980656
DOCUMENT TYPE: Journal; Review RECORD TYPE: Abstract
LANGUAGE: English SUMMARY LANGUAGE: English
NUMBER OF REFERENCES: 109

7/3/47 (Item 45 from file: 73)

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DIALOG(R)File 73:EMBASE
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0081113024 EMBASE/Medline No: 2006174776
Recent developments in C5/C5a inhibitors
Proctor L.M.; Woodruff T.M.; Taylor S.M.
Promics Ltd, PO Box 4578, Eight Mile Plains, QLD 4113, Australia
AUTHOR EMAIL: s.taylor@uq.edu.au
CORRESP. AUTHOR/AFFIL: Taylor S.M.: Department of Pharmacology, School of Biomedical Sciences, University of Queensland, St Lucia, QLD 4072, Australia
CORRESP. AUTHOR EMAIL: s.taylor@uq.edu.au

Expert Opinion on Therapeutic Patents (Expert Opin. Ther. Pat.) (United Kingdom) April 1, 2006, 16/4 (445-458)
CODEN: EOTPE ISSN: 1354-3776
DOI: 10.1517/13543776.16.4.445
DOCUMENT TYPE: Journal; Review RECORD TYPE: Abstract
LANGUAGE: English SUMMARY LANGUAGE: English
NUMBER OF REFERENCES: 106

7/3/48 (Item 46 from file: 73)
DIALOG(R)File 73:EMBASE
(c) 2011 Elsevier B.V. All rts. reserv.

0080688757 EMBASE/Medline No: 2005333075
Novel C5a regulators in inflammatory disease
Mizuno M.; Cole D.S.
Cardiff University, Department of Medical Biochemistry and Immunology, School of Medicine, Henry Wellcome Building, Heath Park, Cardiff CF14 4XN , United Kingdom
AUTHOR EMAIL: MizunoM1@cardiff.ac.uk
CORRESP. AUTHOR/AFFIL: Mizuno M.: Cardiff University, Department of Medical Biochemistry and Immunology, School of Medicine, Henry Wellcome Building, Heath Park, Cardiff CF14 4XN, United Kingdom
CORRESP. AUTHOR EMAIL: MizunoM1@cardiff.ac.uk

Expert Opinion on Investigational Drugs (Expert Opin. Invest. Drugs) (United Kingdom) July 1, 2005, 14/7 (807-821)
CODEN: EOIDE ISSN: 1354-3784
DOI: 10.1517/13543784.14.7.807
DOCUMENT TYPE: Journal; Review RECORD TYPE: Abstract
LANGUAGE: English SUMMARY LANGUAGE: English
NUMBER OF REFERENCES: 179

7/3/49 (Item 47 from file: 73)
DIALOG(R)File 73:EMBASE
(c) 2011 Elsevier B.V. All rts. reserv.

0079380200 EMBASE/Medline No: 2003083933
IDdb News focus

Current Drug Discovery (Curr. Drug Discov.) (United Kingdom) February 1, 2003, -/FEB. (12-15)
CODEN: CDDUA ISSN: 1472-7463
DOCUMENT TYPE: Journal; Note RECORD TYPE: Citation
LANGUAGE: English

Samsung Bioepis Exhibit No. 1002
Page 8934

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 7/3/50     (Item 1 from file: 399)
DIALOG(R)File 399:CA SEARCH(R)
(c) 2011 American Chemical Society. All rts. reserv.

  151286777    CA: 151(13)286777s    JOURNAL
  The effect of C5 inhibition by eculizumab on allergen-induced asthmatic
  responses in patients
  AUTHOR(S): Gauvreau, Gail; Boulet, Louis-Philippe; Severino, Beth;
Watson, Rick; Peng, Tao; Obminski, George; Prince, Philippe; Deschesnes,
Francine; Strinich, Tara; Killian, K. J.; Cote, Joanne; O'Byrne, Paul;
Wang, Yi
  LOCATION: Department of Medicine, Faculty of Health Sciences, McMaster
University, Hamilton, ON, Can.,
  JOURNAL: Mol. Immunol. (Molecular Immunology)  DATE: 2009  VOLUME: 46
  NUMBER: 14  PAGES: 2837-2838  CODEN: MOIMD5  ISSN: 0161-5890
  PUBLISHER ITEM IDENTIFIER: 0161-5890(09)00480-5  LANGUAGE: English
  PUBLISHER: Elsevier Ltd.
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 8/3/1     (Item 1 from file: 73)
DIALOG(R)File  73:EMBASE
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0079380200     EMBASE/Medline No: 2003083933
  IDdb News focus

  Current Drug Discovery ( Curr. Drug Discov. ) (United Kingdom)  February
  1, 2003, -/FEB. (12-15)
  CODEN: CDDUA   ISSN: 1472-7463
  DOCUMENT TYPE: Journal; Note  RECORD TYPE: Citation
  LANGUAGE: English
? t s8/7/all

 8/7/1     (Item 1 from file: 73)
DIALOG(R)File  73:EMBASE
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0079380200     EMBASE/Medline No: 2003083933
  IDdb News focus

  Current Drug Discovery ( Curr. Drug Discov. ) (United Kingdom)  February
  1, 2003, -/FEB. (12-15)
  CODEN: CDDUA   ISSN: 1472-7463
  DOCUMENT TYPE: Journal; Note  RECORD TYPE: Citation
  LANGUAGE: English
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thesaurus.
  File 399:CA SEARCH(R) 1967-2010/UD=15413
         (c) 2011 American Chemical Society
*File 399: Use is subject to the terms of your user/customer agreement.
IPCR/8 classification codes now searchable as IC=. See HELP NEWSIPCR.

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         1676898  ANTAGONI?
         6387990  INHIBIT?
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         3916010  PREVENT?
         1387742  SUPPRESS?
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      S4      47  S3 AND PY<2003
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Samsung Bioepis Exhibit No. 1002
Page 8936

4/3/1 (Item 1 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)
(c) 2011 The Thomson Corporation. All rts. reserv.

17015827 BIOSIS NO.: 200200609338
Contribution of anaphylatoxin C5a to allergic late airway responses after repeated antigen exposure
AUTHOR: Abe Masayoshi (Reprint); Shibata Kazuhiko; Akatsu Hiroyasu; Shimizu Naomi; Katsuragi Takeshi (Reprint); Okada Hidechika
AUTHOR ADDRESS: Department of Pharmacology, Fukuoka University, Fukuoka, 814-0180, Japan**Japan
JOURNAL: International Immunopharmacology 2 (9): p1369 August, 2002 2002
MEDIUM: print
CONFERENCE/MEETING: XIX International Complement Workshop Palermo, Italy September 22-26, 2002; 20020922
ISSN: 1567-5769
DOCUMENT TYPE: Meeting; Meeting Abstract
RECORD TYPE: Citation
LANGUAGE: English

4/3/2 (Item 2 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)
(c) 2011 The Thomson Corporation. All rts. reserv.

16311521 BIOSIS NO.: 200100483360
Anaphylatoxins and infectious and non-infectious inflammatory diseases
AUTHOR: Koehl Joerg (Reprint)
AUTHOR ADDRESS: Institute of Medical Microbiology, Medical School Hannover, Carl-Neubergstrasse 1, 30625, Hannover, Germany**Germany
JOURNAL: Molecular Immunology 38 (2-3): p175-187 August, 2001 2001
MEDIUM: print
ISSN: 0161-5890
DOCUMENT TYPE: Article; Literature Review
RECORD TYPE: Abstract
LANGUAGE: English

4/3/3 (Item 3 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)
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16148495 BIOSIS NO.: 200100320334
Involvement of A3 receptors in the potentiation by adenosine of the inhibitory effect of theophylline on human eosinophil degranulation: Possible novel mechanism of the anti-inflammatory action of theophylline
AUTHOR: Ezeamuzie Charles I (Reprint)
AUTHOR ADDRESS: Department of Pharmacology and Toxicology, Faculty of Medicine, Kuwait University, Safat, 13110, Kuwait**Kuwait
JOURNAL: Biochemical Pharmacology 61 (12): p1551-1559 15 June, 2001 2001
MEDIUM: print
ISSN: 0006-2952
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

4/3/4 (Item 4 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

Samsung Bioepis Exhibit No. 1002
Page 8937

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16119661 BIOSIS NO.: 200100291500
Complement-dependent immune complex-induced bronchial inflammation and hyperreactivity
AUTHOR: Lukacs Nicholas W (Reprint); Glovsky M Michael; Ward Peter A
AUTHOR ADDRESS: Dept. of Pathology, Univ. of Michigan Medical School, 1301 Catherine, Ann Arbor, MI, 48109-0602, USA**USA
JOURNAL: American Journal of Physiology 280 (3 Part 1): pL512-L518 March, 2001 2001
MEDIUM: print
ISSN: 0002-9513
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

4/3/5 (Item 5 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)
(c) 2011 The Thomson Corporation. All rts. reserv.

15978973 BIOSIS NO.: 200100150812
Studies on the effects of adenosine A3 receptor stimulation on human eosinophils isolated from non-asthmatic or asthmatic donors
AUTHOR: Reeves J J (Reprint); Harris C A; Hayes B P; Butchers P R; Sheehan M J
AUTHOR ADDRESS: Receptor Pharmacology Unit, GlaxoWellcome Medicines Research Centre, Gunnels Wood Road, Stevenage, Hertfordshire, SG1 2NY, UK **UK
JOURNAL: Inflammation Research 49 (12): p666-672 December, 2000 2000
MEDIUM: print
ISSN: 1023-3830
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

4/3/6 (Item 6 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)
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15921732 BIOSIS NO.: 200100093571
Identification of complement factor 5 as a susceptibility locus for experimental allergic asthma
AUTHOR: Karp Christopher L; Grupe Andrew; Schadt Eric; Ewart Susan L; Keane-Moore Michelle; Cuomo Peter J; Kohl Jorg; Wahl Larry; Kuperman Douglas; Germer Soren; Aud Dee; Peltz Gary; Wills-Karp Marsha (Reprint)
AUTHOR ADDRESS: Department of Environmental Health Sciences, Johns Hopkins University School of Hygiene and Public Health, Baltimore, 615 N. Wolfe St., Baltimore, MD, 21205, USA**USA
JOURNAL: Nature Immunology 1 (3): p221-226 September, 2000 2000
MEDIUM: print
ISSN: 1529-2908
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

4/3/7 (Item 7 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)
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15033207   BIOSIS NO.: 199900292867
Effect of zafirlukast on cough reflex sensitivity in asthmatics
AUTHOR: Dicpinigaitis Peter V (Reprint); Dobkin Jay B
AUTHOR ADDRESS: Albert Einstein Hospital, 1825 Eastchester Road, Bronx, NY, 10461, USA**USA
JOURNAL: Journal of Asthma 36 (3): p265-270 May, 1999 1999
MEDIUM: print
ISSN: 0277-0903
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

4/3/8   (Item 8 from file: 5)
DIALOG(R)File   5:Biosis Previews(R)
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15023674   BIOSIS NO.: 199900283334
Adenosine A3 receptors on human eosinophils mediate inhibition of degranulation and superoxide anion release
AUTHOR: Ezeamuzie Charles I (Reprint); Philips Elizabeth
AUTHOR ADDRESS: Department of Pharmacology and Toxicology, Faculty of Medicine, Kuwait University, Safat, Kuwait**Kuwait
JOURNAL: British Journal of Pharmacology 127 (1): p188-194 May, 1999 1999
MEDIUM: print
ISSN: 0007-1188
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

4/3/9   (Item 9 from file: 5)
DIALOG(R)File   5:Biosis Previews(R)
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14872644   BIOSIS NO.: 199900132304
Budesonide (BDS) inhibits eosinophil (Eos) chemotaxis through epithelial monolayers and intercellular adhesion molecule (ICAM)-1 expression in C5a-activated bronchial epithelial cells (HBECs)
AUTHOR: Gonzalez R (Reprint); Silvestri M; Cordone A; Morelli M C; Rossi G A
AUTHOR ADDRESS: Pulm Div-Gaslini Inst., Univ. Genoa, Genoa, Italy**Italy
JOURNAL: European Respiratory Journal 12 (SUPPL. 28): p421S Sept., 1998 1998
MEDIUM: print
CONFERENCE/MEETING: European Respiratory Society Annual Congress Geneva, Switzerland September 19-23, 1998; 19980919
SPONSOR: The European Respiratory Society
ISSN: 0903-1936
DOCUMENT TYPE: Meeting; Meeting Abstract
RECORD TYPE: Citation
LANGUAGE: English

4/3/10   (Item 10 from file: 5)
DIALOG(R)File   5:Biosis Previews(R)
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14796287   BIOSIS NO.: 199900055947

LFA-1 expression by blood eosinophils is increased in atopic asthmatic children and is involved in eosinophil locomotion
AUTHOR: Lantero S (Reprint); Alessandri G; Spallarossa D; Scarso L; Rossi G A
AUTHOR ADDRESS: Pulmonary Division, G. Gaslini Institute, Largo G, Gaslini 5, 16147 Genoa, Italy**Italy
JOURNAL: European Respiratory Journal 12 (5): p1094-1098 Nov., 1998 1998
MEDIUM: print
ISSN: 0903-1936
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

4/3/11 (Item 11 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)
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14568578 BIOSIS NO.: 199800362825
Human circulating eosinophils secrete macrophage migration inhibitory factor (MIF): Potential role in asthma
AUTHOR: Rossi Adriano G; Haslett Christopher; Hirani Nikhil; Greening Andrew P; Rahman Irfan; Metz Christine N; Bucala Richard; Donnelly Seamas C (Reprint)
AUTHOR ADDRESS: Respir. Med. Unit, Rayne Lab., Univ. Edinburgh, Med. Sch., Teviot Place, Edinburgh EH8 9AG, UK**UK
JOURNAL: Journal of Clinical Investigation 101 (12): p2869-2874 June 15, 1998 1998
MEDIUM: print
ISSN: 0021-9738
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

4/3/12 (Item 12 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)
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14366033 BIOSIS NO.: 199800160280
Effects of some anti-asthma drugs of human eosinophil superoxide anions release and degranulation
AUTHOR: Ezeamuzie Charles I (Reprint); Al-Hage Mary
AUTHOR ADDRESS: Dep. Pharmacol. Toxicol., Fac. Med., Kuwait Univ., PO Box 24923, Safat 13110, Kuwait**Kuwait
JOURNAL: International Archives of Allergy and Immunology 115 (2): p 162-168 Feb., 1998 ***1998***
MEDIUM: print
ISSN: 1018-2438
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

4/3/13 (Item 13 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)
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14304341 BIOSIS NO.: 199800098588
Differential effects of salbutamol and salmeterol on human eosinophil

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responses
AUTHOR: Ezeamuzie Charles I (Reprint); Al-Hage Mary
AUTHOR ADDRESS: Dep. Pharmacol. Toxicol., Fac. Med., Kuwait Univ., P.O. Box 24923, Safat 13110, Kuwait**Kuwait
JOURNAL: Journal of Pharmacology and Experimental Therapeutics 284 (1): p 25-31 Jan., 1998 ***1998***
MEDIUM: print
ISSN: 0022-3565
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

4/3/14 (Item 14 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)
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13908242 BIOSIS NO.: 199799542302
Identification of neutrophil chemotactic factors in bronchoalveolar lavage fluid of asthmatic patients
AUTHOR: Teran L M; Campos M G; Begishvilli B T; Schroeder J-M; Djukanovic R ; Shute J K; Church M K; Holgate S T (Reprint); Davies D E
AUTHOR ADDRESS: Univ. Med., Level D, Centre Block, Southampton Gen. Hosp., Southampton S016 6YD, UK**UK
JOURNAL: Clinical and Experimental Allergy 27 (4): p396-405 1997 1997
ISSN: 0954-7894
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

4/3/15 (Item 15 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)
(c) 2011 The Thomson Corporation. All rts. reserv.

13551361 BIOSIS NO.: 199699185421
Human eotaxin represents a potent activator of the respiratory burst of human eosinophils
AUTHOR: Elsner Joern (Reprint); Hoechstetter Renate; Kimmig Daniela; Kapp Alexander
AUTHOR ADDRESS: Hannover Med. Sch., Dep. Dermatol., Ricklinger Str. 5, D-3049 Hannover, Germany**Germany
JOURNAL: European Journal of Immunology 26 (8): p1919-1925 1996 1996
ISSN: 0014-2980
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

4/3/16 (Item 16 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)
(c) 2011 The Thomson Corporation. All rts. reserv.

13005856 BIOSIS NO.: 199598473689
PDE isoenzymes as targets for anti-asthma drugs
AUTHOR: Schudt C (Reprint); Tenor H; Hatzelmann A
AUTHOR ADDRESS: Dep. Biochemistry, Byk Gulden, Byk-Gulden-Str. 2, 78467 Konstanz, Germany**Germany
JOURNAL: European Respiratory Journal 8 (7): p1179-1183 1995 1995
ISSN: 0903-1936

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DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

4/3/17 (Item 17 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)
(c) 2011 The Thomson Corporation. All rts. reserv.

12950360 BIOSIS NO.: 199598418193
Elevated intracellular cyclic AMP inhibits chemotaxis in human eosinophils
AUTHOR: Kaneko Takeshi; Alvarez Robert; Ueki Iris F; Nadel Jay A (Reprint)
AUTHOR ADDRESS: Cardiovasc. Res. Inst., Box 0130, Univ. Calif. San Francisco, San Francisco, CA 94143-0130, USA**USA
JOURNAL: Cellular Signalling 7 (5): p527-534 1995 1995
ISSN: 0898-6568
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

4/3/18 (Item 18 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)
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12475460 BIOSIS NO.: 199497496745
Effect of in vivo desensitization to leukotriene B-4 on eosinophil infiltration in response to C5a in guinea-pig skin
AUTHOR: Pettipher E R (Reprint); Salter E D; Showell H J
AUTHOR ADDRESS: Dep. Immunology Infectious Diseases, Central Res. Div., Pfizer Inc., Groton, CT 06340, USA**USA
JOURNAL: British Journal of Pharmacology 113 (1): p117-120 1994 1994
ISSN: 0007-1188
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

4/3/19 (Item 19 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)
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11833093 BIOSIS NO.: 199395135359
Inhibition of cytokine-primed eosinophil chemotaxis by nedocromil sodium
AUTHOR: Warringa Ruud A J; Mengelers Hein J J; Maikoe Tjander; Bruijnzeel P L B; Koenderman L (Reprint)
AUTHOR ADDRESS: Dep. Pulm. Dis., Univ. Hosp. Utrecht, P.O. Box 85500, 3500 GA Utrecht, Netherlands Antilles**Netherlands Antilles
JOURNAL: Journal of Allergy and Clinical Immunology 91 (3): p802-809 1993
ISSN: 0091-6749
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

4/3/20 (Item 20 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)
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11210584 BIOSIS NO.: 199293053475

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COMPLEMENT FRAGMENTS IN PATIENTS WITH BRONCHIAL ASTHMA
AUTHOR: ONODERA H (Reprint); OKAMOTO M; TAKEMURA S; DOI T; KASAMATSU Y; YANAGIDA K; FUKUDA W; TANAKA M; DEGUCHI M; ET AL
AUTHOR ADDRESS: DIV PULMONARY DISEASE, YOSANOUMI KYOTO PREFECTURAL HOSPITAL, KYOTO, JAPAN**JAPAN
JOURNAL: Japanese Journal of Allergology 40 (10): p1272-1281 1991
ISSN: 0021-4884
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: JAPANESE

4/3/21 (Item 21 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)
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08191223 BIOSIS NO.: 198682037610
INHIBITION OF IMMUNOLOGICAL AND NON-IMMUNOLOGICAL HISTAMINE RELEASE FROM HUMAN BASOPHILS AND LUNG MAST CELLS BY FORMOTEROL
AUTHOR: SUBRAMANIAN N (Reprint)
AUTHOR ADDRESS: PHARMACEUTICALS RES DIV, CIBA-GEIGY LTD, POSTFACH, CH-4002 BASEL, SWITZ**SWITZERLAND
JOURNAL: Arzneimittel-Forschung 36 (3): p502-505 1986
ISSN: 0004-4172
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: ENGLISH

4/3/22 (Item 22 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)
(c) 2011 The Thomson Corporation. All rts. reserv.

06583748 BIOSIS NO.: 198274000171
DIGESTION OF THE 5TH COMPONENT OF COMPLEMENT C-5 BY EOSINOPHIL LYSOSOMAL ENZYMES PRODUCTION OF EOSINOPHIL SPECIFIC CHEMO TACTIC ACTIVITY
AUTHOR: OGAWA H (Reprint); KUNKEL S L; FANTONE J C; WARD P A
AUTHOR ADDRESS: DEP PATHOL, UNIV MICHIGAN MED SCH, ANN ARBOR, MICHIGAN 48109, USA**USA
JOURNAL: Virchows Archiv B Cell Pathology Including Molecular Pathology 38 (2): p149-158 1981
ISSN: 0340-6075
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: ENGLISH

4/3/23 (Item 1 from file: 73)
DIALOG(R)File 73:EMBASE
(c) 2011 Elsevier B.V. All rts. reserv.

0079223518 EMBASE/Medline No: 2002387438
Classical and alternative pathways of mast cell activation
Stassen M.; Hultner L.; Schmitt E.
Institut fur Immunologie, Hochhaus am Augustusplatz, D-55101 Mainz, Germany
CORRESP. AUTHOR/AFFIL: Schmitt E.: Institut fur Immunologie, Hochhaus am Augustusplatz, D-55101 Mainz, Germany
CORRESP. AUTHOR EMAIL: eschmitt@mail.uni-mainz.de

Critical Reviews in Immunology (Crit. Rev. Immunol.) (United States)

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Page 8943

November 13, 2002, 22/2 (115-140)
CODEN: CCRID ISSN: 1040-8401
DOCUMENT TYPE: Journal; Review RECORD TYPE: Abstract
LANGUAGE: English SUMMARY LANGUAGE: English
NUMBER OF REFERENCES: 264

4/3/24 (Item 2 from file: 73)
DIALOG(R)File 73:EMBASE
(c) 2011 Elsevier B.V. All rts. reserv.

0078928240 EMBASE/Medline No: 2002091926
Differential mediator release from basophils of allergic and non-allergic asthmatic patients after stimulation with anti-IgE and C5a
Abrahamsen O.; Haas H.; Schreiber J.; Schlaak M.
Medizinische Klnik Borstel, Parkallee 35, D-23845 Borstel, Germany
CORRESP. AUTHOR/AFFIL: Abrahamsen O.: Medizinische Klnik Borstel, Parkallee 35, D-23845 Borstel, Germany
CORRESP. AUTHOR EMAIL: hhaas@fz-borstel.de

Clinical and Experimental Allergy (Clin. Exp. Allergy) (United Kingdom)
December 1, 2001, 31/3 (368-378)
CODEN: CLEAE ISSN: 0954-7894
DOI: 10.1046/j.1365-2222.2001.00965.x
DOCUMENT TYPE: Journal; Article RECORD TYPE: Abstract
LANGUAGE: English SUMMARY LANGUAGE: English
NUMBER OF REFERENCES: 44

4/3/25 (Item 3 from file: 73)
DIALOG(R)File 73:EMBASE
(c) 2011 Elsevier B.V. All rts. reserv.

0078755074 EMBASE/Medline No: 2001361431
Contribution of anaphylatoxin C5a to late airway responses after repeated exposure of antigen to allergic rats
Abe M.; Shibata K.; Akatsu H.; Shimizu N.; Sakata N.; Katsuragi T.; Okada H.
Department of Pharmacology, School of Medicine, Fukuoka University, Fukuoka 814-0180, Japan
CORRESP. AUTHOR/AFFIL: Abe M.: Department of Pharmacology, School of Medicine, Fukuoka University, Fukuoka 814-0180, Japan
CORRESP. AUTHOR EMAIL: abemasa@fukuoka-u.ac.jp

Journal of Immunology (J. Immunol.) (United States) October 15, 2001, 167/8 (4651-4660)
CODEN: JOIMA ISSN: 0022-1767
DOCUMENT TYPE: Journal; Article RECORD TYPE: Abstract
LANGUAGE: English SUMMARY LANGUAGE: English
NUMBER OF REFERENCES: 37

4/3/26 (Item 4 from file: 73)
DIALOG(R)File 73:EMBASE
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0078584430 EMBASE/Medline No: 2001190709
Involvement of A SUB 3 receptors in the potentiation by adenosine of the inhibitory effect of theophylline on human eosinophil degranulation: Possible novel mechanism of the anti-inflammatory action of theophylline
Ezeamuzie C.I.

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Page 8944

Dept. of Pharmacology and Toxicology, Fac. of Med., Kuwait Univ., 13110, Safat, Kuwait
AUTHOR EMAIL: ezeamuzie@hsc.kuniv.edu.kw
CORRESP. AUTHOR/AFFIL: Ezeamuzie C.I.: Dept. of Pharmacology/Toxicology, Faculty of Medicine, Kuwait University, Safat 13110, Kuwait
CORRESP. AUTHOR EMAIL: ezeamuzie@hsc.edu.kw

Biochemical Pharmacology (Biochem. Pharmacol.) (United States) June 15, 2001, 61/12 (1551-1559)
CODEN: BCPCA ISSN: 0006-2952
PUBLISHER ITEM IDENTIFIER: S000629520100613X
DOI: 10.1016/S0006-2952(01)00613-X
DOCUMENT TYPE: Journal; Article RECORD TYPE: Abstract
LANGUAGE: English SUMMARY LANGUAGE: English
NUMBER OF REFERENCES: 44

4/3/27 (Item 5 from file: 73)
DIALOG(R)File 73:EMBASE
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0078431604 EMBASE/Medline No: 2001037439
Studies on the effects of adenosine A SUB 3 receptor stimulation on human eosinophils isolated from non-asthmatic or asthmatic donors
Reeves J.J.; Harris C.A.; Hayes B.P.; Butchers P.R.; Sheehan M.J.
Receptor Pharmacology Unit, GlaxoWellcome Medicines Research Centre, Gunnels Wood Road, Stevenage, Hertfordshire SG1 2NY, United Kingdom
CORRESP. AUTHOR/AFFIL: Reeves J.J.: Receptor Pharmacology Unit, GlaxoWellcome Medicines Res. Ctr., Gunnels Wood Road, Stevenage, Hertfordshire SG1 2NY, United Kingdom

Inflammation Research (Inflamm. Res.) (Switzerland) December 1, 2000, 49/12 (666-672)
CODEN: INREF ISSN: 1023-3830
DOI: 10.1007/s000110050644
DOCUMENT TYPE: Journal; Article RECORD TYPE: Abstract
LANGUAGE: English SUMMARY LANGUAGE: English
NUMBER OF REFERENCES: 29

4/3/28 (Item 6 from file: 73)
DIALOG(R)File 73:EMBASE
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0077674791 EMBASE/Medline No: 1999160983
Adenosine A SUB 3 receptors on human eosinophils mediate inhibition of degranulation and superoxide anion release
Ezeamuzie C.I.; Philips E.
Dept. of Pharmacol. and Toxicology, Faculty of Medicine, Kuwait University, P.O. Box 24923, Safat, Kuwait
AUTHOR EMAIL: ezeamuzie@hsc.kuniv.edu.kw
CORRESP. AUTHOR/AFFIL: Ezeamuzie C.I.: Department Pharmacology Toxicology, Faculty of Medicine, Kuwait University, PO Box 24923, Safat, Kuwait
CORRESP. AUTHOR EMAIL: ezeamuzie@hsc.kuniv.edu.kw

British Journal of Pharmacology (Br. J. Pharmacol.) (United Kingdom) May 19, 1999, 127/1 (188-194)
CODEN: BJPCB ISSN: 0007-1188
DOCUMENT TYPE: Journal; Article RECORD TYPE: Abstract
LANGUAGE: English SUMMARY LANGUAGE: English

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NUMBER OF REFERENCES: 37

4/3/29 (Item 7 from file: 73)
DIALOG(R)File 73:EMBASE
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0077408734 EMBASE/Medline No: 1998319152
Eosinophil degranulation in the presence of lung fibroblasts
Takafuji S.; Shoji S.; Ito K.; Yamamoto K.; Nakagawa T.
Dept. of Med. and Physical Therapy, Faculty of Medicine, University of Tokyo; Department of Internal Medicine, Toyoko Hospital, St. Marianna Univ. Sch. of Medicine, Kawasaki-City, Japan; Department of Internal Medicine, Toyoko Hospital, St. Marianna Univ. Sch. of Medicine, 3-435 Kosugi, Kawasaki-City, Kanagawa 211-0063, Japan
AUTHOR EMAIL: takafu@po.iijnet.or.jp
CORRESP. AUTHOR/AFFIL: Takafuji S.: Department of Internal Medicine, Toyoko Hospital, St. Marianna Univ. School Medicine, 3-435 Kosugi, Kawasaki-City, Kanagawa 211-0063, Japan
CORRESP. AUTHOR EMAIL: takafu@po.iijnet.or.jp

International Archives of Allergy and Immunology (Int. Arch. Allergy Immunol.) (Switzerland) September 1, 1998, 117/SUPPL. 1 (52-54)
CODEN: IAAIE ISSN: 1018-2438
DOCUMENT TYPE: Journal; Conference Paper RECORD TYPE: Abstract
LANGUAGE: English SUMMARY LANGUAGE: English
NUMBER OF REFERENCES: 7

4/3/30 (Item 8 from file: 73)
DIALOG(R)File 73:EMBASE
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0077402613 EMBASE/Medline No: 1998313031
Triple role of platelet-activating factor in eosinophil migration across monolayers of lung epithelial cells: Eosinophil chemoattractant and priming agent and epithelial cell activator
Liu L.; Zuurbier A.E.M.; Mul F.P.J.; Verhoeven A.J.; Lutter R.; Knol E.F.; Roos D.
Ctrl. Lab. Netherlands Red Cross B., Lab. of Exp. and Clinical Immunology, University of Amsterdam, Amsterdam, Netherlands
AUTHOR EMAIL: d; roos@clb.nl
CORRESP. AUTHOR/AFFIL: Roos D.: Central Laboratory, Netherlands Red Cross, Blood Transfusion Service, Plesmanlaan 125, 1066 CX Amsterdam, Netherlands

Journal of Immunology (J. Immunol.) (United States) September 15, 1998, 161/6 (3064-3070)
CODEN: JOIMA ISSN: 0022-1767
DOCUMENT TYPE: Journal; Article RECORD TYPE: Abstract
LANGUAGE: English SUMMARY LANGUAGE: English
NUMBER OF REFERENCES: 54

4/3/31 (Item 9 from file: 73)
DIALOG(R)File 73:EMBASE
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0077208165 EMBASE/Medline No: 1998116870
The effect of salmeterol on human eosinophils is both stimulus- and response-dependent

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Ezeamuzie C.I.; Al-Hage M.; Nwankwoala R.N.P.
Dept. of Pharmacol./Toxicol., Faculty of Medicine, Kuwait University, P.O. Box 24923, Safat, 13110, Kuwait
CORRESP. AUTHOR/AFFIL: Ezeamuzie C.I.: Dept. of Pharmacol./Toxicol., Faculty of Medicine, Kuwait University, P.O. Box 24923, Safat, 13110, Kuwait

International Journal of Immunopharmacology (Int. J. Immunopharmacol.) (United Kingdom) December 1, 1997, 19/8 (421-430)
CODEN: IJIMD ISSN: 0192-0561
PUBLISHER ITEM IDENTIFIER: S0192056197000994
DOI: 10.1016/S0192-0561(97)00099-4
DOCUMENT TYPE: Journal; Article RECORD TYPE: Abstract
LANGUAGE: English SUMMARY LANGUAGE: English
NUMBER OF REFERENCES: 33

4/3/32 (Item 10 from file: 73)
DIALOG(R)File 73:EMBASE
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0077125113 EMBASE/Medline No: 1998033540
Effects of some anti-asthma drugs on human eosinophil superoxide anions release and degranulation
Ezeamuzie C.I.; Al-Hage M.
Dept. of Pharmacology and Toxicology, Faculty of Medicine, Kuwait University, Safat, Kuwait; Dept. of Pharmacology and Toxicology, Faculty of Medicine, Kuwait University, PO Box 24923, Safat 13110, Kuwait
CORRESP. AUTHOR/AFFIL: Ezeamuzie C.I.: Department Pharmacology Toxicology, Faculty of Medicine, Kuwait University, PO Box 24923, Safat 13110, Kuwait

International Archives of Allergy and Immunology (Int. Arch. Allergy Immunol.) (Switzerland) February 1, 1998, 115/2 (162-168)
CODEN: IAAIE ISSN: 1018-2438
DOCUMENT TYPE: Journal; Article RECORD TYPE: Abstract
LANGUAGE: English SUMMARY LANGUAGE: English
NUMBER OF REFERENCES: 27

4/3/33 (Item 11 from file: 73)
DIALOG(R)File 73:EMBASE
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0076905205 EMBASE/Medline No: 1997198322
Eosinophil cationic protein in allergic disease (part one)
Proteina cationica del eosinofilo en enfermedades alergicas (Primera parte)
Miralles Lopez J.C.; Negro J.M.; Hernandez J.; Caravaca F.; Sarrio F.
Plaza Juan XXIII, no. 3, 30008 Murcia, Spain
CORRESP. AUTHOR/AFFIL: Mirales Lopez J.C.: Plaza Juan XXIII, no. 3, 30008 Murcia, Spain

Revista Espanola de Alergologia e Inmunologia Clinica (REV. ESP. ALERGOL. INMUNOL. CLIN.) (Spain) December 1, 1996, 11/2 (77-84)
CODEN: REACE ISSN: 0214-1477
DOCUMENT TYPE: Journal; Review RECORD TYPE: Abstract
LANGUAGE: Spanish SUMMARY LANGUAGE: English; Spanish
NUMBER OF REFERENCES: 47

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4/3/34 (Item 12 from file: 73)
DIALOG(R)File 73:EMBASE
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0074972758 EMBASE/Medline No: 1992124431
Complement activation by house dust: Reduced reactivity of serum complement in patients with bronchial asthma
Castro F.F.M.; Schmitz-Schumann M.; Rother U.; Kirschfink M.
Institute of Immunology, University of Heidelberg, Im Neuenheimer Feld 305, D-W-6900 Heidelberg, Germany
CORRESP. AUTHOR/AFFIL: Kirschfink M.: Institute of Immunology, University of Heidelberg, Im Neuenheimer Feld 305, D-W-6900 Heidelberg, Germany

International Archives of Allergy and Applied Immunology (INT. ARCH. ALLERGY APPL. IMMUNOL.) (Switzerland) December 1, 1991, 96/4 (305-310)
CODEN: IAAAA ISSN: 0020-5915
DOCUMENT TYPE: Journal; Article RECORD TYPE: Abstract
LANGUAGE: English SUMMARY LANGUAGE: English

4/3/35 (Item 13 from file: 73)
DIALOG(R)File 73:EMBASE
(c) 2011 Elsevier B.V. All rts. reserv.

0074963760 EMBASE/Medline No: 1992115433
In vivo priming of platelet-activating factor-induced eosinophil chemotaxis in allergic asthmatic individuals
Warringa R.A.J.; Mengelers H.J.J.; Kuijper P.H.M.; Raaijmakers J.A.M.; Bruijnzeel P.L.B.; Koenderman L.
Pulmonary Diseases Department, University Hospital Utrecht, PO Box 85500, 3500 GA Utrecht, Netherlands
CORRESP. AUTHOR/AFFIL: Koenderman L.: Pulmonary Diseases Department, University Hospital Utrecht, PO Box 85500, 3500 GA Utrecht, Netherlands

Blood (BLOOD) (United States) April 15, 1992, 79/7 (1836-1841)
CODEN: BLOOA ISSN: 0006-4971
DOCUMENT TYPE: Journal; Article RECORD TYPE: Abstract
LANGUAGE: English SUMMARY LANGUAGE: English

4/3/36 (Item 14 from file: 73)
DIALOG(R)File 73:EMBASE
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0072279433 EMBASE/Medline No: 1982022051
Digestion of the fifth component of complement by eosinophil lysosomal enzymes. Production of eosinophil specific chemotactic activity
Ogawa H.; Kunkel S.L.; Fantone J.C.; Ward P.A.
Dept. Pathol., Univ. Michigan Med. Sch., Ann Arbor, MI 48109, United States:
CORRESP. AUTHOR/AFFIL: Dept. Pathol., Univ. Michigan Med. Sch., Ann Arbor, MI 48109, United States

Virchows Archiv Abteilung B Cell Pathology (VIRCHOWS ARCH. ABT. B CELL PATHOL.) (Germany) December 1, 1981, 38/2 (149-157)
CODEN: VAAZA
DOCUMENT TYPE: Journal; Article RECORD TYPE: Abstract
LANGUAGE: English

4/3/37 (Item 15 from file: 73)

Samsung Bioepis Exhibit No. 1002
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DIALOG(R)File 73:EMBASE
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0071514916 EMBASE/Medline No: 1979248367
Late immune reactions in the allergen induced bronchial asthma
ZUR PATHOGENESE VERZOGERTER IMMUNREAKTIONEN BEIM ASTHMA BRONCHIALE
Dorsch W.; Baur X.; Becker Th.
Inst. Poliklin. Arbeitsmed., Klin. Grosshadern, Germany:
CORRESP. AUTHOR/AFFIL: Inst. Poliklin. Arbeitsmed., Klin. Grosshadern, Germany

Atemwegs- und Lungenkrankheiten (ATEMWEGS- LUNGENKR.) (Germany)
December 17, 1979, 5/4 (294-297)
CODEN: ATLUD ISSN: 0341-3055
DOCUMENT TYPE: Journal RECORD TYPE: Abstract
LANGUAGE: German SUMMARY LANGUAGE: English

4/3/38 (Item 16 from file: 73)
DIALOG(R)File 73:EMBASE
(c) 2011 Elsevier B.V. All rts. reserv.

0067846920 EMBASE/Medline No: 9730868
A CD18/ICAM-1-dependent pathway mediates eosinophil adhesion to human bronchial epithelial cells.
Burke-Gaffney A.; Hellewell P.G.
Department of Applied Pharmacology, Imperial College School of Medicine at the National Heart and Lung Institute, London, United Kingdom.
CORRESP. AUTHOR/AFFIL: Burke-Gaffney A.: Department of Applied Pharmacology, Imperial College School of Medicine at the National Heart and Lung Institute, London, United Kingdom.
CORRESP. AUTHOR EMAIL: a.burke-gaffney@ic.ac.uk

American journal of respiratory cell and molecular biology (Am. J. Respir. Cell Mol. Biol.) (United States) September 1, 1998, 19/3 (408-418)
ISSN: 1044-1549
DOCUMENT TYPE: Journal; Article RECORD TYPE: Abstract
FILE SEGMENT: Medline
LANGUAGE: English

4/3/39 (Item 1 from file: 155)
DIALOG(R)File 155:MEDLINE(R)
(c) format only 2011 Dialog. All rts. reserv.

14836962 PMID: 11719302
Effect of wortmannin on human eosinophil responses in vitro and on bronchial inflammation and airway hyperresponsiveness in Guinea pigs in vivo.
Ezeamuzie C I; Sukumaran J; Philips E
Department of Pharmacology and Toxicology, Faculty of Medicine, Kuwait University, Safat, Kuwait. ezeamuzie@hsc.kuniv.edu.kw
American journal of respiratory and critical care medicine (United States) Nov 1 2001, 164 (9) p1633-9, ISSN 1073-449X--Print 1073-449X --Linking Journal Code: 9421642
Publishing Model Print
Document type: Evaluation Studies; In Vitro; Journal Article; Research Support, Non-U.S. Gov't
Languages: ENGLISH
Main Citation Owner: NLM

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Record type: MEDLINE; Completed

4/3/40 (Item 2 from file: 155)
DIALOG(R)File 155:MEDLINE(R)
(c) format only 2011 Dialog. All rts. reserv.

13404955 PMID: 9860239
Eosinophil leukocyte degranulation in response to serum-opsonized beads: C5a and platelet-activating factor enhance ECP release, with roles for protein kinases A and C.
Egesten A; Malm J
Department of Medicine, Lund University, University Hospital MAS, Malmo, Sweden.
Allergy (DENMARK) Nov 1998, 53 (11) p1066-73, ISSN 0105-4538 --Print 0105-4538--Linking Journal Code: 7804028
Publishing Model Print
Document type: Journal Article; Research Support, Non-U.S. Gov't
Languages: ENGLISH
Main Citation Owner: NLM
Record type: MEDLINE; Completed

4/3/41 (Item 3 from file: 155)
DIALOG(R)File 155:MEDLINE(R)
(c) format only 2011 Dialog. All rts. reserv.

12495041 PMID: 8947334
Allergic bronchial asthma: eosinophil chemotaxis and antihistaminic drug modulation.
Ventura M T; Casale G; Cenci L; Tursi A
Department of Allergology and Clinical Immunology, University of Bari, Italy.
Allergy (DENMARK) Nov 1996, 51 (11) p777-81, ISSN 0105-4538--Print 0105-4538--Linking Journal Code: 7804028
Publishing Model Print
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: MEDLINE; Completed

4/3/42 (Item 4 from file: 155)
DIALOG(R)File 155:MEDLINE(R)
(c) format only 2011 Dialog. All rts. reserv.

08766625 PMID: 3608241
Airway responses in vitro following C5a des Arg-induced hyper-responsiveness in vivo in rabbits.
Armour C L; Black J L; Vincenc K S; Johnson P R; Ward H; Berend N
Clinical and experimental pharmacology & physiology (ENGLAND) Jan 1987, 14 (1) p7-14, ISSN 0305-1870--Print 0305-1870--Linking Journal Code: 0425076
Publishing Model Print
Document type: Comparative Study; In Vitro; Journal Article; Research Support, Non-U.S. Gov't
Languages: ENGLISH
Main Citation Owner: NLM
Record type: MEDLINE; Completed

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4/3/43 (Item 5 from file: 155)
DIALOG(R)File 155:MEDLINE(R)
(c) format only 2011 Dialog. All rts. reserv.

08204591 PMID: 2415448
[Cellular and humoral bases of allergic reactions].
Zellulare und humorale Grundlagen allergischer Reaktionen.
Kownatzki E
Immunitat und Infektion (GERMANY, WEST) Sep 1985, 13 (5) p165-70, ISSN 0340-1162--Print 0340-1162--Linking Journal Code: 7505519
Publishing Model Print
Document type: English Abstract; Journal Article
Languages: GERMAN
Main Citation Owner: NLM
Record type: MEDLINE; Completed

4/3/44 (Item 6 from file: 155)
DIALOG(R)File 155:MEDLINE(R)
(c) format only 2011 Dialog. All rts. reserv.

07002752 PMID: 6459046
Immune complex injury of the lung. Symposium held at the 74th annual meeting of the American Thoracic Society, Las Vegas, Nevada, May 1979.
Daniele R P; Henson P M; Fantone J C; Ward P A; Dreisin R B
American review of respiratory disease (UNITED STATES) Dec 1981, 124 (6) p738-55, ISSN 0003-0805--Print 0003-0805--Linking Journal Code: 0370523
Contract/Grant No.: AI-09651; AI; NIAID NIH HHS United States; HL-21565; HL; NHLBI NIH HHS United States; HL-23877; HL; NHLBI NIH HHS United States; +
Publishing Model Print
Document type: Journal Article; Research Support, Non-U.S. Gov't; Research Support, U.S. Gov't, P.H.S.; Review
Languages: ENGLISH
Main Citation Owner: NLM
Record type: MEDLINE; Completed

4/3/45 (Item 1 from file: 399)
DIALOG(R)File 399:CA SEARCH(R)
(c) 2011 American Chemical Society. All rts. reserv.

136068714 CA: 136(5)68714t PATENT
Peptide and polypeptide inhibitors of complement C1s
INVENTOR(AUTHOR): West, Robert R.; Sheppard, Paul O.; Fox, Brian A.
LOCATION: USA
ASSIGNEE: Zymogenetics, Inc.
PATENT: PCT International ; WO 200198365 A2 DATE: 20011227
APPLICATION: WO 2001US19405 (20010618) *US PV212998 (20000621)
PAGES: 99 pp. CODEN: PIXXD2 LANGUAGE: English
PATENT CLASSIFICATIONS:
CLASS: C07K-700/A
DESIGNATED COUNTRIES: AE; AG; AL; AM; AT; AU; AZ; BA; BB; BG; BR; BY; BZ; CA; CH; CN; CO; CR; CU; CZ; DE; DK; DM; DZ; EC; EE; ES; FI; GB; GD; GE; GH; GM; HR; HU; ID; IL; IN; IS; JP; KE; KG; KP; KR; KZ; LC; LK; LR; LS; LT; LU; LV; MA; MD; MG; MK; MN; MW; MX; MZ; NO; NZ; PL; PT; RO; RU; SD; SE; SG; SI; SK; SL; TJ; TM; TR; TT; TZ; UA; UG; UZ; VN; YU; ZA; ZW; AM; AZ; BY; KG; KZ; MD; RU; TJ; TM DESIGNATED REGIONAL: GH; GM; KE; LS; MW; MZ; SD; SL; SZ; TZ; UG; ZW; AT; BE; CH; CY; DE; DK; ES; FI; FR; GB; GR; IE; IT; LU; MC; NL; PT; SE; TR; BF; BJ; CF; CG; CI; CM; GA; GN; GW; ML; MR; NE; SN; TD; TG

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4/3/46 (Item 2 from file: 399)
DIALOG(R)File 399:CA SEARCH(R)
(c) 2011 American Chemical Society. All rts. reserv.

129314955 CA: 129(24)314955q PATENT
Inhibition of B-1 cell mediated immune conditions
INVENTOR(AUTHOR): Askenase, Philip W.; Tsuji, Ryohei; Paliwal, Vipin; Kawikova, Ivana
LOCATION: USA
ASSIGNEE: Yale University
PATENT: PCT International ; WO 9846255 A1 DATE: 19981022
APPLICATION: WO 98US7535 (19980417) *US 45234 (19970417)
PAGES: 66 pp. CODEN: PIXXD2 LANGUAGE: English
PATENT CLASSIFICATIONS:
CLASS: A61K-038/20A; A61K-039/395B; G01N-033/53B
DESIGNATED COUNTRIES: AU; CA; JP; US DESIGNATED REGIONAL: AT; BE; CH; CY ; DE; DK; ES; FI; FR; GB; GR; IE; IT; LU; MC; NL; PT; SE

4/3/47 (Item 3 from file: 399)
DIALOG(R)File 399:CA SEARCH(R)
(c) 2011 American Chemical Society. All rts. reserv.

129157717 CA: 129(13)157717u PATENT
Human c5a-like receptor
INVENTOR(AUTHOR): Coleman, Roger; Bandman, Olga
LOCATION: USA
ASSIGNEE: Incyte Pharmaceuticals, Inc.
PATENT: PCT International ; WO 9833908 A1 DATE: 19980806
APPLICATION: WO 98US1182 (19980120) *US 791974 (19970131)
PAGES: 60 pp. CODEN: PIXXD2 LANGUAGE: English
PATENT CLASSIFICATIONS:
CLASS: C12N-015/12A; C07K-014/705B; C12Q-001/68B; C12N-005/10B; A61K-038/17B; C07K-016/28B; C07K-014/72B
DESIGNATED COUNTRIES: AT; AU; BR; CA; CH; CN; DE; DK; ES; FI; GB; IL; JP; KR; MX; NO; NZ; RU; SE; SG; US; AM; AZ; BY; KG; KZ; MD; RU; TJ; TM
DESIGNATED REGIONAL: GH; GM; KE; LS; MW; SD; SZ; UG; ZW; AT; BE; CH; DE; DK; ES; FI; FR; GB; GR; IE; IT; LU; MC; NL; PT; SE; BF; BJ; CF; CG; CI; CM; GA; GN; ML; MR; NE; SN; TD; TG
? t s4/7/1,4,6,9,12,25,32

4/7/1 (Item 1 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)
(c) 2011 The Thomson Corporation. All rts. reserv.

17015827 BIOSIS NO.: 200200609338
Contribution of anaphylatoxin C5a to allergic late airway responses after repeated antigen exposure
AUTHOR: Abe Masayoshi (Reprint); Shibata Kazuhiko; Akatsu Hiroyasu; Shimizu Naomi; Katsuragi Takeshi (Reprint); Okada Hidechika
AUTHOR ADDRESS: Department of Pharmacology, Fukuoka University, Fukuoka, 814-0180, Japan**Japan
JOURNAL: International Immunopharmacology 2 (9): p1369 August, 2002 2002
MEDIUM: print
CONFERENCE/MEETING: XIX International Complement Workshop Palermo, Italy September 22-26, 2002; 20020922
ISSN: 1567-5769
DOCUMENT TYPE: Meeting; Meeting Abstract

Samsung Bioepis Exhibit No. 1002
Page 8952

RECORD TYPE: Citation
LANGUAGE: English

4/7/4 (Item 4 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)
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16119661 BIOSIS NO.: 200100291500
Complement-dependent immune complex-induced bronchial inflammation and hyperreactivity
AUTHOR: Lukacs Nicholas W (Reprint); Glovsky M Michael; Ward Peter A
AUTHOR ADDRESS: Dept. of Pathology, Univ. of Michigan Medical School, 1301 Catherine, Ann Arbor, MI, 48109-0602, USA**USA
JOURNAL: American Journal of Physiology 280 (3 Part 1): pL512-L518 March, 2001 2001
MEDIUM: print
ISSN: 0002-9513
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: Bronchoconstriction responses in the airway are caused by multiple insults and are the hallmark symptom in ***asthma*** . In an acute lung injury model in mice, IgG immune complex deposition elicited severe airway hyperreactivity that peaked by 1 h, was maintained at 4 h, and was resolved by 24 h. The depletion of complement with cobra venom factor (CVF) markedly reduced the hyperreactive airway responses, suggesting that complement played an important role in the response. Blockade of C5a with specific antisera also significantly reduced airway hyperreactivity in this acute lung model. Complement depletion by CVF treatment significantly reduced tumor necrosis factor and histamine levels in bronchoalveolar lavage fluids, correlating with reductions in airway hyperreactivity. To further examine the role of specific complement requirement, we initiated the immune complex response in C5-sufficient and C5-deficient congenic animals. The airway hyperreactivity response was partially reduced in the C5-deficient mice. Complement depletion with CVF attenuated airway hyperreactivity in the C5-sufficient mice but had a lesser effect on the airway hyperreactive response and histamine release in bronchoalveolar lavage fluids in C5-deficient mice. These data indicate that acute lung injury in mice after deposition of IgG immune complexes induced airway hyperreactivity that is C5 and C5a dependent.

4/7/6 (Item 6 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)
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15921732 BIOSIS NO.: 200100093571
Identification of complement factor 5 as a susceptibility locus for experimental allergic asthma
AUTHOR: Karp Christopher L; Grupe Andrew; Schadt Eric; Ewart Susan L; Keane-Moore Michelle; Cuomo Peter J; Kohl Jorg; Wahl Larry; Kuperman Douglas; Germer Soren; Aud Dee; Peltz Gary; Wills-Karp Marsha (Reprint)
AUTHOR ADDRESS: Department of Environmental Health Sciences, Johns Hopkins University School of Hygiene and Public Health, Baltimore, 615 N. Wolfe St., Baltimore, MD, 21205, USA**USA
JOURNAL: Nature Immunology 1 (3): p221-226 September, 2000 2000
MEDIUM: print
ISSN: 1529-2908

Samsung Bioepis Exhibit No. 1002
Page 8953

DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: The prevalence and severity of allergic asthma continue to rise, lending urgency to the search for environmental triggers and genetic substrates. Using microarray analysis of pulmonary gene expression and single nucleotide polymorphism-based genotyping, combined with quantitative trait locus analysis, we identified the gene encoding complement factor 5 (C5) as a susceptibility locus for allergen-induced airway hyperresponsiveness in a murine model of ***asthma*** . A deletion in the coding sequence of C5 leads to C5-deficiency and susceptibility. Interleukin 12 (IL-12) is able to ***prevent*** or reverse experimental allergic ***asthma*** . ***Blockade*** of the C5a receptor rendered human monocytes unable to produce IL-12, mimicking blunted IL-12 production by macrophages from C5-deficient mice and providing a mechanism for the regulation of susceptibility to ***asthma*** by C5. The role of complement in modulating susceptibility to asthma highlights the importance of immunoregulatory events at the interface of innate and adaptive immunity in disease pathogenesis.

4/7/9 (Item 9 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)
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14872644 BIOSIS NO.: 199900132304
Budesonide (BDS) inhibits eosinophil (Eos) chemotaxis through epithelial monolayers and intercellular adhesion molecule (ICAM)-1 expression in C5a-activated bronchial epithelial cells (HBECs)
AUTHOR: Gonzalez R (Reprint); Silvestri M; Cordone A; Morelli M C; Rossi G A
AUTHOR ADDRESS: Pulm Div-Gaslini Inst., Univ. Genoa, Genoa, Italy**Italy
JOURNAL: European Respiratory Journal 12 (SUPPL. 28): p421S Sept., 1998 1998
MEDIUM: print
CONFERENCE/MEETING: European Respiratory Society Annual Congress Geneva, Switzerland September 19-23, 1998; 19980919
SPONSOR: The European Respiratory Society
ISSN: 0903-1936
DOCUMENT TYPE: Meeting; Meeting Abstract
RECORD TYPE: Citation
LANGUAGE: English

4/7/12 (Item 12 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)
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14366033 BIOSIS NO.: 199800160280
Effects of some anti-asthma drugs of human eosinophil superoxide anions release and degranulation
AUTHOR: Ezeamuzie Charles I (Reprint); Al-Hage Mary
AUTHOR ADDRESS: Dep. Pharmacol. Toxicol., Fac. Med., Kuwait Univ., PO Box 24923, Safat 13110, Kuwait**Kuwait
JOURNAL: International Archives of Allergy and Immunology 115 (2): p 162-168 Feb., 1998 ***1998***
MEDIUM: print
ISSN: 1018-2438
DOCUMENT TYPE: Article
RECORD TYPE: Abstract

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Page 8954

LANGUAGE: English

ABSTRACT: Background: Eosinophil infiltration of bronchial tissues and subsequent release of inflammatory mediators by them are the hallmarks of bronchial asthma but it has not yet been clarified whether anti-***asthma*** drugs affect these cells directly. In this study, we investigated the direct effects of 8 clinically used anti-asthma drugs (salbutamol, salmeterol, theophylline, denbufylline, disodium cromoglycate (DSCG), azelastine, ketotifen and dexamethasone) on superoxide anions (O2-) and eosinophil peroxidase (EPO) release from human blood eosinophils in vitro. Methods: Highly purified eosinophils were stimulated for O2release with platelet-activating factor (PAF) or interleukin-5 (IL-5), while for EPO release complement fragment (C5a) or N-formyl-methionyl-leucyl-phenylalanine (FMLP) was employed. Generated products were assayed by standard techniques. Results: All the drugs, except ketotifen and dexamethasone, inhibited PAF-induced O2- release in a dose-dependent manner. The IC50 values were 0.7, 5.8, 330, 3,500, 4,200 and 6,250 nM for DSCG, denbufylline, salmeterol, azelastine, salbutamol and theophylline, respectively. On IL-5-induced release, the effects were similar except that salbutamol completely failed to inhibit the release induced by this stimulus. In contrast, EPO release was generally poorly ***inhibited*** , especially when the release was induced by ***C5a*** . Only theophylline and azelastine (both at 10-4 M or more) were able to ***inhibit*** EPO release by both ***C5a*** and FMLP. Salbutamol and, to a lesser extent, salmeterol inhibited FMLP-, but not C5a -induced EPO release, while all the other drugs tested were inactive. Conclusions: The results show that some of the anti-asthma drugs, but not all, do exert direct effects on human blood eosinophils but these effects may be stimulus-dependent and by far more pronounced against O2- release than against degranulation.

4/7/25 (Item 3 from file: 73)
DIALOG(R)File 73:EMBASE
(c) 2011 Elsevier B.V. All rts. reserv.

0078755074 EMBASE/Medline No: 2001361431
Contribution of anaphylatoxin C5a to late airway responses after repeated exposure of antigen to allergic rats
Abe M.; Shibata K.; Akatsu H.; Shimizu N.; Sakata N.; Katsuragi T.; Okada H.
Department of Pharmacology, School of Medicine, Fukuoka University, Fukuoka 814-0180, Japan
CORRESP. AUTHOR/AFFIL: Abe M.: Department of Pharmacology, School of Medicine, Fukuoka University, Fukuoka 814-0180, Japan
CORRESP. AUTHOR EMAIL: abemasa@fukuoka-u.ac.jp

Journal of Immunology (J. Immunol.) (United States) October 15, 2001, 167/8 (4651-4660)
CODEN: JOIMA ISSN: 0022-1767
DOCUMENT TYPE: Journal; Article RECORD TYPE: Abstract
LANGUAGE: English SUMMARY LANGUAGE: English
NUMBER OF REFERENCES: 37

We attempted to elucidate the contribution of complement to allergic ***asthma*** . Rat sensitized to OVA received repeated intratracheal exposures to OVA for up to 3 consecutive days, and pulmonary resistance was then estimated for up to 6 h after the last exposure. Whereas the immediate airway response (IAR) in terms of R SUB L tended to decrease in proportion to the number of OVA exposures, late airway response (LAR) became prominent only after three. Although premedication with two kinds of complement

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inhibitors, soluble complement receptor type 1 (sCR1) or nafamostat mesylate, resulted in inhibition of the IAR after either a single or a double exposure, the LAR was ***inhibited*** after the triple. Premedication with a C5a receptor antagonist (C5aRA) before every exposure to OVA also ***inhibited*** the LAR after three. Repeated OVA exposure resulted in eosinophil and neutrophil infiltration into the bronchial submucosa which was suppressed by premedication with sCR1 or C5aRA. Up-regulation of C5aR mRNA was shown in lungs after triple OVA exposure, but almost no up-regulation of C3aR. Pretreatment with sCR1 or C5aRA suppressed the up-regulation of C5aR expression as well as cytokine messages in the lungs. The ***suppression*** of LAR by pretreatment with sCR1 was reversed by intratracheal instillation of rat C5a desArg the action of which was ***inhibited*** by C5aRA. In contrast, rat C3a desArg or cytokine-induced neutrophil chemoattractant-1 induced cellular infiltration into the bronchial submucosa by costimulation with OVA, but these had no influence on the LAR. These differences might be explained by the fact that costimulation with OVA and C5a synergistically potentiated IAR, whereas that with OVA and either C3a or cytokine-induced neutrophil chemoattractant-1 did not. C5a generated by Ag-Ab complexes helps in the production of cytokines and contributes to the LAR after repeated exposure to Ag.

4/7/32 (Item 10 from file: 73)
DIALOG(R)File 73:EMBASE
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0077125113 EMBASE/Medline No: 1998033540
Effects of some anti-asthma drugs on human eosinophil superoxide anions release and degranulation
Ezeamuzie C.I.; Al-Hage M.
Dept. of Pharmacology and Toxicology, Faculty of Medicine, Kuwait University, Safat, Kuwait; Dept. of Pharmacology and Toxicology, Faculty of Medicine, Kuwait University, PO Box 24923, Safat 13110, Kuwait
CORRESP. AUTHOR/AFFIL: Ezeamuzie C.I.: Department Pharmacology Toxicology, Faculty of Medicine, Kuwait University, PO Box 24923, Safat 13110, Kuwait

International Archives of Allergy and Immunology (Int. Arch. Allergy Immunol.) (Switzerland) February 1, 1998, 115/2 (162-168)
CODEN: IAAIE ISSN: 1018-2438
DOCUMENT TYPE: Journal; Article RECORD TYPE: Abstract
LANGUAGE: English SUMMARY LANGUAGE: English
NUMBER OF REFERENCES: 27

Background: Eosinophil infiltration of bronchial tissues and subsequent release of inflammatory mediators by them are the hallmarks of bronchial asthma but it has not yet been clarified whether anti-asthma drugs affect these cells directly. In this study, we investigate the direct effects of 8 clinically used anti-asthma drugs [salbutamol, salmeterol, theophylline, denbufylline, disodium cromoglycate (DSCG), azelastine, ketotifen and dexamethasone] on superoxide anions (O SUB 2 SUP -) and eosinophil peroxidase (EPO) release from human blood eosinophils in vitro. Methods: Highly purified eosinophils were stimulated for O SUB 2 SUP - release with platelet-activating factor (PAF) or interleukin-5 (IL-5), while for EPO release complement fragment (C5a) or N-formyl-methionyl-leucyl-phenylalanine (FMLP) was employed. Generated products were assayed by standard techniques. Results: All the drugs, except ketotifen and dexamethasone, inhibited PAF-induced O SUB 2 SUP - release in a dose-dependent manner. The IC SUB 50 values were 0.7, 5.8, 330, 3500, 4200 and 6250 nM for DSCG, denbufylline, salmeterol, azelastine,

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salbutamol and theophylline, respectively. On IL-5-induced release, the effects were similar except that salbutamol completely failed to inhibit the release induced by this stimulus. In contrast, EPO release was generally poorly inhibited, especially when the release was induced by ***C5a*** . Only theophylline and azelastine (both at 10 SUP -4 M or more) were able to ***inhibit*** EPO release by both ***C5a*** and FMLP. Salbutamol and, to a lesser extent, salmeterol inhibited FMLP-, but not C5a-induced EPO release, while all the other drugs tested were inactive. Conclusions: The results show that some of the anti- ***asthma*** drugs, but not all, do exert direct effects on human blood eosinophils but these effects may be stimulus-dependent and by far more pronounced against O SUB 2 SUP - release than against degranulation.

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? ds

Set     Items   Description
S1        234   (C5 OR C5A)(20N)(ANTI-C5 OR ANTIBOD? OR ANTAGONI? OR INHIB-
                 IT? OR BLOCK? OR PREVENT? OR SUPPRESS?) AND ASTHMA
S2        154   RD S1  (unique items)
S3         57   S2 AND PY<2004
S4         47   S3 AND PY<2003
?
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Refine Search

Search Results

Term	Documents
ANTI-C5	202
ANTI-C5S	0
ECULIZUMAB	218
ECULIZUMABS	0
PEXELIZUMAB	166
PEXELIZUMABS	0
5GA$	0
5GA	58
5GAA	96
5GAAA	1
5GAAAAAAGCTCTGGAAGAAGCTGGCGCTGAAGTTGAAGTTAAACACCACCAC	1
(l10 and (anti-C5 or 5ga$ or eculizumab or pexelizumab)).PGPB.	170

There are more results than shown above. Click here to view the entire set.

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US Patents Full-Text Database
US Patents OCR Backfile
EPO Abstracts Database
JPO Abstracts Database
Derwent World Patents Index
IBM Technical Disclosure Bulletin Database

Search Type: (•) **Prior Art** ( ) **Interference**

Search: L15

Refine Search | Recall Text | Clear | Interrupt

Search History

DATE: Wednesday, March 02, 2011 Purge Queries Printable Copy Create Case

Set Name Side by Side	Query	Hit Count	Set Name Result Set	Set Name Grid
Prior Art Searches				
	DB=PGPB; PLUR=YES; OP=ADJ			
L15	l10 and (anti-C5 or 5ga$ or eculizumab or pexelizumab)	170	L15	L15

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DB=USPT; PLUR=YES; OP=ADJ				
L14	L13 and (anti-C5)	31	L14	L14
L13	L11	312	L13	L13
DB=EPAB,JPAB,DWPI; PLUR=YES; OP=ADJ				
L12	(c5 or anti-c5)same(antibod$ or antagoni$ or inhibit$ or block$ or prevent$ or suppress$) and (asthma$)	61	L12	L12
DB=USPT; PLUR=YES; OP=ADJ				
L11	(c5 or anti-c5)same(antibod$ or antagoni$ or inhibit$ or block$ or prevent$ or suppress$) and (asthma$)	312	L11	L11
DB=PGPB; PLUR=YES; OP=ADJ				
L10	(c5 or anti-c5)same(antibod$ or antagoni$ or inhibit$ or block$ or prevent$ or suppress$) and (asthma$)	1103	L10	L10
L9	L5	121	L9	L9
DB=USPT; PLUR=YES; OP=ADJ				
L8	L6	21	L8	L8
DB=EPAB,JPAB,DWPI; PLUR=YES; OP=ADJ				
L7	L4	16	L7	L7
DB=USPT; PLUR=YES; OP=ADJ				
L6	L4	21	L6	L6
DB=PGPB; PLUR=YES; OP=ADJ				
L5	L4	121	L5	L5
DB=PGPB,USPT,EPAB,JPAB,DWPI; PLUR=YES; OP=ADJ				
L4	(c5 or anti-c5)same(antibod$ or antagoni$ or inhibit$ or block$ or prevent$ or suppress$) and (eculizumab or pexelizumab)	158	L4	L4
L3	L1 and (c5 or anti-c5)same(antibod$ or antagoni$ or inhibit$ or block$ or prevent$ or suppress$) and (eculizumab or pexelizumab)	13	L3	L3
L2	L1 and (c5 or anti-c5)same(antibod$ or antagoni$ or inhibit$ or block$ or prevent$ or suppress$) and (nebulizer or aerosol)	29	L2	L2
L1	wang.in.	450604	L1	L1

END OF SEARCH HISTORY

Samsung Bioepis Exhibit No. 1002
Page 8959

Docket No.: ALXN-P02-102
(PATENT)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of:
Yi Wang

Application No.: 11/127,438 Confirmation No.: 5259

Filed: May 11, 2005 Art Unit: 1644

For: NEBULIZATION OF MONOCLONAL ANTIBODIES FOR TREATING PULMONARY DISEASES Examiner: P. Gambel

AMENDMENT IN RESPONSE TO NON-FINAL OFFICE ACTION

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

Dear Sir:

INTRODUCTORY COMMENTS

In response to the Office Action dated May 2, 2011, please amend the above-identified U.S. patent application as set forth below. Submitted herewith is a Supplement Information Disclosure Statement.

Amendments to the Claims are reflected in the listing of claims which begins on page 2 of this paper.

Remarks/Arguments begin on page 7 of this paper.

AMENDMENTS TO THE CLAIMS

This listing of claims will replace all prior versions and listings of claims in the application.

1-14. (Cancelled)

15. (Currently amended) An aerosol composition comprising an anti-C5 antibody that inhibits the conversion of C5 into C5a and C5b, wherein the composition is suitable for treating a chronic obstructive pulmonary condition or a pulmonary condition characterized with airway inflammation in a subject.

16. (Original) The aerosol composition of claim 15, wherein the antibody is formulated in a composition suitable for aerosolization.

17. (Original) The aerosol composition of claim 15 further comprising an additional active agent.

18. (Currently amended) A biopharmaceutical package comprising: a) an anti-C5 antibody that inhibits the conversion of C5 into C5a and C5b; and b) a nebulizer, wherein the antibody is suitable for treating a chronic obstructive pulmonary condition or a pulmonary condition characterized with airway inflammation in a subject.

19. (Original) The biopharmaceutical package of claim 18, wherein the nebulizer is selected from the group consisting of a jet air nebulizer, an ultrasonic nebulizer, a vibrating mesh nebulizer and a shockwave nebulizer.

20. (Original) The biopharmaceutical package of claim 19 further comprising instructions for use.

21. (Original) The biopharmaceutical package of claim 19 further comprising an additional active agent.

22. (Previously presented) A pulmonary drug delivery kit comprising: a) an inhaler; and b) an anti-C5 antibody formulated for inhalation delivery, wherein said antibody inhibits the conversion of C5 into C5a and C5b.

23. (Original) The kit of claim 22, wherein said inhaler is a metered dose inhaler.

24. (Previously presented) The kit of claim 23, wherein the metered dose inhaler is a pressurized metered dose inhaler.

25. (Original) The kit of any one of claims 22 or 23, wherein said inhaler further comprises a holding chamber.

26. (Original) The kit of claim 22, wherein said inhaler is a nebulizer.

27. (Original) The kit of claim 26, wherein said nebulizer is an ultrasonic nebulizer.

28. (Original) The kit of claim 26, wherein said nebulizer is a jet air nebulizer.

29. (Original) The kit of claim 22, wherein said inhaler is a dry powder inhaler.

30. (Canceled)

31. (Withdrawn) A method for preventing or treating a pulmonary condition in a subject, the method comprising administering to the subject an effective amount of the aerosol composition of claim 15 to prevent or treat the pulmonary condition.

32. (Withdrawn) The method of claim 31 wherein an additional active agent is administered.

33. (Withdrawn) The method of claim 31, wherein the pulmonary condition is selected from the group consisting of: asthma, bronchitis, a chronic obstructive pulmonary disease (COPD), interstitial lung diseases, lung malignancies, α-1 anti-trypsin deficiency, emphysema,

bronchiectasis, bronchiolitis obliterans, sarcoidosis, pulmonary fibrosis, and collagen vascular disorders.

34. (Withdrawn) The method of claim 31, wherein the subject is a human.

35-37. (Canceled)

38. (Withdrawn) The method of claim 31, wherein the antibody is eculizumab or pexelizumab.

39. (Withdrawn) The method of claim 31, wherein the antibody is selected from the group consisting of: a full length immunoglobulin, a single chain antibody, a domain antibody, a Fab fragment, and an antibody having a Fab fragment and a mutated Fc portion.

40. (Withdrawn) The method of claim 39, wherein the mutated Fc portion does not activate complement.

41. (Withdrawn) The method of claim 31, wherein the antibody is administered prior to manifestation of the pulmonary condition, during manifestation of the pulmonary condition, or after manifestation of the pulmonary condition.

42. (Withdrawn) The method of claim 32, wherein the additional active agent is a corticosteroid.

43. (Withdrawn) The method of claim 42, wherein the corticosteroid is dexamethasone.

44. (Withdrawn) The method of claim 32, wherein the antibody and the additional active agent are administered to the subject by the same delivery method or route.

45. (Withdrawn) The method of claim 32, wherein the antibody and the additional active agent are administered to the subject by different delivery methods or routes.

46. (Previously presented) The composition of claim 15, wherein the pulmonary condition is asthma.

47. (Previously presented) The biopharmaceutical package of claim 18, wherein the pulmonary condition is asthma.

48. (Previously presented) The method of claim 31, wherein the pulmonary condition is asthma.

49. (Previously presented) The composition of claim 15, wherein the antibody is eculizumab or pexelizumab.

50. (Previously presented) The composition of claim 15, wherein the antibody is selected from the group consisting of: a full length immunoglobulin, a single chain antibody, a domain antibody, a Fab fragment, and an antibody having a Fab fragment and a mutated Fc portion.

51. (Previously presented) The composition of claim 50, wherein the mutated Fc portion does not activate complement.

52. (Previously presented) The biopharmaceutical package of claim 18, wherein the antibody is eculizumab or pexelizumab.

53. (Previously presented) The biopharmaceutical package of claim 18, wherein the antibody is selected from the group consisting of: a full length immunoglobulin, a single chain antibody, a domain antibody, a Fab fragment, and an antibody having a Fab fragment and a mutated Fc portion.

54. (Previously presented) The biopharmaceutical package of claim 53, wherein the mutated Fc portion does not activate complement.

55. (Previously presented) The pulmonary drug delivery kit of claim 22, wherein the antibody is eculizumab or pexelizumab.

56. (Previously presented) The pulmonary drug delivery kit of claim 22, wherein the antibody is selected from the group consisting of: a full length immunoglobulin, a single chain antibody, a domain antibody, a Fab fragment, and an antibody having a Fab fragment and a mutated Fc portion.

57. (Previously presented) The pulmonary drug delivery kit of claim 56, wherein the mutated Fc portion does not activate complement.

REMARKS

Claims 15-29 and 46-57 are currently pending and under consideration. By virtue of this amendment, claims 15 and 18 have been amended. Support for the claim amendments may be found throughout the application as filed as well as the underlying provisional applications. In particular, support for the amendments to claims 15 and 18 may be found, for example, in paragraphs [0002], [0046], and [0057] of the published application (U.S. Publication No. 2005/0271660) as well as page 1, lines 10-13 of both U.S. Provisional Application Nos. 60/408,571 and 60/469,189. No new matter has been introduced.

Amendments of the claims should in no way be construed as an acquiescence to any of the Examiner's rejections. The amendments are being made solely to expedite prosecution of the present application. Applicant reserves the option to further prosecute the same or similar claims in the instant or subsequent application.

Applicant respectfully requests reconsideration in view of the following remarks. Issues raised by the Examiner will be addressed below in the order they appear in the prior Office Action.

Priority

At pages 4-6 of the Office Action, Applicant's asserted effective priority date of September 6, 2002 was refused. According to the Office Action, the priority applications do not support sufficient written description for the instant claims, including limitations such as "aerosol composition … suitable for treating a pulmonary condition in a subject", "biopharmaceutical package …" and "pulmonary drug delivery kit …" as well as various limitations of the dependent claims (e.g., "jet air/ultrasonic/shockwave nebulizer"). Applicant respectfully disagrees. As indicated in detail below, Applicant submits that the instant claims find full written description support in the present application and in the priority applications (i.e., U.S. Provisional Patent Application Nos. 60/408,571, filed on September 6, 2002, and 60/469,189, filed on May 9, 2003).

In accordance with M.P.E.P. § 2163.02, "[t]he subject matter of [a] claim need not be described literally (using the same terms or *in haec verba*) in order for the disclosure to satisfy the written description requirement." The M.P.E.P. also cites *Martin v. Johnson*, 424 F.2d 746, 751

(CCPA 1972) that "the description need not be *ipsis verbis* [i.e., in the same words] to be sufficient." M.P.E.P. § 2163 (3)(a). Moreover, "[m]ere rephrasing of a passage does not constitute new matter…[and] a rewording of a passage where the same meaning remains intact is permissible." M.P.E.P. § 2163.07 (I). In view of these principles, Applicant asserts that the priority documents provide ample support for the terms "compositions / kits / packages", "antibody specificities", and "chronic obstructive pulmonary conditions or pulmonary conditions characterized with airway inflammation."

For example, Applicant respectfully submits that the Examiner concedes that the provisional applications disclose "treating 'chronic obstructive pulmonary diseases' such as 'asthma' …" (page 4 of the Office Action). Indeed, each of the priority documents discloses that:

> [a]sthma, bronchitis and emphysema are known collectively as Chronic Obstructive Pulmonary Diseases…characterized as generalized airway obstruction, especially of the small airways, associated with varying degrees of symptoms of chronic bronchitis, asthma, and emphysema.

See, e.g., U.S. provisional patent application Nos. 60/408,571 and 60/469,189 both at page 1, lines 10 to 13. Notably, the above-quoted language is maintained *ipsis verbis* in the present specification. Paragraph [0002] of U.S. Patent Application Publication No. 2005/0271660.

The priority documents further state that the pulmonary diseases can also be associated with airway hyper-responsiveness to specific and/or non-specific stimuli and inflammation. U.S. 60/408,571 at page 1, lines 19 and 20, and page 3, lines 1 to 18. Thus one of ordinary skill in the art would easily and readily recognize that the priority applications describe a genus of "obstructive pulmonary disorders" sharing common clinical manifestations such as inflammation, airway hyper-responsiveness, and obstruction of, e.g., the small airways. It would have been equally clear to the artisan that the priority documents provide a representative number of species of that genus (such as, e.g., asthma, bronchitis, and emphysema) such that the artisan would understand that Applicant was in full possession of the genus at the asserted earliest priority date of September 6, 2002.

Fully consistent with and supported by both priority documents, the present claims cover compositions suitable for treating ***chronic obstructive pulmonary conditions*** or ***pulmonary conditions characterized with airway inflammation***. Under the section entitled "Pulmonary

Diseases or Conditions, and the Complement System" (paragraphs [0046] to [0057] of the published application), the specification states that "pulmonary diseases or conditions such as asthma can be characterized by a combination of chronic airway inflammation, airway obstruction and airway hyper-responsiveness." The specification further provides a number of species within the genus of pulmonary conditions, the species including, among others, asthma, bronchitis, and emphysema (see, e.g., paragraph [0002] of the published application).

In view of the foregoing, it is clear that the skilled artisan would fully appreciate the unmistakable harmony between the terms "pulmonary diseases," as recited in the priority documents, and "pulmonary condition," as recited in the instant specification. That is, the two genus terms are characterized by the same clinical manifestations and comprise the same species. Any distinction between these two clearly synonymous terms is at most nothing more than a "mere rephrasing" without a difference. Thus, Applicant asserts that the genus term "***chronic obstructive pulmonary conditions*** or ***pulmonary conditions characterized with airway inflammation"*** is fully supported in the priority documents as filed.

The Examiner further asserts that the terms "'kits' and 'packages' do not appear to be described prior to the instant application." Office Action at page 4. Applicant respectfully disagrees and asserts that the priority applications provide ample written support for the claimed kits, biopharmaceutical packages, and compositions. For example, the priority documents each describe that a "compound that inhibits production and/or activity of at least one complement component will generally be in an aerosol form with a suitable pharmaceutical carrier[.]" U.S. 60/408,571 at page 14, lines 12 to 14. See also U.S. 60/469,189 at page 18, lines 15 to 17. The priority documents further state that this "complement-inhibiting compound … can be administered via … aerosol[.]" U.S. 60/408,571 at page 4, lines 5 to 11. A skilled artisan at the filing date of the '571 provisional application would have appreciated that administering the described aerosol compositions requires something more than the composition itself – namely: a delivery device such as an inhaler or a nebulizer – just as the artisan would have appreciated that an intravenous form of a composition would require, e.g., a syringe useful for intravenous delivery. While an applicant may not rely on obviousness per se as evidence of written description, "[i]nformation which is well known in the art need not be described in detail in the specification." M.P.E.P. § 2163 (II)(A)(2).

Thus, from this disclosure alone, it is clear that the artisan would have easily and readily appreciated that Applicant was in full possession of the instantly claimed kits, packages, and compositions.

Notwithstanding these considerations, the priority documents specifically exemplify the use of such an aerosol composition – namely, an anti-C5 antibody formulated for, and administered to mammals, by way of aerosol and nebulization. U.S. 60/408,571 at pages 17-18 (Example 3), and Fig. 4a. According to the M.P.E.P, adequate written description may be shown where, as here, an actual reduction to practice of the claimed invention is fully described. M.P.E.P. § 2163 (3)(a). In view of the foregoing, Applicant asserts that the terms kits, biopharmaceutical packages, and compositions are fully supported in the priority documents as filed.

The Examiner further asserts that the description of "eculizumab or pexelizumab" as well as "the mutated Fc portions" in the priority documents is not readily apparent. Office Action at page 4. Applicant respectfully disagrees and asserts that the priority applications provide ample written support for the claimed descriptions. For example, the priority documents each describe that "Particularly useful anti-C5 antibodies are h5G1.1, h5G1.1-scFv and functional fragments of h5G1.1 are described in U.S. Patent No. 6,355,245 and 'Inhibition of Complement Activity by Humanized Anti-C5 antibody and Single Chain Fv', Thomas et al., *Molecular Immunology*, Vol. 33, No. 17/18, pages 1389-1401, 1996, the disclosures of which are incorporated herein in their entirely by this reference." See page 11, lines 13-20, of U.S. 60/408,571 and page 13, lines 2-9, of U.S. 60/469,189. Applicant submits that h5G1.1 and h5G1.1-scFv were well-known to one of ordinary skill in the art as eculizumab and pexelizumab, respectively, at the time of filing of priority applications. For example, see the abstract of Kaplan (2002) *Curr Opin Investig Drugs* 3(7):1017-1023, submitted herewith as Exhibit A, and the abstract of Whiss (2002) *Curr Opin Investig Drugs* 3(6):870-877, submitted herewith as Exhibit B. Specifically, the amino acid sequence of pexelizumab was disclosed as SEQ ID NO: 8 in U.S. 6,355,245. Thus, according to M.P.E.P. § 2163 (II)(A)(2), "[i]nformation which is well known in the art need not be described in detail in the specification." Applicant therefore submits that the description of "eculizumab or pexelizumab" is fully supported by the priority applications. Applicant further submits that eculizumab was first constructed in the IgG4 isotype, see, e.g., the bridging paragraph of the left and right columns of page 1396 of Thomas et al. (1996), *Id.*, a copy of which is submitted herewith as Exhibit C, and

then into the G2/G4 format, see Mueller et al. (1997) *Molecular Immunology*, Vol. 34, No. 6, pages 441-452, a copy of which is submitted herewith as Exhibit D, while in either form the h5G1.1 antibody was well known to be incapable to activate human complement, see, e.g., the right column, lines 27-28, of page 1399 of Thomas et al., 1996, *Id.*, and the bridging paragraphs of pages 446 to 448 and 450 to 451 of Mueller et al, 1997, *Id.* Thus, Applicant submits that it was well-known to one of ordinary skill in the art at the time of filing of priority applications that eculizumab has a G2/G4 Fc portion, i.e., a mutated Fc portion. Therefore, according to M.P.E.P. § 2163 (II)(A)(2), Applicant submits that the description of "the mutated Fc portion" is fully supported by the priority applications.

Finally, the priority applications also provide ample support for the claimed "antibody specificities." The instant claims are drawn to various compositions, kits, and packages comprising an anti-C5 antibody that inhibits conversion of C5 into C5a and C5b. *Ipsis verbis* support for such an antibody is provided in both priority documents. See U.S. 60/408,571 at page 10, second full paragraph stating "[p]articularly useful compounds for use herein are antibodies that reduce … the conversion of complement component C5 into complement components C5a and C5b." Nothing more is required under the law.

For at least the foregoing reasons, provisional patent application nos. 60/408,571 and 60/469,189 clearly provide sufficient support under 35 U.S.C. § 112, first paragraph for the claims of the instant application. Accordingly, the instant claims are entitled to an effective date of at least September 6, 2002, based upon the disclosure of provisional application no. 60/408,571.

The Wang Declaration

At page 5 of the Office Action, Applicant's asserted effective priority date of at least 20 December 2001 was refused. According to the Office Action, "the Wang 131 declaration"[1] and its supporting materials [hereinafter collectively the Declaration], upon which the asserted priority claim is based, allegedly do "not provide for the generic anti-C5 antibodies that inhibit the conversion of C5 into C5a and C5b, as currently claimed." Office Action at page 5 (underlining in original). The Examiner urges that:

[1] The Declaration was submitted with Applicant's 17 December 2011 Amendment and Response to Non-final Office Action.

> there is no disclosure [in the Declaration] that the generic properties of anti-C5 antibodies…in the context of the claimed invention was [sic] described in a manner that provides for conception, diligence and reduction to practice prior to the claimed invention in a manner that obviates the prior art teachings.

Id. (underlining in original). Moreover, the Examiner casts doubt as to whether BB5.1, a specific anti-C5 antibody recited in the Declaration, is actually a member of the instantly claimed genus of anti-C5 antibodies. Applicant respectfully disagrees with this position.

At bottom, the Examiner's refusal of the priority claim sounds in written description – that the Declaration allegedly fails to provide: (a) literal support for the properties of the claimed genus of antagonist anti-C5 antibodies (i.e., anti-C5 antibodies that inhibit the conversion of complement component C5 into C5a and C5b); and/or (b) sufficient representative species to support the genus. As an initial matter, a proper legal analysis of whether written description is satisfied "calls for the examiner to compare the scope of the claim with the scope of the description to determine whether applicant has demonstrated possession of the claimed invention." M.P.E.P. § 2163 (II)(A)(2). This analysis should be "conducted from the standpoint of one of skill in the art [at the relevant time]…and should include a determination of the field of the invention and the level of skill and knowledge in the art." *Id.*

Applying this legal rubric, it is clear that the Examiner's position simply cannot stand under the weight of an objective reading of the Declaration in conjunction with the common scientific knowledge in the art on or around 20 December 2001. A skilled artisan would have readily, easily, and completely understood from the Declaration that Applicant conceived of a therapeutic use of a genus of antagonist anti-C5 antibodies that inhibit cleavage of C5 into fragments C5a and C5b at least by 20 December 2001.

Exhibit A of the Declaration, for example, leads with a broadly stated purpose: to "Evaluate the efficacy of ***anti-C5*** (BB5.1) on asthma mouse model." (Emphasis added.) Save once, the inventor consistently refers to an "anti-C5" antibody, rather than a specific antibody (e.g., BB5.1), throughout Exhibits A and B of the Declaration.

The Examiner, in this aspect of his argument, reads the term "anti-C5" narrowly; one of ordinary skill in the art on or around 20 December 2001 would not have. Rather the skilled artisan would have readily and unambiguously appreciated that "anti-C5" and/or "anti-C5 antibody" were terms of art referring to a genus of antibodies that inhibit the cleavage of C5 into fragments C5a and C5b, as is instantly claimed. To bolster Applicant's position, Wang et al. (September 1995) *Proc Natl Acad Sci USA* 92:8955-8959[2] [hereinafter Wang et al.] and PCT application publication no. WO 95/29697[3] [hereinafter the '697 PCT] are submitted herewith for consideration[4]. As elaborated on below, each reference demonstrates that: (i) the term "anti-C5" antibody is and was on or around 20 December 2001 used to describe a genus of antibodies that inhibit C5 cleavage into fragments C5a and C5b; and (ii) specific anti-C5 antibodies, such as BB5.1, were tested in animal models primarily to establish proof of concept for therapeutic C5 inhibition in human disease.

For example, Wang et al. describes the results of experiments evaluating the role of terminal complement in arthritis. As in the instant case, the authors of Wang et al. test a specific murine anti-C5 antibody (BB5.1) in a mouse model of disease. To remove any doubt, BB5.1 is, and was well-known in the art for many years to be, "an inhibitory mAb specific for murine C5" that "effectively inhibits terminal complement activation *in vivo*." *Id.*, at 8955, column 2. *See also* the '697 PCT, at Example 4, page 46.

Analogous to the Declaration, the therapeutic objective of the Wang et al. authors was not to treat arthritis in *mice*. Rather, the aim was generally "[t]o target complement activation in immune-mediated joint inflammation [using] monoclonal antibodies that inhibit the complement cascade at C5, blocking the generation of…C5a and C5b-9." Wang et al., at page 8955, Abstract. Wang et al.'s results provided "persuasive evidence that C5-specific mAb therapy may be an effective approach to the treatment of inflammatory joint disease" and supported "the derivation of a potent anti-human C5-blocking mAb[.]" Wang et al., at page 8959, column 2. In other words, *a specific*

[2] Wang et al. *Proc Natl Acad Sci USA* 92:8955-8959 (1995) was previously submitted on the Form PTO/SB/08b filed in connection with the instant application on September 22, 2006.
[3] Submitted herewith as Exhibit E.
[4] Each reference published more than six years before the priority date presently asserted by Applicants. Yi Wang, the author of the Declaration, is the first author of Wang et al. and an inventor named in the '697 PCT.

anti-C5 antibody served as a surrogate to establish proof of concept for use of functionally-related anti-C5 antibodies in human disease.

Similarly, the '697 PCT relates to, among other things, methods for treating a human afflicted with glomerulonephritis (GN). The '697 PCT at page 1. The inventors of the '697 PCT evaluated the antagonist anti-C5 antibody BB5.1 in a GN mouse model. *Id.*, at pages 43 to 46 (anti-C5 monoclonal antibodies used in the experiment are described at page 41, line 34 to page 42, line 1). As with Wang et al., treating mice was not the core objective. Based, at least in part, on the experimental evidence in the '697 PCT's specification, the PCT's inventors concluded that "antibodies [that] block the generation…of complement components C5a and C5b" are useful for treating glomerulonephritis in humans. *Id.*, at page 11, lines 7 to 31.

Thus, it is clear that a skilled artisan on or around 20 December 2001 reading the notebook pages of the Declaration would have at once understood that "[evaluating] the efficacy of ***anti-C5*** (BB5.1) on asthma mouse model", as asserted by the inventors, referred to the surrogate evaluation of BB5.1 as indicative of the therapeutic effect of a genus of functionally-related anti-C5 antibodies, rather than to use of BB5.1 *per se*. Accordingly, the artisan would have appreciated that the instant inventor had conceived of the therapeutic use of antagonist anti-C5 antibodies at least by 20 December 2001. Moreover, as evidenced by the working examples of the priority application (U.S. patent application serial no. 60/408,571), the inventor diligently carried out and completed the experiments described in the Declaration.

Notwithstanding these considerations, and in an alternative argument, the Office finds enormous breadth in the term "anti-C5" in order to conclude that Applicant impermissibly claims an unsupported subgenus (namely antagonist anti-C5 antibodies that inhibit the conversion of complement component C5 into C5a and C5b) within the broader genus of anti-C5 antibodies. Office Action at page 5. Under the Examiner's definition, ostensibly, "anti-C5 antibodies" as used in the Declaration include those antibodies that inhibit C5 cleavage (antagonist antibodies) and those that do not. In this embodiment of the argument, the Examiner alleges that BB5.1, an anti-C5 antibody that inhibits C5 cleavage, is simply not enough to support this "subgenus" of antagonist

anti-C5 antibodies. Applicant disagrees with the Examiner's characterization for at least the following reasons.

First, it is simply axiomatic that Applicant is free to be his own lexicographer when his description makes clear the definition of the claim term at issue. M.P.E.P § 2173.05(a)(III). As discussed *supra*, a skilled artisan on or around 20 December 2001 would have readily and unambiguously understood that the term "anti-C5" antibody – as used by the inventor in the Declaration, the instant application, and the art for years prior to the instantly asserted priority date – is and was coextensive with a genus of antagonist anti-C5 antibodies that inhibit the cleavage of C5 into fragments C5a and C5b. In fact, it defies reason that a skilled artisan in the complement field would have believed that the inventor, who has investigated the therapeutic role of C5 inhibition for decades, conceived of the *therapeutic* use of antibodies that do not inhibit C5 cleavage.

Furthermore, in contrast to the Office's position, a skilled artisan on or around 20 December 2001 would have been well aware of numerous, well-known species of antagonist anti-C5 antibodies embraced by the instant claims. The Office Action, for example, acknowledges that at least one example, BB5.1, is expressly provided in the Declaration. And, even if not explicitly recited in the Declaration, the skilled artisan would also have been well aware that additional "anti-C5 antibodies that have the desirable ability to block complement hemolytic activity and to block the generation of C5a…***have been known in the art since at least 1982***." The '697 PCT, at page 28 (emphasis added).

The Court of Appeals for the Federal Circuit (CAFC) has stated that "[i]nformation", such as information relating to additional antagonist anti-C5 antibodies embraced by the claims, "which is well known in the art need not be described in detail in the specification." *Hybritech, Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1379, 1380 (Fed. Cir. 1986). In this case, such well-known information includes, e.g., the antagonist anti-C5 antibodies 5G1.1 and 5G1.1 scFv as described in, e.g., the '697 PCT at page 28. The well-known information also includes the N19/8 and N19/8 scFv antibodies (see, e.g., the '697 PCT) as well as the antagonist anti-C5 antibodies described in Moongkarndi et al. (1982) *Immunobiol* 162:397 and Moongkarndi et al. (1983)

Immunobiol 165:323, copies of each of which are also submitted herewith as Exhibits F and G, respectively. In fact, the Office Action acknowledges that "eculizumab or pexelizumab, which are the same anti-C5 antibodies recited in instant claim 49 and encompassed by anti-C5 antibodies that inhibit the conversion of C5 into fragments C5a and C5b", were also known in the art on or around 20 December 2001.

Thus, whether express or implicit by virtue of common scientific knowledge, the Declaration materials adequately describe a sufficient number of species representative of the claimed genus to legally establish possession. *See*, e.g., M.P.E.P. § 2163 II(A)(3)(a)(ii). It is clear that a skilled artisan on or around 20 December 2001 would have readily and easily understood from the Declaration that Applicant has possession of a genus of antagonist anti-C5 antibodies, as is instantly claimed. Accordingly, acknowledgement of Applicant's asserted priority date of at least 20 December 2001 is requested.

Claims Rejected Under 35 U.S.C. §102(b)

Claims 15-17 and 46-50 were rejected under 35 U.S.C. § 102(b) as allegedly being anticipated by Wang et al., International Publication No. WO 2004/022096, ("Wang"). Wang was published on March 18, 2004; it also claims priority to U.S. Provisional Application Nos. 60/408,571 and 60/469,189, as does the present application. As detailed above, Applicant asserts that the instant claims (including claims 15-17 and 46-50 at issue here) are entitled to an effective filing date of September 6, 2002. Accordingly, Applicant submits that Wang cannot serve as the basis for a rejection of the claims under 35 U.S.C. § 102(b). Reconsideration and withdrawal of the rejection are respectfully requested.

Claims Rejected Under 35 U.S.C. §102(e)

Claims 15-18, 30, 46-50, 52, 53, and 55-57 were rejected under 35 U.S.C. § 102(e) as allegedly being anticipated by Krause (U.S. patent application publication no. 2004/0014782) [hereinafter Krause]. Applicant respectfully disagrees.

First, Applicant maintains that Krause is not properly § 102(e) prior art against the instant application for the reasons of record and those provided herein. In short, the Declaration clearly

establishes that Applicant conceived of the instant invention prior to March 29, 2002, the filing date of the priority application of Krause, and was diligent from prior to March 29, 2002 to at least September 6, 2002. Accordingly, Krause cannot serve as a § 102(e) reference against the instant application, and reconsideration and withdrawal of this rejection are respectfully requested.

Assuming *arguendo* that Krause could serve as prior art against the instant application Applicant maintains that Krause does not disclose a method for treating asthma or other pulmonary diseases using an anti-C5 antibody as is instantly claimed.

In order to anticipate the instant claims, Krause must disclose, either expressly or inherently, each and every element of the claimed methods. *See*, e.g., *Verdegaal Bros. v. Union Oil Co. of California*, 814 F.2d 628 (Fed. Cir. 1987) as cited in M.P.E.P. § 2131. Krause does not satisfy these requirements.

Krause discloses candidate small molecule C5a antagonists and their use, alone or in combination with other "C5a receptor-inactive agents", to treat inflammatory and/or autoimmune disorders such as rheumatoid arthritis (RA), skin injuries, infections, and lung diseases such as asthma. At paragraphs [0027] and [0277], eculizumab and pexelizumab are recited as one of many different examples of other "C5a receptor-inactive agents" that can be used in combination with the small molecules for treating RA. Anti-C5 antibodies have no effect on preformed C5a; the antibodies are not embraced by Krause's definition of C5a antagonist. At page 3, the Examiner appears to concede these points.

The legal standard for inherent anticipation is well established – "the extrinsic evidence 'must make clear that the missing descriptive matter is *necessarily* present in the thing described in the reference, and that it would be so recognized by persons of ordinary skill.'" *In re Robertson*, 169 F.3d 743, 745 (Fed. Cir. 1999) (citations omitted) (emphasis added). "The fact that a certain result or characteristic <u>may</u> occur or be present in the prior art is not sufficient to establish the inherency of that result or characteristic." M.P.E.P. § 2112 citing *In re Rijckaert*, 9 F.3d 1531, 1534 (Fed. Cir. 1993) (emphasis in original). The initial burden of proof falls upon the Office. *See*, e.g., M.P.E.P. § 2112 (IV) (stating "'In relying upon a theory of inherency, the examiner must provide a basis in fact and/or technical reasoning to reasonably support the determination that the allegedly

inherent characteristic necessarily flows from the teachings of the prior art.'") (Emphasis in original.) Applicant asserts that the Office has not established a *prima facie* case of inherent anticipation for at least the following reasons.

First, as discussed in Applicant's 17 December 2010 Amendment and Response to Non-final Office Action, Krause discloses in a distinct and modular way specific combination therapies useful for treating different types of inflammation. That is, in each therapeutic "module" related to the treatment of a specific inflammatory condition (e.g., rheumatoid arthritis), Krause discloses specific C5a receptor-inactive agents that can be used in combination with the C5a receptor antagonists of its disclosure. For example, at pages 17 and 18, Krause discloses a combination therapy for treating rheumatoid arthritis, which therapy includes "at least one C5a antagonist and a C5a receptor-inactive agent that is an anti-arthritic agent (i.e., a C5a receptor-inactive anti-arthritic agent)." *Id.* at paragraph [0202]. In another therapeutic module, Krause provides a combination therapy for treating lung disorders using at least one C5a antagonist and a C5a receptor-inactive agent "useful in the treatment of asthma." *Id.* at paragraph [0227] and paragraph [0279].

Eculizumab and pexelizumab are recited only two times in Krause, and in each instance only in "rheumatoid arthritis" therapeutic modules and only as one of a laundry list of well-known, potential C5a receptor-inactive anti-arthritic agents. In contrast, the two therapeutic modules drawn to treating lung disorders – at pages 18, 19, and 23 of Krause – do not mention eculizumab or pexelizumab, or any other anti-C5 antibodies, as being one of the C5a receptor-inactive agents useful for treating asthma. Instead, the lung disorder-related therapeutic modules recite a lung disorder-specific laundry list of well-known asthma treatments. Krause at paragraphs [0227] to [0229].

Since Krause does not expressly describe the use of anti-C5 antibodies, alone or in combination, to treat lung disorders such as asthma, the only way it can anticipate the claims, if at all, is by inherency. Yet neither eculizumab nor pexelizumab are ***necessarily*** part of the expansive genus of "C5a receptor inactive agents" embraced by Krause's asthma-related disclosure, as is required under the law for inherency. In fact, in view of the myriad, diverse C5a receptor-inactive agents specifically recited in paragraphs [0027] to [0029], one of ordinary skill in the art at the

effective filing date of Krause would certainly not have at once placed eculizumab and/or pexelizumab, let alone even anti-C5 antibodies in general, in Krause's laundry list of C5a receptor-inactive agents useful for treating asthma.

The term "C5a receptor-inactive agent", for example, imparts no structural or functional constraints on the types of compounds embraced by the genus – other than what its members are not. Rather, the specific examples of C5a receptor-inactive agents recited in Krause's asthma-related sections are functionally and structurally diverse. For example, the genus of functionally-diverse asthma-related C5a receptor-inactive agents includes, without limitation, leukotriene modifiers, mast cell stabilizers, phosphodiesterase 4 (PDE4) inhibitors, beta adrenergic receptor agonists, and thrombin inhibitors. *Id.* The C5a receptor-inactive agents embraced by Krause's asthma-related disclosure also have no apparent unifying structural features (e.g., steroidal compounds as compared to methylxanthines or cromolyns). *Id.* Given the broad range of function and physical attributes of the specific C5a receptor-inactive agents recited at paragraphs [0027 to [0029], it can hardly be said that eculizumab and pexelizumab, or any other anti-C5 antibody, are ***necessarily*** members of the genus of C5a receptor-inactive agents useful for treating asthma, which is required under the law.

On the other hand, eculizumab and pexelizumab are actually dissimilar from Krause's C5a receptor-inactive agents for at least one important reason – neither antibody was well known, clinically approved, or the subject of clinical trials for treating asthma or any related lung condition at the effective filing date of Krause. This is, of course, in stark contrast to the specific C5a receptor-inactive agents recited at paragraphs [0227] to [0229], all of which were well-known, clinically approved, and/or the subject of clinical trials for treating asthma. For example, Aerolate®, as recited in paragraph [0227] of Krause, was FDA approved on 3 December 1986; Accolate™, as recited in paragraph [0227] of Krause, was FDA approved on 26 September 1996; Nasalcrom™, as recited in paragraph [0227] of Krause, was FDA approved on 3 January 1997; Zyflo™, as recited in paragraph [0227] of Krause, was FDA approved on 9 December 1996; Atrovent™, as recited in paragraph [0227] of Krause, was FDA approved on 29 December 1986; Vanceril™, as recited in paragraph [0228] of Krause, was FDA approved on 12 May 1976;

Advair™, as recited in paragraph [0228] of Krause, was FDA approved on 24 August 2000; and Flovent™, as recited in paragraph [0228], was FDA approved on 27 March 1996. *See*, e.g., U.S. Food and Drug Administration Website (Drugs@FDA, original approval or tentative approval date). Eculizumab was, at the effective filing date of Krause, the subject of a clinical trial for the treatment of RA (hence it is included in the RA-related sections of Krause). But the skilled artisan reading Krause would not have at once grouped these anti-C5 antibodies with well-known, asthma-related secondary agents such as those disclosed by Krause. At a minimum, such antibodies would not ***necessarily*** be members of Krause's genus of C5a receptor-inactive agents useful for treating asthma, which is required under the law.

In view of the foregoing, Applicant respectfully submits that Krause fails to expressly or inherently anticipate the instant claims. Accordingly, reconsideration and withdrawal of the rejection is respectfully requested.

Claims Rejected Under 35 U.S.C. §103(a)

Claims 15-29 and 46-57 were rejected under 35 U.S.C. § 103(a) as allegedly being obvious over Krause (*supra*) in view of Evans et al. (U.S. Patent No. 6,355,245) [hereinafter Evans], Fung et al. (U.S. Patent No. 6,956,107) [hereinafter Fung (a)], Fung et al. (U.S. Patent No. 6,998,468) [hereinafter Fung (b)], West et al. (U.S. Patent No. 7,071,299) [hereinafter West], Babington et al. (U.S. Patent No. 4,228,795) [hereinafter Babington], Lobb et al. (U.S. Patent No. 5,871,734) [hereinafter Lobb], and Winter et al. (U.S. Patent No. 5,648,260) [hereinafter Winter]. Applicant respectfully traverses.

The Examiner, relying on the obviousness standard articulated by the U.S. Supreme Court in *KSR International Co. v. Teleflex Inc.*, 550 U.S. 398 (2007), concluded that

> [g]iven that the goal was to inhibit complement activation in order to treat pulmonary diseases…incorporating…anti-C5 antibodies into therapeutic regiments [sic] to treat…pulmonary conditions such as asthma would have been routine to the ordinary skilled artisan at the time the invention was made and therefore obvious[.]

Id., at page 12. Applicant respectfully disagrees with the Examiner's position.

While the *KSR* court did foreclose the use of argumentation based solely upon a lack of teaching, suggestion, or motivation – the *TSM test* – the Court emphasized that there must still be an *apparent reason* for the skilled artisan to combine references to arrive at the claimed invention. *KSR International Co.*, 550 U.S. at page 417 and 418. *See also* M.P.E.P. § 2143.01 (IV) (the P.T.O. stating that just "because the references relied upon teach that all aspects of the claimed invention were individually known in the art is not sufficient to establish a prima facie case of obviousness without some objective reason to combine the teachings of the references.") Furthermore, the Examination Guidelines Update (2010) promulgated by the U.S.P.T.O. state that "familiar lines of argument still apply including teaching away from the claimed invention from the prior art…and unexpected results. Indeed, they have taken on ***added importance*** in view of the recognition in *KSR* of a variety of possible rationales." Examination Guidelines Update: Developments in the Obviousness Inquiry After KSR v. Teleflex, *Federal Register* 75(169):53643, 53645, column 3 (emphasis added).

Applicant maintains that Krause is not properly § 102(e) prior art against the instant application. Assuming *arguendo* that Krause could serve as prior art against the instant application, Applicant asserts that, absent the teachings of the instant specification, there would have been no apparent reason for a skilled artisan to modify the teachings of this reference, in view of the secondary references, and arrive at the claimed methods.

The instant claims are drawn to an aerosol composition comprising an anti-C5 antibody that inhibits the conversion of C5 into C5a and C5b, wherein the composition is suitable for treating a chronic obstructive pulmonary condition or a pulmonary condition characterized with airway inflammation. The instant claims are also drawn to a biopharmaceutical package and a pulmonary drug delivery kit comprising said anti-C5 antibody.

The claimed compositions are based, in part, on actual experimental data provided in the application exemplifying use of a terminal complement component C5 inhibitor (an anti-C5 antibody) to treat established respiratory disease. *See* instant Specification at, e.g., paragraphs [0119] to [0173]. For example, the inventor demonstrated, using a mouse asthma model, that administration of an anti-C5 antibody to mice with established airway inflammation significantly

lowered the development of AHR and the on-going airway responses in these mice. *See* specification at, e.g., paragraphs [0050] to [0057] and [0149] to [0166], and Figs. 4-8. The specification also describes detailed formulations for nebulization of the disclosed anti-C5 antibody. *See* specification at, e.g., paragraphs [0170] to [0173], and Figs. 10-15.

These results indicate that an aerosol composition of an anti-C5 antibody is useful for treating subjects with established airway disease (e.g., a chronic obstructive pulmonary condition or a pulmonary condition characterized with airway inflammation, such as asthma), as is presently claimed.

In contrast to Applicant's disclosure, Krause describes a series of candidate small molecule C5a receptor antagonists and suggests, but does not experimentally demonstrate, that they may be useful for treating inflammatory diseases. As discussed above, the reference twice recites eculizumab and pexelizumab (at paragraphs [0207] and [0277]), in each instance listed, along with a laundry list of other well-known putative anti-arthritic agents[5], for use in treating rheumatoid arthritis. The reference does not expressly or inherently disclose methods for using anti-C5 antibodies as instantly claimed (*supra*).

The Office Action, however, advances the following syllogism: Krause discloses that inhibiting C5a receptor signaling (using candidate small molecule compounds) may be useful for treating asthma; anti-C5 antibodies inhibit the production of C5a; therefore, a skilled artisan reading Krause allegedly would have believed that anti-C5 antibodies are useful for treating asthma. Yet "[a] person of ordinary skill is…not an automaton." *KSR International Co.*, 550 U.S. at 421. The artisan would have considered ***all teachings in the analogous prior art*** and what the combined teachings suggested. The Examiner, by proxy, must do the same. M.P.E.P. § 2143.01 (II). According to the CAFC,

> [w]here the teachings of two or more prior art references conflict, the examiner must weigh the power of each reference to suggest solutions to one

[5] Notably, at the effective date of Krause, Alexion Pharmaceuticals, Inc. was engaged in a well-known phase II clinical trial evaluating an anti-C5 antibody in rheumatoid arthritis. *See, e.g.*, PR Newswire article dated 4 August 1999 and Abstract of Kaplan (2002) (stating that - "Eculizumab … is under development by Alexion as a potential treatment for … rheumatoid arthritis (RA) … In January 2002, a phase IIb trial was initiated for RA") *Id.*

> of ordinary skill in the art, considering the degree to which one reference might accurately discredit another.

In re Young, 927 F.2d 588 (Fed. Cir. 1991). Such is the case at bar.

At the effective filing date of the instant application, the art was, at best, conflicted about the role of complement component C5 in asthma. As evidence of the state of the art at the priority date of the application, Applicant again provides Karp et al. (2000) *Nature Immunology* 1(3):221[6] [hereinafter Karp], a reference published two years prior to the effective filing date of Krause. Karp's authors found that lower expression of C5 protein is associated with more severe OVA-induced inflammation in mouse lung (see Figure 1). These actual experimental results, of course, are in stark contrast to what a skilled artisan would have expected under the Examiner's interpretation of the Krause reference.

In addition, Karp discloses that inhibition of C5a receptor, as is at issue in Krause, results in a marked reduction in IL-12 production by monocytes *in vitro* (see Figure 3). IL-12 is a cytokine that is able to prevent or reverse experimental allergic asthma (see Abstract of Karp). This disclosure would very likely lead a skilled artisan to believe that inhibition of C5 would, if anything, exacerbate asthma, rather than treat it. Thus, Applicant submits that Karp ***teaches away*** from the notion that inhibition of C5a or C5 would reduce the severity of OVA-induced inflammation in mouse lung. Accordingly, the skilled artisan reading Karp would have believed that C5 was protective against asthma and that inhibition of C5 or C5a receptor would not be beneficial for treating asthma.

Such a belief is consistent with other reports published proximal to the filing date of the instant application, and further teaching away from any benefit of using C5 inhibitors to treat respiratory disorders such as asthma. For example, Humbles et al. (2000) *Nature* 406:998-1001 [hereinafter Humbles], a reference published two years before the effective filing date of Krause, demonstrates that mice deficient in C3a receptor alone were protected against methacholine-induced airway hyperresponsiveness in a mouse model of asthma. *See* Humbles at, e.g., page 999, Figure 3, submitted concurrently herewith as Exhibit H.

[6] Karp was provided by Applicant as Exhibit A in the 8 December 2008 Amendment and Response to Office Action.

C3a is a cleavage product of complement component C3, which is upstream of C5. As expressly acknowledged by the Office Action, C5 blockade preserves the critical immunoregulatory functions of upstream components such as C3. Office Action at page 10. Given the art-recognized critical role for C3a/C3a receptor in asthma, and that the pathophysiological action of C3a is not inhibited by C5 antagonists, one of skill in the art at the effective date of this application would very likely have believed that inhibition of C5a alone, or C5, would not prevent C3-driven airway hyperresponsiveness in asthma.

Krause's disclosure does not surmount the contrary teachings in the art. For example, Krause provides absolutely no experimental evidence that its C5a receptor antagonists are effective at treating asthma in an animal model, let alone in humans. On its face, Krause does not even experimentally demonstrate that its compounds are capable of inhibiting C5a receptor signaling. To wit: although Krause describes through a series of prophetic examples how one *could* test its small molecule compounds for *in vitro* activity (e.g., inhibition of C5a receptor-mediated signal transduction), there is no evidence that any of its putative C5a receptor antagonists *were actually tested* and confirmed to have such activity. The skilled artisan steeped in the art would have recognized Krause as espousing little more than hypothetical, conjectural, and/or hoped-for results.

Notably, Neurogen, the assignee of the Krause application, supported a randomized clinical trial involving 142 patients with mild-to-moderate asthma, who were treated with a small molecule C5a antagonist – NGD-2000-1 – in a manner consistent with the Krause disclosure. The trial failed in 2004 with results showing no therapeutic benefit. *See*, e.g., Press Release dated 13 January 2004 (a copy of which is submitted herewith as Exhibit I). The Krause disclosure simply would not have been sufficient in the mid of a skilled artisan to overcome the strong contrary experimental evidence present in the art. The artisan's reticence was vindicated by Neurogen's failed clinical trial. Thus, absent the express teachings of the instant application, the skilled artisan reading Krause would not have had the requisite reason to practice the instantly claimed methods.

The secondary references cited by the Office do not cure the large deficiencies of Krause. For example, Fung (a), as acknowledged by the Office Action, relates to anti-factor D antibodies.

The Office asserts that Fung (a), particularly at column 9, teaches the role of C5a, and inhibition thereof, in the context of severe asthma. Applicant respectfully disagrees.

In contrast to the Office Action's characterization, of Fung (a) at column 9 discloses textbook knowledge that anti-factor D antibodies, by virtue of acting upon the C3 convertase step of the complement cascade, inhibit downstream complement activation including the generation of C5a and C5b-9. Column 9, lines 39 to 41. Notably, inhibition of factor D using anti-factor D antibodies inhibits the production of C3a (Fung (a) at column 9, line 40), which, as noted above, was described by Humbles to play a critical role in airway hyperreactivity. There is simply no disclosure or suggestion in Fung (a) that C5a receptor antagonists, let alone anti-C5 antibodies, are, or would be, useful for treating asthma as is instantly claimed.

Fung (b) exhibits similar deficiencies. The reference relates to anti-C2a antibodies and their use in treating complement-associated diseases. At page 10 the Office Action urges that Fung (b) teaches that anti-C2a antibodies, by virtue of acting upon the C3 convertase step of the complement cascade, inhibit downstream complement activation including the generation of C5a and C5b-9. Yet there is no disclosure or suggestion in this reference that inhibition of C5 is therapeutically useful as claimed.

Evans discloses and claims a genus of new anti-C5 antibodies. The reference, as cited by the Examiner, states that the antibodies can be used "for treatment of other inflammatory conditions involving pathogenic activation of complement system." Lobb does not even relate to inhibition of the complement cascade, but is offered by the Examiner as evidence of combination therapies and that an antibody can be delivered to the lungs of a subject (see the Office Action at page 12). The above references do not, however, disclose or suggest the instantly claims or otherwise suggest an alternative view to that advanced by Humbles and Karp. West and Babington are directed to compositions suitable for nasal inhalation. Winter generally teaches antibodies with altered Fc functions. However, none of these cited references cures the deficiency of Krause vis-à-vis the instant claims.

In conclusion, it is clear that absent the teachings of the instant specification, there would have been no apparent reason for a skilled artisan to modify the teachings of Krause, in view of the

secondary references, and arrive at the claimed methods. None of the cited references, including Krause, sets forth any data evidencing use of any C5 inhibitor, let alone an anti-C5 antibody, in the instantly claimed methods. The cited references also fail to surmount the teachings of, e.g., Humbles and Karp, which argued against therapeutic C5 inhibition in asthma. Accordingly, Applicant respectfully requests reconsideration and withdrawal of the rejection under 35 U.S.C. § 103.

CONCLUSION

In view of the foregoing amendments and remarks, Applicant submits that the pending claims are in condition for allowance. Early and favorable consideration is respectfully solicited.

The Examiner may address any questions raised by this submission to the undersigned at 617-951-7000. Applicant believes no fees are due other than specifically itemized on the accompanying fee transmittal. However, should an extension of time be required, Applicant hereby petition for same and request that the extension fee and any other fee required for timely consideration of this submission be charged to Deposit Account No. 18-1945, under Order No. ALXN-P02-102 from which the undersigned is authorized to draw.

Dated: August 2, 2011

Respectfully submitted,

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Attorneys/Agents For Applicant

Docket No.: ALXN-P02-102
(PATENT)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of:
Wang et al.

Application No.: 11/127,438 Confirmation No.: 5259

Filed: May 11, 2005 Art Unit: 1644

For: NEBULIZATION OF MONOCLONAL ANTIBODIES FOR TREATING PULMONARY DISEASES Examiner: P. Gambel

SUPPLEMENTAL INFORMATION DISCLOSURE STATEMENT (IDS)

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

Dear Sir:

Pursuant to 37 CFR 1.56, 1.97 and 1.98, the attention of the Patent and Trademark Office is hereby directed to the references listed on the attached PTO/SB/08. It is respectfully requested that the information be expressly considered during the prosecution of this application, and that the references be made of record therein and appear among the "References Cited" on any patent to issue therefrom.

This Supplemental Information Disclosure Statement is filed more than three months after the U.S. filing date, and after the mailing date of the first Office Action on the merits, whichever occurs first, but before the mailing date of any of a Final Office Action, a Notice of Allowance (37 CFR 1.97(c)) or an action that otherwise closes prosecution in the application.

Applicant submits herewith copies of non-patent literature in accordance with 37 CFR 1.98(a)(2).

Those documents which are marked with a double asterisk (**) next to the Cite No. in the attached form PTO/SB/08 are not supplied because they were previously cited by or submitted to the Office in prior application number 10/655,861 filed September 5, 2003 and relied upon in this application for an earlier filing date under 35 U.S.C. 120.

In accordance with 37 CFR 1.97(g), the filing of this Supplemental Information Disclosure Statement shall not be construed to mean that a search has been made or that no other material information as defined in 37 CFR 1.56(a) exists. In accordance with 37 CFR 1.97(h), the filing of this Supplemental Information Disclosure Statement shall not be construed to be an admission that any patent, publication or other information referred to therein is "prior art" for this invention unless specifically designated as such.

It is submitted that the Supplemental Information Disclosure Statement is in compliance with 37 CFR 1.98 and the Examiner is respectfully requested to consider the listed references.

Please charge our Deposit Account No. 18-1945 in the amount of $180.00 covering the fee set forth in 37 CFR 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 (or with any paper hereafter filed in this application by this firm) to our Deposit Account No. 18-1945, under Order No. ALXN-P02-102.

Dated: August 2, 2011

Respectfully submitted,

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PTO/SB/08a (07-09)
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Substitute for form 1449/PTO

INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Use as many sheets as necessary)

Sheet 1 of 2

Complete if Known	
Application Number	11/127,438
Filing Date	May 11, 2005
First Named Inventor	Yi Wang
Art Unit	1644
Examiner Name	P. Gambel
Attorney Docket Number	ALXN-P02-102

U.S. PATENT DOCUMENTS

Examiner Initials*	Cite No.[1]	Document Number Number-Kind Code[2] (if known)	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear

FOREIGN PATENT DOCUMENTS

Examiner Initials*	Cite No.[1]	Foreign Patent Document Country Code[3]-Number[4]-Kind Code[5] (if known)	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages Or Relevant Figures Appear	T[6]
	**	WO 95/29697	11-09-1995	Alexion Pharmaceuticals, Inc.		

Examiner Signature		Date Considered	

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant. ** CITE NO.: Those document(s) which are marked with an double asterisk (**) next to the Cite No. are not supplied because they were previously cited by or submitted to the Office in a prior application relied upon in this application for an earlier filing date under 35 U.S.C. 120. [1] Applicant's unique citation designation number (optional). [2] See Kinds Codes of USPTO Patent Documents at www.uspto.gov or MPEP 901.04. [3] Enter Office that issued the document, by the two-letter code (WIPO Standard ST.3). [4] For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. [5] Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16 if possible. [6] Applicant is to place a check mark here if English language Translation is attached.

PTO/SB/08b (07-09)
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U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
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INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Use as many sheets as necessary)

Sheet	2	of	2

Complete if Known	
Application Number	11/127,438
Filing Date	May 11, 2005
First Named Inventor	Yi Wang
Art Unit	1644
Examiner Name	P. Gambel
Attorney Docket Number	ALXN-P02-102

NON PATENT LITERATURE DOCUMENTS

Examiner Initials*	Cite No.[1]	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, page(s), volume-issue number(s), publisher, city and/or country where published.	T[2]
		Humbles et al., "A role for the C3a anaphylatoxin receptor in the effector phase of asthma," Letters to Nature, Vol. 406; pp. 998-1001 (2000).	
	**	Kaplan, Mariana, "Eculizumab," Current Opinion in Investigational Drugs, Vol. 3(7); pp. 1017-1023 (2002).	
	**	Moongkarndi et al., "Immunological and functional properties of two monoclonal antibodies against human C5," Immunobiol. Vol. 165, page 323 (1983).	
	**	Moongkarndi et al., "Monoclonal antibodies against the fifth component of human complement," Immunobiol, Vol 162; page 397 (1982).	
		Mueller et al., "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), pp. 441-452 (1997).	
	**	Neurogen Reports Phase IIa Clinical Trial Results for Oral Asthma Drug, Press Release dated January 13, 2004.	
		Thomas et al., "Inhibition of Complement Activity By Humanized Anti-C5 Antibody and Single-Chain Fv.," Molecular Immunology, Vol. 33(17/18), pp. 1389-1401 (1996).	
		Whiss, P.A., "Pexelizumab Alexion," Current Opinion Investig. Drugs, Vol. 3(6); pp. 870-877 (2002). (abstract)	

Examiner Signature		Date Considered	

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant. ** CITE NO.: Those document(s) which are marked with an double asterisk (**) next to the Cite No. are not supplied because they were previously cited by or submitted to the Office in a prior application relied upon in this application for an earlier filing date under 35 U.S.C. 120.

[1]Applicant's unique citation designation number (optional). [2]Applicant is to place a check mark here if English language Translation is attached.

Electronic Patent Application Fee Transmittal	
Application Number:	11127438
Filing Date:	11-May-2005
Title of Invention:	Nebulization of monoclonal antibodies for treating pulmonary diseases
First Named Inventor/Applicant Name:	Yi Wang
Filer:	Jason S. Cathelyn/ginny blundell
Attorney Docket Number:	ALXN-P02-102
Filed as Large Entity	

Utility under 35 USC 111(a) Filing Fees

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

Samsung Bioepis Exhibit No. 1002
Page 8991

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Miscellaneous:				
Submission- Information Disclosure Stmt	1806	1	180	180
		Total in USD ($)		**180**

Samsung Bioepis Exhibit No. 1002
Page 8992

Electronic Acknowledgement Receipt	
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Application Number:	11127438
International Application Number:	
Confirmation Number:	5259
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First Named Inventor/Applicant Name:	Yi Wang
Customer Number:	28120
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Filer Authorized By:	Jason S. Cathelyn
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1	Miscellaneous Incoming Letter	AXLN_P02_102_Transmittal.pdf	92112 05a45970a42ee15ce6590402edf7c3bf2b536198	no	1
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2	Miscellaneous Incoming Letter	ALXN_P02_102_Exhibit_A.pdf	1633871 51da1afa554129a2ad3c5a2409fd984683133bfb	no	7
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7	Miscellaneous Incoming Letter	ALXN_P02_102_Exhibit_G.pdf	1509555 b3017fe79061da2691e5b1b85ae9df54a3441674	no	1
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8	Miscellaneous Incoming Letter	ALXN_P02_102_Exhibit_H.pdf	965627 65d1ba94d0b924a70a0446b2dc068bd7e2edc061	no	4
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9	Non Patent Literature	Humbles.pdf	961276 fb77433bb9a1c464c948f59c2ffe6cb41f07eea0	no	4
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12	Non Patent Literature	Mueller.pdf	2724674 310d4548d40cb616e4f4042dccb9d57ac928f179	no	12
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13		ALXN_P02_102_Reply.pdf	208214 1e2d58751ed3d8d26ee3b2584c77283523bfdaf1	yes	27

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Claims	2	6
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14	Miscellaneous Incoming Letter	ALXN_P02_102_Exhibit_D.pdf	2726541 a07dbfb05e9a28376adcff3d3c3d9fb8bf90e7ef	no	12
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15	Miscellaneous Incoming Letter	ALXN_P02_102_Exhibit_I.pdf	105217 d4b572d0e25ab0dae19028a4d1baa7894c6abfbb	no	1
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16	Transmittal Letter	ALXN_P02_102_IDS_Statement.pdf	71133 97c4404643a013b71e6193b61545d8193d2d18d3	no	2
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17	Information Disclosure Statement (IDS) Form (SB08)	ALXN_P02_102_SB08.pdf	127794 f5b28935c4b06624d9b4734366df79b6be821e01	no	2
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18	Fee Worksheet (SB06)	fee-info.pdf	30218 bee3d9cf5a5250b12d8e9af82d06b41d51fe851b	no	2
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AMENDMENT TRANSMITTAL LETTER			Docket No. ALXN-P02-102
Application No. 11/127,438	Filing Date May 11, 2005	Examiner P. Gambel	Art Unit 1644

Applicant(s): Wang et al.

Invention: NEBULIZATION OF MONOCLONAL ANTIBODIES FOR TREATING PULMONARY DISEASES

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Transmitted herewith is an amendment in the above-identified application.

The fee has been calculated and is transmitted as shown below.

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/Jason S. Cathelyn/ Dated: August 2, 2011

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(57) Abstract

The use of anti-C5 antibodies, e.g., monoclonal antibodies, to treat glomerulonephritis (GN) is disclosed. The administration of such antibodies at low dosage levels has been found to significantly reduce glomerular inflammation/enlargement and other pathologic conditions associated with GN. Also disclosed are novel anti-C5 antibodies and anti-C5 antibody-encoding nucleic acid molecules. These antibodies are useful in the treatment of GN and other inflammatory conditions involving pathologic activation of the complement system.

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METHODS AND COMPOSITIONS FOR THE TREATMENT OF GLOMERULONEPHRITIS AND OTHER INFLAMMATORY DISEASES

FIELD OF THE INVENTION

The present invention relates to the treatment of glomerulonephritis (GN) and other inflammatory diseases, and more generally to therapeutic treatments involving the pharmacologic inhibition of a patient's complement system. In particular, the invention relates to the use of antibodies specific to human complement component C5 to accomplish such therapeutic treatment. The invention also relates to compositions comprising native monoclonal antibodies (mAbs) specific to human complement component C5 that block complement hemolytic activity and C5a generation at concentrations that substantially reach the theoretical one to two stoichiometric limit of antibody to antigen that can be achieved by a bivalent antibody. The invention further provides recombinant mAbs that are derivatives (including monovalent derivatives) of these native mAbs that provide substantially the same blocking activities as the native mAbs.

BACKGROUND OF THE INVENTION

I. Immune Complex Mediated Disease

The formation of immune complexes is the typical consequence of the interaction of antigens with specific antibodies. The inflammatory response that ensues when such complexes accumulate in a limited area is an important element of normal host defenses, leading to immune complex clearance and antigen destruction by phagocytic cells. In contrast, immune complex diseases are reflections of excess complex formation or retarded clearance, usually under conditions of exceptional antigen challenge or immunologic dysregulation. Under such circumstances, immune complexes are deposited or formed at specific tissue sites and resulting inflammatory responses lead to disease states due to localized or systemic tissue damage. The kidney, and more specifically the kidney structure known as the glomerulus, is a particularly important

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site of immune complex deposition resulting in the development of serious disease conditions.

Human studies, and studies using animal models of human diseases, have implicated the complement system in the pathologies associated with a number of immune complex associated disorders. The activation of complement that mediates the pathology associated with these disorders may be a consequence of an autoimmune mechanism, or can be non-immunologic in origin.

The hypersensitivity response that occurs when antibodies bind to antigens either in tissues or in the circulation results from the activation of complement and the release of molecules that mediate inflammation. This process is classified as either being mediated by the binding of antibody to fixed tissue or cell bound antigens (Type II hypersensitivity) or to circulating antigens, resulting in the formation of circulating immune complexes and their subsequent pathogenic deposition in tissues (Type III hypersensitivity).

Type II hypersensitivity is mediated through the activation of complement following the binding of antibodies to fixed tissue antigens. The inflammatory response that ensues results from the activation of the proinflammatory and lytic components of the complement system and the subsequent recruitment of stimulated leukocytes to the sites of immune complex formation. The increased vascular permeability that results from the anaphylatoxic activities of C3a and C5a further enhances immune complex deposition and leukocyte recruitment.

The cross-linking of antibody bound cells or tissues to effector cells such as neutrophils, platelets, NK cells, and monocytes via their Fc receptors also plays a proinflammatory role. Such cross-linking activates effector cells, stimulating the release of oxygen radicals, prostaglandins, and leukotrienes, which release is further potentiated by the actions of activated complement components.

Examples of Type II hypersensitivity-mediated conditions include hyperacute rejection of transplanted organs, autoimmune hemolytic and thrombocytopenic states,

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Goodpasture's syndrome (and associated glomerulonephritis and pulmonary hemorrhage), myasthenia gravis, pathologic sequellae associated with insulin-dependent diabetes melitus, and pemphigus vulgaris.

Type III hypersensitivity reactions involving circulating antigens can also result in the development of numerous pathologic conditions. These include glomerulonephritis (discussed in detail below), vasculitis (a potentially life-threatening inflammatory condition of large and/or small blood vessels), rheumatoid arthritis, dermatitis, and other disorders.

Other diseases associated with type III hypersensitivity reactions include autoimmune diseases such as systemic lupus erythematosis (SLE), many infectious diseases, neoplastic diseases, and a wide variety of other conditions (Dixon, et al. Immune Complex Injury, in Samter, (ed.) Immunological Diseases, 4th ed. Little Brown & Co. Boston, 1987).

II. Glomerulonephritis

The glomerulus is a key structural and functional element of the kidney. Each glomerulus is found as part of a larger structure that serves as the main functional unit of the kidney and is called a nephron. About a million nephrons are found in each kidney. Each glomerulus is a network of up to fifty parallel capillaries encased in a structure known as Bowman's capsule. The area inside Bowman's capsule that is not taken up by the glomerular capillaries is known as Bowman's space. The glomerulus functions as a filter, separating water and certain solutes from the proteins and cells of the blood into Bowman's space for further processing in the convoluted tubules, loop of Henle, and collecting duct of the nephron.

Glomerulonephritis (GN) is a disease of the kidney characterized by inflammation and resulting enlargement of the glomeruli that is typically due to immune complex formation. The accumulation of immune complexes in the glomeruli results in inflammatory responses, involving inter alia hypercellularity, that can cause total or partial blockage of the glomerulus through, among other factors, narrowing of

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capillary lumens. One result of this process is the inhibition of the normal filtration function of the glomerulus. Blockage may occur in large numbers of glomeruli, directly compromising kidney function and often causing the abnormal deposition of proteins in the walls of the capillaries making up the glomerulus. Such deposition can, in turn, cause damage to glomerular basement membranes. Those glomeruli that are not blocked develop increased permeability, allowing large amounts of protein to pass into the urine, a condition referred to as proteinuria.

In many cases of severe GN, pathological structures called crescents are formed within the Bowman's space, further impeding glomerular filtration. These structures can only be seen by microscopic examination of tissue samples obtained by biopsy or necropsy, and are thus not always observed in those patients in which they occur. Crescents are a manifestation of hypercellularity and are thought to arise from the extensive abnormal proliferation of parietal epithelial cells, the cells that form the inner lining of the Bowman's capsule. Clinical research has shown that there is a rough correlation between the percentage of glomeruli with crescents and the clinical severity of the disease, and thus the patient's prognosis. When present in large numbers, crescents are a poor prognostic sign.

Symptoms of GN include: proteinuria; reduced glomerular filtration rate (GFR); serum electrolyte changes including azotemia (uremia, excessive blood urea nitrogen - BUN) and salt retention, leading to water retention resulting in hypertension and edema; hematuria and abnormal urinary sediments including red cell casts; hypoalbuminemia; hyperlipidemia; and lipiduria.

In 1990, over 210,000 patients in the United States required hemodialysis or transplantation for chronic renal failure at an annual cost in excess of 7 billion dollars, according to the United States Renal Data System (USRDS). The USRDS compiles data on kidney disease in the United States in conjunction with the National Institute of Diabetes and Digestive and Kidney Diseases, Division of Kidney, Urologic,

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and Hematologic Diseases, of the National Institutes of Health (NIDDKD). The USRDS estimates that the costs of treatment for renal failure are now increasing by 20 percent annually.

GN is the third leading cause of death in end-stage renal disease patients, exceeded only by diabetes and hypertension. As a result, there is a clear and long felt need in the medical community for effective treatments for this condition. Research aimed at the development of new treatments for GN is ongoing worldwide. In the United States, the NIDDKD, the National Kidney Foundation, and several other public and private organizations sponsor research in this area. The National Kidney Foundation alone supplies over two million dollars annually to fund the efforts of kidney researchers.

III. Current Treatments for GN

Corticosteroid administration, typically as high doses of "pulse" intravenous methylprednisolone or oral prednisone therapy, is currently considered the most effective pharmacologic agent available for the treatment of GN. Such steroid therapy is often administered in combination with cytotoxic general immunosuppressive agents such as azathioprine or cyclophosphamide. The overall immune suppression and resulting increased susceptibility to infection, along with other debilitating side effects associated with both steroid and cytotoxic drug administration, limit the effective use of these drugs.

Aspirin-like non-steroidal anti-inflammatory drugs (NSAIDs) have also been used to reduce the glomerular inflammation and enlargement of GN. These drugs are not routinely used for this purpose, however, probably because of their relatively weak anti-inflammatory effects and propensity to cause gastrointestinal and other side effects in many patients.

The administration of anticoagulants such as heparin or warfarin sodium, and antithrombotic agents such as cyproheptadine, dipyridamole, or sulfinpyrazone, has been used on the basis of evidence suggesting the involvement of the coagulation process in the genesis of glomerular crescents. However, objective evidence of benefit from such therapies in

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animals afflicted with experimentally induced crescentic GN has been inconsistent. Also, anticoagulants are dangerous drugs, as they can potentiate life-threatening bleeding episodes. They are especially hazardous in this regard in patients with advanced renal failure.

In addition to pharmacologic approaches, intensive plasma exchange (plasmapheresis) of 2 to 4 liters of plasma daily (or in some cases three times a week) can dramatically reduce high levels of circulating immune complexes when acute intervention in the inflammatory process is needed. Such treatment is expensive and requires that the patient be connected to the plasmapheresis machine for many hours each week. In addition, all procedures in which blood is removed from and returned to a patient are associated with an increased risk of infection. Nonetheless, plasma exchange is currently considered the most effective non-pharmacological treatment for removal of circulating immune complexes which can cause GN.

Circulating immune complex levels can also be decreased by eliminating or reducing the source of the antigen or antigens contained in the complexes by, for example, effective therapy of an underlying infection or change in an antibiotic. However, while such therapy is almost always a treatment of choice, great care must be taken since reduction of the antigen load alters the molar ratio of antigen to antibody involved in forming immune complexes and thus a dangerous temporary exacerbation of the inflammatory process may occur (see discussion below in Background Physiology & Pathology).

IV. Antibody Engineering

Native antibodies are multi-subunit animal protein molecules with highly specific antigen-binding properties. Animals make multiple classes of antibodies. There are five major classes (IgA, IgD, IgE, IgG and IgM) and a variety of subclasses. Native antibodies are made up of two or more heterodimeric subunits each containing one heavy (H) and one light (L) chain. The differences between antibody classes derive from their different H chains. H chains have a molecular weight of about 53 kDa, while L chains are about 23 kDa in mass.

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Every individual native antibody has one type of L chain and one type of H chain, which are held together by disulfide bonds to form a heterodimeric subunit. Typically a native antibody (e.g., an IgG) has two such subunits, which are also held together by disulfide bonds. Within each chain, units of about 110 amino acid residues fold so as to form compact domains. Each domain is held together by a single intrachain disulfide bond. L chains have two domains, while H chains have four or five. Most H chains have a hinge region after the first (i.e., most amino-terminally located) two domains. The disulfide bonds linking together the heterodimeric subunits are located at the hinge regions. The hinge region is particularly sensitive to proteolytic cleavage, such proteolysis yielding two or three fragments (depending on the precise site of cleavage), a non-antigen binding fragment containing only H chain C regions (Fc) and one bivalent (Fab'2) or two monovalent (Fab) antigen binding fragments. The hinge region allows the antigen binding regions (each made up of a light chain and the first two domains of a heavy chain) to move freely relative to the rest of the native antibody, which includes the remaining heavy chain domains.

The first domain of each chain is highly variable in amino acid sequence, providing the vast spectrum of antibody binding specificities found in each individual. These are known as variable heavy (VH) and variable light (VL) domains. The second and subsequent (if any) domains of each chain are relatively invariant in amino acid sequence. These are known as constant heavy (CH) and constant light (CL) domains.

Each variable region contains three loops of hypervariable sequence that provide a complementary structure to that of the antigen and are critical in determining the antigen binding specificity of the antibody, as they are the contact sites for binding to the antigen. These loops are known as complementarity determining regions, or CDRs. Each variable domain is made up of three CDRs embedded in four much less variable framework segments (FRs). Together, the sets of collinear CDRs and FRs are in large part responsible for determining the three dimensional conformation of the variable

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regions of antibody molecules.

CDRs and FRs are features that have been deduced from structural properties of antibody variable regions. Both amino acid sequence (primary structure) and three dimensional modeling (deduced secondary and tertiary structure) of antibody variable regions have been used by various researchers to define CDRs and, by default, FRs. While the positions of the CDRs are beyond question, not all workers in the art agree upon the precise locations of the boundaries of each CDR in VH or VL regions; there is no clear cut structural marker delineating CDR/FR boundaries.

Two definitions of CDR location are currently in general use in the art. These are the "sequence variability" definition of Kabat et al. ("Sequences of Proteins of Immunological Interest," 4th ed. Washington, D.C.: Public Health Service, N.I.H.) and the "structural variability" definition of Chothia and Lesk (J. Mol. Biol. 1987, 196:901). As used herein, the terms VL CDR1, VL CDR2, VL CDR3, VH CDR1, VH CDR2, and VH CDR3 refer minimally to the region of overlap between the regions designated for each CDR by each of these two definitions, and maximally to the total region spanned by the combination of the regions designated for each CDR by each of these two definitions.

One problem that antibody engineering attempts to address is the immune activity of a human patient that occurs in response to a native murine (or other non-human animal) antibody, typically a mAb, that is being administered to the patient for therapeutic purposes. This activity against murine antibodies is characterized by a human anti-mouse antibody (HAMA) response that can have deleterious effects on treatment efficacy and patient health. It has been found that almost all such human anti-non-human antibody ("HAMA type") activity is directed at the constant domains and at the FR regions of the variable domains of native non-human antibodies.

By manipulating the nucleic acid molecules encoding antibody H and L chains it is possible to incorporate non-human variable regions into antibodies otherwise made up of

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human constant regions. The resulting antibodies are referred to as "chimeric antibodies," and are typically less prone to eliciting HAMA type responses than are the non-human antibodies from which the variable regions are derived.

An even more effective approach to eliminating the potential of a non-human antibody to elicit a HAMA type response is to "humanize" it, i.e., to replace its non-human framework regions with human ones. One way of achieving such humanization involves the insertion of polynucleotide fragments encoding the non-human CDRs of the antibody to be humanized into a nucleic acid molecule encoding an otherwise human antibody (with human constant regions if desired) so as to replace the human CDRs and to use the resulting nucleic acid molecule to express the encoded "humanized" antibody.

Unfortunately, however, humanization of non-human antibodies has unpredictable effects on antibody antigen interactions, e.g., antigen binding properties. Some of this unpredictability stems from the properties of the CDRs. Certain CDRs may be more amenable to the construction of humanized antibodies that retain the properties of the non-human CDR donor antibody than others. While the CDRs are key to the antigen binding properties of an antibody, CDRs and FRs must interact appropriately if the antigen specificity of an antibody is to be retained following humanization. The effects of combination with particular human FRs on uncharacterized non-human CDRs cannot be reliably predicted by any known method. However, the successful humanization of an antibody provides information that, in general, facilitates the successful humanization of the CDRs of that antibody using other human or altered human FRs. In addition, approaches are available that facilitate tailoring human FRs to enhance the likelihood of successful humanization.

Other problems addressed by antibody engineering include efficient antibody production and alteration of antibody pharmacokinetics. Recombinant protein production is generally most efficiently carried out in bacterial hosts. The large size and multimeric nature of native antibodies makes their production in bacteria difficult. One approach to dealing

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with production problems is to use recombinant DNA methods to construct antibodies that have their H and L chains joined by a linker peptide to form a single chain (sc) antibody. As described below, there are several types of sc antibodies that can be constructed.

As is the case for humanization, the effects on antigen binding properties of constructing a particular type of sc antibody using H and L chains that have not been characterized with regard to their ability to function as part of an sc antibody cannot be reliably predicted by any known method. However, the successful construction of any one type of sc antibody from a particular native antibody provides information that, in general, facilitates the successful construction of other types of sc antibodies from that native antibody.

Single chain antibodies may include one each of only VH and VL domains, in which case they are referred to as scFv antibodies; they may include only one each of VH, VL, CH, and CL domains, in which case they are referred to as scFab antibodies; or they may contain all of the variable and constant regions of a native antibody, in which case they are referred to as full length sc antibodies.

The differing sizes of these antibodies imparts each with differing pharmacokinetic properties. In general, smaller proteins are cleared from the circulation more rapidly than larger proteins of the same general composition. Thus, full length sc antibodies and native antibodies generally have the longest duration of action, scFab antibodies have shorter durations of action, and scFv antibodies have even shorter durations of action. Of course, depending upon the illness being treated, longer or shorter acting therapeutic agents may be desired. For example, therapeutic agents for use in the prevention of immune and hemostatic disorders associated with extracorporeal circulation procedures (which are typically of brief duration) are preferably relatively short acting, while antibodies for the treatment of long term chronic conditions (such as inflammatory joint disease or GN) are preferably relatively long acting.

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Detailed discussions of antibody engineering may be found in numerous recent publications including: Borrebaek, "Antibody Engineering, A Practical Guide," 1992, W.H. Freeman and Co. NY; and Borrebaek, "Antibody Engineering," 2nd ed. 1995, Oxford University Press, NY, Oxford.

SUMMARY OF THE INVENTION

In view of the foregoing, it is an object of the present invention to provide a new approach for reducing the glomerular inflammation and kidney dysfunction associated with GN.

The method of the invention involves the use of preparations containing antibodies to human complement component C5 as pharmaceutical agents. More particularly, the invention provides for the use of anti-C5 antibodies that bind to complement component C5 or active fragments thereof. Preferably, the antibodies block the generation and/or activity of complement components C5a and C5b. For most applications, the antibody is a monoclonal antibody.

In the preferred embodiments of the invention, the administration of the anti-C5 antibody preparation is started after the appearance of GN symptoms, e.g., after the appearance of proteinuria. Alternatively, the invention can be used prophylactically to treat patients who are at risk for an acute exacerbation of existing GN, e.g., patients experiencing a flare-up of symptoms of systemic lupus erythematosus or similar autoimmune diseases that have resulted in GN.

As shown in the examples presented below, anti-C5 antibodies administered subsequent to the onset of GN essentially eliminate glomerular inflammation/enlargement and reduce kidney dysfunction (see Examples 1 and 2).

Although not wishing to be bound by any particular theory of operation, it is believed that the anti-C5 antibodies have these and other therapeutic effects through their activity in blocking the generation or activity of the C5a and/or C5b active fragments of complement component C5. Through this blocking effect, the antibodies inhibit the proinflammatory (anaphylatoxic) effects of C5a and the generation of the C5b-9

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membrane attack complex (MAC). Significantly, the blockage effected by the anti-C5 antibodies, since it occurs at the level of complement component C5, has the advantage of maintaining important opsonic, anti-infective, and immune complex clearance functions of the complement system mediated by, inter alia, complement component C3.

The invention additionally provides compositions comprising anti-C5 antibodies that block complement hemolytic activity and C5a generation. These antibodies are useful for the treatment of GN as well as a number of other conditions. These include treatment of immune and hemostatic dysfunctions associated with extracorporeal circulation (see copending US patent application Serial No. 08/217,391, which is incorporated herein by reference), treatment of inflammatory joint diseases (see copending US patent application Serial No. 08/311,489, which is incorporated herein by reference), and other complement associated conditions, particularly inflammatory diseases.

Although other antibodies can be used to treat GN in accordance with the present invention, the novel antibodies of the invention are preferred. Preferably, these novel antibodies bind to the alpha chain of C5, but do not exhibit substantial binding to the alpha chain cleavage product C5a (referred to hereinafter and in the claims as "free C5a"). Other preferred targets for antibody binding include fragments of the alpha chain of human C5 that are immunoreactive with the most preferred antibody of the invention, the 5G1.1 antibody discussed below. Such preferred targets include the 46 kDa acid hydrolysis fragment of C5 (the "5G46k" fragment), the 27 kDa tryptic digestion fragment of C5 (the "5G27k" fragment), the 325aa peptide spanning amino acid residues 725-1049 of SEQ ID NO:2 (the "5G325aa" peptide), the 200 amino acid peptide spanning amino acids residues 850 to 1049 of SEQ ID NO:2 (the "5G200aa" peptide) -- as discussed below in Example 13.

The novel antibodies of the invention include antibodies that bind to an epitope within the amino acid sequence Val Ile Asp His Gln Gly Thr Lys Ser Ser Lys Cys Val Arg Gln Lys Val

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Glu Gly Ser Ser, (SEQ ID NO:1) hereinafter referred to as the KSSKC epitope. These novel antibodies that bind to the KSSKC epitope are hereinafter referred to as anti-KSSKC antibodies, and monoclonal antibodies binding to the KSSKC epitope are hereinafter referred to as anti-KSSKC mAbs.

The novel antibodies of the invention have many advantages over other anti-C5 antibodies, particularly with regard for their use as anti-inflammatory therapeutic agents. These include the ability to substantially block both complement hemolytic activity and the generation of the proinflammatory complement cleavage product C5a to substantially the same extent at the same concentration of antibody. Some of the preferred antibodies of the invention have the additional advantageous property of blocking the binding of C5 to C3 or C4.

Particularly preferred antibodies of the invention are monospecific native anti-KSSKC antibodies. The 5G1.1 native anti-KSSKC mAb has the distinct advantage of substantially blocking both complement hemolytic activity and the generation of C5a at a stoichiometric ratio of antibody to C5 that approaches the theoretical one to two (antibody to antigen) limit of binding that can be achieved by a bivalent antibody. This is a desirable property because it allows smaller doses of antibody to achieve therapeutic effects than would be required of otherwise similar antibodies that cannot function at such a ratio.

The invention further provides recombinant mAbs that are derivatives (including monovalent derivatives) of these native mAbs. These include anti-KSSKC recombinant mAbs. Preferably the antibodies of the invention provide a level of blockade of both complement hemolytic activity and C5a generation (on a per mole of binding site basis) that is obtained when the antibody concentration is within an order of magnitude of that of the native mAbs. Particularly preferred anti-KSSKC recombinant mAbs provide a level of such blockade when the antibody concentration is no more than three fold that of the native mAbs of the invention.

The invention further provides nucleic acid sequences of

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polynucleotides encoding such recombinant anti-KSSKC mAbs, as well as amino acid sequences of the polypeptides encoded by these nucleic acid molecules of the invention.

The invention further provides CDR sequences that are useful in the construction of the humanized antibodies of the invention, as well as peptides and oligopeptides that are useful in the preparation and characterization of the antibodies of the invention.

Anti-C5 antibodies of the invention have activity in blocking the generation or activity of the C5a and/or C5b active fragments of complement component C5. Through this blocking effect, the antibodies inhibit the proinflammatory (anaphylatoxic) effects of C5a and the generation of the C5b-9 membrane attack complex (MAC). Significantly, the blockage effected by the anti-C5 antibodies, since it occurs at the level of complement component C5, has the advantage of maintaining important opsonic, anti-infective, and immune complex clearance functions of the complement system mediated by, inter alia, complement component C3.

The accompanying figures, which are incorporated in and constitute part of the specification, illustrate certain aspects of the invention, and together with the description, serve to explain the principles of the invention. It is to be understood, of course, that both the figures and the description are explanatory only and are not restrictive of the invention.

BRIEF DESCRIPTION OF THE DRAWINGS

Figures 1A, 1B, and 1C -- Photomicrographs of PAS stained sections of mouse kidneys. Fig 1A -- uninduced untreated mouse. Fig. 1B -- GN-induced PBS-(control)-treated mouse. Fig. 1C -- GN-induced anti-C5 treated mouse. Magnification for each is the same, approximately 400X.

Figures 2A, 2B, and 2C -- Photomicrographs of immunofluorescence stained sections of mouse kidneys. Fig 2A- - uninduced untreated mouse. Fig. 2B -- GN-induced PBS-(control)-treated mouse. Fig. 2C -- GN-induced anti-C5 treated mouse. Magnification for each is the same, approximately 200X.

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Figure 3 -- Results of hemolytic (cell lysis) assays of serum from GN-induced animals treated with either anti-C5 antibodies in PBS ("Anti-C5") or PBS alone ("PBS control"). Also shown are the results of assays performed with normal serum.

Figure 4 -- Results of soluble C5b-9 ("sC5b-9") assays. "ND" indicates not determined.

Figures 5A, 5B, and 5C -- Immunofluorescence photomicrographs of kidney sections stained for mouse C3. Fig 5A -- uninduced untreated mouse. Fig. 5B -- GN-induced PBS-(control)-treated mouse. Fig. 5C -- GN-induced anti-C5 treated mouse. Magnification for each is the same, approximately 400X.

Figure 6 -- Results of C3a assays of samples of circulating human blood. "ND" indicates not determined.

Figures 7A and 7B -- Pharmacokinetic analyses of the reduction of the cell lysis ability of mouse (Fig. 7A) or human (Fig. 7B) blood after treatment with anti-C5 antibodies.

The immunofluorescent staining of Figures 2 and 5 is confined to the glomerular capillary network (tuft) and thus the enlargement of the glomerulus seen in Figure 1B is not visible in Figures 2B and 5B.

Figure 8 -- Scatchard analysis of native 5G1.1 binding to C5.

Figure 9 -- Scatchard analysis of native N19/8 binding to C5.

Figure 10 -- C3a generation in samples of circulating human blood in the presence of native 5G1.1.

Figure 11 -- sC5b-9 generation in samples of circulating human blood in the presence of native 5G1.1.

Figure 12 -- Serum hemolytic activity of samples of circulating human blood in the presence of native 5G1.1.

Figure 13 -- Serum hemolytic activity in the presence of m5G1.1 scFv.

Figure 14 -- C5a generation in the presence of m5G1.1 scFv.

Figure 15 -- C3a generation in samples of circulating human blood in the presence of m5G1.1 scFv.

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Figure 16 -- Serum hemolytic activity of samples of circulating human blood in the presence of 5G1.1 scFv.

Figure 17 -- sC5b-9 generation in samples of circulating human blood in the presence of m5G1.1 scFv.

Figure 18 -- The light chain variable region of the antibody 5G1.1. Sequence derived from the 5' oligonucleotide primer used for PCR amplification of the variable region is shown in lower case. Amino acids are number according to Kabat et al., *supra*. Boxed amino acids correspond to peptide sequences obtained from the mature 5G1.1 light chain or from an endoproteinase Lys C peptide of 5G1.1. The complementarity determining region (CDR) residues according to the sequence variability definition and the structural variability definition are underlined and overlined, respectively.

Figure 19 -- The heavy chain variable region of the antibody 5G1.1. Sequence derived from the 5' oligonucleotide primer used for PCR amplification of the variable region is shown in lower case. Amino acids are numbered using the scheme of Kabat et al. *supra* with +1 denoting the first amino acid of the processed mature variable region. Boxed amino acids correspond to peptide sequence obtained from the 5G1.1 heavy chain after treatment with pyroglutamate aminopeptidase. The complementarity determining region (CDR) residues according to the sequence variability definition or according to the structural variability definition are underlined and overlined, respectively.

BACKGROUND PHYSIOLOGY & PATHOLOGY

The discussion in this section is not limited to subject matter that qualifies as "prior art" against the present invention. Therefore, no admission of such prior art status shall be implied or inferred by reason of inclusion of particular subject matter in this discussion, and no declaration against the present inventors' interests shall be implied by reason of such inclusion.

I. Introduction

As described above, the present invention relates to therapeutic treatments for GN and other immune complex

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mediated diseases, as well as to the treatment of other complement mediated diseases and to the inhibition of complement component C5. To provide background for the description of the preferred embodiments and the examples presented below, we turn first to general discussions of the complement arm of the immune system, the pathophysiologic features of GN, and previous studies of the role of complement in GN pathogenesis.

General discussions of the complement system and GN can be found in, for example, Glassock and Brenner, 1994; Couser, 1993; Couser, 1992; Couser, et al, 1992; Rich, 1992; Glassock and Brenner, 1987; Robbins and Cotran, 1979; and Guyton, 1971.

II. The Complement System

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

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the sequence of events leading to various aspects of complement function.

C3a is an anaphylatoxin (see discussion below). 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, in Intensive Review of Internal Medicine, 2nd Ed. Fanta and Minaker, eds. Brigham and Women's and Beth Israel Hospitals, 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., 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.

C5 is a 190 kDa beta globulin found in normal serum at approximately 75µg/ml (0.4µM). 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. 1991, 146:362-368). 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 (SEQ ID NO:2).

The pro-C5 precursor is cleaved after amino acid 655 and 659, to yield the beta chain as an amino terminal fragment

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(amino acid residues +1 to 655 of SEQ ID NO:2) and the alpha chain as a carboxyl terminal fragment (amino acid residues 660 to 1658 of SEQ ID NO:2), with four amino acids (amino acid residues 656-659 of SEQ ID NO:2) 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 of SEQ ID NO:2). 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 of SEQ ID NO:2. 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. 1977, 119:1597-1602; Wetsel and Kolb, J. Immunol. 1982, 128:2209-2216) and acid treatment (Yammamoto and Gewurz, J. Immunol. 1978, 120:2008; Damerau et al., Molec. Immunol. 1989, 26:1133-1142) can also cleave C5 and produce active C5b.

C5a is another anaphylatoxin (see discussion below). 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

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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.

III. Pathophysiology of GN

Although GN may accompany an extraordinary range of pathologic processes, in general it is encountered most commonly in the course of infectious diseases, in autoimmunity, and as a consequence of therapy for some other disease process. The causative mechanism for GN is typically the deposit of circulating immune complexes in the kidney. Factors involved in the pathogenesis of GN include the specific antigen and antibody involved and the inflammatory processes that occur as a consequence of immune complex deposition.

Antigens Involved in the Formation of Immune Complexes That Cause GN: Antigens involved in the development of GN can be broadly classified as endogenous, infectious, and iatrogenic (those encountered as a consequence of medical practice). In many cases the specific antigen is unknown, although the general class can usually be identified.

The best known example of the formation of endogenous immune complexes is the DNA anti-DNA complexes produced in connection with systemic lupus erythematosus (lupus, SLE). Other important sources of endogenous antigens include malignancies in which immune complex formation may contribute to the development of paraneoplastic syndromes.

Infections with organisms of many types, particularly chronic infections, are also associated with the development of immune complexes that can cause GN. Bacterial and fungal infections that can produce such complexes include infection with certain strains of streptococci, Pseudomonas, disseminated gonococcal infection, lepromatous leprosy, subacute bacterial endocarditis, bronchopulmonary aspergillosis, secondary syphilis, and chronic infections in patients with cystic fibrosis.

Viral diseases in which immune complex deposition may be a prominent feature include hepatitis B infection, dengue,

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infectious mononucleosis, and subacute sclerosing panencephalitis. GN is also a prominent feature of many parasitic infestations such as the GN seen in children with quartan malaria, as well as toxoplasmosis, trypanosomiasis, and schistosomiasis.

Iatrogenic antigens constitute a special class of exogenous antigens. These include those responsible for the prototype immune complex disease, serum sickness, which follows formation of immune complexes between heterologous serum constituents and autologous antibodies. Serum sickness was regularly seen earlier in this century when infectious diseases were frequently treated with heterologous antisera.

An iatrogenic disease essentially indistinguishable from classic serum sickness can occur as a consequence of high-dose antibiotic therapy. The serum sickness-like manifestations of immune responses to these drugs include GN and reflect the fact that certain drugs, particularly the ß-lactam and sulfonamide antibiotics, are effective haptens that are capable of inducing antibody responses upon spontaneous conjugation to autologous proteins.

Factors Affecting Immune Complex Formation and Deposition: Features of both antigen and antibody determine the likelihood of pathologic immune complex formation and subsequent deposition in the kidney. Chief among these are the absolute concentrations of the reactants and their relative molar ratios.

Most antigens display multiple epitopes and typically stimulate a polyclonal antibody response. All naturally occurring antibody molecules are at least bivalent. These properties allow for the formation of an extensive antigen-antibody lattice, the size of which is determined largely by the affinity of the antibodies and the molar ratio of antigen to antibody.

In general, antibody responses begin under conditions in which antigen is present in excess to antibody, and this relative ratio changes as the antibody response increases in magnitude. Complexes formed initially are usually small and exhibit little or no pathogenic activity. In contrast, very

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large complexes are often formed as the amount of antigen becomes limiting, late in the course of an antibody response under conditions of antibody excess. Because these very large complexes are readily cleared by the reticuloendothelial system in the liver, they are also relatively nonpathogenic.

The formation of immune complexes that can cause GN is believed to occur during conditions of slight antigen excess or near the point of antibody-antigen equivalence, where lattice formation is maximal and lattice size is large, but not very large.

Several factors influence the speed and location of immune complex precipitation. Interactions between Fc regions of antibody molecules promote rapid precipitation of immune complexes. The role of Fc-Fc interactions in immune complex precipitation is illustrated by studies of the properties of F(ab')2 antibody fragments, which do not contain Fc regions. Although the valence of F(ab')2 fragments does not differ from that of most whole immunoglobulins, F(ab')2 antibody fragments form lattices more slowly.

Antigen charge plays a role in determining the tissue localization of sites of deposition of immune complex precipitates. Complexes with a substantial positive charge are preferentially attracted to the strong negative charge of basement membranes, particularly in the renal glomerulus.

Localized presence of antigen may largely account for certain cases of organ specific immune complex deposition. Diseases such as Goodpasture's syndrome (a rare form of GN) are typically not classified as immune complex diseases because the complexes are formed <u>in situ</u> in the kidney rather than being preformed in the circulation and then deposited. Once the immune complexes are formed, the subsequent inflammatory process is believed to be essentially the same as that seen following deposition of preformed complexes. However, the different mode of deposition distinguishes this syndrome from typical GN caused by circulating immune complexes.

Features of blood flow and vascular structure are also important in determining the localization of immune complex

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deposits. Chief among these is capillary permeability. Because their capillary endothelium is fenestrated, renal glomeruli are preferential sites for the deposition of immune complexes. Hemodynamic variables enhancing immune complex localization include turbulence of flow and increased blood pressure, both of which are present in the renal glomeruli.

Complement and Complement Receptors as Regulators of Immune Complex Deposition: In addition to their proinflammatory functions, complement components can also inhibit immune complex deposition and resolubilize immune complex precipitates from sites of deposition. In addition, it is known that erythrocyte receptors for C3b, e.g., CR1, are important for reticuloendothelial clearance of opsonized circulating immune complexes.

Analysis of the clinical pattern of immune complex disease in patients with deficiencies of particular complement components provides information regarding the normal role of these components in the prevention of complex deposition. The incidence of immune complex disease in patients with deficiencies of Clq, Clr, Cls, C4, C2, or C3 varies from 60 to 90 percent, with the majority of these patients exhibiting a lupus-like syndrome. Immune complex disease is rarely associated with deficiencies of late-acting or alternative pathway components.

The binding of complement components to immune complexes prevents the formation of large antigen-antibody lattices and inhibits immune precipitation. This process requires activation via the classical pathway; serum that is deficient for Clq, C4, or C2 does not effectively inhibit lattice formation and complex precipitation. Classical pathway dependence may reflect the initial binding of C1 components, impeding the Fc-Fc interactions between IgG molecules that contribute to immune precipitation. This is followed by covalent binding of C3b to the complexes, which further inhibits immune precipitation and leads to solubilization of previously deposited complexes.

The solubilization process also depends upon activation of components of the alternative pathway. Consequently, by

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promoting clearance of immune complexes and inhibiting their deposition at sites of inflammation, complement components and their receptors serve as negative regulators of immune complex diseases that may retard disease development.

It should be noted that the present invention involves blocking the activities of complement component C5. The targeting of this component does not alter the functions of the early complement components, and thus does not compromise the negative regulatory effects on immune complex deposition of those early components.

Immune Complex-Mediated Inflammation: Basophils are important in the initiation of immune complex-mediated inflammatory responses, as capillary permeability is markedly increased by the action of vasoactive amines such as histamine and platelet-activating factor, which are released by these cells. Vascular permeability is also promoted by aggregation of platelets at sites of an inflammatory lesion, with the release of platelet-activating factor and the formation of microthrombi.

Basophil degranulation may reflect the effects of IgE antibodies, as well as the elaboration of the anaphylatoxin components of complement, C3a and C5a.

In addition to basophils and platelets, the primary cellular effectors of immune complex-mediated inflammation are polymorphonuclear leukocytes, monocytes, and macrophages.

IV. Previous Studies of the Role of Complement in GN Pathogenesis

Extensive work has been performed in an attempt to understand the possible role of complement in the development of GN. This work has included studies of GN using a number of animal models by, among others, Unanue, et al., (1964); Cochrane, et al., (1965); Kniker, et al., (1965); Salant, et al., (1980); Groggel, et al., (1983); Falk and Jennette (1986); Jennette, et al., (1987); Passwell, et al., (1988); Schrijver, et al., (1988); Baker, et al., (1989); Schrijver, et al., (1990); Couser, et al., (1991); and Couser, et al., (1992).

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These studies have shown that complement plays a role in GN pathogenesis. However, they have not established specific unequivocal roles for the various complement components. In particular, the relative roles of C3 and other anaphylatoxins compared to the roles of the terminal complement components in GN pathogenesis have not been unequivocally established. Also, some researchers have reported that complement depletion does not diminish glomerular injury. See Kniker, et al., (1965).

The foregoing work includes that of Falk and Jennette (1986), who reported results of experiments in which attempts were made to induce GN in mice having a genetic defect that resulted in a deficiency of complement component C5. The report concludes that C5 or some terminal complement component dependent on C5 plays a role in the pathogenesis of GN.

Significantly, with regard to the present invention, Falk and Jennette in no way disclose or suggest that an antibody to C5 can be used to treat GN. Indeed, it would be counterintuitive to use an antibody to treat disease which typically involves the formation and deposition of circulating antibody-antigen immune complexes. Plainly, the creation of more circulating immune complexes would seem to be the last way to go to solve a problem that can be caused by circulating immune complexes. Yet, as demonstrated by the surprising results presented below, anti-C5 antibodies have been found to effectively block GN, even though the creation of additional circulating immune complexes is inherent in their mode of action.

Baker et al. (1989), Couser et al. (1991), and Couser et al. (1992) (hereinafter referred to collectively as the "C6" work) discuss experiments in which high levels of an anti-C6 polyclonal antibody preparation were administered to rats, following which immune complexes were formed <u>in situ</u> in the rats' kidneys. Significantly, with regard to the present invention, the anti-C6 antibody preparation was not administered to animals with pre-existing kidney disease, i.e., it was not used as a therapeutic treatment. Moreover, the experimental protocol used in the C6 experiments did not

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involve circulating immune complexes, but rather involved complexes formed in situ. Accordingly, the experiments did not disclose or suggest the counterintuitive approach of the present invention wherein more circulating immune complexes are formed in the process of treating a disease state caused by circulating immune complexes.

Further, the anti-C6 antibody dosages used in the C6 work were too high for practical medical use. Specifically, these antibodies were used at a dosage of 1 gm/kg, a dosage which would correspond to 70 gm of antibody for a 70 kg (155 lb) individual. In contrast, the anti-C5 antibodies used in the practice of the present invention are used at concentrations at or below 0.1 gm/kg, i.e., a factor of at least ten times less than used in the C6 work. Indeed, as shown by the examples presented below, anti-C5 antibody dosages as low as 0.03 gm/kg, i.e., 33 times less than those used in the C6 work, have been found to achieve the therapeutic effects of the invention in treating GN. For a 70 kg individual, this antibody level corresponds to a dose of just 2.1 gms.

The novel anti-KSSKC antibodies of the invention allow the use of even lower dosage levels to treat GN and other inflammatory conditions. Based upon their level of activity in human blood, they are expected to provide complete complement inhibition at dosages below 0.005g/kg, and to provide therapeutically effective complement inhibition at dosages below 0.003g/kg. This 3mg/kg dosage is one tenth the dosage discussed below in Examples 4 and 5 for the for the anti-C5 (beta chain specific) mAb N19/8. Some of the full length anti-KSSKC mabs of the invention will provide therapeutic benefits even at dosages below 0.0022g/kg. This is the minimum dose providing complete complement inhibition as calculated from the data obtained using the anti-KSSKC 5G1.1 mAb in human blood in a CPB circuit, as discussed below in Example 9.

Accordingly, dosages of less than 0.005g/kg are preferred, with dosages of below 0.003g/kg being more preferred, and dosages below 0.0022g/kg being particularly preferred. For a 70 kg individual, these antibody dosage levels correspond to a

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dose of less than 0.35 gms for the highest dosage of the preferred dosages, less than 0.21 gms for the more preferred dosage, and less than or equal to 0.15 gms for the most preferred dosage.

Of course, dosage levels of single chain and other recombinant mAbs of the invention must be adjusted according to their level of activity (e.g., their binding affinity, their ability to block C5 activation, and/or their ability to block complement hemolytic activity), their valency, and their molecular weight. For example, the humanized scFv anti-KSSKC mAbs of Example 11 are approximately 27 kDa, about one sixth the approximately 155 kDa mass of a native, full length IgG antibody. These antibodies completely block complement hemolytic activity and C5a generation at a ratio of 3:1, six fold greater than for native 5G1.1 (but only three fold greater when viewed in terms of numbers of antibody-antigen binding sites).

Thus, the number of molecules of each of these scFvs required to equal the effect of a single molecule of native 5G1.1 must be increased by a factor of six to adjust for the ratio at which blocking is complete. Since the mass of these molecules is approximately one sixth of the mass of native 5G1.1, dosages of the scFvs are in the same range as those for the native 5G1.1 mAb.

In addition to lowering dosage levels, the anti-C5 antibodies used in the practice of the present invention (i.e., in treating GN) achieve important therapeutic effects not achieved with the anti-C6 antibodies. Specifically, the control and test animals in the C6 work exhibited both hypercellularity and narrowing of capillary lumens. In direct contrast, no such hypercellularity or narrowing of capillary lumens was seen when diseased individuals were treated with anti-C5 antibodies (see Figure 1).

Moreover, the anti-C5 antibodies used in the present invention achieve a reduction in glomerular enlargement, thus providing a clear demonstration of the unexpectedly powerful anti-inflammatory effects of the anti-C5 antibodies used in the practice of the invention. Nowhere in the C6 work is

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there any disclosure or suggestion of such a powerful anti-inflammatory effect.

V. Anti-C5 Monoclonal Antibodies That Block Complement Hemolytic Activity and Block the Generation of C5a:

Anti-C5 mAbs that have the desirable ability to block complement hemolytic activity and to block the generation of C5a (and are thus preferred for use in the treatment of GN and other inflammatory conditions in accordance with the present invention) have been known in the art since at least 1982 (Moongkarndi et al. Immunobiol. 1982, 162:397; Moongkarndi et al. Immunobiol. 1983, 165:323). Antibodies known in the art that are immunoreactive against C5 or C5 fragments include antibodies against the C5 beta chain (Moongkarndi et al. Immunobiol. 1982, 162:397; Moongkarndi et al. Immunobiol. 1983, 165:323; Wurzner et al. 1991, *supra*; Mollnes et al. Scand. J. Immunol. 1988, 28:307-312); C5a (see for example, Ames et al. J. Immunol. 1994, 152:4572-4581, U.S. patent No. 4,686,100, and European patent publication No. 0 411 306); and antibodies against non-human C5 (see for example, Giclas et al. J. Immunol. Meth. 1987, 105:201-209). Significantly, none of these anti-C5 mAbs has the properties of the novel anti-C5 mAbs of the invention, i.e., none of them binds to the C5 alpha chain but not to the C5 cleavage product C5a, none of them has the ability to substantially block both complement hemolytic activity and the generation of C5a to substantially the same extent at the same concentration of antibody. It is noteworthy that an scFv derivative of the N19/8 antibody of Wurzner et al. 1991, *supra*, has been prepared, and that the N19/8 scFv has 50% less inhibitory activity towards C5a generation than the native N19/8 antibody (see Example 15). This is in contrast to the 5G1.1 scFv, which retained substantially all of its inhibitory activity towards C5a generation (see Example 12).

While not wishing to be bound by any particular theory of operation, it is believed that these distinctions are due to the specific binding characteristics of the antibodies of the invention. Accordingly, antibodies that do not bind to sites within the alpha chain of C5, and antibodies that bind to the

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are preferably in the range from about 25 µg/ml to about 500 µg/ml.

Subject to the judgement of the physician, a typical therapeutic treatment includes a series of doses, which will usually be administered concurrently with the monitoring of clinical endpoints such as BUN levels, proteinuria levels, etc., with the dosage levels adjusted as needed to achieve the desired clinical outcome. Alternatively, levels of serum complement activity available in the patient's blood are monitored using the techniques set forth below under the heading "Cell Lysis Assays" to determine if additional doses or higher or lower dosage levels of antibodies are needed, with such doses being administered as required to maintain at least about a 50% reduction, and preferably about a 95% or greater reduction of serum complement activity. Other protocols can, of course, be used if desired as determined by the physician.

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. 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.

The formulations of the invention can be distributed as articles of manufacture comprising packaging material and the anti-C5 antibodies. When prepared for use in the treatment of GN, the packaging material will include a label which indicates that the formulation is for use in the treatment of kidney disease and may specifically refer to nephritis or glomerulonephritis.

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C5 cleavage product C5a (free C5a), are believed to lack the ability to substantially block both complement hemolytic activity and the generation of C5a to substantially the same extent at the same concentration of antibody.

DESCRIPTION OF THE PREFERRED EMBODIMENTS

As discussed above, the present invention relates to the use of anti-C5 antibodies in treating patients suffering from GN and other diseases, and to specific C5 antibodies and antibody preparations. Preferably, and when used to treat GN, the anti-C5 antibodies are used in an amount effective to substantially reduce (e.g., reduce by at least about 50%) the cell-lysing ability of complement present in the patient's blood (the "cell-lysing ability of complement present in the patient's blood" is also referred to herein as the "serum complement activity of the patient's blood"). Reduction of the cell-lysing ability of complement present in the patient's blood can be measured by methods well known in the art such as, for example, by the chicken erythrocyte hemolysis method described below under the heading "Cell Lysis Assays."

To achieve the desired reductions, the 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 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

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The anti-C5 antibody is preferably a monoclonal antibody, although polyclonal antibodies produced and screened by conventional techniques can also be used if desired. As discussed above, the anti-C5 antibodies must be effective in reducing the cell-lysing ability of complement present in human blood. As also discussed above, this property of the antibodies can be determined by methods well known in the art such as, for example, by the chicken erythrocyte hemolysis method described below under the heading "Cell Lysis Assays".

The anti-C5 antibodies used in the practice of the invention bind to C5 or fragments thereof, e.g., C5a or C5b. Preferably, the anti-C5 antibodies are immunoreactive against epitopes on the beta chain of purified human complement component C5 and are capable of blocking the conversion of C5 into C5a and C5b by C5 convertase. This capability can be measured using the techniques described in Wurzner, et al., Complement Inflamm 8:328-340, 1991. Preferably, the anti-C5 antibodies are used to treat GN in an amount effective to reduce the C5 convertase activity available in the patient's blood by at least about 50%.

In a particularly preferred embodiment of the invention, the anti-C5 antibodies are not immunoreactive against epitopes on the beta chain, but rather are immunoreactive against epitopes within the alpha chain of purified human complement component C5. In this embodiment the antibodies are also capable of blocking the conversion of C5 into C5a and C5b by C5 convertase. In an especially preferred example of this embodiment they can provide this blockade at substantially the same concentrations needed to block hemolytic activity.

Within the alpha chain, the most preferred antibodies bind to an amino-terminal region, however, they do not bind to free C5a. Particularly preferred targets for these antibodies within the alpha chain include the 5G46k fragment, the 5G27k fragment, the 5G325aa peptide, the 5G200aa peptide, or the KSSKC epitope. The scope of the invention also includes the 5G46k fragment, the 5G27k fragment, the 5G325aa peptide, the 5G200aa peptide, or the KSSKC epitope that are useful as immunogens and screening ligands for producing the antibodies

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of the invention.

Hybridomas producing monoclonal antibodies reactive with complement component C5 can be obtained according to the teachings of Sims, et al., U.S. Patent No. 5,135,916. As discussed therein, antibodies are prepared using purified components of the complement membrane attack complex as immunogens. In accordance with the present invention, complement component C5 or C5b is preferably used as the immunogen. In accordance with a particularly preferred aspect of the present invention, the immunogen is the alpha chain of C5. Within the alpha chain, the most preferred immunogens include the 5G46k fragment, the 5G27k fragment, the 5G325aa peptide, or the 5G200aa peptide. A less preferred immunogen is the KSSKC epitope.

In accordance with the invention, the antibodies of the invention all share certain required functional properties. These are the ability to substantially inhibit complement hemolytic activity and to substantially inhibit the conversion of C5 to produce C5a. Preferably, but not requisitely, they provide these functions when used at a molar ratio of antibody to antigen (C5) of 3:1 or less.

A particularly preferred antibody of the invention is the 5G1.1 antibody (5G1.1, produced by the 5G1.1 hybridoma, ATCC designation HB-11625). Other particularly preferred antibodies of the present invention share the required functional properties discussed in the preceding paragraph and have any of the following characteristics:

(1) they compete with 5G1.1 for binding to portions of C5 -- the C5 alpha chain, the 5G46k fragment, the 5G27k fragment, the 5G325aa peptide, the 5G200aa" peptide, or the KSSKC peptide -- that are specifically immunoreactive with 5G1.1; and

(2) they specifically bind to the C5 alpha chain, the 5G46k fragment, the 5G27k fragment, the 5G325aa peptide, the 5G200aa" peptide, and/or the KSSKC peptide. Such specific binding, and competition for binding can be determined by various methods well known in the art, including the plasmon surface resonance method (Johne et al., J. Immunol. Meth.

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1993, 160:191-198).

(3) they block the binding of C5 to either C3 or C4 (which are components of C5 convertase).

Also in accordance with the invention, the antibodies preferably should 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. In a particularly preferred embodiment, these anti-C5 antibodies will not impair the opsonization function associated with the activation of complement component C3 by a C3 convertase. Plasma C3 convertase activity can be measured by assaying plasma for the presence of C3a as described below under the heading "Histology." Preferably, the anti-C5 antibody produces essentially no reduction in plasma C3a levels.

General methods for the immunization of animals (in this case with C5 or C5b or another preferred immunogen), isolation of polyclonal antibodies or 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 C5 or C5b or another preferred 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.

As used herein, the term "antibodies" refers to immunoglobulins produced in vivo, as well as those produced in vitro by a hybridoma, and antigen binding fragments (e.g.,

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Fab' preparations) of such immunoglobulins, as well as to recombinantly expressed antigen binding proteins, including immunoglobulins, chimeric immunoglobulins, "humanized" immunoglobulins, antigen binding fragments of such immunoglobulins, single chain antibodies, and other recombinant proteins containing antigen binding domains derived from immunoglobulins. As used herein,"antibodies" also refers to antigen binding synthetic peptides comprising sequences derived from the sequences of immunoglobulin antigen binding domains. As used herein, the term "recombinant mAbs" refers to recombinantly expressed antigen binding proteins. As used herein, the term "antibody-antigen binding site" refers to an antigen binding site of an antibody comprising at least one CDR sequence.

Antibodies whose amino acid sequences are full length immunoglobulin sequences that have not been truncated (e.g., to produce an scFv or an Fab) or mutated (e.g., spliced to form a chimeric antibody or humanized) are referred to herein as "native" antibodies. Publications describing methods for the preparation of such antibodies, in addition to those listed immediately above, include: Reichmann, et al., Nature, 332:323-327, 1988; Winter and Milstein, Nature, 349:293-299, 1991; Clackson, et al., Nature, 352:624-628, 1991; Morrison, Annu Rev Immunol, 10:239-265, 1992; Haber, Immunol Rev, 130:189-212, 1992; and Rodrigues, et al., J Immunol, 151:6954-6961, 1993.

While treatment of GN in accordance with the process of the present invention may be carried out using polyclonal or monoclonal antibodies, monospecific antibodies are preferred. As used herein "monospecific antibodies" refer to antibodies that bind to a specific region of a particular antigen. All monoclonal antibodies are monospecific, but polyclonal antibodies are typically not monospecific.

As is known in the art, however, monospecific polyclonal antibodies may be prepared by various methods. For example, a peptide (e.g., an oligopeptide -- as used hereinafter and in the claims, a polymer of 5 to 200 amino acids) may be used as an immunogen. Another procedure allowing the preparation of

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monospecific polyclonal antibodies is the use of antigen affinity purification techniques to isolate a monospecific antibody population from a polyclonal antibody mixture. In accordance with the present invention, peptides are preferred as immunogens for the production and as affinity ligands for the purification of monospecific polyclonal anti-KSSKC antibodies.

The native (i.e., non-engineered) monoclonal antibodies of the invention are preferably prepared by conventional means, with the 5G46k fragment, the 5G27k fragment, the 5G200aa peptide, the 5G325aa peptide, and/or the KSSKC peptide (e.g., immobilized on a polypropylene membrane as described below in Example 13) being used as screening ligand(s). This involves testing hybridoma supernatants for binding to each screening ligand.

In one preferred embodiment, the native mAbs of the invention are prepared using the alpha chain of human C5, or fragments thereof, as immunogen. Preferred fragments of the alpha chain of human C5 for this purpose include the 5G46k fragment, the 5G27k fragment, and/or the 5G200aa fragment. Although less preferred, the KSSKC peptide may also be used as an immunogen.

Another (albeit less preferred) immunogen and screening ligand for the preparation of antibodies within the scope of the novel antibodies of the present invention is the "cleavage site peptide," i.e., the peptide spanning amino acids 725 through 754 of SEQ ID NO:2 (the C5a cleavage site), as discussed below in Example 13.

In another preferred embodiment of the invention, the native mAbs of the invention are prepared in transgenic mice expressing human immunoglobulins (see, for example, Green et al., Nature Genet. 1994, 7:13-21). In this case, the same preferred immunogens and screening ligands are used as described for the preparation of other native mAbs.

In another preferred embodiment of the invention, the recombinant mAbs of the invention are prepared by screening phage display libraries expressing recombinant mAb-encoding polynucleotides (preferably encoding human recombinant mAbs).

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See, for example, Ames et al., 1994, *supra*; Smith and Scott, Meth. Enzymol. 1993, 217:228; Kay et al., Gene, 1993, 128:59-65. This screening is carried out with the screening ligands described above for the preparation of native mAbs. The recombinant mAbs of the invention are prepared by subcloning the recombinant mAb-encoding polynucleotides into a suitable expression vector, expressing them in a suitable host (as described below), and isolating the recombinant mAbs.

The present invention provides recombinant expression vectors which include the synthetic, genomic, or cDNA-derived nucleic acid fragments of the invention, i.e. polynucleotides encoding the mAbs of the invention. The nucleotide sequence coding for any of the mAbs of the invention 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. The necessary transcriptional and translational signals can also be supplied by the native or source gene and/or its flanking regions.

A variety of host vector systems may be utilized to express the recombinant expression vectors of the invention. These include, but are not limited to, mammalian cell systems infected with recombinant virus (e.g., vaccinia virus, adenovirus, retroviruses, etc.); mammalian cell systems transfected with recombinant plasmids; insect cell systems infected with recombinant virus (e.g., baculovirus); microorganisms such as yeast containing yeast expression vectors, or bacteria transformed with recombinant bacteriophage DNA, recombinant plasmid DNA, or cosmid DNA (see, for example, Goeddel, 1990).

Useful expression vectors for bacterial use can comprise a selectable marker and bacterial origin of replication derived from commercially available plasmids comprising genetic elements of the well-known cloning vector pBR322 (American Type Culture Collection -"ATCC"-, 12301 Parklawn Drive, Rockville, Maryland 20852, United States of America; ATCC Accession No. 37017). These pBR322 "backbone sections," or functionally equivalent sequences, are combined with an

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appropriate promoter and the structural gene to be expressed. Promoters commonly used in recombinant microbial expression vectors include, but are not limited to, the lactose promoter system (Chang, et al., Nature 275:615), the tryptophan (trp) promoter (Goeddel, et al., 1980, Gene Expression Technology, Volume 185. Academic Press, Inc., San Diego, CA) and the tac promoter, or a fusion between the tac and trp promoters referred to as the trc promoter (Maniatis, 1982, Molecular Cloning: A Laboratory Manual, Cold Spring Harbor Laboratory, Cold Spring Harbor, NY). Particularly preferred promoters include the T7 promoter, which is used in conjunction with host cell expression of a T7 RNA polymerase (see Studier et al. 1990, Meth. Enzymol. 185:60-89), and the trc promoter, which is found in several commercially available vectors, as described below.

Preferred bacterial expression vectors include, but are not limited to, the pET vectors (see Studier et al. 1990, *supra*) and the Trc vectors. Many of the pET vectors are commercially available from Stratagene Cloning Systems (La Jolla, CA). A particularly preferred vector is the pET Trc SO5/NI vector described below (SEQ ID NO:18). A Trc vector, pTrc 99A, is available from Pharmacia. Other Trc vectors include the pSE vectors (Invitrogen, San Diego, CA).

Preferred bacteria for expression of recombinant mAbs include Bacillus subtilis and, most preferably, Escherichia coli. A particularly preferred strain of E. coli is strain W3110 (ATCC designation 27325). Under certain unusual conditions it may be necessary to use standard bacterial genetics methods to prepare derivative strains of W3110, for example, when a contaminating bacteriophage ("phage") is present in the laboratory where the bacterial manipulations are being carried out. Generally, and particularly for large scale preparation of the recombinant anti-KSSKC mAbs of the invention, it is preferred to use unmodified W3110, or another fully characterized strain.

In cases where phage contamination is a problem and disinfection is not practicable or desirable, it is preferred to identify the phage contaminant and to then use a fully

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characterized bacterial strain having a known mutation rendering the bacterium resistant to the phage. Preferably the mutation is a null mutant for the receptor for the phage. In some instances, however, the generation use of a relatively uncharacterized phage-resistant derivative strain may be acceptable, particularly in small scale experimental work. When such derivative strains are desired, they may be prepared using the methods described below in Example 11.

For most purposes the use of unmodified W3110 or another fully characterized bacterial strain is generally preferred. This is particularly true for the preparation of pharmaceutical agents comprising the recombinant anti-KSSKC mAbs of the invention. This is because of the problems, well known in the art, of using bacterial strains containing uncharacterized or partially characterized mutations for the production of ingredients of pharmaceutical agents.

The recombinant mAbs of the invention may also be expressed in fungal hosts, preferably yeast of the Saccharomyces genus such as S. cerevisiae. Fungi of other genera such as Aspergillus, Pichia or Kluyveromyces may also be employed. Fungal vectors will generally contain an origin of replication from the 2 μm yeast plasmid or another autonomously replicating sequence (ARS), a promoter, DNA encoding a mAb of the invention, sequences directing polyadenylation and transcription termination, and a selectable marker gene. Preferably, fungal vectors will include an origin of replication and selectable markers permitting transformation of both E. coli and fungi.

Suitable promoter systems in fungi include the promoters for metallothionein, 3-phosphoglycerate kinase, or other glycolytic enzymes such as enolase, hexokinase, pyruvate kinase, glucokinase, the glucose-repressible alcohol dehydrogenase promoter (ADH2), the constitutive promoter from the alcohol dehydrogenase gene, ADH1, and others. See, for example, Schena, et al. 1991 Meth. Enzymol. 194:389-398. Secretion signals, such as those directing the secretion of yeast alpha-factor or yeast invertase, can be incorporated into the fungal vector to promote secretion of a soluble

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recombinant mAb into the fungal growth medium. See Moir, et al., 1991, Meth. Enzymol. 194:491-507.

Preferred fungal expression vectors can be assembled using DNA sequences from pBR322 for selection and replication in bacteria, and fungal DNA sequences, including the ADH1 promoter and the alcohol dehydrogenase ADH1 termination sequence, as found in vector pAAH5 (Ammerer, 1983, Meth. Enzymol. 101:192). The ADH1 promoter is effective in yeast in that ADH1 mRNA is estimated to be 1 - 2% of total poly(A) RNA.

Various mammalian or insect cell culture systems can be employed to express recombinant mAbs. Suitable baculovirus systems for production of heterologous proteins in insect cells are reviewed by Luckow, et al., 1988. Examples of suitable mammalian host cell lines include the COS cell of monkey kidney origin, mouse L cells, murine C127 mammary epithelial cells, mouse Balb/3T3 cells, Chinese hamster ovary cells (CHO), human 293 EBNA and HeLa cells, myeloma, and baby hamster kidney (BHK) cells, with myeloma cells, CHO cells, and human 293 EBNA cells being particularly preferred.

Mammalian expression vectors may comprise non-transcribed elements such as origin of replication, a suitable promoter and enhancer linked to the recombinant mAb gene to be expressed, and other 5' or 3' flanking sequences such as ribosome binding sites, a polyadenylation sequence, splice donor and acceptor sites, and transcriptional termination sequences.

The transcriptional and translational control sequences in mammalian expression vector systems to be used in transforming vertebrate cells may be provided by viral sources. For example, commonly used promoters and enhancers are derived from Polyoma virus, Adenovirus, Simian Virus 40 (SV40), and human cytomegalovirus, including the cytomegalovirus immediate-early gene 1 promoter and enhancer (CMV).

Particularly preferred eukaryotic vectors for the expression of recombinant anti-KSSKC mAbs are pAPEX-1 (SEQ ID NO:3 and, more preferably, pAPEX-3p, SEQ ID NO:4. The vector pAPEX-1 is a derivative of the vector pcDNAI/Amp (Invitrogen) which was modified to increase protein expression levels.

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First, the 3'-untranslated SV40 small-t antigen intron was removed by deletion of a 601 base pair *Xba*I/*Hpa*I fragment since this intron is susceptible to aberrant splicing into upstream coding regions (Evans and Scarpulla, 1989 Gene 84:135; Huang and Gorman, 1990, Molec. Cell Biol. 10:1805). Second, a chimeric adenovirus-immunoglobulin hybrid intron was introduced into the 5'-untranslated region by replacing a 484 base pair *Nde*I-*Not*I fragment with a corresponding 845 base pair *Nde*I-*Not*I fragment from the vector pRc/CMV7SB (Sato et al., 1994, J. Biol. Chem. 269:17267). Finally, to increase plasmid DNA yields from E. coli, the resulting CMV promoter expression cassette was shuttled into the vector pGEM-4Z (Promega Corp. Madison, WI).

The vector pAPEX-3 is a derivative of the vector pDR2 (Clontech Laboratories, Inc. Palo Alto, CA) in which the EBNA gene was first removed by deletion of a 2.4 kb *Cla*I/*Acc*I fragment. The RSV promoter was then replaced with the CMV promoter and the adenovirus/immunoglobulin chimeric intron by exchanging a 450 bp *Mlu*I/*Bam*HI fragment from pDR2 with a 1.0 kb *Mlu*I/*Bam*HI fragment from the vector pAPEX-1. For construction of pAPEX-3P, a 1.7 kb *Bst*BI/*Swa*I fragment containing the HSV tk promoter and hygromycin phosphotransferase (hyg) gene was removed from pAPEX-3 and replaced with a 1.1 kb *Sna*BI/*Nhe*I fragment containing the SV40 early promoter and puromycin acetyltransferase (pac) gene (Morgenstern and Land, 1990, Nucleic Acids Res. 18:3587-3596) plus a 137 bp *Xba*I/*Cla*I fragment containing an SV40 polyadenylation signal from the vector pAPEX-1.

A particularly preferred host cell for the expression of recombinant mAb-encoding inserts in the pAPEX vectors is the human 293 EBNA cell line (Invitrogen, San Diego, CA).

Another preferred eukaryotic vector for the expression of recombinant mAbs is pcDNAI/Amp (Invitrogen Corporation, San Diego, California). The pcDNAI/Amp expression vector contains the human cytomegalovirus immediate-early gene I promoter and enhancer elements, the Simian Virus 40 (SV40) consensus intron donor and acceptor splice sequences, and the SV40 consensus polyadenylation signal. This vector also contains an SV40

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origin of replication that allows for episomal amplification in cells (e.g., COS cells, MOP8 cells, etc.) transformed with SV40 large T antigen, and an ampicillin resistance gene for propagation and selection in bacterial hosts.

Purified recombinant mAbs are prepared by culturing suitable host/vector systems to express the recombinant mAb translation products of the nucleic acid molecules of the present invention, which are then purified from the culture media or cell extracts of the host system, e.g., the bacteria, insect cells, fungal, or mammalian cells. Fermentation of fungi or mammalian cells that express recombinant mAb proteins containing a histidine tag sequence (a sequence comprising a stretch of at least 5 histidine residues) as a secreted product greatly simplifies purification. Such a histidine tag sequence enables binding under specific conditions to metals such as nickel, and thereby to nickel (or other metal) columns for purification. Recombinant mAbs may also be purified by protein G affinity chromatography (Proudfoot et al., 1992, Protein Express. Purif. 3:368).

Without intending to limit it in any manner, the present invention will be more fully described by the following examples. The methods and materials which are common to various of the examples are as follows.

Materials and Methods

Induction of GN in Mice

Four month old female B10.D2/nSnJ mice averaging approximately 25 gms each were obtained from the Jackson Laboratory, Bar Harbor, ME. Mice were injected with 0.1 mL daily (six days per week) of a 40 mg/mL solution of horse apoferritin (HAF), which was prepared by dilution of a saline solution of HAF (Sigma Chemical Company Catalog No. A-3641) with PBS.

Anti-C5 Monoclonal Antibodies

Monoclonal antibodies that bind to complement component C5 of the mouse were prepared by standard methods as an IgG fraction from supernatants of cultures of hybridoma BB5.1 (Frei, et al., 1987), which was obtained from Dr. Brigitta Stockinger of the National Institute for Medical Research,

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Mill Hill, London, England.

Histology

Kidneys were subjected to microscopic analysis using standard histochemical staining and immunofluorescence techniques. Periodic Acid Schiff (PAS) staining of 5μ paraffin sections was by standard methods using a HARLECO PAS histochemical reaction set (EM Diagnostic Systems, Gibbstown, NJ, number 64945/93) according to the manufacturer's directions.

Immunofluorescence staining of 5μ cryostat sections was carried out by standard methods using FITC conjugated sheep anti-mouse C3 (Biodesign International, Kennebunk, ME, Catalog No. W90280F) to detect murine complement component C3, or FITC conjugated goat anti-mouse IgG, IgA, and IgM (Zymed Laboratories, South San Francisco, CA, Catalog No. 65-6411) to detect immune complexes.

Urine Assays

Protein and glucose levels were determined by spotting urine samples on CHEMSTRIP 2GP dipsticks (Boehringer Mannheim Diagnostics, Indianapolis, IN, Catalog No. 200743). The detection areas of these strips change color when exposed to urine containing protein or glucose; a lack of color change indicates no detectable protein or glucose is present. The level of analyte in the urine being tested is read out by matching changed colors with color charts supplied by the manufacturer. The urine protein chart shows colors corresponding to trace, 30, 100, and 500 mg/dL.

Cell Lysis Assays

The cell-lysing ability of complement in blood can be determined using hemolytic assays that are performed as follows: Chicken erythrocytes are washed well in GVBS (Rollins, et al., J Immunol 144:3478-3483, 1990, Sigma Chemical Co. St. Louis, MO, catalog No. G-6514) and resuspended to $2x10^8$/mL in GVBS. Anti-chicken erythrocyte antibody (IgG fraction of anti-chicken-RBC antiserum, Intercell Technologies, Hopewell, NJ) is added to the cells at a final concentration of 25 μg/mL and the cells are incubated for 15 min. at 23°C. The cells are washed 2x with GVBS and

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$5x10^6$ cells are resuspended to 30 µL in GVBS. A 100 µL volume of serum test solution is then added to yield a final reaction mixture volume of 130 µL. As used herein, reference to the serum percentage and/or serum input in these assays indicates the percent serum in the 100 µL volume of serum test solution.

For assays of mouse serum activity, the 100 µL volume of serum test solution contained 50 µL of diluted (in GVBS) mouse serum and 50 µL of human C5 deficient serum (Quidel Corporation, San Diego, CA). For assays of human serum activity, the serum test solution may contain up to 100% human plasma or serum, with hybridoma supernatants and/or GVBS being added to yield the 100 µL volume. For the assays used to screen hybridoma supernatants discussed below in Example 7, each 100µL volume of serum test solution contained 50µL of hybridoma supernatant and 50µL of a 10% solution of human serum in GVBS, yielding a 5% human serum input.

After incubation for 30 min. at 37°C, percent hemolysis was calculated relative to a fully lysed control sample. Hemolysis was determined by spinning the cells down and measuring released hemoglobin in the supernatant as the optical density at 415nm.

A 50% reduction in hemolysis after treatment with the anti-C5 antibodies used in the practice of the invention means that the percent hemolysis after treatment is one half of the percent hemolysis before treatment.

EXAMPLE 1

Anti-C5 Antibodies Inhibit Glomerular Inflammation and Enlargement

This example illustrates that anti-C5 antibodies will inhibit glomerular inflammation and enlargement.

The protocol for these experiments was as follows. GN-induced mice were treated with anti-C5 antibodies or with PBS as a control after 2 weeks of GN induction. Each mouse received 750 µg of anti-C5 monoclonal antibodies in PBS (30 mg/kg in a 25 gm mouse) or an equal volume of PBS alone. The amount injected was from 0.25 to 0.365 mL (the concentration of antibodies in PBS varied), which was administered by intraperitoneal injection once a day, six days a week.

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After an additional 2 weeks of induction and treatment, the animals were sacrificed and kidneys were harvested and prepared for histological examination as described above. Kidneys were also obtained from age-matched uninduced and untreated control mice.

Figure 1 shows sections of mouse kidneys with a single glomerulus located centrally amidst surrounding interstitium and cross sections of convoluted tubules in each section. As can be seen therein, the kidneys of the GN-induced, PBS-treated mice (Fig. 1B) developed severe crescentic glomerular pathology, including inflammatory glomerular hypercellularity, apparent basement membrane thickening, and glomerular enlargement, while the glomeruli of the GN-induced, anti-C5-treated animals (Figure 1C) were essentially indistinguishable from the glomeruli of the normal healthy kidneys of the uninduced untreated mice (Figure 1A).

Note that in the glomeruli with severe crescentic pathology, the size of the glomerular capillary network (glomerular tuft) is not enlarged, but shows signs of compression by a crescentic-shaped proliferation of epithelial cells and PAS-positive material, and the Bowman's capsule is dramatically enlarged. Also note that in the section of diseased glomerulus shown in Fig. 1B, the capillary network is split in half by a projection of the hypercellular crescentic mass.

The non-inflamed glomerulus of the uninduced untreated mouse shown in Figure 1A is approximately 100 μ in diameter; the inflamed glomerulus of the GN-induced, PBS treated mouse shown in Fig. 1B is approximately 175 μ in diameter; the non-inflamed glomerulus of the GN-induced, anti-C5-treated mouse shown in Fig. 1C is approximately 90 μ in diameter.

EXAMPLE 2

Anti-C5 Antibodies Prevent/Reduce Proteinuria Associated with GN

This example demonstrates that treatment with anti-C5 antibodies results in the prevention/reduction of kidney damage as evidenced by the lack of significant amounts of protein in the urine (i.e. the presence of less than 100mg/dL

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of protein in the urine).

The protocol for the experiments of this example was the same as that used in the experiments of Example 1. Five PBS-treated, GN-induced mice, 6 anti-C5-treated, GN-induced mice, and 4 age-matched untreated uninduced mice were used in this study. A first set of urine samples was analyzed prior to treatment after the initial 2 week induction period. A second set of urine samples was analyzed after the 2 week treatment period. None of the untreated uninduced control animals had detectable protein in their urine at either of these timepoints.

The results obtained with the GN-induced mice are set forth in Table 1. As shown therein, at the end of the 2 week PBS treatment period, 4 out of the 5 PBS treated (control) animals developed significant proteinuria, i.e., at least 100mg/dL of protein in the urine. The fifth animal (mouse D in Table 1) did not have detectable protein in the urine at either timepoint but, unlike the other mice in the study, was found to have very high levels of glucose in the urine after the 2 week PBS treatment period, suggesting that this animal was physiologically compromised.

In the anti-C5-treated, GN-induced group, the one mouse that developed significant proteinuria at the end of the initial 2 week induction period (mouse 6 in Table 1) improved by the end of the 2 week antibody treatment period. In addition, in contrast to the development of significant proteinuria in 4 out of 5 PBS-treated, GN-induced mice, none of the anti-C5-treated, GN-induced mice exhibited significant proteinuria at the end of the 2 week antibody treatment period.

EXAMPLE 3

Anti-C5 Antibodies Do Not Inhibit Glomerular Immune Complex Deposition

This example demonstrates that anti-C5 antibodies used in the practice of the invention achieve their therapeutic effects even though immune complexes are deposited in the glomeruli of treated animals at equivalent levels to those seen in the glomeruli of PBS-treated animals. The example

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further illustrates that the mechanism of operation of the anti-C5 antibodies is not through the inhibition of immune complex deposition in the glomerulus.

The protocol used in the experiments of this example was the same as that used in the experiments of Example 1. Immunofluorescence staining as described above was performed on sections from the same kidneys harvested in Example 1.

The results are shown in Figure 2. As can be seen in this figure, equivalent amounts of immune complexes were deposited in the glomeruli of the kidneys of both the PBS-treated, GN-induced mice (Figure 2B) and the anti-C5-treated, GN-induced mice (Figure 2C), but not in the untreated uninduced controls (Figure 2A). Kidneys of GN-induced mice harvested after the 2 week induction period, but before treatment, showed immune complex deposits in the glomeruli, but at lower levels (as indicated by lower fluorescence intensity) than in the kidney sections shown in Fig. 2B and Fig. 2C.

EXAMPLE 4

Anti-C5 Antibodies Inhibit C5b-9 Generation

This example demonstrates that the anti-C5 antibodies used in the practice of the invention inhibit C5b-9 generation. C5b-9 generation was assayed in 2 ways: (1) by testing the cell-lysing (hemolytic) ability of blood samples, and (2) by measuring levels of soluble C5b-9 in blood samples.

Fig. 3 shows the results of cell lysis assays performed as described above, with mouse serum added to the percentage indicated on the X axis ("serum input %"). In these assays, serum from GN-induced animals treated with either anti-C5 antibodies in PBS or PBS alone (see above) was assayed at the end of the two week treatment period. Serum from normal, uninduced, uninjected mice ("normal mouse serum") obtained from Sigma Chemical Company (St. Louis, MO, Catalog No. S-3269) was also assayed as an additional control. These results indicate that the anti-C5 monoclonal antibody administered to mice at a dosage of 30 mg/Kg completely blocked the cell lysing ability of mouse blood at serum input levels 4-fold higher than the levels of normal serum that produce maximum hemolysis in the assay.

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The effects of an anti-C5 monoclonal antibody raised to human C5 was evaluated in circulating human blood. Hybridoma N19/8 (Wurzner, et al., 1991) was obtained from Dr. Otto Götze, Department of Immunology, University of Göttingen, FRG. The C5 monoclonal antibody was prepared following immunization of mice with purified human C5 protein as described in Wurzner, et al., (1991). The hybridoma was propagated in mice, and the monoclonal antibody recovered and purified as an IgG fraction from mouse ascites fluid (Antibodies, A Laboratory Manual, Cold Spring Harbor Laboratory, New York, 1988; Current Protocols In Immunology, John Wiley & Sons, New York, 1992).

To carry out these experiments, as well as others described below in Examples 5 and 6, 300 mL of whole human blood was drawn from a healthy human donor and additionally a 1 mL sample was removed as a control sample for later analysis. The blood was diluted to 600 mL by the addition of Ringer's lactate solution containing 10 U/mL heparin. The anti-C5 mAb (30 mg in sterile PBS) was added to the diluted blood to a final concentration of 50 µg/mL (results using test samples obtained in this way are labeled "+anti-C5 sample" in Fig. 4 and Fig. 6). In a control experiment, an equal volume of sterile PBS was added to diluted blood (results using control samples obtained in this way are labeled "-anti-C5 sample" in Fig. 4 and Fig. 6).

The blood was then used to prime the extracorporeal circuit of a COBE CML EXCEL membrane oxygenator cardiopulmonary bypass (CPB) machine (Cobe BCT, Inc., Lakewood, CO) and circulation through the circuit was started. The circuit was cooled to 28°C and circulated for 60 minutes. The circuit was then warmed to 37°C and circulated for an additional 30 minutes, after which time the experiment was terminated. Mechanical circulation of blood in this fashion activates the complement cascade. Samples were taken at several time points.

At each time point an aliquot of blood was taken, and subaliquots were centrifuged to remove all cells and the remaining plasma diluted 1:1 in Quidel sample preservation

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solution (Quidel Corporation, San Diego, CA) and stored at-80°C for subsequent evaluation of soluble C5b-9 (sC5b-9) generation. Diluted subaliquots of plasma were also frozen for evaluation of C3a generation (see Example 5, below). Undiluted subaliquots of plasma were frozen at - 80°C for analysis in hemolytic assays to evaluate the pharmacokinetics of the effects of the anti-C5 antibodies on the cell lysing ability of complement present in the blood (see Example 6, below). These experiments are also discussed in copending US patent application Serial No. 08/217,391, filed March 23, 1994.

sC5b-9 assays were performed before the addition of the antibody or the commencement of the CPB circuit (labeled "Pre Tx" in Fig. 4 and Fig. 6) using undiluted blood (i.e. blood from the 1mL sample taken before the blood was diluted with Ringer's lactate solution -- labeled "undil" in Fig. 4 and Fig. 6) and Ringer's lactate solution diluted blood (labeled "dil" in Fig. 4 and Fig. 6). Samples of Ringer's lactate solution diluted blood to which the antibody had been added (labeled "Post Tx" in Fig. 4 and Fig. 6) were assayed at the times indicated after starting the CPB circuit.

As can be seen in Figure 4, while sC5b-9 levels were more than 4-fold higher in untreated samples after 90 minutes of circulation than before circulation, the anti-C5 antibody completely inhibited C5b-9 generation throughout the 90 minute time course of circulation so that sC5b-9 levels during circulation were essentially equivalent to control, uncirculated samples, at all timepoints.

EXAMPLE 5

Anti-C5 Antibodies Do Not Inhibit C3 Deposition Or Activation

This example demonstrates that treatment with anti-C5 antibodies does not result in the inhibition of the activation of complement component C3 or in the deposition of C3 or its activated fragments in glomeruli.

The deposition of C3, or the fragments generated by its activation (e.g., C3a and C3b), in the glomeruli of GN-induced and GN-uninduced mice was visualized by immunofluorescence

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staining with a FITC-conjugated sheep anti-mouse C3 antibody preparation using standard methods, as described above. As can be seen in Fig. 5, kidneys of the PBS-treated (Fig. 5B) and the anti-C5 antibody-treated (Fig. 5C) GN-induced mice had roughly equivalent levels of C3 immunoreactive material in the glomeruli, while the uninduced untreated control mice had only traces of C3 immunoreactive material in their kidneys (Fig. 5A).

Note that the print shown in Fig. 5A was overexposed compared to those of Fig. 5B and Fig. 5C to show the very slight levels of reactivity present in normal uninduced kidneys. Kidneys of GN-induced mice harvested after the 2 week induction period, but before treatment, showed C3 immunoreactive materials in the glomeruli, but at lower levels (as indicated by lower fluorescence intensity) than in the kidney sections shown in Fig. 5B and Fig. 5C.

Anti-human C5 antibodies were also tested for possible inhibition of C3 activation in human blood prepared and circulated as described above in Example 4. Activation of complement component C3 was indicated by the presence in the blood of the C3 activation product C3a. C3a assays were performed as follows.

The plasma samples that had previously been diluted in Quidel sample preservation solution and frozen (see Example 4) were assayed for the presence of C3a by using the Quidel C3a EIA kit (Quidel Corporation, San Diego, CA) according to the manufacturers specifications. Concentrations of C3a in the samples is expressed as ng/well as determined by comparison to a standard curve generated from samples containing known amounts of human C3a.

As seen in Fig. 6, the addition of the anti-C5 mAb had no inhibitory effect on the production of C3a during the circulation of human blood in this experiment.

EXAMPLE 6

Pharmacokinetics of Anti-C5 Antibodies

The in vivo duration of action of mAb BB5.1, and a Fab' fragment of mAb BB5.1 (prepared by standard methods) was determined in normal female BALB/cByJ mice (averaging

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approximately 20 gms each) which were obtained from the Jackson Laboratory, Bar Harbor, ME. The mice were given a single intravenous injection (at 35 mg/kg body weight) of the mAB or the Fab' fragment of the mAb (or an equal volume of PBS as a control). Blood samples were collected from the retroorbital plexus at 1, 4, 24, 96, and 144 hours after administration of PBS; 4, 16, and 24 hours after administration of the Fab' fragment of mAb BB5.1; and 4, 24, 48, 72, 96, and 144 hours after administration of intact mAb BB5.1.

Fig. 7A shows the time course of inhibition of the cell-lysing ability of complement in mouse blood (determined, by testing serum obtained from the blood and diluted to 2.5%, as described above) after the in vivo administration of the mAb, the Fab' fragment, or the PBS. As shown in the figure, the mAb almost completely inhibited the hemolytic activity of the blood throughout the 6 day test period. The Fab', however, had a half-life of approximately 24 hours.

In addition to the above experiments, at the end of the 6 day testing period all of the mice were sacrificed. Kidneys, lungs, and livers were harvested and examined by gross inspection, as well as by microscopic examination of stained sections. All of the organs of the anti-C5 antibody treated animals appeared the same as those taken from PBS control treated animals. The overall appearance of the test and control mice was also indistinguishable prior to necropsy.

Anti-human C5 antibodies were also tested for pharmacokinetic properties in circulating human blood as described above in Example 4. As described therein, the hemolysis inhibiting effects of an anti-human C5 monoclonal antibody were assayed over a 90 minute period of circulation. The results of these assays are charted in Fig. 7B, and show that the N19/8 anti-C5 mAb essentially completely inhibited the cell lysing ability of the human blood during the entire 90 minute period of circulation.

The results of these experiments demonstrate that the anti-C5 antibodies will survive in the bloodstream for a substantial period of time, thus making periodic

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administration practical.

EXAMPLE 7

Preparation of Anti-C5 Monoclonal Antibodies

A monoclonal antibody suitable for use in the practice of the present invention was prepared in accordance with the teachings of Sims, et al., U.S. Patent No. 5,135,916, as follows.

Balb/c mice were immunized three times by intraperitoneal injection with human C5 protein (Quidel Corporation, San Diego, CA, Cat # A403). The first injection contained 100µg of C5 protein in a complete Freund's adjuvant emulsion, the second immunization contained 100µg of C5 protein in an incomplete Freund's adjuvant emulsion, and the third immunization was 100µg of protein in PBS. The mice were injected at roughly 2 month intervals.

Fusions of splenocytes to myeloma cells to generate hybridomas were performed essentially as described in Current Protocols in Immunology (John Wiley & Sons, New York, 1992, pages 2.5.1 to 2.5.17). One day prior to fusion the mice were boosted IV with 100µg of C5 protein. On the day of fusion, the immunized mice were sacrificed and spleens was harvested. SP2/0-AG14 myeloma cells (ATCC CRL#1581) were used as the fusion partner. SP2/0-AG14 cultures were split on the day before the fusion to induce active cell division. A ratio of 1:10 (myeloma cells:splenocytes) was used in the fusions.

The cells were fused using PEG 1450 in PBS without calcium (Sigma Chemical Company, St. Louis, MO, Catalog No. P-7181) and plated at 1-2.5 x 10^5 cells per well. Selection in EX-CELL 300 medium (JRH Biosciences, Lexena, KS, Catalog No. 14337-78P) supplemented with 10% heat inactivated fetal bovine serum (FBS); glutamine, penicillin and streptomycin (GPS); and HAT (Sigma Chemical Company, St. Louis, MO, Catalog No. H-0262) was started the following day. The fusions were then fed every other day with fresh FBS, GPS, and HAT supplemented medium. Cell death could be seen as early as 2 days and viable cell clusters could be seen as early as 5 days after initiating selection. After two weeks of selection in HAT, surviving hybridomas chosen for further study were transferred

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to EX-CELL 300 medium supplemented with FBS, GPS, and HT (Sigma Chemical Company, St. Louis, MO, Catalog No. H-0137) for 1 week and then cultured in EX-CELL 300 medium supplemented with FBS and GPS.

Hybridomas were screened for reactivity to C5 and inhibition of complement-mediated hemolysis 10-14 days after fusion, and were carried at least until the screening results were analyzed. The screen for inhibition of hemolysis was the chicken erythrocyte lysis assay described above. The screen for C5 reactivity was an ELISA, which was carried out using the following protocol:

A 50 µL aliquot of a 2 µg/mL solution of C5 (Quidel Corporation, San Diego, CA) in sodium carbonate/bicarbonate buffer, pH 9.5, was incubated overnight at 4°C in each test well of a 96 well plate (Nunc-Immuno F96 Polysorp, A/S Nunc, Roskilde, Denmark). The wells were then subjected to a wash step. (Each wash step consisted of three washes with TBST.) Next, test wells were blocked with 200 µL of blocking solution, 1% BSA in TBS (BSA/TBS), for 1 hour at 37°C. After an additional wash step, a 50 µL aliquot of hybridoma supernatant was incubated in each test well for 1 hour at 37°C with a subsequent wash step. As a secondary (detection) antibody, 50 µL of a 1:2000 dilution of horseradish peroxidase (HRP) conjugated goat anti-mouse IgG in BSA/TBS, was incubated in each test well for 1 hour at 37°C, followed by a wash step. Following the manufacturer's procedures, 10 mg of O-phenylenediamine (Sigma Chemical Company, St. Louis, MO, Catalog No. P-8287) was dissolved in 25 mLs of phosphate-citrate buffer (Sigma Chemical Company, St. Louis, MO, Catalog No. P-4922), and 50 µL of this substrate solution was added to each well to allow detection of peroxidase activity. Finally, to stop the peroxidase detection reaction, a 50 µL aliquot of 3N hydrochloric acid was added to each well. The presence of antibodies reactive with C5 in the hybridoma supernatants was read out by a spectrophotometric OD determination at 490 nm.

The supernatant from a hybridoma designated as 5G1.1 tested positive by ELISA and substantially reduced the cell-lysing ability of complement present in normal human blood in

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the chicken erythrocyte hemolysis assay. Further analyses revealed that the 5G1.1 antibody reduces the cell-lysing ability of complement present in normal human blood so efficiently that, even when present at roughly one-half the molar concentration of human C5 in the hemolytic assay, it can almost completely neutralize serum hemolytic activity.

Immunoblot analysis was undertaken to further characterize the 5G1.1 mAb. Human C5 (Quidel Corporation, San Diego, CA, Catalog No. A403) was subjected to polyacrylamide gel electrophoresis under reducing conditions, transferred to a nitrocellulose membrane, and probed with the 5G1.1 mAb as a purified IgG preparation. Two bands were immunoreactive with the 5G1.1 mAb at apparent molecular weights corresponding to those of the alpha and beta chains of the human C5 protein. The two 5G1.1 immunoreactive bands seen on this Western blot were subsequently found to result from the binding of the 5G1.1 antibody to the 115 kDa C5 alpha chain and to a large fragment of the alpha chain that had the same apparent molecular weight (approximately 75 kDa) as the beta chain of C5 and was present in the C5 preparations used for the experiment.

Assays were performed to determine the relative activity of the N19/8 mAb discussed in Examples 4 and 5 with the 5G1.1 mAb in functional hemolytic assays and to assess whether these mAbs blocked the cleavage of C5 to yield C5a. To this end, the N19/8 and 5G1.1 mAbs were directly compared in human complement hemolytic and C5a release assays.

Hemolytic assays performed in the presence of 20% v/v human serum revealed that the 5G1.1 mAb effectively blocked serum hemolytic activity at a final concentration of 6.25µg/ml (0.5 / 1 molar ratio of 5G1.1 / C5) whereas the N19/8 mAb blocked at a higher concentration of 25.0µg/ml (2.0 / 1 molar ratio of N19/8 / C5). When the supernatants from these assays were tested for the presence of C5a, the 5G1.1 mAb was found to have effectively inhibited C5a generation at doses identical to those required for the blockade of C5b-9 mediated hemolytic activity.

In contrast, the N19/8 mAb was 10 fold less effective in

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blocking the release of C5a in these assays when compared to the 5G1.1 mAb. Furthermore, the ability of the N19/8 mAb to block complement mediated hemolysis was not equivalent to its capacity to block C5a generation in that a dose of 25µg/ml of N19/8 completely blocked hemolysis while only reducing C5a generation by 37%.

Hybridoma 5G1.1 was deposited with the American Type Culture Collection, 12301 Parklawn Drive, Rockville, Maryland, 20852, United States of America, on April 27, 1994, and has been assigned the designation HB-11625. This deposit were made under the Budapest Treaty on the International Recognition of the Deposit of Micro-organisms for the Purposes of Patent Procedure (1977).

EXAMPLE 8

Determination of the affinity constants (K_D) for the anti-human C5 monoclonal antibodies 5G1.1 and N19/8

The procedure utilized to determine the dissociation constant (K_D) of antibody-antigen equilibria in solution was that described by Friguet et al., J. Immunol. Meth. 1985, 77:305-319. This method was used to determine the K_D for the anti-human C5 monoclonal antibodies N19/8 and 5G1.1. The monoclonal antibodies were incubated with the antigen (C5) in solution until the equilibrium was reached. The proportion of antibody that remains unbound (free) at equilibrium was measured using a conventional Enzyme Linked Immunosorbant Assay (ELISA). The experimental values of K_D obtained by this method have been shown to be equivalent to those obtained by other methods (immunoprecipitation of the radiolabeled antigen and fluorescence transfer). This method offers the advantage of dealing with unmodified antigen.

Figures 8 and 9 show the Scatchard plots of the binding of the anti-human C5 monoclonal antibodies 5G1.1 and N19/8 to human C5 as measured by ELISA. In each graph (v) represents the fraction of bound antibody and (a) represents the concentration of free antigen at equilibrium. The calculated K_D for the 5G1.1 mAb was 30pM while the calculated K_D for the N19/8 mAb was 43pM. These results indicate that the K_D for

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the 5G1.1 and N19/8 mAb's are similar, and therefore the functional disparity between the two antibodies cannot be explained simply by the differences in affinity for the C5 antigen.

EXAMPLE 9

Effect of 5G1.1 mAb on Complement Activation During CPB

Experiments involving recirculation of human blood in an CPB circuit, as described above in Examples 4 and 5, were carried out using three doses of the 5G1.1 mAb (15mg, 7.5mg, 3.75mg) as well as controls in the absence of the 5G1.1 mAb. In five such control experiments performed in this series, C3a Fig. 10) and sC5b-9 (Fig. 11) levels increased during the first 30 min and continued to rise throughout the entire experiment. Addition of the 5G1.1 mAb to the CPB circuit had no effect on the generation of C3a in these experiments.

Conversely, addition of the two highest doses (15mg and 7.5mg) of the 5G1.1 mab completely blocked the generation of sC5b-9 in these experiments while the lowest dose (3.75mg) only partially blocked sC5b-9 generation. Hemolytic assays performed on serum samples drawn throughout the time course of these experiments revealed that total serum complement activity was not affected in control experiments (Fig. 12). In contrast, the highest dose of the 5G1.1mAb (15mg) completely blocked complement hemolytic activity, while the two lower doses (7.5mg and 3.75mg), failed to block hemolytic activity.

These results show that the 7.5mg dose effectively blocked C5b-9 generation in the CPB circuit but failed to block C5b-9-mediated hemolytic activity, suggesting that hemolytic assays alone may not accurately reflect the complement activation that occurs during CPB. These results further indicate that the 5G1.1 mAb can completely block complement activation in human blood, as measured by either criterion, at a dosage of 15mg/500ml, a dose that is approximately equivalent to a dose of 150mg for a 70kg patient.

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EXAMPLE 10

Cloning of Anti-C5 Recombinant Anti-KSSKC Variable Region Genes

Amino Acid Sequencing:

To determine the N-terminal amino acid sequence of the 5G1.1 mAb, a 12% acrylamide gel (37.5:1 acrylamide/N,N'-methylene-bisacrylamide) was prepared and pre-electrophoresed for 45 minutes at 10 mA using 1x pre-electrophoresis buffer (123 mM bis-Tris, pH 6.6, with the cathode buffer reservoir supplemented with 1 mM reduced glutathione). The following day, the pre-electrophoresis buffer in the cathode reservoir was replaced with cathode reservoir buffer (44 mM N-tris-(hydroxymethyl)-methyl-2-aminoethanesulfonic acid, 113 mM bis-Tris, 0.1% (w/v) sodium dodecyl sulfate (SDS), 0.067% (w/v) thioglycolic acid) and the pre-electrophoresis buffer in the anode reservoir was replaced with anode reservoir buffer (63 mM bis-Tris, pH 5.9).

75 µg 5G1.1 monoclonal antibody was added to Laemmli sample buffer (30 mM Tris-HCl pH 6.8, 3% (w/v) SDS, 10 mM EDTA, 0.02% (w/v) bromophenol blue, 5% (v/v) glycerol, 2.5% (v/v) beta-mercaptoethanol) and electrophoresed at 10 mA until the bromophenol blue tracking dye reached the bottom of the gel. The protein was transferred to a PROBLOTT membrane (Applied Biosystems, Foster City, CA) using 1X transfer buffer (10 mM cyclohexylaminopropane sulfonic acid, 0.05% (w/v) dithiothreitol, 15% (v/v) methanol) at 50 V for one hour.

Protein bands were localized by staining with 0.2% Ponceau S (in 3% trichloroacetic acid, 3% sulfosalicylic acid) followed by destaining with water. Bands were excised and subjected to amino acid sequence analysis using Edman chemistry performed on a pulsed liquid protein sequencer (ABI model 477A), with the PTH amino acids thereby obtained being analyzed with an on-line microbore HPLC system (ABI model 120A).

To deblock the amino terminus of the 5G1.1 heavy chain, 10 mg 5G1.1 monoclonal antibody was exchanged into reducing buffer (5 M guanidine-HCl, 50 mM Tris-HCl, 10 mM dithiothreitol, pH 8.5) using a PD-10 column (Pharmacia,

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Piscataway, NJ). After a one hour incubation at room temperature, 50 mM iodoacetamide was added and the incubation allowed to continue for 30 minutes. The carbamidomethylated light and heavy chains thus obtained were separated by size exclusion chromatography on a SUPEROSE 12 (Pharmacia) column equilibrated with 5 M guanidine-HCl, 50 mM Tris-HCl pH 8.5. The carbamidomethylated heavy chain was exchanged into 50 mM sodium phosphate, pH 7.0 using a PD-10 column, subjected to digestion with pyroglutamate aminopeptidase (PanVera, Madison, WI; 0.5 mU per nmol of heavy chain protein), and sequenced as described above.

For determination of internal amino acid sequence, the carbamidomethylated 5G1.1 light chain was exchanged into 2 M urea, 25 mM Tris-HCl, 1 mM EDTA, pH 8.0 and incubated with endoproteinase Lys-C (Promega, Madison, WI; protease:protein ratio of 1:40) at 37°C overnight. The digested material was run on a C18 reversed phase HPLC column (Beckman Instruments, Fullerton, CA) and eluted using a linear 0-50% acetonitrile gradient in 0.1% trifluoroacetic acid. Peaks were subjected to amino acid sequence analysis as described above.

PCR Cloning:

Cloning of the 5G1.1 variable heavy region was performed using a set of commercially available primers (Mouse Ig-PRIMER SET, catalogue number 69831-1, Novagen, Madison, WI). Total RNA was isolated from 5G1.1 hybridoma cells using the acid/guanidinium thiocyanate technique (Chomczynski and Sacchi, Anal. Biochem. 1987, 162:156-159). For first strand cDNA synthesis, ten micrograms total RNA were denatured at 65°C for 5 min., chilled on ice, and added to a 100 µl reaction containing 10 mM Tris pH 8.3, 50 mM KCl, 1.5 mM $MgCl_2$, 10 mM dithiothreitol, 250 µM each dNTP, 20 units AMV reverse transcriptase (Seikagaku America, Rockville, MD), and 10 pmole of the appropriate 3' primer (as described in the Ig-PRIMER SET kit protocol). After incubation at 37°C for one hour, five microliters of the cDNA synthesis reaction were added to a 100 microliter PCR reaction containing: 10 mM Tris-HCl pH 9.0 at 25°C, 50 mM KCl, 1.5 mM $MgCl_2$, 0.1% (w/v) gelatin, 1.0% (v/v) Triton X-100, 200 µM each dNTP, 2.5 U

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AMPLITAQ DNA polymerase (Perkin-Elmer-Cetus, Norwalk, CT) and 25 pmoles of the appropriate 5′ and 3′ primers (as described in the Ig-PRIMER SET kit protocol). The reaction conditions were 1 minute at 95°C, 1 minute at 42°C, and 1 minute at 72°C for 30 cycles, followed by a final extension at 72°C for 10 minutes.

PCR products having the expected size (approximately 450 bp) were cloned into the vector pCRII (Invitrogen, San Diego, CA) using a T/A cloning kit (Invitrogen). DNA sequence analysis of cloned DNA fragments was performed by the dideoxy chain-termination method using double-stranded plasmid DNA as a template. A unique heavy chain variable region was isolated by this procedure, with the resulting plasmid designated p5G1.1 VH 2-1-3. Several clones obtained from independent replicate PCR reactions were sequenced to detect any mutations introduced during the PCR amplification of this variable region.

To clone the 5G1.1 light chain variable region, PCR primers were designed by using the UWGCG program TFASTA (University of Wisconsin, Madison, WI) to search the GenBank rodent subdirectory with the 19mer query amino acid sequence Ile Gln Met Thr Gln Ser Pro Ala Ser Leu Ser Ala Ser Val Gly Glu Thr Val Thr, that was obtained by amino acid sequencing as described above. An exact match to this sequence was located in the murine germline gene encoding the v-kappa k2 variable region (Seidman et al. Proc. Natl. Acad. Sci. USA 1978 75:3881-3885). The DNA sequence of this germline gene was used to design the oligonucleotide UDEC690 (SEQ ID NO:5) for use as a variable region 5′-primer. A murine kappa gene constant region primer, UDEC395 (SEQ ID NO:6) was also synthesized and used in this reaction. Cloning of the 5G1.1 variable light region was performed using the UDEC690 variable region 5′-primer and the UDEC395 murine kappa gene constant region primer.

PolyA mRNA was isolated from hybridoma 5G1.1. The acid/guanidinium thiocyanate procedure (Chomczynski and Sacchi, *supra*) was used to isolate total RNA, and was followed by oligo(dT)-cellulose chromatography of 1 mg of total RNA.

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For first strand cDNA synthesis, one microliter of the 25 microliters of oligo(dT)-cellulose eluate (containing approximately 2 micrograms of purified 5G1.1 mRNA) was denatured at 65°C for 5 min., chilled on ice, and incubated in extension buffer (10 mM Tris pH 8.3, 50 mM KCl, 1 mM dithithreitol, 240 µM each dNTP) containing 100 nM UDEC395 (SEQ ID NO:6) and 25 units AMV reverse transcriptase (Seikagaku America, Rockville, MD) at 42°C for one hour. Five microliters of the completed first strand reaction was subjected to PCR amplification using amplification buffer supplemented with 2.5 units AMPLITAQ DNA polymerase (Perkin Elmer, Foster City, CA) and 500 nM each of primer UDEC690 (SEQ ID NO:5) and UDEC395 (SEQ ID NO:6). Amplification was performed using 30 cycles each consisting of 1 minute at 95°C, 1 minute at 52°C, and 1 minute at 72°C, followed by a single ten minute incubation at 72°C.

The resulting PCR product was purified using GENECLEAN according to the manufacturer's directions (Bio 101, La Jolla, CA), digested with *Sse*8387 I and *Hind* III, gel purified, and ligated into the vector Bluescript II SK+ (Stratagene, La Jolla, CA). Ligated plasmids were transformed into the bacterial strain DH10B by electroporation.

Plasmid DNA was purified from cultures of transformed bacteria by conventional methods including column chromatography using a QUIAGEN-TIP-500 column according to the manufacturer's directions (Quiagen, Chatsworth, CA) and sequenced by the Sanger dideoxy chain termination method using SEQUENASE enzyme (U.S. Biochemical, Cleveland, OH). Clones obtained from a second independent PCR reaction verified that no mutations were introduced during the amplification process. The resulting plasmid containing the cloned variable region was designated SK (+) 690/395. This light chain encoding insert in this plasmid coded for both the N-terminal and internal light chain sequences determined by amino acid sequencing of 5G1.1, as described above.

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EXAMPLE 11

Construction and Expression of Recombinant mAbs

Recombinant DNA constructions encoding the recombinant mAbs comprising the 5G1.1 CDRs are prepared by conventional recombinant DNA methods including restriction fragment subcloning and overlapping PCR procedures. The resulting recombinant mAb-encoding DNAs include:

(1) one encoding a non-humanized (murine) scFv designated 5G1.1M1 scFv (SEQ ID NO:7), wherein CDR L1 is amino acid residues 28-34 of SEQ ID NO:7, CDR L2 is amino acid residues 52-54 of SEQ ID NO:7, CDR L3 is amino acid residues 93-98 of SEQ ID NO:7, CDR H1 is amino acid residues 156-159 of SEQ ID NO:7, CDR H2 is amino acid residues 179-183 of SEQ ID NO:7, and CDR H3 is amino acid residues 226-236 of SEQ ID NO:7;

(2) one encoding a humanized (CDR grafted) scFv designated 5G1.1 scFv CB (SEQ ID NO:8), wherein CDR L1 is amino acid residues 26-36 of SEQ ID NO:8, CDR L2 is amino acid residues 52-58 of SEQ ID NO:8, CDR L3 is amino acid residues 91-99 of SEQ ID NO:8, CDR H1 is amino acid residues 152-161 of SEQ ID NO:8, CDR H2 is amino acid residues 176-192 of SEQ ID NO:8, H3 is amino acid residues 225-237 of SEQ ID NO:8;

(3) one encoding a chimeric light chain (which can form the light chain portion of an Fab) designated 5G1.1M1 VL HuK (SEQ ID NO:9);

(4) one encoding a chimeric Fd (the heavy chain portion of an Fab) designated 5G1.1M1 VH HuG1 (SEQ ID NO:10);

(5) one encoding a humanized (CDR grafted and framework sequence altered) Fd designated 5G1.1 VH + IGHRL (SEQ ID NO:11), wherein CDR H1 is amino acid residues 26-35 of SEQ ID NO:11, CDR H2 is amino acid residues 50-60 of SEQ ID NO:11, and CDR H3 is amino acid residues 99-111 of SEQ ID NO:11;

(6) one encoding a humanized (CDR grafted, not framework altered) Fd designated 5G1.1 VH + IGHRLC (SEQ ID NO:12), CDR H1 is amino acid residues 26-35 of SEQ ID NO:12, CDR H2 is amino acid residues 50-66 of SEQ ID NO:12, and CDR H3 is amino acid residues 99-111 of SEQ ID NO:12;

(7) one encoding a humanized (CDR grafted and framework sequence altered) light chain designated 5G1.1 VL + KLV56 (SEQ

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ID NO:13), wherein CDR L1 is amino acid residues 26-36 of SEQ ID NO:13, CDR L2 is amino acid residues 52-58 of SEQ ID NO:13, and CDR L3 is amino acid residues 91-99 of SEQ ID NO:13;

(8) one encoding a humanized (CDR grafted, not framework altered) light chain designated 5G1.1 VL + KLV56B (SEQ ID NO:14), wherein CDR L1 is amino acid residues 26-36 of SEQ ID NO:14, CDR L2 is amino acid residues 52-58 of SEQ ID NO:14, and CDR L3 is amino acid residues 91-99 of SEQ ID NO:14;

(9) one encoding a humanized (CDR grafted, not framework altered) light chain designated 5G1.1 VL + 012 (SEQ ID NO:15), wherein CDR L1 is amino acid residues 24-34 of SEQ ID NO:15, CDR L2 is amino acid residues 50-56 of SEQ ID NO:15, and CDR L3 is amino acid residues 89-97 of SEQ ID NO:15; and

(10) one encoding a humanized (CDR grafted, not framework altered) Fd designated 5G1.1 VH + IGHRLD (SEQ ID NO:16), wherein CDR H1 is amino acid residues 26-35 of SEQ ID NO:16, CDR H2 is amino acid residues 50-60 of SEQ ID NO:16, and CDR H3 is amino acid residues 99-111 of SEQ ID NO:16.

(11) one encoding a humanized (CDR grafted, not framework altered) scFv designated 5G1.1 scFv DO12 (SEQ ID NO:17), wherein CDR L1 is amino acid residues 26-36 of SEQ ID NO:17, CDR L2 is amino acid residues 52-58 of SEQ ID NO:17, CDR L3 is amino acid residues 91-99 of SEQ ID NO:17, CDR H1 is amino acid residues 152-161 of SEQ ID NO:17, CDR H2 is amino acid residues 176-186 of SEQ ID NO:17, and CDR H3 is amino acid residues 225-237 of SEQ ID NO:17;

In accordance with the invention, one each of the various L1, L2 and L3 CDRs discussed in (1) to (11) above may be combined with any of the other light chain CDRs so as to make a set of 3 light chain CDRs comprising one L1, one L2, and one L3 CDR, as part of a recombinant antibody or synthetic peptide antibody (i.e., a synthetic peptide with the sequence of a recombinant peptide of the invention).

In accordance with the invention, one each of the various H1, H2 and H3 CDRs discussed in (1) to (11) above may be combined with any of the other light chain CDRs so as to make a set of 3 light chain CDRs comprising one H1, one H2, and one H3 CDR, as part of a recombinant antibody or synthetic peptide

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antibody (i.e., a synthetic peptide with the sequence of a recombinant peptide of the invention).

In accordance with the invention, matched pairs of the variable regions (e.g., a VL and a VH region) of the various antibody molecules, Fds, and light chains described above may be combined with constant region domains by recombinant DNA or other methods known in the art to form full length antibodies of the invention. Particularly preferred constant regions for this purpose are IgG constant regions, which may be unaltered, or constructed of a mixture of constant domains from IgGs of various subtypes, e.g., IgG1 and IgG 4.

Matched pairs of the Fd and light chain encoding DNAs described immediately above -- i.e. (3) and (4), (5) and (7), (6) and (8), and (6) and (9) -- were subcloned together into the APEX-3P vector, essentially as described below in Example 15 for N19/8. The scFv constructs of (1) and (2) were subcloned into pET Trc S05/NI using conventional techniques.

Plasmids so obtained were introduced by into the bacterial strain ME2 (pET plasmids) by conventional electroporation, or into human 293 EBNA cells (APEX plasmids) by lipofection using 2-3 microliters of TRANSFECTAM reagent (Promega, Madison, WI) per microgram of DNA according to the manufacturer's directions. Bacterial strains ME1 and ME2 are derivatives of *Escherichia coli* strain W3110 (ATCC designation 27325) prepared as follows.

Preparation of W3110 Derivatives ME1 and ME2:

The non-humanized, non-chimeric murine 5G1.1-scFv "m5G1.1-scFv" -- made up of light chain (3) and Fd (4) -- was expressed in a derivative of *E. coli* K12 strain W3110. This derivative was prepared by inactivating an uncharacterized gene to provide protection against infections by a lytic bacteriophage. *E. coli* strain W3110 is a particularly preferred strain because it is fully characterized and is commonly used for recombinant DNA product fermentations.

A single colony of *E. coli* strain W3110 was grown overnight in L medium at 30°C. The cells were collected by centrifugation and resuspended in 10 mM $MgSO_4$. A total of 0.1 ml of the culture was added to 2.5 ml 0.7% L soft agar at 45°C

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and quickly poured on an L plate. Fifty microliter aliquots of a plaque purified phage lysate, undiluted, diluted 10^{-2} and diluted 10^{-4}, were spotted onto the agar surface. Phage lysates had previously been filtered through 0.45 µm membranes and stored in sterile tubes with a drop of chloroform at 4°C. The spots were allowed to dry on the soft agar surface and incubated overnight at 37°C.

The next day L plates were spread with 10^9 phage PFU and allowed to dry. Using a sterile, flat toothpick, cells from isolated colonies growing in the zones of phage lysis on the spot plates were streaked for single colonies on the plates spread with 10^9 phage PFU and incubated overnight at 37°C. Single colonies were rechecked for phage resistance by cross-streaking after single colony purification. The cross streak test for phage sensitivity was performed as follows. Fifty µl of phage (10^8 pfu/ml) was spread in a vertical line in the left hand portion of the plate using a Pasteur pipette. Additional phage were tested parallel to the first and to the right. The plate was allowed to dry, and strains to be checked for sensitivity or resistance were spread perpendicular to and across the lines of all phages in a single swath from the left to the right. Resistant strains grow in the area of the phage streaks while sensitive strains lyse.

The phage resistant mutant strain ME1 was tested for phage production after overnight growth in L medium and treatment with the DNA damaging agent, mitomycin C. The strain failed to produce viable phage utilizing a standard plaque assay and *E. coli* W3110 as the phage sensitive indicator strain. These results suggest that strain ME1 does not harbor a resident prophage.

Strain ME2 was constructed by site specific integration of the lambdaDE3 prophage (Studier et al. 1990, Meth. Enzymol. 185:60-89) into the ME1 chromosome. Expression of the T7 RNA polymerase, directed by the prophage, allows expression of target genes cloned into pET vectors (Studier et al., *supra*) under the control of the T7 promoter in the lysogenized host. Lysogenization was accomplished in a three way infection with

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lambdaDE3, the lambda helper phage, lambdaB10 and the selection phage, lambdaB482 (Studier et al., *supra*).

lambdaDE3 (*imm*21) was constructed by Studier and colleagues (1990, Meth. Enzymol. 185:60-89) by inserting the T7 RNA polymerase gene behind the *E. coli lacUV5* promoter into the *Bam*HI cloning site of lambdaD69(*imm*21). Since cloning into the *Bam*HI site of lambdaD69 interrupts the integrase gene, lambdaDE3 cannot integrate or excise from the chromosome by itself. The helper phage lambdaB10 provides the integrase function that lambdaDE3 lacks but cannot form a lysogen by itself. The selection phage, lambdaB482, lyses any lambdaDE3 host range mutants that otherwise would be among the surviving cells, but it can neither integrate into susceptible cells nor lyse lambdaDE3 lysogens since it has the same immunity region as lambdaDE3 (*imm*21).

Lysogenization protocol:

Strain ME1 was grown in L medium supplemented with 0.2% maltose and 10 mM $MgSO_4$ at 37°C to a density of approximately 10^8 cells/ml. One µl of ME1 cells were incubated with 2 x 10^8 plaque forming units (pfu) of lambdaDE3 and 10^8 pfu of lambdaB10 and lambdaB482. The host/phage mixture was incubated at 37°C for 20 min to allow phage adsorption to ME1 cells. Several dilutions of the cell/phage suspension were spread on L plates to produce plates containing approximately 30-200 candidate lysogens as isolated colonies. The plates were inverted and incubated at 37°C overnight. Several isolated colonies were screened for the acquisition of the lambdaDE3 prophage as described below.

Verification of lambdaDE3 lysogens:

lambdaDE3 lysogen candidates were tested for their ability to support the growth of the T7 phage 4107, a T7 phage deletion mutant that is completely defective unless active T7 RNA polymerase is provided in *trans*. Only lambdaDE3 lysogens will support the normal growth of the phage in the presence of IPTG (isopropyl-beta-thiogalactopyranoside). The T7 phage produces very large plaques on lambdaDE3 lysogens in the presence of IPTG, while very small plaques are observed in the absence of inducer. The size of the plaque in the absence of

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IPTG is an indication of the basal level of T7 RNA polymerase expression in the lysogen. Putative lambdaDE3 lysogens were grown in L broth supplemented with 0.2 % maltose and 10 mM $MgSO_4$ at 37°C to a cell density of approximately 10^8 cells/ml. A total of 0.5 ml of cells was centrifuged and the pellet was resuspended in 0.2 ml of a T7 phage lysate containing 2 x 10^4 pfu. The phage was allowed to adsorb for 30 min at 37°C. One-half of suspension (0.1 ml) was added to 3.0 ml of molten top agarose at 47°C and poured onto L plates. The remaining aliquot of cell/phage suspension was poured onto an L plate supplemented with 0.4 mM IPTG to check for induction of T7 RNA polymerase. The plates were inverted and incubated at 37°C overnight.

Strains were also tested for the presence of the lambdaDE3 lysogen by demonstrating that each strain was resistant to infection by the phage lambdaB482, which is in the same immunity group (*imm*21), by the cross streak method described above. A lysogen was chosen with a low basal expression level for protein production from pET vectors. The resulting strain, designated ME2, is phage resistant and overexpresses T7 RNA polymerase in the presence of IPTG.

Purification of Humanized 5G1.1-scFv from E. coli:

The humanized 5G1.1-scFv (h5G1.1-scFv) cDNA construct was cloned into the bacterial expression plasmid pET Trc SO5/NI (SEQ ID NO:18) and transformed into E. coli strain ME1. The resulting strain expressing h5G1.1 scFv was grown at 37°C in 2 liter Applikon glass vessel fermentors containing Terrific Broth (1.2 % (w/v) bacto-tryptone, 2.4% (w/v) bacto-yeast extract, 0.4% (v/v) glycerol, 90 mM KPO_4, pH 7.0) supplemented with 100 µg/ml ampicillin. The production of recombinant scFv was induced by the addition of 1 mM IPTG when the $O.D._{550}$ of the culture reached 10. After an additional 3 h incubation at 37°C, the cells were harvested by centrifugation and the cell pellets stored at -80°C.

Cells were resuspended in 1 mM EDTA, pH 5.0 at 10 ml per gram weight and lysed by a single pass through a microfluidizer (Model M110T, Microfluidics Corp., Newton, MA). After centrifugation at 17,500 x g for 15 min, the resulting

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inclusion body pellet was washed by resuspension in 20 mM Tris-HCl pH 8.0, 1 mM EDTA, 100 mM NaCl, 0.15% (w/v) deoxycholate at 10 ml per gram inclusion body using a Tekmar POLYTRON. The inclusion bodies were again pelleted by centrifugation at 17,500 x g for 15 min and resuspended in 20 mM Tris-HCl pH 9.0, 8 M urea at 10 ml per g. After stirring for 1 h, the sample was centrifuged at 14,000 x g for 30 min to pellet remaining insoluble material.

The extract supernatant was diluted 10-fold with 20 mM Tris-HCl pH 9.0, 7 M urea, 50 µM cupric sulfate and allowed to stir for at least 16 hours at 4°C to refold the scFv. After addition of Biocryl BPA-1000 (TosoHaas, Montgomeryville, PA) as a flocculating agent at 3 µl per ml, the sample was centrifuged at 15,000 x g for 10 minutes to remove insoluble material. The refolding mixture was exchanged into 20 mM Tris, pH 9.0, 1mM EDTA by diafiltration and concentrated by ultrafiltration using a stirred cell fitted with a YM10 membrane (Amicon, Beverly, MA).

The properly refolded scFv was then separated from aggregated material and contaminating proteins by anion exchange chromatography using Q Sepharose Fast Flow (Pharmacia, Piscataway, NJ). Bound scFv was eluted with 20 mM Tris-HCL pH 9.0, 1 mM EDTA containing a linear NaCl gradient (0 to 0.5 M). The fractions containing the scFv were combined, concentrated by ultrafiltration using a stirred cell fitted with a YM10 membrane, and applied to a Sephacryl S200 HR 26/100 column (Pharmacia) equilibrated in 20 mM Tris-HCl pH 9.0, 1 mM EDTA, 150 mM NaCl. Fractions containing the scFv were combined, exchanged into phosphate-buffered saline by diafiltration, concentrated by ultrafiltration, filtered through a 0.22 µm Millex-GV filter (Millipore, Bedford, MA), and stored at 4C.

Purification of m5G1.1-scFv from E. coli:

Frozen bacterial cell paste was thawed and resuspended in 2.5 ml of 1 mM EDTA (pH 5) per gram of cell paste. This suspension of cells was lysed by passage through a Microfluidizer (Microfluidics) with the interaction chamber in line and a backpressure of approximately 18000 psi. The cell

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lysate was then centrifuged at 10,000 rpm in a JA-10 centrifuge rotor at 4°C for 15 min. The supernatant was decanted and discarded.

The pellet was resuspended in 10 ml of 20 mM Tris, pH 8.0, 100 mM NaCl, 1 mM EDTA, 0.15% sodium deoxycholate per gram of pellet. This suspension was centrifuged as above for 10 min. Again the supernatant was decanted and discarded. This detergent washed pellet was then resuspended in 10 ml of 8 M urea, 20 mM Tris-HCl, pH 9, 1 mM EDTA. The suspension was stirred at 4°C for 1 hr. and was then diluted 10 fold with 7 M urea, 20 mM Tris-HCl, pH 9 and stirred at 4°C. $CuSO_4$ was then added to a final concentration of 50 µM and stirring was continued overnight at 4°C.

The majority of contaminating proteins (including incorrectly folded versions of m5G1.1 scFv) were then removed by precipitation by diluting (with stirring) the refolded sample five fold with buffer such that the final concentrations after dilution were 1.4 M urea, 25 mM NaCl, 1 mM EDTA, and 20 mM sodium acetate at 4°C. The pH of the dilution buffer when prepared at room temperature was pH 5.0. Prior to dilution the pH of the dilution buffer is determined at 4°C. After the dilution the pH of the sample was greater than pH 5.5. The pH of the sample was then adjusted with 6 N HCl to the initial pH 5.0 of the buffer. The solution immediately became cloudy and it was left stirring at 4-8°C for 0.5 to 24 hours.

The precipitate was removed by filtering the sample through a 300 kDa cut-off ultrafiltration membrane (Millipore Corporation, Bedford, MA). The permeate was collected and concentrated 5 fold using a 10 kDa cutoff ultrafiltration membrane (Millipore). This concentrated retentate was then diluted 2 fold with 20 mM sodium acetate, 1 mM EDTA, pH 5.0 in order to lower the NaCl concentration to 12.5 mM.

The diluted retentate was then loaded at 4°C onto a SP Sepharose FF column (Pharmacia) equilibrated in 0.7 M urea, 1 mM EDTA, 10 mM NaCl, 20 mM sodium acetate, pH 5.0, at a linear flowrate of 5 cm/min. Bed height was equal to or greater than 3.5 cm. Following loading the column was washed with 40

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column volumes (CV) of equilibration buffer. The column was then washed with 20 CV of 20 mM sodium acetate, pH 5.0, 1 mM EDTA. The bound scFv was then eluted using 20 mM sodium citrate, pH 5.8, 1 mM EDTA. A single peak was collected in approximately 4 column volumes.

The SP Sepharose eluate was then adjusted to 20 mM Tris-HCl by addition of 1 M Tris-HCl, pH 8. The pH of the sample was adjusted to 8.0 by addition of 1 N NaOH. This sample was loaded onto a Q Sepharose FF column (Pharmacia) equilibrated in 20 mM Tris-HCl, pH 8.0, 1 mM EDTA at room temperature at a flowrate of 5 cm/min. The flow through fraction containing the scFv was collected.

The Q Sepharose flow through fraction was then adjusted to 150 mM NaCl and concentrated to 10 mg of scFv per ml using a 10 kDa cutoff ultrafiltration membrane. This concentrated sample was then loaded onto a Sephacryl S200 column equilibrated in phosphate buffered saline, pH 7.4 and eluted at 0.4 cm/min. The fractions were analyzed by SDS-PAGE and silver staining. Peak fractions were combined after discarding the front and back shoulder fractions that contained the majority of contaminants.

EXAMPLE 12

Functional Analysis of the m5G1.1 scFv

Titration of the m5G1.1 scFv in hemolytic assays revealed that the m5G1.1 scFv inhibited human complement-mediated lysis in a dose dependent fashion (Fig. 13). Direct comparison of the efficacy of the m5G1.1 scFv to the 5G1.1mAb and Fab demonstrated that the m5G1.1 scFv completely blocked C5b-9-mediated hemolysis in 20% human serum at 0.15μM while the 5G1.1 mAb and Fab blocked at 0.06-0.08μM. Analysis of C5a generation in these assays revealed similar results in that the 5G1.1 scFv completely blocked C5a generation at 0.15μM while the 5G1.1 mAb and Fab blocked at 0.06-0.08μM (Fig. 14). Taken together these experiments indicated that unlike N19/8, which lost half of its effectiveness at blocking C5a generation upon being engineered as an scFv (SEQ ID NO:19), the 5G1.1 murine scFv retained the capacity to block the generation of both C5a and C5b-9.

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Additionally, these data demonstrate that the m5G1.1 scFv retained similar activity to that of the parent molecule (the native murine 5G1.1 mAb) in that the molar concentration of 5G1.1 murine scFv required to completely block C5a and C5b-9 (0.15μM) was within two-fold of that required for the 5G1.1 mAb and Fab (0.06-0.08μM).

In order to determine whether the m5G1.1 scFv retained the capacity to block the activation of complement in the *ex vivo* model of cardiopulmonary bypass, 4.5mg of the purified bacterially produced 5G1.1 murine scFv was added to the CPB circuit and complement activation was monitored. In control experiments, both C3a and C5b-9 levels increased throughout the time course of the experiment. In a single experiment, addition of 4.5mg of the m5G1.1 scFv to the CPB circuit had no effect on the generation of C3a (Fig. 15). Conversely, complement hemolytic activity as well as the generation of sC5b-9 was completely blocked in this experiment (Fig. 16 and Fig. 17).

Example 13

Characterization of the Epitope Recognized by 5G1.1

Tryptic digestion: Twenty micrograms of purified human C5 (Advanced Technologies, San Diego, CA) was subjected to enzymatic digestion with 1 μg of TPCK-treated trypsin (Worthington Biochemical Corp., Freehold, NJ). The digestion was allowed to continue for 3 minutes, after which time it was stopped by the addition of 20 μg soy bean trypsin inhibitor (Worthington). The reaction was then denatured and reduced by the addition of protein sample buffer and immediately boiled for 5 min. The digested fragments were size fractionated through a SDS-PAGE on a 12 % gel. The gel was then electroblotted in transfer buffer (20% (v/v) methanol, 25 mM Tris-base pH 8.0, and 192 mM glycine) to nitrocellulose (Bio-Rad Laboratories, Hercules, CA) and subjected to ECL western blot analysis using either 5G1.1 or a C5a specific monoclonal antibody (G25/2, obtained from Dr. Otto Götze, Department of Immunology, University of Göttingen, Germany).

The filters were incubated twice for 30 minutes each in blocking solution (500 mM NaCl, 5 mM Tris pH 7.4, 10% (v/v)

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nonfat dry milk, and 0.2% (v/v) Tween-20). The filters were then changed to fresh blocking solution (20 ml) containing the primary antibody and incubated for 40 minutes on a rocking platform. The filters were rinsed briefly with washing solution (500 mM NaCl, 35 mM Tris pH7.4, 0.1% SDS, 1% NP40, and 0.5% deoxycholic acid) to remove any milk, and then fresh wash solution was added and incubated for two 20 minute intervals on an orbiting shaker. The filters were rinsed briefly with 10 to 20 mls of secondary antibody solution (500 mM NaCl, 5 mM Tris pH 7.4, 10% (v/v) Nonfat dry milk, 0.2% (v/v) Tween-20, and 1% NP-40) and then incubated with fresh secondary antibody solution containing a 1:2000 dilution of HRP conjugated goat anti-mouse for 20 minutes on a rocking platform. The filters were then washed as described above, incubated in ECL reagent (Amersham Corp., Arlington Heights, IL) for 1 minute and then exposed to ECL Hyperfilm (Amersham).

Acid Hydrolysis: Twenty micrograms of purified human C5 (Advanced Technologies) was subjected to hydrolysis in 1N acetic acid. The 20 µg of human C5 (1µg/µl) was added to 20 µl of 2N acetic acid and incubated for 10 min at 100°C. The sample was denatured and reduced with protein sample buffer, also at 100°C, for 5 minutes. The acid was neutralized by dropwise addition of a saturated tris base solution until the sample turned blue. The cleavage products were then size fractionated by SDS-PAGE and western blotted as described above. For N-terminal sequencing, the gel fractionated acid hydrolysate was transferred to PVDF membrane. N-terminal sequence was obtained by excising the 46 kDa acid hydrolysis fragment band from a PVDF membrane and subjecting it to amino acid sequence analysis as discussed above in Example 10.

Deglycosylation: Reduced and denatured acid hydrolyzed or tryptic fragments of human C5 were subjected to deglycosylation with N-Glycosidase F (Peptide-N-Glycosidase F, Boehringer Mannheim Corp., Indianapolis, IN) according to the manufacture's directions.

Results: Acid hydrolysis of human C5 yielded a fragment with an apparent molecular weight by SDS-PAGE of 46 kDa that was immunoreactive for both the anti-C5a mAb G25/2 and the

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anti-C5 alpha chain mAb 5G1.1. Western blots probed with both antibodies simultaneously, as well as silver stain SDS-PAGE analysis, confirmed the presence of a single 46 kDa fragment that was immunoreactive with both antibodies. The presence of a single immunoreactive fragment containing binding sites for both 5G1.1 and G25/2 strongly suggested that the 5G1.1 epitope was contained within approximately the first 46 kDa of the N-terminus of the alpha chain of C5.

As discussed above in the description of the complement system under the heading "Background Physiology & Pathology," a compound (e.g., an antibody) that binds to a site at or immediately adjacent to the C5a cleavage site would have the potential to act as a terminal complement inhibitor. The potential inhibitory activity of antibodies binding to this site led to the expectation that the C5 alpha chain-binding 5G1.1 antibody would bind to an epitope at or near the C5a cleavage site. The finding that 5G1.1 bound to the 46 kDa acid hydrolysis fragment of C5 lent support to this expectation.

Western blot analysis of the tryptic digestion products identified one proteolytic fragment migrating at approximately 27 kDa that was immunoreactive with 5G1.1. Likewise, one immunoreactive proteolytic fragment migrating at approximately 29 kDa was observed following western blot analysis with the anti-C5a mAb G25/2. Experiments in which a blot was simultaneously probed with both 5G1.1 and G25/2 demonstrated that each band was distinct and that their apparent differential mobility was not a gel anomaly. This was surprising, because the 5G1.1 mAb was thought likely to bind to the C5 convertase cleavage site. 5G1.1 was thus expected to be immunoreactive with any fragment of C5 of over 12 kDa that exhibited immunoreactivity with G25/2. Such a fragment would contain enough of the extreme amino terminus of the C5 alpha chain to bind specifically to the anti-C5a mAb, and enough beyond that to encompass a region including and extending beyond the C5 convertase cleavage site.

The immunoreactivity of G25/2 with the 29 kDa fragment indicated that that fragment contains the N-terminal region of

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the alpha chain of C5 that is cleaved off to yield C5a. Furthermore, because 5G1.1 was not immunoreactive with this band, the 5G1.1 epitope was not likely to be contained within approximately the first 29 kDa of the N-terminus of the alpha chain of C5, and therefore could not be located near the C5 convertase cleavage site.

These tryptic digestion and acid hydrolysis mapping data suggested that the 5G1.1 epitope was contained within a region starting about 29 kDa (including post-translational modifications) from the N-terminus of the alpha chain of C5 and continuing 17 kDa in a C-terminal direction, i.e., ending 46 kDa from the N-terminus, a surprising finding in view of the expectation, discussed above, that the antibody would bind at or immediately adjacent to the point at which C5a is cleaved off of the C5 alpha chain, i.e., at or immediately adjacent to amino acid residue 733 of SEQ ID NO:2.

Post-translational modifications can alter the mobility of proteins during SDS-PAGE electrophoresis. One such modification is the addition of carbohydrate via N-linked glycosylation. As discussed above under the heading "Background Physiology & Pathology", C5 is glycosylated, as is C5a. C5a is glycosylated at an asparagine residue corresponding to amino acid number 723 of the full length pro-C5 precursor of human C5 (SEQ ID NO:2).

Computer analysis of the human C5 alpha chain suggests potential N-linked glycosylation sites at positions corresponding to amino acid numbers 893, 1097, and 1612 of SEQ ID NO:2. In order to determine the contribution of carbohydrate to the electrophoretic mobility of both the tryptic and acid fragments, enzymatic deglycosylation of the fragments was performed and followed by western blot analysis. It was determined that each tryptic fragment lost approximately 3 kDa in apparent molecular weight while the acid fragment lost approximately 6 kDa.

This result was interpreted as indicating that the tryptic fragments were each glycosylated at a single site and that the 46 kDa acid fragment was glycosylated at two sites (one of which was the known glycosylation site in C5a referred to

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above). The diminished mobility observed following deglycosylation agrees with the computed prediction of a second N-linked glycosylation site within the first 233 amino acids of the C5 alpha chain.

N-terminal sequence analysis determined that the first four amino acids of the 46 kDa fragment generated by 1N acetic acid treatment was Thr Leu Gln Lys. This sequence is found only once in the full length human pro-C5 precursor molecule- - at a position corresponding to amino acids 660 through 663 of SEQ ID NO:2. This four amino acid sequence also corresponds to the sequence of the amino-terminus of the alpha chain of human C5 and, thus to the amino-terminus of human C5a.

In order to more precisely map the binding site of 5G1.1, overlapping peptide analysis was performed. The sequence predicted to be contained within the 17 kDa section of human C5 described above (SEQ ID NO:2; amino acids 893 through 1019) together with an extension of 43 amino acids towards the N-terminus and 30 amino acids towards the C-terminus (a total of 200 amino acids) was synthesized as a series of 88 overlapping peptides by solid phase synthesis on polypropylene filters (Research Genetics Inc., Huntsville, AL).

The 43 and 30 amino acid extensions were added to allow for possible inaccuracies in the prediction of the span of this 17 kDa region. Such inaccuracies are likely due to the uncertainty of the specific extent of glycosylation of each of the various regions of C5a, as well as to the aberrant gel mobility that is commonly seen when highly charged polypeptides (such as the 5G46k fragment and the 5G27k fragment) are analyzed by SDS-PAGE. As discussed above in the Summary of the Invention, a 200 amino acid peptide corresponding to the region covered by these overlapping peptides is referred to herein as the "5G200aa" peptide.

Because of the expectation that the 5G1.1 antibody would bind at the C5a cleavage site, an additional set of 8 overlapping peptides was synthesized that spanned a 30 amino acid section spanning the C5a cleavage site (amino acids 725 through 754 of SEQ ID NO:2). A peptide having the sequence of

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this 30 amino acid section is referred to herein as the "cleavage site peptide". A 325aa peptide spanning amino acid residues 725-1049 of SEQ ID NO:2 (this peptide spans the region covered by the cleavage site peptide and the 5G200aa peptide) is referred to herein as the "5G325aa" peptide.

These filters were probed with 5G1.1 as described above for ECL western blot analysis, and a set of 4 overlapping peptides spanning the region corresponding to amino acid residues 3-19 of the KSSKC peptide (SEQ ID NO:1) each gave a positive signal indicative of monoclonal antibody binding, while peptides corresponding to the C5a cleavage site did not bind to the 5G1.1 antibody.

EXAMPLE 14

C3/C4 Binding Assay

C3 and C4 are both key components of classical C5 convertase, and C3 is also a key component of alternative C5 convertase. These C5 convertases are required for the conversion of C5 to active C5a and C5b. The ability to block C5 binding to C3 and C4 is thus a desirable property for an antibody to be used in treatment of complement mediated diseases in accordance with the present invention.

96 well microtiter plates were coated with 50µl/well, 10µg/ml of either purified human C3 or C4 (Quidel) for 1 hour at 37°C. The plates were then blocked with 200µl/well of TBS containing 1% BSA for 1 hour at room temperature. After three washes in TBS .1% BSA, purified human C5 (Quidel, 20µg/ml in TBS 1% BSA) was added to the plates in the presence (20µg/ml) or absence of a 5G1.1 Fab (derived from 5G1.1 by conventional papain digestion) and allowed to incubate for 1 hour at 37°C. After three washes in TBS/.1% BSA, a monoclonal antibody directed against the C5 beta chain (N19/8, 5µg/ml) was added to the wells to detect C5 bound to either C3 or C4. After three final washes in TBS/.1% BSA, the plate was developed using a horseradish peroxidase-conjugated secondary antibody and the appropriate substrate.

The results of these assays showed that the 5G1.1 mAb inhibited the binding of purified human C5 to either C3 or C4 by at least 60% to 90%. As used herein and in the claims,

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such a 60% to 90% reduction in C3 or C4 binding is a "substantial reduction" in C3 or C4 binding.

EXAMPLE 15

Construction and Functional Analysis of N19/8 Chimeric Fab

The heavy chain and light chain variable regions from the hybridoma N19-8 were cloned by PCR using the Ig-Prime System (Novagen) as described by the manufacturer. Clones from multiple independent PCR reactions were sequenced to detect mutations introduced during the PCR amplification. An N19-8 VL/human kappa constant region chimeric cDNA was created by using a plasmid containing the N19-8 light chain variable region and the plasmid pHuCK (Hieter et al., 1980 Cell, 22:197-207) as templates in an overlapping PCR reaction.

Similarly, an N19-8 VH/human IgG1 Fd chimeric cDNA was created using a plasmid containing the N19-8 heavy chain variable region and a plasmid containing the human IgG1 gene (obtained from Ilan R. Kirsch, National Cancer Institute, Bethesda, MD) as templates. This Fd construct contained the first nine amino acids of the IgG1 hinge region, including the cysteine residue which normally forms a disulfide bond with the terminal cysteine residue of the kappa light chain.

The resulting chimeric cDNAs were separately cloned into the APEX-1 vector using appropriate flanking restriction enzyme sites introduced during the PCR amplification procedure and sequenced. A fragment containing the promoter, intron, and cDNA insert from one of these APEX vectors was subsequently subcloned into the polylinker of the other to produce a single vector directing the expression of both the light chain and Fd. The tandem expression cassette from this APEX-1 vector was subsequently subcloned into APEX-3P, which was transfected into 293 EBNA cells for expression of the chimeric Fab.

When tested for the ability to block complement hemolytic activity and C5a generation, the chimeric N19/8 Fab retained the ability to block hemolytic activity, but lost 50% of its C5a generation blocking capacity.

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Throughout this application various publications and patent disclosures are referred to. The teachings and disclosures thereof, in their entireties, are hereby incorporated by reference into this application to more fully describe the state of the art to which the present invention pertains.

Although preferred and other embodiments of the invention have been described herein, further embodiments may be perceived by those skilled in the art without departing from the scope of the invention as defined by the following claims.

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TABLE 1

Prevention/Reduction of Proteinuria by Treatment With Anti-C5 Antibodies

	Before Treatment	After Treatment
	Urine Protein (mg/dL)	Urine Protein (mg/dL)
PBS Control		
mouse A	none	100
mouse B	none	500
mouse C	none	500
mouse D*	trace	trace
mouse E	100	100
Anti-C5 Treated		
mouse 1	none	none
mouse 2	none	30
mouse 3	30	trace
mouse 4	30	30
mouse 5	30	30
mouse 6	100	30

* Mouse D had more than 500mg/dL urine glucose after treatment

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SEQUENCE LISTING

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(A) MEDIUM TYPE: 3.5 inch, 1.4Mb storage
(B) COMPUTER: Macintosh Cetris 610
(C) OPERATING SYSTEM: System 7
(D) SOFTWARE: WordPerfect 3.0
(vi) CURRENT APPLICATION DATA:
(A) APPLICATION NUMBER:
(B) FILING DATE:
(C) CLASSIFICATION:

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Page 9079

(vii) PRIOR APPLICATION DATA:
(A) APPLICATION NUMBER: US 08/236,208
(B) FILING DATE: 02-MAY-1994

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(2) INFORMATION FOR SEQ ID NO:1:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 21 amino acids
(B) TYPE: Amino Acid
(C) STRANDEDNESS: Single
(D) TOPOLOGY: Linear
(A) DESCRIPTION: KSSKC peptide
(iii) HYPOTHETICAL: No
(iv) ANTI-SENSE: No

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:1:

Val Ile Asp His Gln Gly Thr Lys Ser Ser
5 10

Lys Cys Val Arg Gln Lys Val Glu Gly Ser Ser
15 20

(2) INFORMATION FOR SEQ ID NO:2:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 1658 Amino Acids
(B) TYPE: Amino Acid

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(C) STRANDEDNESS: Single
(D) TOPOLOGY: Linear
(A) DESCRIPTION: Pro-C5 Polytpeptide
(iii) HYPOTHETICAL: No
(iv) ANTIISENSE: No
(vi) ORIGINAL SOURCE:
(A) ORGANISM: Homo sapiens
(x) PUBLICATION INFORMATION:
(A) AUTHORS: Haviland, D.L.
Haviland, J.C.
Fleischer, D.T.
Hunt, A.
Wetsel, R.A.

(B) TITLE: Complete cDNA Sequence of Human Complement Pro-C5
(C) JOURNAL: Journal of Immunology
(D) VOLUME: 146
(F) PAGES: 362-368
(G) DATE: 1991

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:2:

```
                Met Gly Leu Leu Gly Ile Leu Cys Phe Leu
                           -15                 -10

Ile Phe Leu Gly Lys Thr Trp Gly Gln Glu Gln Thr Tyr Val
            -5              -1                   5

Ile Ser Ala Pro Lys Ile Phe Arg Val Gly Ala Ser Glu Asn
            10                  15                  20

Ile Val Ile Gln Val Tyr Gly Tyr Thr Glu Ala Phe Asp Ala
                25                  30

Thr Ile Ser Ile Lys Ser Tyr Pro Asp Lys Lys Phe Ser Tyr
```


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35 40 45

Ser Ser Gly His Val His Leu Ser Ser Glu Asn Lys Phe Gln
50 55 60

Asn Ser Ala Ile Leu Thr Ile Gln Pro Lys Gln Leu Pro Gly
65 70 75

Gly Gln Asn Pro Val Ser Tyr Val Tyr Leu Glu Val Val Ser
80 85 90

Lys His Phe Ser Lys Ser Lys Arg Met Pro Ile Thr Tyr Asp
95 100

Asn Gly Phe Leu Phe Ile His Thr Asp Lys Pro Val Tyr Thr
105 110 115

Pro Asp Gln Ser Val Lys Val Arg Val Tyr Ser Leu Asn Asp
120 125 130

Asp Leu Lys Pro Ala Lys Arg Glu Thr Val Leu Thr Phe Ile
135 140 145

Asp Pro Glu Gly Ser Glu Val Asp Met Val Glu Glu Ile Asp
150 155 160

His Ile Gly Ile Ile Ser Phe Pro Asp Phe Lys Ile Pro Ser
165 170

Asn Pro Arg Tyr Gly Met Trp Thr Ile Lys Ala Lys Tyr Lys
175 180 185

Glu Asp Phe Ser Thr Thr Gly Thr Ala Tyr Phe Glu Val Lys
190 195 200

Glu Tyr Val Leu Pro His Phe Ser Val Ser Ile Glu Pro Glu
205 210 215

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```
Tyr Asn Phe Ile Gly Tyr Lys Asn Phe Lys Asn Phe Glu Ile
            220                 225                 230

Thr Ile Lys Ala Arg Tyr Phe Tyr Asn Lys Val Val Thr Glu
                235                 240

Ala Asp Val Tyr Ile Thr Phe Gly Ile Arg Glu Asp Leu Lys
245                 250                 255

Asp Asp Gln Lys Glu Met Met Gln Thr Ala Met Gln Asn Thr
    260                 265                 270

Met Leu Ile Asn Gly Ile Ala Gln Val Thr Phe Asp Ser Glu
        275                 280                 285

Thr Ala Val Lys Glu Leu Ser Tyr Tyr Ser Leu Glu Asp Leu
            290                 295                 300

Asn Asn Lys Tyr Leu Tyr Ile Ala Val Thr Val Ile Glu Ser
                305                 310

Thr Gly Gly Phe Ser Glu Glu Ala Glu Ile Pro Gly Ile Lys
315                 320                 325

Tyr Val Leu Ser Pro Tyr Lys Leu Asn Leu Val Ala Thr Pro
    330                 335                 340

Leu Phe Leu Lys Pro Gly Ile Pro Tyr Pro Ile Lys Val Gln
        345                 350                 355

Val Lys Asp Ser Leu Asp Gln Leu Val Gly Gly Val Pro Val
            360                 365                 370

Ile Leu Asn Ala Gln Thr Ile Asp Val Asn Gln Glu Thr Ser
                375                 380

Asp Leu Asp Pro Ser Lys Ser Val Thr Arg Val Asp Asp Gly
385                 390                 395
```


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UTILITY PATENT APPLICATION TRANSMITTAL

(ONLY FOR NEW NONPROVISIONAL APPLICATIONS UNDER 37 CFR 1.53(B))

Attorney Docket No.	ALXN-P08-114
First Inventor	Leonard Bell
Title	TREATMENT OF PAROXYSMAL NOCTURNAL HEMOGLOBINURIA PATIENTS BY AN INHIBITOR OF COMPLEMENT
Express Mail Label No.	

APPLICATION ELEMENTS

See MPEP chapter 600 concerning utility patent application contents.

1. [X] **Fee Transmittal Form** (e.g., PTO/SB/17)
2. [ ] **Applicant claims small entity status.** See 37 CFR 1.27.
3. [X] **Specification** [*Total Pages* 56]
   Both the claims and abstract must start on a new page
   (For information on the preferred arrangement, see MPEP 608.01(a))
4. [X] **Drawing(s)** *(35 U.S.C. 113)* [*Total Sheets* 4]
5. **Oath or Declaration** [*Total Sheets* 4]
   a. [ ] Newly executed (original or copy)
   b. [X] A copy from a prior application (37 CFR 1.63(d)) *(for continuation/divisional with Box 18 completed)*
      i. [ ] DELETION OF INVENTOR(S)
      Signed statement attached deleting inventor(s) name in the prior application, see 37 CFR 1.63(d)(2) and 1.33(b).
6. [X] **Application Data Sheet**. See 37 CFR 1.76
7. [ ] **CD-ROM or CD-R** in duplicate, large table or Computer Program *(Appendix)*
   [ ] Landscape Table on CD
8. **Nucleotide and/or Amino Acid Sequence Submission** *(if applicable, items a. – c. are required)*
   a. [ ] Computer Readable Form (CRF)
   b. Specification Sequence Listing on:
      i. [ ] CD-ROM or CD-R (2 copies); or ii. [ ] Paper
   c. [ ] Statements verifying identity of above copies

ADDRESS TO: **Commissioner for Patents**
P.O. Box 1450
Alexandria, VA 22313-1450

ACCOMPANYING APPLICATION PARTS

9. [ ] **Assignment Papers** (cover sheet & document(s))
   Name of Assignee: Alexion Pharmaceuticals, Inc.
10. [ ] **37 CFR 3.73(b) Statement** *(when there is an assignee)* [ ] **Power of Attorney**
11. [ ] **English Translation Document** *(if applicable)*
12. [ ] **Information Disclosure Statement** (PTO/SB/08 or PTO-1449)
    [ ] Copies of citations attached
13. [X] **Preliminary Amendment**
14. [ ] **Return Receipt Postcard** (MPEP 503) *(Should be specifically itemized)*
15. [ ] **Certified Copy of Priority Document(s)** *(if foreign priority is claimed)*
16. [ ] **Nonpublication Request** under 35 U.S.C.122 (b)(2)(B)(i). Applicant must attach form PTO/SB/35 or equivalent.
17. [ ] Other:

18. If a CONTINUING APPLICATION, *check appropriate box, and supply the requisite information below and in the first sentence of the specification following the title, or in an Application Data Sheet under 37 CFR 1.76:*

[X] Continuation [ ] Divisional [ ] Continuation-in-part (CIP) of prior application No.: 12/225,040

Prior application information: Examiner J. L. Rogers *Art Unit:* 1644

19. CORRESPONDENCE ADDRESS

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Signature	/Jason S. Cathelyn/	Date	March 22, 2012
Name (Print/Type)	Jason S. Cathelyn, Ph.D.	Registration No. (Attorney/Agent)	68,195

29891335_1

Application Data Sheet

Application Information

Application Type::	Regular
Subject Matter::	Utility
Suggested Group Art Unit::	1644
CD-ROM or CD-R?::	None
Sequence submission?::	None
Computer Readable Form (CRF)?::	No
Title::	TREATMENT OF PAROXYSMAL NOCTURNAL HEMOGLOBINURIA PATIENTS BY AN INHIBITOR OF COMPLEMENT
Attorney Docket Number::	ALXN-P08-114
Request for Early Publication?::	No
Request for Non-Publication?::	No
Total Drawing Sheets::	4
Small Entity?::	No
Petition included?::	No
Secrecy Order in Parent Appl.?::	No

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Representative Information

Representative Customer Number:: 28120

Domestic Priority Information

Application::	Continuity Type::	Parent Application::	Parent Filing Date::
This Application	Continuation	12/225,040	05/13/09
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)	60/783,070	03/15/06

Foreign Priority Information

Assignee Information

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Postal or Zip Code of mailing address:: 06410

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DECLARATION FOR UTILITY OR DESIGN PATENT APPLICATION (37 CFR 1.63)		
☐ Declaration Submitted With Initial Filing OR ☒ Declaration Submitted after Initial Filing (surcharge (37 CFR 1.16 (f)) required)	Attorney Docket Number	ALXN-P04-114
	First Named Inventor	Leonard Bell
	COMPLETE IF KNOWN	
	Application Number	12/225,040
	Filing Date	September 12, 2008
	Art Unit	1645
	Examiner Name	Not Yet Assigned

I hereby declare that: (1) Each inventor's residence, mailing address, and citizenship are as stated below next to their name; and (2) I believe the inventor(s) named below to be the original and first inventor(s) of the subject matter which is claimed and for which a patent is sought on the invention entitled:

TREATMENT OF PAROXYSMAL NOCTURNAL HEMOGLOBINURIA PATIENTS BY AN INHIBITOR OF COMPLEMENT

(Title of the Invention)

the specification of which

☐ is attached hereto

OR

☒ was filed on (MM/DD/YYYY) 03/15/2007 as United States Application Number or PCT International Application Number PCT/US2007/006606 and filed as a national stage filing under 35 U.S.C. 371 and assigned Application No. 12/225,040

I hereby state that I have reviewed and understand the contents of the above identified specification, including the claims, as amended by any amendment specifically referred to above.

I acknowledge the duty to disclose information which is material to patentability as defined in 37 CFR 1.56, including for continuation-in-part applications, material information which became available between the filing date of the prior application and the national or PCT international filing date of the continuation-in-part application.

Authorization To Permit Access To Application by Participating Offices

☐ If checked, the undersigned hereby grants the USPTO authority to provide the European Patent Office (EPO), the Japan Patent Office (JPO), and any other intellectual property offices in which a foreign application claiming priority to the above-identified application is filed access to the above-identified patent application. See 37 CFR 1.14(c) and (h). This box should not be checked if the applicant does not wish the EPO, JPO, or other intellectual property office in which a foreign application claiming priority to the above-identified application is filed to have access to the application.

In accordance with 37 CFR 1.14(h)(3), access will be provided to a copy of the application-as-filed with respect to: 1) the above-identified application, 2) any foreign application to which the above-identified application claims priority under 35 USC 119(a)-(d) if a copy of the foreign application that satisfies the certified copy requirement of 37 CFR 1.55 has been filed in the above-identified US application, and 3) any U.S. application from which benefit is sought in the above-identified application.

In accordance with 37 CFR 1.14(c), access may be provided to information concerning the date of filing the Authorization to Permit Access to Application by Participating Offices.

DECLARATION — Utility or Design Patent Application

Claim of Foreign Priority Benefits

I hereby claim foreign priority benefits under 35 U.S.C. 119(a)-(d) or (f), or 365(b) of any foreign application(s) for patent, inventor's or plant breeder's rights certificate(s), or 365(a) of any PCT international application which designated at least one country other than the United States of America, listed below and have also identified below, by checking the box, any foreign application for patent, inventor's or plant breeder's rights certificate(s), or any PCT international application having a filing date before that of the application on which priority is claimed.

Prior Foreign Application Number(s)	Country	Foreign Filing Date (MM/DD/YYYY)	Priority Not Claimed	Certified Copy Attached? YES	NO
PCT/US2007/006606	PCT	03/15/2007	☐	☐	☒
			☐	☐	☐
			☐	☐	☐
			☐	☐	☐

☐ Additional foreign application numbers are listed on a supplemental priority data sheet PTO/SB/02B attached hereto.

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DECLARATION — Utility or Design Patent Application

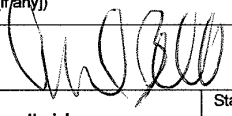
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I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements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

NAME OF SOLE OR FIRST INVENTOR:		[ ] A petition has been filed for this unsigned inventor	
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[X] Additional inventors or a legal representative are being named on the 1 supplemental sheet(s) PTO/SB/02A or 02LR attached hereto.

PTO/SB/02A (07-07)
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DECLARATION

ADDITIONAL INVENTOR(S)
Supplemental Sheet

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Docket No.: ALXN-P08-114
(PATENT)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of:
Bell et al.

Application No.: Not Yet Assigned

Confirmation No.: Not Yet Assigned

Filed: Concurrently Herewith

Art Unit: Not Yet Assigned

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

Examiner: Not Yet Assigned

FIRST PRELIMINARY AMENDMENT UNDER 37 C.F.R. 1.115

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

Dear Madam:

INTRODUCTORY COMMENTS

Prior to examination on the merits, please amend the above-identified U.S. patent application as set forth below.

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

Amendments to the Claims are reflected in the listing of claims which begins on page 3 of this paper.

Remarks begin on page 7 of this paper.

29890638_1

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AMENDMENTS TO THE SPECIFICATION

On Page 1, please insert the following paragraph immediately after the title:

RELATED APPLICATIONS

This application is a continuation of U.S. Application No. 12/225,040, filed May 13, 2009, which is a national stage filing under 35 U.S.C. 371 of International Application No. PCT/US2007/006606, filed March 15, 2007, which claims the benefit of U.S. Application No. 60/783,070, filed March 15, 2006. The specifications of each of the foregoing applications are incorporated herein by reference in their entirety.

AMENDMENTS TO THE CLAIMS

1-90. (Cancelled)

91. (New) 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 complement component C5 into fragments C5a and C5b.

92. (New) The method according to claim 91, wherein the anti-C5 antibody is a whole antibody or a C5-binding fragment thereof.

93. (New) The method according to claim 91, wherein the anti-C5 antibody is eculizumab.

94. (New) The method according to claim 92, wherein the C5-binding fragment is a Fab, a F(ab)', a $F(ab')_2$, an scFv, or a diabody.

95. (New) The method according to claim 91, wherein the anti-C5 antibody is pexelizumab.

96. (New) The method according to claim 91, wherein the antibody comprises an altered constant region that exhibits decreased effector function relative to the corresponding native constant region.

97. (New) The method according to claim 96, wherein the effector function is selected from the group consisting of antibody-dependent cell-mediated cytotoxicity (ADCC) and complement-dependent cytotoxicity (CDC).

98. (New) The method according to claim 91, wherein the anti-C5 antibody is administered to the patient for at least 6 months.

99. (New) The method according to claim 91, wherein the hemolytic disease is paroxysmal nocturnal hemoglobinuria (PNH).

100. (New) The method according to claim 99, wherein the patient has a hemoglobin level less than (i) 14 g/dL if a man or (ii) 12 g/dL if a woman.

101. (New) The method according to claim 99, wherein the patient has a hemoglobin level less than (i) 13 g/dL if a man or (ii) 11 g/dL if a woman.

102. (New) The method according to claim 99, wherein the patient has a hemoglobin level less than (i) 12 g/dL if a man or (ii) 10 g/dL if a woman.

103. (New) The method according to claim 99, wherein the patient suffers from hemolysis due to a C3b-mediated, extravascular clearance of PNH erythrocytes through the reticuloendothelial system.

104. (New) The method according to claim 99, 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.

105. (New) The method according to claim 99, wherein the patient is at least 18 years of age and has: (i) a PNH type III erythrocyte population of $\geq$ 10% and (ii) received at least four transfusions during the 12 months immediately preceding the first treatment with the anti-C5 antibody.

106. (New) The method according to claim 91, wherein the patient has aplastic anemia or myelodysplastic syndrome.

107. (New) The method according to claim 92, wherein the method comprises administering to the patient a pharmaceutical composition comprising a single unit dosage form of the whole anti-C5 antibody or C5-binding fragment thereof, and wherein the single unit dosage form comprises 300 mg of the whole anti-C5 antibody or C5-binding fragment thereof.

108. (New) The method according to claim 107, wherein the single unit dosage form has a volume of 30 mL.

109. (New) The method according to claim 107, wherein the single unit dosage form comprises a 10 mg/mL solution of the anti-C5 antibody or C5-binding fragment thereof.

110. (New) The method according to claim 107, wherein the single unit dosage form is a preservative free formulation.

111. (New) The method according to claim 91, wherein the anti-C5 antibody is to be administered to the patient under the following treatment schedule: (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 ± 2 days after (i), and (iii) 900 mg of the antibody every 14 ± 2 days thereafter, and wherein administration of the antibody to the patient occurs via 25 to 45 minute intravenous infusion.

112. (New) A method for treating a patient afflicted with a hemolytic disease, the method comprising:

vaccinating the patient against *Neisseria meningitides*; and

administering to the patient an effective amount of an anti-C5 antibody that inhibits cleavage of complement component C5 into fragments C5a and C5b.

113. (New) A method for treating a patient afflicted with a hemolytic disease, the method comprising administering to the patient an effective amount of an anti-C5 antibody that: (i) inhibits cleavage of complement component C5 into fragments C5a and C5b and (ii) comprises an altered constant region that exhibits decreased effector function relative to the corresponding native constant region.

114. (New) The method according to claim 113, wherein the effector function is selected from the group consisting of antibody-dependent cell-mediated cytotoxicity (ADCC) and complement-dependent cytotoxicity (CDC).

115. (New) A method for treating a patient afflicted with a hemolytic disease, the method comprising administering to the patient an anti-C5 antibody under the following treatment schedule: (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 ± 2 days after (i), and (iii) 900 mg of the antibody every 14 ± 2 days thereafter, wherein

administration of the antibody to the patient is to occur via 25 to 45 minute intravenous infusion, and wherein the antibody inhibits cleavage of complement component C5 into fragments C5a and C5b.

REMARKS

The Related Applications paragraph has been added to include a specific reference to the parent and other related priority applications.

Claims 1-90 have been cancelled. Claims 91-115 have been newly added. Support for new claims 91-115 can be found in the original claims and throughout the specification (PCT application publication no. WO 2007106585) as filed, e.g., at page 2, line 10 to page 3, line 30; page 4, line 19 to page 5, line 18; page 6, lines 17-25; page 27, lines 7-15; page 38, lines 20-30; and page 22, lines 13-17. No new matter has been introduced.

In view of the above amendments and remarks, Applicants believe the pending application is in condition for allowance.

The Examiner may address any questions raised by this submission to the undersigned at 617-951-7000. Applicant believes no fee is due with this response in addition to the fees provided for on the Fee Transmittal sheet. However, if a fee is due, please charge our Deposit Account No. 18-1945, under Order No. ALXN-P08-114 from which the undersigned is authorized to draw.

Dated: March 22, 2012

Respectfully submitted,

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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

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.

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		P Value
		< 4	>= 4	
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)

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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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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 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.

2. The method of claim 1 wherein said quality of life is measured by a FACIT-Fatigue score.

3. The method of claim 2 wherein the FACIT-Fatigue score increases by at least 3 points.

4. The method of claim 2 wherein the FACIT-Fatigue score increases by $\geq$ 4 points.

5. The method of claim 1 wherein said quality of life is measured by an EORTC QLQ-C30 score.

6. The method of claim 5 wherein said EORTC QLQ-C30 score improves by $\geq$ 10% of the pretreatment score.

7. The method of claim 5 wherein 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.

8. The method of claim 7 wherein said aspect of quality of life is fatigue.

9. The method of claim 1 wherein 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.

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10. The method of claim 1 wherein said compound is a steroid that suppresses complement.

11. The method of claim 1 wherein 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.

12. The method of claim 11 wherein said compound is an antibody or an active antibody fragment.

13. The method of claim 12 wherein 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.

14. The method of claim 12 wherein said antibody or active antibody fragment blocks C5 cleavage.

15. The method of claim 12 wherein said antibody or active antibody fragment inhibits the formation of C5b-9.

16. The method of claim 12 wherein said antibody is eculizumab.

17. The method of claim 12 wherein said antibody or active antibody fragment is administered for at least 6 months.

18. The method of claim 1 wherein said patient has aplastic anemia or myelodysplastic syndrome.

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19. The method of claim 1 wherein said patient is anemic

20. The method of claim 19 wherein said patient remains anemic following treatment.

21. The method of claim 19 wherein said patient has a hemoglobin level less than i) 14 g/dL if a man or ii) 12 g/dL if a woman.

22. The method of claim 19 wherein said patient has a hemoglobin level less than i) 13 g/dL if a man or ii) 11 g/dL if a woman.

23. The method of claim 19 wherein said patient has a hemoglobin level less than i) 12 g/dL if a man or ii) 10 g/dL if a woman.

24. 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 intravascular hemolysis.

25. The method of claim 24 wherein said method results in a greater than 30% reduction in LDH in said patient.

26. The method of claim 24 wherein said quality of life is measured by a FACIT-Fatigue score.

27. The method of claim 26 wherein the FACIT-Fatigue score increases by at least 3 points.

28. The method of claim 26 wherein the FACIT-Fatigue score increases by ≥ 4 points.

29. The method of claim 24 wherein said quality of life is measured by an EORTC QLQ-C30 score.

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30. The method of claim 29 wherein said EORTC QLQ-C30 score improves by ≥ 10% of the pretreatment score.

31. The method of claim 29 wherein said aspect of the quality of life 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.

32. The method of claim 31 wherein said aspect of quality of life is fatigue.

33. The method of claim 24 wherein 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.

34. The method of claim 24 wherein said compound is a steroid that suppresses complement.

35. The method of claim 24 wherein 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.

36. The method of claim 35 wherein said compound is an antibody or an active antibody fragment.

37. The method of claim 36 wherein 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.

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38. The method of claim 36 wherein said antibody or active antibody fragment blocks C5 cleavage.

39. The method of claim 36 wherein said antibody or active antibody fragment is administered for at least 6 months.

40. The method of claim 24 wherein said compound inhibits complement or inhibits the formation of C5b-9.

41. The method of claim 40 wherein said compound is an antibody or active antibody fragment.

42. The method of claim 41 wherein said antibody is eculizumab.

43. The method of claim 24 wherein said patient has aplastic anemia or myelodysplastic syndrome.

44. 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.

45. The method of claim 44 wherein said method results in a greater than 30% reduction in LDH in said patient.

46. The method of claim 44 wherein said patient has a hemoglobin level less than i) 14 g/dL if a man or ii) 12 g/dL if a woman.

47. The method of claim 44 wherein said patient has a hemoglobin level less than i) 13 g/dL if a man or ii) 11 g/dL if a woman.

48. The method of claim 44 wherein said patient has a hemoglobin level less than i) 12 g/dL if a man or ii) 10 g/dL if a woman.

49. The method of claim 44 wherein said patient suffers from paroxysmal nocturnal hemoglobinuria.

50. The method of claim 44 wherein said quality of life is measured by a FACIT-Fatigue score.

51. The method of claim 50 wherein the FACIT-Fatigue score increases by at least 3 points.

52. The method of claim 50 wherein the FACIT-Fatigue score increases by $\geq$ 4 points.

53. The method of claim 44 wherein said quality of life is measured by an EORTC QLQ-C30 score.

54. The method of claim 53 wherein said EORTC QLQ-C30 score improves by $\geq$ 10% of the pretreatment score.

55. The method of claim 53 wherein said aspect of the quality of life 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.

56. The method of claim 55 wherein said aspect of quality of life is fatigue.

57. The method of claim 44 wherein 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.

58. The method of claim 44 wherein said compound is a steroid that suppresses complement.

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59. The method of claim 44 wherein 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.

60. The method of claim 59 wherein said compound is an antibody or an active antibody fragment.

61. The method of claim 60 wherein 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.

62. The method of claim 60 wherein said antibody or active antibody fragment blocks C5 cleavage.

63. The method of claim 60 wherein said antibody or active antibody fragment is administered for at least 6 months.

64. The method of claim 44 wherein said compound inhibits complement or inhibits the formation of C5b-9.

65. The method of claim 64 wherein said compound is an antibody or an active antibody fragment.

66. The method of claim 65 wherein said antibody is eculizumab.

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67. The method of claim 44 wherein said patient has aplastic anemia or myelodysplastic syndrome.

68. 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.

69. The method of claim 68 wherein said patient is anemic.

70. The method of claim 69 wherein said patient remains anemic following treatment.

71. The method of claim 68 wherein said patient has a hemoglobin level less than i) 14 g/dL if a man or ii) 12 g/dL if a woman.

72. The method of claim 68 wherein said patient has a hemoglobin level less than i) 13 g/dL if a man or ii) 11 g/dL if a woman.

73. The method of claim 68 wherein said patient has a hemoglobin level less than i) 12 g/dL if a man or ii) 10 g/dL if a woman.

74. The method of claim 68 wherein said patient suffers from paroxysmal nocturnal hemoglobinuria.

75. The method of claim 68 wherein 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.

76. The method of claim 75 wherein the health-adjusted life expectancy in a subject is prolonged by at least one day.

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77. The method of claim 75 wherein the health-adjusted life expectancy in a subject is prolonged by at least week.

78. The method of claim 75 wherein the health-adjusted life expectancy in a subject is prolonged by at least one month.

79. The method of claim 75 wherein the health-adjusted life expectancy in a subject is prolonged by at least one year.

80. The method of claim 68 wherein 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.

81. The method of claim 68 wherein said compound is a steroid that suppresses complement.

82. The method of claim 68 wherein 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.

83. The method of claim 82 wherein said compound is an antibody or an active antibody fragment.

84. The method of claim 83 wherein 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.

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85. The method of claim 83 wherein said antibody or active antibody fragment blocks C5 cleavage.

86. The method of claim 83 wherein said antibody or active antibody fragment is administered for at least 6 months.

87. The method of claim 68 wherein said compound inhibits complement or inhibits the formation of C5b-9.

88. The method of claim 87 wherein said compound is an antibody or an active antibody fragment.

89. The method of claim 88 wherein said antibody is eculizumab.

90. The method of claim 68 wherein said patient has aplastic anemia or myelodysplastic syndrome.

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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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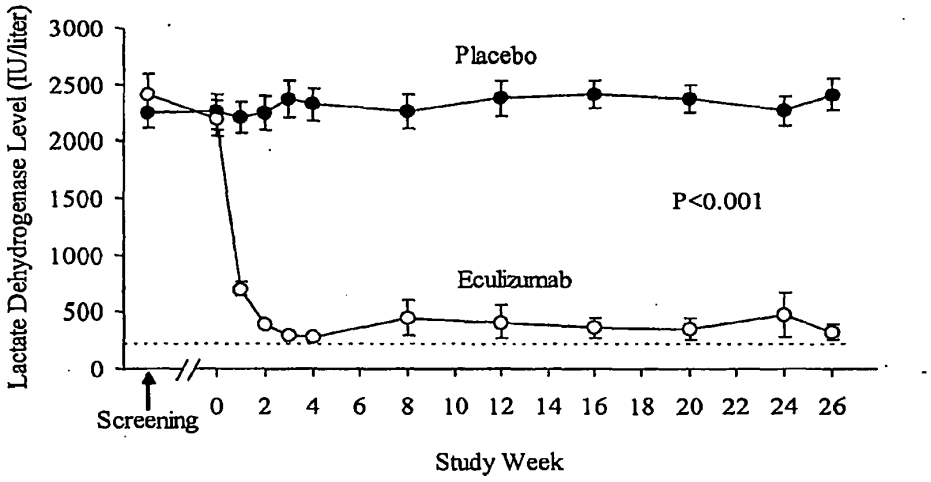


FIGURE 1A

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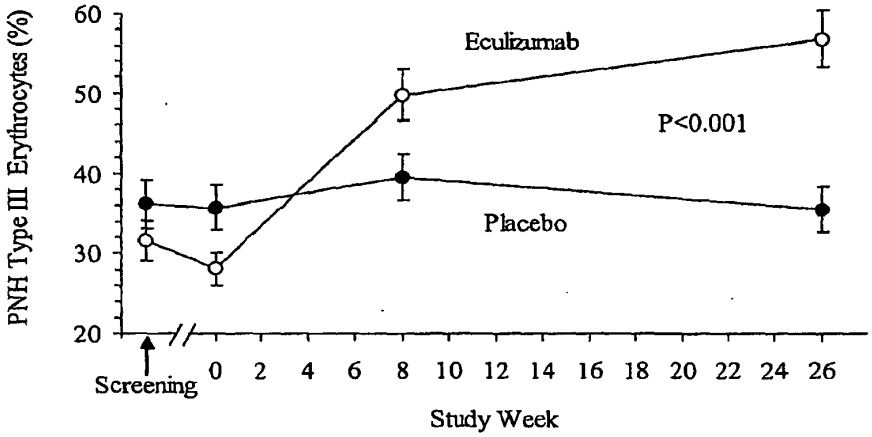


FIGURE 1B

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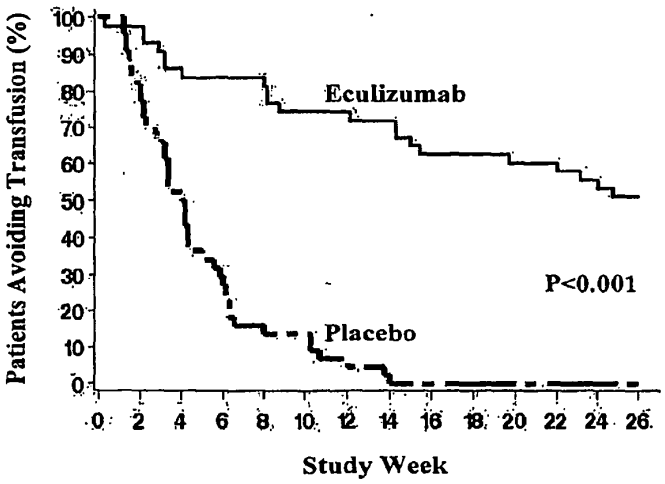


FIGURE 2

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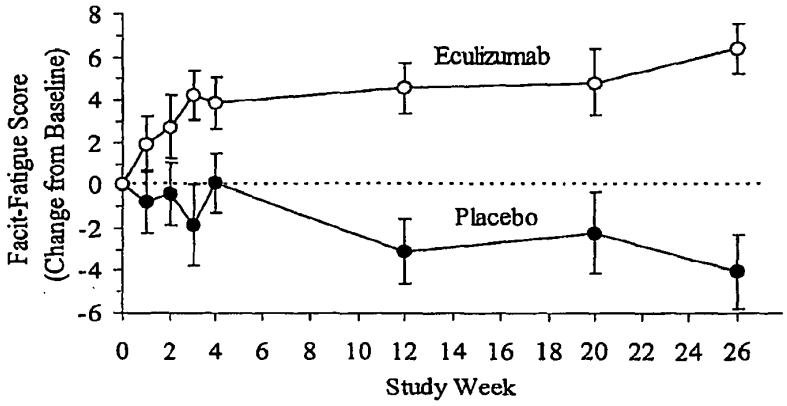


FIGURE 3

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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:	Jason S. Cathelyn/ginny blundell
Attorney Docket Number:	ALXN-P08-114
Filed as Large Entity	

Utility under 35 USC 111(a) Filing Fees

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Basic Filing:				
Utility application filing	1011	1	380	380
Utility Search Fee	1111	1	620	620
Utility Examination Fee	1311	1	250	250
Pages:				
Claims:				
Claims in excess of 20	1202	5	60	300
Independent claims in excess of 3	1201	1	250	250
Miscellaneous-Filing:				

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Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Petition:				
Patent-Appeals-and-Interference:				
Post-Allowance-and-Post-Issuance:				
Extension-of-Time:				
Miscellaneous:				
		Total in USD ($)		**1800**

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Electronic Acknowledgement Receipt	
EFS ID:	12364887
Application Number:	13426973
International Application Number:	
Confirmation Number:	8851
Title of Invention:	TREATMENT OF PAROXYSMAL NOCTURNAL HEMOGLOBINURIA PATIENTS BY AN INHIBITOR OF COMPLEMENT
First Named Inventor/Applicant Name:	Leonard Bell
Customer Number:	28120
Filer:	Jason S. Cathelyn/ginny blundell
Filer Authorized By:	Jason S. Cathelyn
Attorney Docket Number:	ALXN-P08-114
Receipt Date:	22-MAR-2012
Filing Date:	
Time Stamp:	13:46:45
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	yes
Payment Type	Deposit Account
Payment was successfully received in RAM	$1800
RAM confirmation Number	71
Deposit Account	181945
Authorized User	

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)

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1	Transmittal of New Application	ALXN-P08-114_transmittal.pdf	108881 1bf6187fe1b392da2eb0f62d9871f7982de73a93	no	1
Warnings:					
Information:					
2	Application Data Sheet	ALXN-P08-114_ADS.pdf	57548 609d0748d1f270fc5dc99e8f6950779c6f314c93	no	3
Warnings:					
Information:					
This is not an USPTO supplied ADS fillable form					
3	Oath or Declaration filed	ALXN-P08-114_Declaration.pdf	435859 22edceb614517b3e678c1286c14dba9e2f02dab1	no	4
Warnings:					
Information:					
4		ALXN-P08-114_amendment.pdf	114206 24cf30bd40a79ca462995027ee0308ecf8f6a3ab	yes	7

	Multipart Description/PDF files in .zip description		
	Document Description	**Start**	**End**
	Preliminary Amendment	1	1
	Specification	2	2
	Claims	3	6
	Applicant Arguments/Remarks Made in an Amendment	7	7

Warnings:					
Information:					
5		ALXN-P08-114_application.pdf	15127994 ecec8962c16bfcd484c8da651fab1312740e31d3	yes	56

	Multipart Description/PDF files in .zip description		
	Document Description	**Start**	**End**
	Specification	1	40
	Claims	41	55
	Abstract	56	56

Warnings:					

Samsung Bioepis Exhibit No. 1002
Page 9162

Information:					
6	Drawings-only black and white line drawings	ALXN-P08-114_figures.pdf	139143 0faee64ce43f2ceb78ca740067e0e438512e0299	no	4
Warnings:					
Information:					
7	Fee Worksheet (SB06)	fee-info.pdf	38092 7214787c32c2a2712419196df9c2d7f114c94c09	no	2
Warnings:					
Information:					
			Total Files Size (in bytes):	16021723	

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

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

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

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

Samsung Bioepis Exhibit No. 1002
Page 9163

PTO/SB/06 (07-06)
Approved for use through 1/31/2007. OMB 0651-0032
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number.

PATENT APPLICATION FEE DETERMINATION RECORD Substitute for Form PTO-875	Application or Docket Number 13/426,973	Filing Date 03/22/2012	☐ To be Mailed

APPLICATION AS FILED – PART I

	(Column 1)	(Column 2)	SMALL ENTITY ☐		OR	OTHER THAN SMALL ENTITY	
FOR	NUMBER FILED	NUMBER EXTRA	RATE ($)	FEE ($)		RATE ($)	FEE ($)
☐ BASIC FEE (37 CFR 1.16(a), (b), or (c))	N/A	N/A	N/A			N/A	
☐ SEARCH FEE (37 CFR 1.16(k), (i), or (m))	N/A	N/A	N/A			N/A	
☐ EXAMINATION FEE (37 CFR 1.16(o), (p), or (q))	N/A	N/A	N/A			N/A	
TOTAL CLAIMS (37 CFR 1.16(i))	minus 20 =	*	X $ =		OR	X $ =	
INDEPENDENT CLAIMS (37 CFR 1.16(h))	minus 3 =	*	X $ =			X $ =	
☐ APPLICATION SIZE FEE (37 CFR 1.16(s))	If the specification and drawings exceed 100 sheets of paper, the application size fee due is $250 ($125 for small entity) for each additional 50 sheets or fraction thereof. See 35 U.S.C. 41(a)(1)(G) and 37 CFR 1.16(s).						
☐ MULTIPLE DEPENDENT CLAIM PRESENT (37 CFR 1.16(j))							
* If the difference in column 1 is less than zero, enter "0" in column 2.			TOTAL			TOTAL	

APPLICATION AS AMENDED – PART II

		(Column 1)		(Column 2)	(Column 3)	SMALL ENTITY		OR	OTHER THAN SMALL ENTITY	
	03/22/2012	CLAIMS REMAINING AFTER AMENDMENT		HIGHEST NUMBER PREVIOUSLY PAID FOR	PRESENT EXTRA	RATE ($)	ADDITIONAL FEE ($)		RATE ($)	ADDITIONAL FEE ($)
AMENDMENT	Total (37 CFR 1.16(i))	* 25	Minus	** 25	= 0	X $ =		OR	X $60=	0
	Independent (37 CFR 1.16(h))	* 4	Minus	***4	= 0	X $ =		OR	X $250=	0
	☐ 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	0

		(Column 1)		(Column 2)	(Column 3)					
		CLAIMS REMAINING AFTER AMENDMENT		HIGHEST NUMBER PREVIOUSLY PAID FOR	PRESENT EXTRA	RATE ($)	ADDITIONAL FEE ($)		RATE ($)	ADDITIONAL FEE ($)
AMENDMENT	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 number found in the appropriate box in column 1.

Legal Instrument Examiner:
/CHERRI FITZGERALD/

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

If you need assistance in completing the form, call 1-800-PTO-9199 and select option 2.

Samsung Bioepis Exhibit No. 1002
Page 9164

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NUMBER	FILING OR 371(C) DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO./TITLE
13/426,973	03/22/2012	Leonard Bell	ALXN-P08-114

CONFIRMATION NO. 8851

28120
ROPES & GRAY LLP
IPRM - Floor 43
PRUDENTIAL TOWER
800 BOYLSTON STREET
BOSTON, MA 02199-3600

FORMALITIES LETTER

OC000000053488810

Date Mailed: 04/04/2012

NOTICE TO FILE CORRECTED APPLICATION PAPERS

Filing Date Granted

An application number and filing date have been accorded to this application. The application is informal since it does not comply with the regulations for the reason(s) indicated below. Applicant is given TWO MONTHS from the date of this Notice within which to correct the informalities indicated below. Extensions of time may be obtained by filing a petition accompanied by the extension fee under the provisions of 37 CFR 1.136(a).

The required item(s) identified below must be timely submitted to avoid abandonment:

- Replacement drawings in compliance with 37 CFR 1.84 and 37 CFR 1.121(d) are required. The drawings submitted are not acceptable because:
  - The drawings must be reasonably free from erasures and must be free from alterations, overwriting, interlineations, folds, and copy marks. See Figure(s) 2.
- This application does not contain, as a separate part of the disclosure on paper copy, a "Sequence Listing" as required by 37 CFR 1.821(c) Applicant must provide an initial paper or compact disc copy of the "Sequence Listing", **as well as an amendment specifically directing its entry into the application** and a statement that the content of the sequence listing information recorded in computer readable form is identical to the written (on paper or compact disc) sequence listing and, where applicable, includes no new matter, as required by 37 CFR 1.821(e), 1.821(f), 1.821(g), 1.825(b), or 1.825(d). If the effective filing date is on or after September 8, 2000, see the final rulemaking notice published in the Federal Register at 65 FR 54604 (September 8, 2000) and 1238 OG 145 (September 19, 2000).
- A copy of the "Sequence Listing" in computer readable form has not been submitted as required by 37 CFR 1.821(e). If the effective filing date is on or after September 8, 2000, see the final rulemaking notice published in the Federal Register at 65 FR 54604 (September 8, 2000) and 1238 OG 145 (September 19, 2000). Applicant must provide an initial computer readable form (CRF) copy of the "Sequence Listing" and a statement that the content of the sequence listing information recorded in computer readable form is identical to the written (on paper or compact disc) sequence listing and, where applicable, includes no new matter, as required by 37 CFR 1.821(e), 1.821(f), 1.821(g), 1.825(b), or 1.825(d). If applicant desires the sequence listing in the instant application to be identical with that of another application on file in the U.S. Patent and Trademark Office, such request in accordance with 37 CFR 1.821(e) may be submitted in lieu of a new CRF.

To Download Patentin Software, visit http://www.uspto.gov/web/patents/software.htm
For questions regarding compliance to these requirements, please contact:

- **For Rules Interpretation, call (571) 272-0623**
- **For Patentin Software Program Help, call Patent EBC at 1-866-217-9197 between the hours of 6 a.m. and 12 midnight, Monday through Friday, EST.**

• **Send e-mail correspondence for Patentin Software Program Help to ebc@uspto.gov**

Applicant is cautioned that correction of the above items may cause the specification and drawings page count to exceed 100 pages. If the specification and drawings exceed 100 pages, applicant will need to submit the required application size fee.

Replies should be mailed to:

Mail Stop Missing Parts
Commissioner for Patents
P.O. Box 1450
Alexandria VA 22313-1450

Registered users of EFS-Web may alternatively submit their reply to this notice via EFS-Web.
https://sportal.uspto.gov/authenticate/AuthenticateUserLocalEPF.html

For more information about EFS-Web please call the USPTO Electronic Business Center at **1-866-217-9197** or visit our website at http://www.uspto.gov/ebc.

If you are not using EFS-Web to submit your reply, you must include a copy of this notice.

/afessehaye/

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

PATENT APPLICATION FEE DETERMINATION RECORD

Substitute for Form PTO-875

Application or Docket Number: 13/426,973

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	380
SEARCH FEE (37 CFR 1.16(k), (i), or (m))	N/A	N/A	N/A			N/A	620
EXAMINATION FEE (37 CFR 1.16(o), (p), or (q))	N/A	N/A	N/A			N/A	250
TOTAL CLAIMS (37 CFR 1.16(i))	25 minus 20 =	* 5			OR	x 60 =	300
INDEPENDENT CLAIMS (37 CFR 1.16(h))	4 minus 3 =	* 1				x 250 =	250
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	1800

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.

Samsung Bioepis Exhibit No. 1002
Page 9167

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
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Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NUMBER	FILING or 371(c) DATE	GRP ART UNIT	FIL FEE REC'D	ATTY.DOCKET.NO	TOT CLAIMS	IND CLAIMS
13/426,973	03/22/2012	1629	1800	ALXN-P08-114	25	4

CONFIRMATION NO. 8851

28120
ROPES & GRAY LLP
IPRM - Floor 43
PRUDENTIAL TOWER
800 BOYLSTON STREET
BOSTON, MA 02199-3600

FILING RECEIPT

OC000000053488809

Date Mailed: 04/04/2012

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**

Applicant(s)

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

Assignment For Published Patent Application

Alexion Pharmaceuticals, Inc., Cheshire, CT

Power of Attorney: None

Domestic Priority data as claimed by applicant

This application is a CON of 12/225,040 05/13/2009
which is a 371 of PCT/US2007/006606 03/15/2007
which claims benefit of 60/783,070 03/15/2006

Foreign Applications (You may be eligible to benefit from the **Patent Prosecution Highway** program at the USPTO. Please see http://www.uspto.gov for more information.)

If Required, Foreign Filing License Granted: 04/02/2012

The country code and number of your priority application, to be used for filing abroad under the Paris Convention, is **US 13/426,973**

Projected Publication Date: To Be Determined - pending completion of Corrected Papers

Non-Publication Request: No

Early Publication Request: No

Title

TREATMENT OF PAROXYSMAL NOCTURNAL HEMOGLOBINURIA PATIENTS BY AN INHIBITOR OF COMPLEMENT

Preliminary Class

514

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 (1-866-999-4158).

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Title 35, United States Code, Section 184

Title 37, Code of Federal Regulations, 5.11 & 5.15

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This license is to be retained by the licensee and may be used at any time on or after the effective date thereof unless it is revoked. This license is automatically transferred to any related applications(s) filed under 37 CFR 1.53(d). This license is not retroactive.

The grant of a license does not in any way lessen the responsibility of a licensee for the security of the subject matter as imposed by any Government contract or the provisions of existing laws relating to espionage and the national security or the export of technical data. Licensees should apprise themselves of current regulations especially with respect to certain countries, of other agencies, particularly the Office of Defense Trade Controls, Department of State (with respect to Arms, Munitions and Implements of War (22 CFR 121-128)); the Bureau of Industry and Security, Department of Commerce (15 CFR parts 730-774); the Office of Foreign AssetsControl, Department of Treasury (31 CFR Parts 500+) and the Department of Energy.

NOT GRANTED

No license under 35 U.S.C. 184 has been granted at this time, if the phrase "IF REQUIRED, FOREIGN FILING LICENSE GRANTED" DOES NOT appear on this form. Applicant may still petition for a license under 37 CFR 5.12, if a license is desired before the expiration of 6 months from the filing date of the application. If 6 months has lapsed from the filing date of this application and the licensee has not received any indication of a secrecy order under 35 U.S.C. 181, the licensee may foreign file the application pursuant to 37 CFR 5.15(b).

SelectUSA

The United States represents the largest, most dynamic marketplace in the world and is an unparalleled location for business investment, innovation and commercialization of new technologies. The USA offers tremendous resources and advantages for those who invest and manufacture goods here. Through SelectUSA, our nation works to encourage, facilitate, and accelerate business investment. To learn more about why the USA is the best country in the world to develop technology, manufacture products, and grow your business, visit SelectUSA.gov.

Docket No.: ALXN-P08-114
(PATENT)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of:
Bell et al.

Application No.: 13/426,973

Filed: March 22, 2012

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

Confirmation No.: 8851

Art Unit: 1629

Examiner: Not Yet Assigned

RESPONSE TO NOTICE TO FILE CORRECTED APPLICATION PAPERS

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

Dear Madam:

In response to the Notice to File Corrected Application Papers mailed April 4, 2012, Applicants respectfully submit a replacement drawing (1 figure, 1 sheet; specifically Figure 2), a computer readable copy of the Sequence Listing (ASCII text file), and a Second Preliminary Amendment.

As required by 37 CFR § 1.821(g), Applicants state that the submission includes no new matter. Please enter the sequence listing as part of the application.

30722506_1

Samsung Bioepis Exhibit No. 1002
Page 9171

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. 18-1945, under Order No. ALXN-P08-114.

Dated: May 30, 2012

Respectfully submitted,

By_/Jason S. Cathelyn/__
Jason S. Cathelyn, Ph.D.
Registration No.: 68,195
ROPES & GRAY LLP
Prudential Tower
800 Boylston Street
Boston, Massachusetts 02199
(617) 951-7000
(617) 235-9492 (Fax)
Attorneys/Agents For Applicant

Docket No.: ALXN-P08-114
(PATENT)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of:
Bell et al.

Application No.: 13/426,973 | Confirmation No.: 8851

Filed: March 22, 2012 | Art Unit: 1629

For: TREATMENT OF PAROXYSMAL NOCTURNAL HEMOGLOBINURIA PATIENTS BY AN INHIBITOR OF COMPLEMENT | Examiner: Not Yet Assigned

SECOND PRELIMINARY AMENDMENT UNDER 37 C.F.R. 1.115

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

Dear Madam:

INTRODUCTORY COMMENTS

Prior to examination on the merits, please amend the above-identified U.S. patent application as set forth below.

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

Remarks begin on page 3 of this paper.

30722630_1

Samsung Bioepis Exhibit No. 1002
Page 9173

AMENDMENTS TO THE SPECIFICATION

Please insert the paragraph below on page 1, after the "Related Applications" paragraph (as amended via the First Preliminary Amendment filed with the application on March 22, 2012).

SEQUENCE LISTING

The instant application contains a Sequence Listing which has been submitted via EFS-Web and is hereby incorporated by reference in its entirety. Said ASCII copy, created on May 30, 2012, is named ALXN-P08-114Seq.txt, and is 10,437 bytes in size.

REMARKS

The specification has been amended to incorporate by reference the Sequence Listing filed concurrently herewith. No new matter has been introduced.

Applicants believe no fee is due with this response. However, if a fee is due, please charge our Deposit Account No. 18-1945, under Order No. ALXN-P08-114 from which the undersigned is authorized to draw.

Dated: May 30, 2012

Respectfully submitted,

By_/Jason S. Cathelyn/____
Jason S. Cathelyn, Ph.D.
Registration No.: 68,195
ROPES & GRAY LLP
Prudential Tower
800 Boylston Street
Boston, Massachusetts 02199
(617) 951-7000
(617) 235-9492 (Fax)
Attorneys/Agents For Applicant

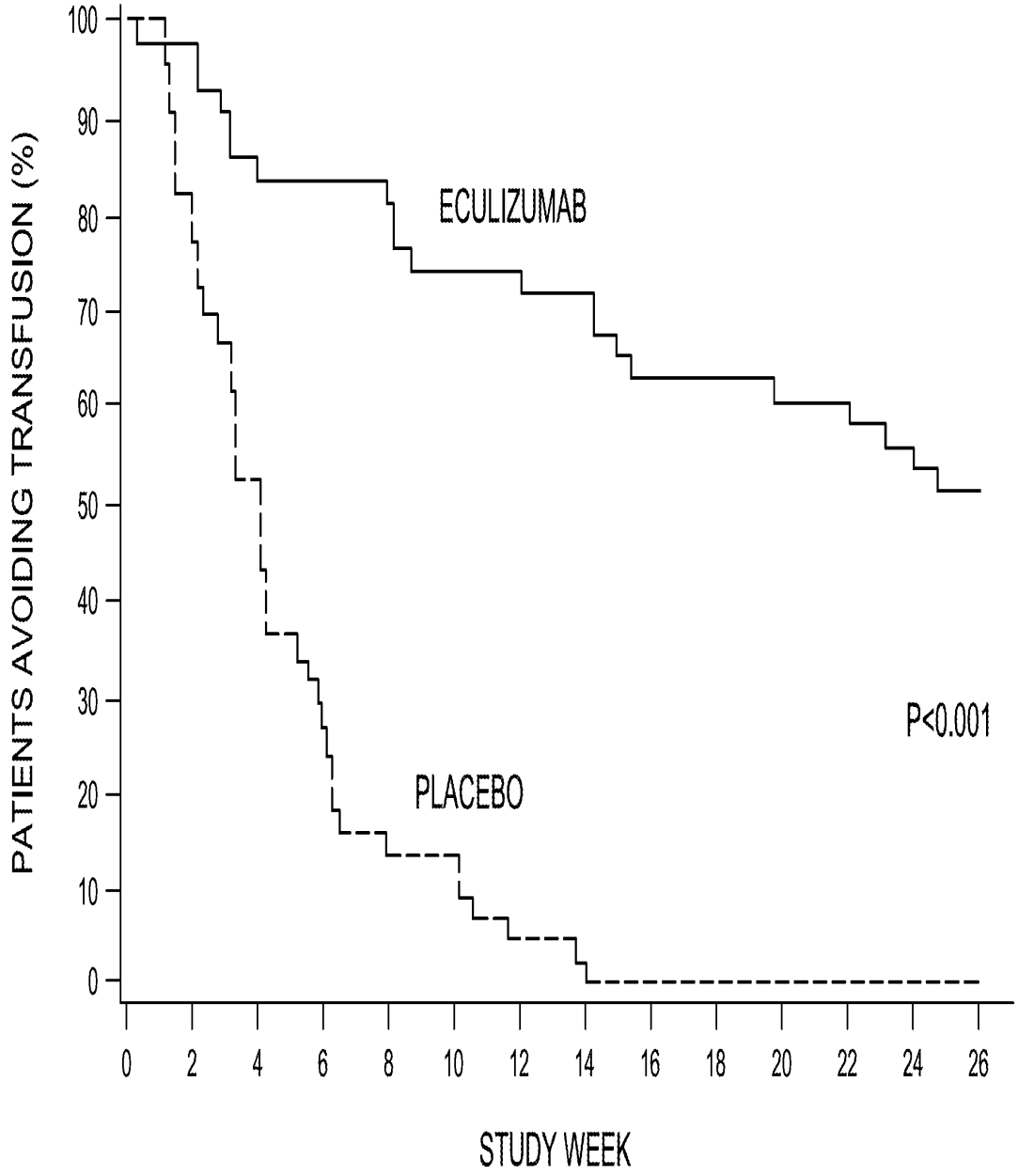


FIGURE 2

Replacement Sheet 3/4

Electronic Acknowledgement Receipt	
EFS ID:	12890650
Application Number:	13426973
International Application Number:	
Confirmation Number:	8851
Title of Invention:	TREATMENT OF PAROXYSMAL NOCTURNAL HEMOGLOBINURIA PATIENTS BY AN INHIBITOR OF COMPLEMENT
First Named Inventor/Applicant Name:	Leonard Bell
Customer Number:	28120
Filer:	Jason S. Cathelyn/ginny blundell
Filer Authorized By:	Jason S. Cathelyn
Attorney Docket Number:	ALXN-P08-114
Receipt Date:	30-MAY-2012
Filing Date:	22-MAR-2012
Time Stamp:	15:52:02
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	Applicant Response to Pre-Exam Formalities Notice	ALXN-P08-114_reply.pdf	68295 abaf88a0f94a5c232a57330ed475ef60a62ba01d	no	2

Warnings:
Information:

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Page 9177

2		ALXN-P08-114_amendment.pdf	96518 086931fc9c1cf6b99ae1eb95a8ee4b349dbfda4f	yes	3
	Multipart Description/PDF files in .zip description				
	Document Description		**Start**	**End**	
	Preliminary Amendment		1	1	
	Specification		2	2	
	Applicant Arguments/Remarks Made in an Amendment		3	3	
Warnings:					
Information:					
3	Sequence Listing (Text File)	ALXN-P08-114Seq.TXT	10437	no	0
Warnings:					
Information:					
4	Drawings-only black and white line drawings	ALXN-P08-114_replacement_figure.pdf	118694 0c3bbc548249abee4d4f28ba5899fc1ef6a648c5	no	1
Warnings:					
Information:					
		Total Files Size (in bytes):	293944		

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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DocCode – SCORE

SCORE Placeholder Sheet for IFW Content

Application Number: 13426973 Document Date: 05/30/2012

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

- Design Drawing

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

To access the documents in the SCORE database, refer to instructions developed by SIRA.

At the time of document entry (noted above):

- Examiners may access SCORE content via the eDAN interface.
- Other USPTO employees can bookmark the current SCORE URL (http://es/ScoreAccessWeb/).
- External customers may access SCORE content via the Public and Private PAIR interfaces.

Form Revision Date: February 8, 2006

DocCode – SEQ.TXT

SCORE Placeholder Sheet for IFW Content

Application Number: 13426973 Document Date: 05/30/2012

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

- Sequence Listing

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

To access the documents in the SCORE database, refer to instructions developed by SIRA.

At the time of document entry (noted above):

- Examiners may access SCORE content via the eDAN interface.
- Other USPTO employees can bookmark the current SCORE URL (http://es/ScoreAccessWeb/).
- External customers may access SCORE content via the Public and Private PAIR interfaces.

Form Revision Date: February 8, 2006

PTO/SB/06 (07-06)
Approved for use through 1/31/2007. OMB 0651-0032
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
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PATENT APPLICATION FEE DETERMINATION RECORD
Substitute for Form PTO-875

Application or Docket Number	Filing Date	☐ To be Mailed
13/426,973	03/22/2012	

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	
☐ SEARCH FEE (37 CFR 1.16(k), (i), or (m))	N/A	N/A	N/A			N/A	
☐ EXAMINATION FEE (37 CFR 1.16(o), (p), or (q))	N/A	N/A	N/A			N/A	
TOTAL CLAIMS (37 CFR 1.16(i))	minus 20 =	*	X $ =		OR	X $ =	
INDEPENDENT CLAIMS (37 CFR 1.16(h))	minus 3 =	*	X $ =			X $ =	
☐ APPLICATION SIZE FEE (37 CFR 1.16(s))	If the specification and drawings exceed 100 sheets of paper, the application size fee due is $250 ($125 for small entity) for each additional 50 sheets or fraction thereof. See 35 U.S.C. 41(a)(1)(G) and 37 CFR 1.16(s).						
☐ MULTIPLE DEPENDENT CLAIM PRESENT (37 CFR 1.16(j))							
* If the difference in column 1 is less than zero, enter "0" in column 2.			TOTAL			TOTAL	

APPLICATION AS AMENDED – PART II

AMENDMENT 05/30/2012	(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	SMALL ENTITY RATE ($)	SMALL ENTITY ADDITIONAL FEE ($)	OR	OTHER THAN SMALL ENTITY RATE ($)	OTHER THAN SMALL ENTITY ADDITIONAL FEE ($)
Total (37 CFR 1.16(i))	* 25	Minus	** 25	= 0	X $ =		OR	X $60=	0
Independent (37 CFR 1.16(h))	* 4	Minus	***4	= 0	X $ =		OR	X $250=	0
☐ 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	0

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

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

Legal Instrument Examiner:
/CHERRI FITZGERALD/

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

If you need assistance in completing the form, call 1-800-PTO-9199 and select option 2.

Samsung Bioepis Exhibit No. 1002
Page 9181

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Sequence Listing was accepted.
If you need help call the Patent Electronic Business Center at (866)
217-9197 (toll free).
Reviewer: Anne Corrigan
Timestamp: [year=2012; month=6; day=6; hr=7; min=49; sec=26; ms=454; ]
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Samsung Bioepis Exhibit No. 1002
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Validated By CRFValidator v 1.0.3

Application No: 13426973 Version No: 1.0

Input Set:

Output Set:

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Finished: 2012-05-30 15:52:41.644
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Total Warnings: 10
Total Errors: 0
No. of SeqIDs Defined: 10
Actual SeqID Count: 10

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Page 9183

SEQUENCE LISTING

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ROTHER, RUSSELL P.

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BY AN INHIBITOR OF COMPLEMENT

<130> ALXN-P08-114

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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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            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
    130                 135                 140
```


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```
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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            20                  25                  30

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        35                  40                  45

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

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

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

Ile Ser Ser Leu Gln Pro Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Asn
            100                 105                 110
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Val Leu Asn Thr Pro Leu Thr Phe Gly Gln Gly Thr Lys Val Glu Ile
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            20                  25                  30


Leu Ser Ala Ser Val Gly Asp Arg Val Thr Ile Thr Cys Gly Ala Ser
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Glu Asn Ile Tyr Gly Ala Leu Asn Trp Tyr Gln Gln Lys Pro Gly Lys
    50                  55                  60


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


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


Ile Ser Ser Leu Gln Pro Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Asn
            100                 105                 110


Val Leu Asn Thr Pro Leu Thr Phe Gly Gln Gly Thr Lys Val Glu Ile
        115                 120                 125


Lys Arg Thr Val Ala Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp
    130                 135                 140


Glu Gln Leu Lys Ser Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn
145                 150                 155                 160
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Phe Tyr Pro Arg Glu Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu
165 170 175

Gln Ser Gly Asn Ser Gln Glu Ser Val Thr Glu Gln Asp Ser Lys Asp
180 185 190

Ser Thr Tyr Ser Leu Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr
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Glu Lys His Lys Val Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser
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Page 9189

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1 5

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Page 9190

PATENT APPLICATION FEE DETERMINATION RECORD

Substitute for Form PTO-875

Application or Docket Number: 13/426,973

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	380
SEARCH FEE (37 CFR 1.16(k), (i), or (m))	N/A	N/A	N/A			N/A	620
EXAMINATION FEE (37 CFR 1.16(o), (p), or (q))	N/A	N/A	N/A			N/A	250
TOTAL CLAIMS (37 CFR 1.16(i))	25 minus 20 =	* 5			OR	x 60 =	300
INDEPENDENT CLAIMS (37 CFR 1.16(h))	4 minus 3 =	* 1				x 250 =	250
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	1800

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	SMALL ENTITY RATE($)	SMALL ENTITY ADDITIONAL FEE($)	OR	OTHER THAN SMALL ENTITY RATE($)	OTHER THAN SMALL ENTITY ADDITIONAL FEE($)
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

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
13/426,973	03/22/2012	1629	1800	ALXN-P08-114	25	4

CONFIRMATION NO. 8851

UPDATED FILING RECEIPT

28120
ROPES & GRAY LLP
IPRM - Floor 43
PRUDENTIAL TOWER
800 BOYLSTON STREET
BOSTON, MA 02199-3600

OC000000054709737

Date Mailed: 06/12/2012

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**

Applicant(s)

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

Assignment For Published Patent Application

Alexion Pharmaceuticals, Inc., Cheshire, CT

Power of Attorney: None

Domestic Priority data as claimed by applicant

This application 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 (You may be eligible to benefit from the **Patent Prosecution Highway** program at the USPTO. Please see http://www.uspto.gov for more information.)

If Required, Foreign Filing License Granted: 04/02/2012

The country code and number of your priority application, to be used for filing abroad under the Paris Convention, is **US 13/426,973**

Projected Publication Date: 09/20/2012

Non-Publication Request: No

Early Publication Request: No

Title

TREATMENT OF PAROXYSMAL NOCTURNAL HEMOGLOBINURIA PATIENTS BY AN INHIBITOR OF COMPLEMENT

Preliminary Class

514

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.

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Substitute for form 1449/PTO

INFORMATION DISCLOSURE STATEMENT BY APPLICANT

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Sheet 1 of 6

Complete if Known	
Application Number	13/426,973
Filing Date	March 22, 2012
First Named Inventor	Leonard Bell
Art Unit	1644
Examiner Name	J. L. Rogers
Attorney Docket Number	ALXN-P08-114

U.S. PATENT DOCUMENTS

Examiner Initials*	Cite No.[1]	Document Number Number-Kind Code[2] (*if known*)	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear
		2003/0049683	03-13-2003	Bowdish et al.	
		2005/191298	09-01-2005	Bell et al.	
		2005/221382	10-06-2005	Rother	
		4,686,100	08-11-1987	Raffin et al.	
		5,135,916	08-04-1992	Sims et al.	
		5,660,825	08-26-1997	Sims et al.	
		6,355,245	03-12-2002	Evans et al.	
		7,361,339	04-22-2008	Bell	
		7,482,435	01-27-2009	Bowdish et al.	

FOREIGN PATENT DOCUMENTS

Examiner Initials*	Cite No.[1]	Foreign Patent Document Country Code[3]-Number[4]-Kind Code[5] (*if known*)	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages Or Relevant Figures Appear	T[6]
	**	EP 0 411 306 A1 (ABSTRACT)	06-22-1991	Gotze		
	**	WO 2005/074607 A2	08-18-2005	Alexion Pharmaceuticals, Inc.		

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				Filing Date	March 22, 2012
				First Named Inventor	Leonard Bell
				Art Unit	1644
(Use as many sheets as necessary)				Examiner Name	J. L. Rogers
Sheet	2	of	6	Attorney Docket Number	ALXN-P08-114

NON PATENT LITERATURE DOCUMENTS			
Examiner Initials*	Cite No.[1]	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, page(s), volume-issue number(s), publisher, city and/or country where published.	T[2]
	**	Alexion Announces Presentation of Preliminary Results from Phase I Pilot Study of Eculizumab Treatment of Patients with Paroxysmal Nocturnal Hemoglobinuria"; [online]; Alexion Pharmaceuticals: News; [Retrieved on 2003-06-18]. Retrieved from the world wide web at alexionpharmaceuticals.com/news/sub_press.cfm?prid=242&selectyear=2002.	
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				Filing Date	March 22, 2012
				First Named Inventor	Leonard Bell
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Sheet	4	of	6	Attorney Docket Number	ALXN-P08-114

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				First Named Inventor	Leonard Bell
				Art Unit	1644
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Sheet	5	of	6	Attorney Docket Number	ALXN-P08-114

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	**	Inoue et al., "Molecular genetics of paroxysmal nocturnal hemoglobinuria," Int J Hematol. 2003 Feb;77(2):107-112.	
	**	Kaplan, M. "Eculizumab (Alexion)" Curr Opin Investig Drugs, 2002 Jul;2(7):1017-23.	
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Sheet	6	of	6	Attorney Docket Number	ALXN-P08-114

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	**	Paroxysmal nocturnal hemoglobinuria, included; PNH, included phosphatidylinositol glycan, class A, pseudogene 1, included; pigap1, included piga-related processed gene, included [online]. OMIM-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...	
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Page 9200

Electronic Acknowledgement Receipt	
EFS ID:	13481360
Application Number:	13426973
International Application Number:	
Confirmation Number:	8851
Title of Invention:	TREATMENT OF PAROXYSMAL NOCTURNAL HEMOGLOBINURIA PATIENTS BY AN INHIBITOR OF COMPLEMENT
First Named Inventor/Applicant Name:	Leonard Bell
Customer Number:	28120
Filer:	Jason S. Cathelyn/ginny blundell
Filer Authorized By:	Jason S. Cathelyn
Attorney Docket Number:	ALXN-P08-114
Receipt Date:	13-AUG-2012
Filing Date:	22-MAR-2012
Time Stamp:	16:55:12
Application Type:	Utility under 35 USC 111(a)

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Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Transmittal Letter	ALXN-P08-114_IDS_Statement.pdf	69853 800e3594c03e79c9731f7ea5b742e5510fffa5ec	no	2
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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.

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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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Docket No.: ALXN-P08-114
(PATENT)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of:
Bell et al.

Application No.: 13/426,973 | Confirmation No.: 8851

Filed: March 22, 2012 | Art Unit: 1644

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

INFORMATION DISCLOSURE STATEMENT (IDS)

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

Dear Madam:

Pursuant to 37 CFR 1.56, 1.97 and 1.98, the attention of the Patent and Trademark Office is hereby directed to the references listed on the attached PTO/SB/08. It is respectfully requested that the information be expressly considered during the prosecution of this application, and that the references be made of record therein and appear among the "References Cited" on any patent to issue therefrom.

This Information Disclosure Statement is filed before the mailing date of a first Office Action on the merits as far as is known to the undersigned (37 CFR 1.97(b)(3)).

In accordance with 37 CFR 1.98(a)(2)(ii), Applicant has not submitted copies of U.S. patents and U.S. patent applications. Applicant submits herewith a copy of non-patent literature in accordance with 37 CFR 1.98(a)(2).

31534121_1

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Those documents which are marked with a double asterisk (**) next to the Cite No. in the attached form PTO/SB/08 are not supplied because they were previously cited by or submitted to the Office in prior application number 12/225,040, filed May 13, 2009, and relied upon in this application for an earlier filing date under 35 U.S.C. 120.

In accordance with 37 CFR 1.97(g), the filing of this Information Disclosure Statement shall not be construed to mean that a search has been made or that no other material information as defined in 37 CFR 1.56(a) exists. In accordance with 37 CFR 1.97(h), the filing of this Information Disclosure Statement shall not be construed to be an admission that any patent, publication or other information referred to therein is "prior art" for this invention unless specifically designated as such.

It is submitted that the Information Disclosure Statement is in compliance with 37 CFR 1.98 and the Examiner is respectfully requested to consider the listed references.

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. 18-1945, under Order No. ALXN-P08-114.

Dated: August 13, 2012

Respectfully submitted,

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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

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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

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 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 ¶)

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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).

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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).

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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 ¶).

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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.

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August 15, 2012

/JAMES ROGERS/
Examiner, Art Unit 1644

/Maher M. Haddad/
Primary Examiner, Art Unit 1644

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Page 9216

Notice of References Cited	Application/Control No. 13/426,973	Applicant(s)/Patent Under Reexamination BELL ET AL.	
	Examiner JAMES ROGERS	Art Unit 1644	Page 1 of 3

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*		Document Number Country Code-Number-Kind Code	Date MM-YYYY	Name	Classification
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	B	US-			
	C	US-			
	D	US-			
	E	US-			
	F	US-			
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	N					
	O					
	P					
	Q					
	R					
	S					
	T					

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	U	Kato et al. "Deconstructing sickle cell disease: reappraisal of the role of hemolysis in the development of clinical subphenotypes" Blood Reviews, 21, 2007, 37-47
	V	Hill et al. "Effect of Eculizumab on hemolysis and transfusion requirements in patients with paroxysmal nocturnal hemoglobinuria" N Engl J Med, 350(6), 2004, 552-559Hill et al. "Sustained response and long-term safety of eculizumab in paroxysmal noctural hemoglobinuria" Blood, 106(7), October 2005, 2559-2565
	W	Hill et al. "Improvement in the symptoms of smooth muscle dystonia during eculizumab therapy in paroxysmal nocturnal hemoglobinuria" Haematologica, 90(online), 2005, 111-113
	X	Jasinski et al. "a novel mechanisms of complement-independent clearance of red cells deficient in glycosyl phosphatidylinositol-linked proteins" Blood, April 2004, 103(7), 2827-2834

*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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	P					
	Q					
	R					
	S					
	T					

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*		Include as applicable: Author, Title Date, Publisher, Edition or Volume, Pertinent Pages)
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	V	
	W	
	X	

*A copy of this reference is not being furnished with this Office action. (See MPEP § 707.05(a).)
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Search Notes	Application/Control No.	Applicant(s)/Patent Under Reexamination
	13426973	BELL ET AL.
	Examiner	Art Unit
	JAMES ROGERS	1644

SEARCHED			
Class	Subclass	Date	Examiner

SEARCH NOTES		
Search Notes	Date	Examiner
STN: DISSABS MEETINGS BIOSCI CAPLUS MEDICINE	7/30/2012	JR
EAST: PGPUB, USPAT, JPO, EPO, DRWNT, INVENTOR SEARCH	7/30/2012	JR

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SERIAL NUMBER	FILING or 371(c) DATE	CLASS	GROUP ART UNIT	ATTORNEY DOCKET NO.
13/426,973	03/22/2012 RULE	424	1644	ALXN-P08-114

APPLICANTS

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

**** CONTINUING DATA ***************************

This application 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 ***************************

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Foreign Priority claimed	35 USC 119(a-d) conditions met	Verified and Acknowledged	Met after Allowance	STATE OR COUNTRY	SHEETS DRAWINGS	TOTAL CLAIMS	INDEPENDENT CLAIMS
☐ Yes ☑ No	☐ Yes ☑ No	/JAMES L ROGERS/ Examiner's Signature	☐ JR Initials	CT	4	25	4

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UNITED STATES

TITLE

TREATMENT OF PAROXYSMAL NOCTURNAL HEMOGLOBINURIA PATIENTS BY AN INHIBITOR OF COMPLEMENT

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Sheet 1 of 6

Complete if Known	
Application Number	13/426,973
Filing Date	March 22, 2012
First Named Inventor	Leonard Bell
Art Unit	1644
Examiner Name	J. L. Rogers
Attorney Docket Number	ALXN-P08-114

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Examiner Initials*	Cite No.[1]	Document Number Number-Kind Code[2] (*if known*)	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear
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	**	EP 0 411 306 A1 (ABSTRACT)	06-22-1991	Gotze		
	**	WO 2005/074607 A2	08-18-2005	Alexion Pharmaceuticals, Inc.		

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Filing Date	March 22, 2012
First Named Inventor	Leonard Bell
Art Unit	1644
Examiner Name	J. L. Rogers
Attorney Docket Number	ALXN-P08-114

NON PATENT LITERATURE DOCUMENTS

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Sheet	4	of	6	Attorney Docket Number	ALXN-P08-114

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	**	Inoue et al., "Molecular genetics of paroxysmal nocturnal hemoglobinuria," Int J Hematol. 2003 Feb;77(2):107-112.	
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31534139_1

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Samsung Bioepis Exhibit No. 1002
Page 9226

PTO/SB/08b (07-09)
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Substitute for form 1449/PTO

INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Use as many sheets as necessary)

Sheet	6	of	6

Complete if Known	
Application Number	13/426,973
Filing Date	March 22, 2012
First Named Inventor	Leonard Bell
Art Unit	1644
Examiner Name	J. L. Rogers
Attorney Docket Number	ALXN-P08-114

NON PATENT LITERATURE DOCUMENTS

Examiner Initials*	Cite No.[1]	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, page(s), volume-issue number(s), publisher, city and/or country where published.	T[2]
	**	Paroxysmal nocturnal hemoglobinuria, included; PNH, included phosphatidylinositol glycan, class A, pseudogene 1, included; pigap1, included piga-related processed gene, included [online]. OMIM-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...	
	**	Reiter et al., "Cell-free hemoglobin limits nitric oxide bioavailability in sickle-cell disease," Nature Medicine 8(12):1383-1389 (2002).	
	**	Richards et al., "Evolution of GPI-Deficient Clones Predicts Clinical Course in Paroxysmal Nocturnal Haemoglobinuria," Blood, 104:Abstract 172 (2004).	
		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).	
	**	Rosse et al., Immune-mediated hemolytic anemia, Hematology Am Soc Hematol Educ Program, 48-62 (2004) XP002497825.	
	**	Rother et al., The clinical sequelae of intravascular hemolysis and extracellular plasma hemoglobin, JAMA 293(13):1653-1662 (2005).	
	**	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).	
	**	Tang and Pikal, Design of Freeze-Drying Processes for Pharmaceuticals: Practical Advice, Pharmaceutical Research, Vol. 21(2), pp. 191-200 (2004).	
	**	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).	
	**	Vakeva, et al., "Myocardial infarction and apoptosis after myocardial ischemia and reperfusion," Circulation 97:2259-2267 (1998).	

Examiner Signature	/James Rogers/	Date Considered	08/15/2012

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant. ** CITE NO.: Those document(s) which are marked with an double asterisk (**) next to the Cite No. are not supplied because they were previously cited by or submitted to the Office in a prior application relied upon in this application for an earlier filing date undser 35 U.S.C. 120.

[1]Applicant's unique citation designation number (optional). [2]Applicant is to place a check mark here if English language Translation is attached.

31534139_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
13/426,973	03/22/2012	Leonard Bell	ALXN-P08-114

CONFIRMATION NO. 8851

28120
ROPES & GRAY LLP
IPRM - Floor 43
PRUDENTIAL TOWER
800 BOYLSTON STREET
BOSTON, MA 02199-3600

PUBLICATION NOTICE

OC00000056651412

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

Publication No.US-2012-0237515-A1
Publication Date:09/20/2012

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

PTO/SB/81 (01-09)
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POWER OF ATTORNEY OR REVOCATION OF POWER OF ATTORNEY WITH A NEW POWER OF ATTORNEY AND CHANGE OF CORRESPONDENCE ADDRESS

Application Number	13/426,973
Filing Date	March 22, 2012
First Named Inventor	Leonard Bell
Title	TREATMENT OF PAROXYSMAL NOCTURNAL HEMOGLOBINURIA PATIENTS BY AN, etc.
Art Unit	1644
Examiner Name	J. L. Rogers
Attorney Docket No.	ALXN-P08-114

I hereby revoke all previous powers of attorney given in the above-identified application.

☐ A Power of Attorney is submitted herewith.

OR

☒ I hereby appoint Practitioner(s) associated with the following Customer Number as my/our attorney(s) or agent(s) to prosecute the application identified above, and to transact all business in the United States Patent and Trademark Office connected therewith:

28120

OR

☐ I hereby appoint Practitioner(s) named below as my/our attorney(s) or agent(s) to prosecute the application identified above, and to transact all business in the United States Patent and Trademark Office connected therewith:

Practitioner(s) Name	Registration Number	Practitioner(s) Name	Registration Number

Please recognize or change the correspondence address for the above-identified application to:

☒ The address associated with the above-mentioned Customer Number:

OR

☐ The address associated with Customer Number:

OR

☐ Firm or Individual Name

Address					
City		State		Zip	
Country		Telephone		Email	

I am the:

☐ Applicant/Inventor.

OR

☒ Assignee of record of the entire interest. See 37 CFR 3.71.

Statement under 37 CFR 3.73(b) (Form PTO/SB/96) submitted herewith or filed on _____

SIGNATURE of Applicant or Assignee of Record

Signature	S	Date	3 OCT 12
Name	STEPHEN P. SQUINTO, PhD	Telephone	203-272-2596
Title and Company	EXEC. VP AND HEAD OF R&D, ALEXION PHARMACEUTICALS, INC.		

NOTE: Signatures of all the inventors or assignees of record of the entire interest or their representative(s) are required. Submit multiple forms if more than one signature is required, see below*

☒ *Total of 1 forms are submitted.

PTO/SB/96 (07-09)
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STATEMENT UNDER 37 CFR 3.73(b)

Applicant/Patent Owner: Alexion Pharmaceuticals, Inc.

Application No./Patent No.: 13/426,973 Filed/Issue Date: March 22, 2012

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

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

states that it is:

1. [x] the assignee of the entire right, title, and interest in;

2. [ ] an assignee of less than the entire right, title, and interest in
(The extent (by percentage) of its ownership interest is _____ %); or

3. [ ] an assignee of an undivided interest in the entirety of (a complete assignment from one of the joint inventors was made) the patent application/patent identified above by virtue of either:

A. [x] An assignment from the inventor(s) of the patent application/patent identified above. The assignment was recorded in the United States Patent and Trademark Office at Reel 028696, Frame 0909, or for which a copy thereof is attached.

OR

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

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

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

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

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

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

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

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

Signature	30 OCT 12 Date
STEPHEN P. SQUINTO, Ph.D. Printed or Typed Name	EXEC. VP AND CHIEF R&D Title

317983288_1

Samsung Bioepis Exhibit No. 1002
Page 9230

Electronic Acknowledgement Receipt	
EFS ID:	13960252
Application Number:	13426973
International Application Number:	
Confirmation Number:	8851
Title of Invention:	TREATMENT OF PAROXYSMAL NOCTURNAL HEMOGLOBINURIA PATIENTS BY AN INHIBITOR OF COMPLEMENT
First Named Inventor/Applicant Name:	Leonard Bell
Customer Number:	28120
Filer:	Jason S. Cathelyn/ginny blundell
Filer Authorized By:	Jason S. Cathelyn
Attorney Docket Number:	ALXN-P08-114
Receipt Date:	11-OCT-2012
Filing Date:	22-MAR-2012
Time Stamp:	12:57:16
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	Power of Attorney	ALXN-P08-114_POA.pdf	1338730 057ad77fc3251f4a3c150d6c3065d837cb8c42c8	no	1
Warnings:					
Information:					

Samsung Bioepis Exhibit No. 1002
Page 9231

2	Assignee showing of ownership per 37 CFR 3.73.	ALXN-P08-114_373b.pdf	1261598 6388785e4133bbc1bfa7bbd0c0890bb822ab155e	no	1

Warnings:	
Information:	
Total Files Size (in bytes):	2600328

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

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

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

Samsung Bioepis Exhibit No. 1002
Page 9232

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APPLICATION NUMBER	FILING OR 371(C) DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO./TITLE
13/426,973	03/22/2012	Leonard Bell	ALXN-P08-114

CONFIRMATION NO. 8851

POA ACCEPTANCE LETTER

28120
ROPES & GRAY LLP
IPRM - Floor 43
PRUDENTIAL TOWER
800 BOYLSTON STREET
BOSTON, MA 02199-3600

OC00000057184744

Date Mailed: 10/22/2012

NOTICE OF ACCEPTANCE OF POWER OF ATTORNEY

This is in response to the Power of Attorney filed 10/11/2012.

The Power of Attorney in this application is accepted. Correspondence in this application will be mailed to the above address as provided by 37 CFR 1.33.

/qtran/

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

PTO/SB/08a (07-09)
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INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Use as many sheets as necessary)

Sheet 1 of 2

Complete if Known	
Application Number	13/426,973
Filing Date	March 22, 2012
First Named Inventor	Leonard Bell
Art Unit	1644
Examiner Name	J. L. Rogers
Attorney Docket Number	ALXN-P08-114

U.S. PATENT DOCUMENTS

Examiner Initials*	Cite No.[1]	Document Number Number-Kind Code[2] (if known)	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear

FOREIGN PATENT DOCUMENTS

Examiner Initials*	Cite No.[1]	Foreign Patent Document Country Code[3]-Number[4]-Kind Code[5] (if known)	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages Or Relevant Figures Appear	T[6]

Examiner Signature		Date Considered	

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant. [1] Applicant's unique citation designation number (optional). [2] See Kinds Codes of USPTO Patent Documents at www.uspto.gov or MPEP 901.04. [3] Enter Office that issued the document, by the two-letter code (WIPO Standard ST.3). [4] For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. [5] Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16 if possible. [6] Applicant is to place a check mark here if English language Translation is attached.

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Page 9234

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INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Use as many sheets as necessary)

Sheet	2	of	2

Complete if Known	
Application Number	13/426,973
Filing Date	March 22, 2012
First Named Inventor	Leonard Bell
Art Unit	1644
Examiner Name	J. L. Rogers
Attorney Docket Number	ALXN-P08-114

NON PATENT LITERATURE DOCUMENTS

Examiner Initials*	Cite No.[1]	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, page(s), volume-issue number(s), publisher, city and/or country where published.	T[2]
		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).	

Examiner Signature		Date Considered	

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

[1]Applicant's unique citation designation number (optional). [2]Applicant is to place a check mark here if English language Translation is attached.

Electronic Patent Application Fee Transmittal	
Application Number:	13426973
Filing Date:	22-Mar-2012
Title of Invention:	TREATMENT OF PAROXYSMAL NOCTURNAL HEMOGLOBINURIA PATIENTS BY AN INHIBITOR OF COMPLEMENT
First Named Inventor/Applicant Name:	Leonard Bell
Filer:	Anita Varma/Joanne Ryan
Attorney Docket Number:	ALXN-P08-114
Filed as Large Entity	

Utility under 35 USC 111(a) Filing Fees

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Basic Filing:				
Pages:				
Claims:				
Miscellaneous-Filing:				
Petition:				
Patent-Appeals-and-Interference:				
Post-Allowance-and-Post-Issuance:				
Extension-of-Time:				
Extension - 2 months with $0 paid	1252	1	570	570

Samsung Bioepis Exhibit No. 1002
Page 9236

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Miscellaneous:				
Submission- Information Disclosure Stmt	1806	1	180	180
		Total in USD ($)		**750**

Samsung Bioepis Exhibit No. 1002
Page 9237

Electronic Acknowledgement Receipt	
EFS ID:	14762569
Application Number:	13426973
International Application Number:	
Confirmation Number:	8851
Title of Invention:	TREATMENT OF PAROXYSMAL NOCTURNAL HEMOGLOBINURIA PATIENTS BY AN INHIBITOR OF COMPLEMENT
First Named Inventor/Applicant Name:	Leonard Bell
Customer Number:	28120
Filer:	Anita Varma/Joanne Ryan
Filer Authorized By:	Anita Varma
Attorney Docket Number:	ALXN-P08-114
Receipt Date:	22-JAN-2013
Filing Date:	22-MAR-2012
Time Stamp:	19:11:27
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	yes
Payment Type	Deposit Account
Payment was successfully received in RAM	$750
RAM confirmation Number	7136
Deposit Account	181945
Authorized User	

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)

Samsung Bioepis Exhibit No. 1002
Page 9238

1	Extension of Time	ALXN-P08-114_Extension.pdf	88947 16018be486e2f16886e6d3384746d75c6683fbb6	no	1
Warnings:					
Information:					
2		ALXN-P08-114_NonFinal_Response.pdf	138605 773a0ec789e6ffec8b4308e9033b55bbfd866332	yes	10
	Multipart Description/PDF files in .zip description				
	Document Description		**Start**	**End**	
	Amendment/Req. Reconsideration-After Non-Final Reject		1	1	
	Claims		2	4	
	Applicant Arguments/Remarks Made in an Amendment		5	10	
Warnings:					
Information:					
3	Transmittal Letter	ALXN-P08-114_IDS.pdf	70440 b3f0350fa010d2020012c58b2a0e94c140ec2381	no	2
Warnings:					
Information:					
4	Information Disclosure Statement (IDS) Form (SB08)	ALXN-P08-114_SB08.pdf	126228 2273423fccc0744cf8825840e295ee857cc17cf5	no	2
Warnings:					
Information:					
This is not an USPTO supplied IDS fillable form					
5	Non Patent Literature	Rother_pp_197.pdf	108853 b1b1bf78dbaf0079adc82668321fb797b84da6fa	no	1
Warnings:					
Information:					
6	Fee Worksheet (SB06)	fee-info.pdf	32556 bc237a4440cfb2eb8b04bdfa39c7812abca711e7	no	2
Warnings:					
Information:					
		Total Files Size (in bytes):	565629		

Samsung Bioepis Exhibit No. 1002
Page 9239

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

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

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

Samsung Bioepis Exhibit No. 1002
Page 9240

PTO/SB/22 (10-12)
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PETITION FOR EXTENSION OF TIME UNDER 37 CFR 1.136(a)	Docket Number (Optional) ALXN-P08-114
Application Number 13/426,973	Filed March 22, 2012
For TREATMENT OF PAROXYSMAL NOCTURNAL HEMOGLOBINURIA PATIENTS BY AN INHIBITOR OF COMPLEMENT	
Art Unit 1644	Examiner J. L. Rogers

This is a request under the provisions of 37 CFR 1.136(a) to extend the period for filing a reply in the above identified application.

The requested extension and fee are as follows (check time period desired and enter the appropriate fee below):

		Fee	Small Entity Fee	
☐	One month (37 CFR 1.17(a)(1))	$150	$75	$
☒	Two months (37 CFR 1.17(a)(2))	$570	$285	$ 570.00
☐	Three months (37 CFR 1.17(a)(3))	$1,290	$645	$
☐	Four months (37 CFR 1.17(a)(4))	$2,010	$1,005	$
☐	Five months (37 CFR 1.17(a)(5))	$2,730	$1,365	$

☐ Applicant claims small entity status. See 37 CFR 1.27.

☐ A check in the amount of the fee is enclosed.

☐ Payment by credit card. Form PTO-2038 is attached.

☒ The Director has already been authorized to charge fees in this application to a Deposit Account.

☒ The Director is hereby authorized to charge any fees which may be required, or credit any overpayment, to Deposit Account Number 18-1945 .

☒ Payment made via EFS-Web.

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.

I am the

☐ applicant/inventor.

☐ assignee of record of the entire interest. See 37 CFR 3.71. 37 CFR 3.73(b) statement is enclosed (Form PTO/SB/96).

☒ attorney or agent of record. Registration Number 43,221 .

☐ attorney or agent under 37 CFR 1.34. Registration number _____ .

/Anita Varma/	January 22, 2013
Signature	Date
Anita Varma, Esq.	(617) 951-7796
Typed or printed name	Telephone Number

NOTE: This form must be signed in accordance with 37 CFR 1.33. See 37 CFR 1.4 for signature requirements and certifications. Submit multiple forms if more than one signature is required, see below*.

☒ *Total of 1 forms are submitted.

33013661_1

Docket No.: ALXN-P08-114
(PATENT)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of:
Bell et al.

Application No.: 13/426,973 | Confirmation No.: 8851

Filed: March 22, 2012 | Art Unit: 1644

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

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

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

Dear Madam:

INTRODUCTORY COMMENTS

This submission responds to the Office Action dated August 20, 2012, in the above-identified U.S. patent application. Applicants' Petition for a two-month extension of time and a Supplemental Information Disclosure Statement are submitted concurrently herewith. Please amend the above-identified U.S. patent application as set forth below.

Amendments to the Claims are reflected in the listing of claims which begins on page 2 of this paper.

Remarks/Arguments begin on page 5 of this paper.

AMENDMENTS TO THE CLAIMS

This listing of claims will replace all prior versions and listings of the claims in the application.

1-90. (Cancelled)

91. (Currently Amended) A method for treating a patient that: (i) is afflicted with paroxysmal nocturnal hemoglobinuria (PNH) ~~a hemolytic disease~~ and (ii) has been vaccinated against *Neisseria meningitides*, the method comprising administering to the patient an effective amount of a pharmaceutical composition comprising a single unit dosage form of an anti-C5 antibody that inhibits cleavage of complement component C5 into fragments C5a and C5b, 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.

92-97. (Cancelled)

98. (Previously Presented) The method according to claim 91, wherein the anti-C5 antibody is administered to the patient for at least 6 months.

99. (Cancelled)

100. (Currently Amended) The method according to claim 91[[99]], wherein the patient has a hemoglobin level less than (i) 14 g/dL if a man or (ii) 12 g/dL if a woman.

101. (Currently Amended) The method according to claim 91[[99]], wherein the patient has a hemoglobin level less than (i) 13 g/dL if a man or (ii) 11 g/dL if a woman.

102. (Currently Amended) The method according to claim 91[[99]], wherein the patient has a hemoglobin level less than (i) 12 g/dL if a man or (ii) 10 g/dL if a woman.

103. (Currently Amended) The method according to claim 91[[99]], wherein the patient suffers from hemolysis due to a C3b-mediated, extravascular clearance of PNH erythrocytes through the reticuloendothelial system.

104. (Currently Amended) The method according to claim 91[[99]], 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.

105. (Currently Amended) The method according to claim 91[[99]], wherein the patient is at least 18 years of age and has: (i) a PNH type III erythrocyte population of ≥ 10% and (ii) received at least four transfusions during the 12 months immediately preceding the first treatment with the anti-C5 antibody.

106. (Previously Presented) The method according to claim 91, wherein the patient has aplastic anemia or myelodysplastic syndrome.

107-109. (Cancelled)

110. (Currently Amended) The method according to claim 91[[107]], wherein the single unit dosage form is a preservative free formulation.

111. (Currently Amended) The method according to claim 91, wherein the pharmaceutical composition ~~anti-C5 antibody~~ is ~~to be~~ administered to the patient under the following treatment schedule: (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 ± 2 days after (i), and (iii) 900 mg of the antibody every 14 ± 2 days thereafter, and wherein the administration ~~of the antibody to the patient~~ occurs via 25 to 45 minute intravenous infusion.

112. (Currently Amended) A method for treating a patient afflicted with paroxysmal nocturnal hemoglobinuria (PNH) ~~a hemolytic disease~~, the method comprising:

vaccinating the patient against *Neisseria meningitides*; and

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administering to the patient an effective amount of a pharmaceutical composition comprising a single unit dosage form of an anti-C5 antibody that inhibits cleavage of complement component C5 into fragments C5a and C5b, 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.

113. (Currently Amended) A method for treating a patient afflicted with paroxysmal nocturnal hemoglobinuria (PNH) ~~a hemolytic disease~~, the method comprising administering to the patient an effective amount of a pharmaceutical composition comprising a single unit dosage form of an anti-C5 antibody that [[: (i)]] inhibits cleavage of complement component C5 into fragments C5a and C5b ~~and (ii) comprises an altered constant region that exhibits decreased effector function relative to the corresponding native constant region~~, 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.

114. (Cancelled)

115. (Currently Amended) A method for treating a patient afflicted with paroxysmal nocturnal hemoglobinuria (PNH) ~~a hemolytic disease~~, the method comprising administering to the patient a pharmaceutical composition comprising a single unit dosage form of an anti-C5 antibody under the following treatment schedule: (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 ± 2 days after (i), and (iii) 900 mg of the antibody every 14 ± 2 days thereafter, wherein the administration ~~of the antibody to the patient~~ is to occur via 25 to 45 minute intravenous infusion, 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 antibody inhibits cleavage of complement component C5 into fragments C5a and C5b, and wherein the anti-C5 antibody is eculizumab.

REMARKS

Claims 91-115 are pending and under consideration in this application. Claims 91, 100-105, 110-113, and 115 have been amended. Claims 92-97, 99, 107-109, and 114 have been cancelled herein. The amendments and cancellations have been made without prejudice or disclaimer and Applicants reserve the right to pursue the cancelled subject matter in this application, or in one or more divisional or continuation applications. Following entry of the amendments and cancellations made herein, claims 91, 98, 100-106, 110-113, and 115 will be pending and under consideration in this application.

Support for the amendments made herein can be found in the original claims and throughout the specification (U.S. patent application publication no. 2012/0237515), e.g., at paragraphs [0005], [0009], [0010], [0018], [0019], [0024], [0085], [0103], and [0128]. No new matter has been added.

Applicants respectfully request reconsideration in view of the following comments. Issues raised by the Examiner will be addressed in the order they appear in the Office Action.

Claims Rejected Under 35 U.S.C. § 112, First Paragraph (Enablement)

At pages 2 and 3 of the Office Action, claims 91-98 and 106-115 were rejected under 35 U.S.C. § 112, first paragraph as allegedly lacking enablement. According to the Examiner, "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, [the specification] does not reasonably provide enablement for a method for treatment of **any hemolytic disease** by administering an anti-C5 antibody." Office Action at page 2 (emphasis added). While Applicants do not concede to any aspect of the Examiner's stated reasons for rejection, the claims have been amended to incorporate the limitations of claim 99 and are now drawn to methods for treating patients afflicted with PNH. As noted above, the Office Action expressly acknowledges enabling support for such methods. Accordingly, reconsideration and withdrawal of the rejection are respectfully requested.

Claims Rejected under 35 U.S.C. § 102(b)

I. At pages 3 and 4 of the Office Action, claims 113-115 were rejected under 35 U.S.C. § 102(b) as allegedly lacking novelty in view of Rosse et al. (2004) *Hematology Am Soc Hematol Educ Program* 48-62. While not conceding to any aspect of the Examiner's stated reasons for rejection, claims 113-115 have been amended. The instant claims, as amended, require the administration to a PNH patient of a pharmaceutical composition comprising a single unit dosage form of an antagonist anti-C5 antibody, wherein the single unit dosage form comprises 300 mg of the anti-C5 antibody or C5-binding fragment thereof. Rosse et al., which is a review article discussing the underlying biology and diagnosis of, as well as treatment options for, PNH, does not disclose or suggest such pharmaceutical compositions. Accordingly, the reference does not anticipate the instant claims. Reconsideration and withdrawal of the rejection under 35 U.S.C. § 102(b) are therefore respectfully requested.

II. At pages 4 and 5 of the Office Action, claims 91-93, 96-97, 99, 103-105, and 112-115 were rejected under 35 U.S.C. § 102(b) as allegedly being anticipated by Hillmen et al. (2004) *N Engl J Med* 350:552-559 as evidenced by Jasinski (2004) *Blood* 103:2827-2834 and Rosse et al. (*supra*). While not conceding to any aspect of the Examiner's stated reasons for rejection, claims 113-115 have been amended. The instant claims, as amended, require the administration to a PNH patient of a pharmaceutical composition comprising a single unit dosage form of an antagonist anti-C5 antibody, wherein the single unit dosage form comprises 300 mg of the anti-C5 antibody or C5-binding fragment thereof. None of the cited references disclose or suggest such compositions.

Hillmen et al. describes the results of clinical trials in which eculizumab, an antagonist anti-C5 antibody, was evaluated as a treatment for PNH. Eculizumab was found to be safe for, and well tolerated by, such patients and that the antibody reduced intravascular hemolysis, hemoglobinuria, and the need for transfusions. *See* Hillmen et al. (Abstract). The reference does not, however, disclose or suggest 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 or more of the anti-C5 antibody or C5-binding fragment thereof, as is instantly claimed. Accordingly, the reference does not anticipate the instant claims.

Rosse et al., discussed above, is offered as proof that eculizumab "has a completely nonfunctional Fc domain" and Jasinski as evidencing "the shortened survival of PIGA negative RBCs which causes PNH is mediated by macrophage clearance." Office Action at pages 4 and 5, respectively. However, neither reference discloses nor suggests 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 or more of the anti-C5 antibody or C5-binding fragment thereof, as is instantly claimed. Therefore, these references do not provide the requisite disclosure to support a finding of anticipation based on Hillmen et al. Accordingly, Applicants respectfully request reconsideration and withdrawal of the rejection under 35 U.S.C. § 102(b).

Claims Rejected Under 35 U.S.C. § 103(a)

I. Claims 91-93, 96-106, and 111-115 were rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Rosse et al. (*supra*), "Hill (1)" [Hill et al. (2005) *Blood* 106(7):2559-2565)], or "Hill (2)" [Hill et al. (2005) *Haematologica* 90:e111-e113], each in view of Hillmen et al. (*supra*) as evidenced by Jasinski (*supra*). While not conceding to any aspect of the Examiner's stated reasons for rejection, the rejected claims have been amended and now include the limitations of claims 107-109. Claim 107, which embraced embodiments in which a pharmaceutical composition comprising a single unit dosage form of an antagonist anti-C5 antibody is administered to a PNH patient, was not subject to rejection under this subsection of the Office Action. Accordingly, instant claims 91, 98, 100-106, 110-113, and 115 are ostensibly nonobvious in view of the cited references and remarks of this subsection of the Office Action and, thus, reconsideration and withdrawal of the rejection are respectfully requested.

II. At pages 8 and 9 of the Office Action, claims 107-110 were rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Rosse et al. (*supra*), Hill (1) (*supra*), or Hill (2) (*supra*), as applied to claims 91-93, 96-102, 105, 106, and 111-115 (above), and further in view of Garcia et al. (2002) *Biologicals* 30:143-151. As noted above, claims 107-109 have been cancelled, but their limitations are now included in independent claims 91, 112, 113, and 115. According to the Examiner, "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…the claimed dosage forms are simply a matter of convenience". Office Action at page 9. Applicants traverse in view of the instant amendments and the following remarks.

In order for the cited references to render the claimed invention obvious, there must have been an *apparent reason* for the skilled artisan to combine those references and arrive at the claimed invention. *KSR International Co. v. Teleflex Inc.*, 550 U.S. 398, 417, 418 (2007) (emphasis added). *See also* M.P.E.P. § 2143.01 (IV) (the P.T.O. stating that just "because the references relied upon teach that all aspects of the claimed invention were individually known in the art is not sufficient to establish a prima facie case of obviousness without some objective reason to combine the teachings of the references").

With regard to previously pending claims 107-110, the Examiner acknowledges that 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….and comprises a 10 mg/mL solution". In essence, however, the Examiner asserts that it would have been obvious nonetheless for a skilled artisan to select from the genus of potential pharmaceutical compositions the specific single unit dosage form claimed because such forms *are convenient*. Yet, the instant claims specify a distinct subgenus of pharmaceutical compositions comprising a single unit dosage form of an anti-C5 antibody that inhibits cleavage of complement component C5 into fragments C5a and C5b, 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, and wherein the single unit dosage form has a volume of 30 mL. And "[s]ome motivation to select the claimed…subgenus must be taught by the prior art." M.P.E.P. § 2144.08(II)(A)(4)(a).

It is well known in the art that the dose of an antibody will "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" (paragraph [0084] of the published application), to list just a few factors. This is especially true for a chronic condition such as PNH, since, in addition to the above factors, one has to also take into account the possibility of

toxicity from over-dosing. Applicants respectfully submit that optimizing the dosage form is neither routine nor a mere matter of "convenience". At a minimum, in order to arrive at the claimed solutions at all, the inventors had to know that the claimed antibody, eculizumab, was soluble. In order to produce a solution of eculizumab at 10 mg/mL, the inventors had to know the solubility of the eculizumab and that eculizumab was sufficiently soluble for a 10 mg/mL formulation. Moreover, in order for a pharmaceutical solution to be commercially viable, the inventors had to know the shelf-life stability of eculizumab in solution; for if its stability was too low, a pharmaceutical solution would not have been an option. Even assuming *arguendo* that the instantly claimed compositions are convenient, it is clear that skilled artisans reading the cited references could not have arrived at the particular instantly-claimed compositions by convenience. They would have required the knowledge supporting the instant invention. And none of that knowledge is disclosed or even suggested by the cited references.

Thus, the cited references do not render the claimed invention obvious and reconsideration and withdrawal of the rejection are respectfully requested.

III. At page 10 of the Office Action, claims 94 and 95 were rejected under35 U.S.C. § 103(a) as allegedly being unpatentable over Rosse et al. (*supra*), Hill (1) (*supra*), Hill (2) (*supra*), and Hillmen et al. (*supra*), as applied to claims 91-93, 96-102, 105-106, and 111-115 (above), and further in view of Kaplan (2002) *Curr Opin Investig Drugs* 3(7):1017-1023. While not conceding to any aspect of the Examiner's stated reasons for rejection, the rejected claims have been amended and now include the limitations of claims 107-109. Claim 107, which embraced embodiments in which a pharmaceutical composition comprising a single unit dosage form of an antagonist anti-C5 antibody is administered to a PNH patient, was not rejected under this subsection of the Office Action. Accordingly, instant claims 91, 98, 100-106, 110-113, and 115 are ostensibly nonobvious in view of the cited references and remarks under this subsection of the Office Action and, thus, reconsideration and withdrawal of the rejection are respectfully requested.

CONCLUSION

In view of the above amendment and remarks, Applicants believe the pending application is in condition for allowance. The Examiner may address any questions raised by this submission to the undersigned at 617-951-7000.

Applicants believe no fee is due with this response other than those listed on the accompanying transmittal. However, if a fee is due, please charge our Deposit Account No. 18-1945, under Order No. ALXN-P08-114 from which the undersigned is authorized to draw.

Dated: January 22, 2013

Respectfully submitted,

By____/Anita Varma/_____
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Docket No.: ALXN-P08-114
(PATENT)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of:
Bell et al.

Application No.: 13/426,973 | Confirmation No.: 8851

Filed: March 22, 2012 | Art Unit: 1644

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

SUPPLEMENTAL INFORMATION DISCLOSURE STATEMENT (IDS)

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

Dear Madam:

Pursuant to 37 CFR 1.56, 1.97 and 1.98, the attention of the Patent and Trademark Office is hereby directed to the references listed on the attached PTO/SB/08. It is respectfully requested that the information be expressly considered during the prosecution of this application, and that the references be made of record therein and appear among the "References Cited" on any patent to issue therefrom.

This Supplemental Information Disclosure Statement is filed more than three months after the U.S. filing date, OR more than three months after the date of entry of the national stage of a PCT application, AND after the mailing date of the first Office Action on the merits, whichever occurs first, but before the mailing date of any of a Final Office Action, a Notice of Allowance (37 CFR 1.97(c)) or an action that otherwise closes prosecution in the application.

Applicants submit herewith a copy of non-patent literature in accordance with 37 CFR 1.98(a)(2).

In accordance with 37 CFR 1.97(g), the filing of this Supplemental Information Disclosure Statement shall not be construed to mean that a search has been made or that no other material information as defined in 37 CFR 1.56(a) exists. In accordance with 37 CFR 1.97(h), the filing of this Supplemental Information Disclosure Statement shall not be construed to be an admission that any patent, publication or other information referred to therein is "prior art" for this invention unless specifically designated as such.

It is submitted that the Supplemental Information Disclosure Statement is in compliance with 37 CFR 1.98 and the Examiner is respectfully requested to consider the listed reference.

Please charge our Deposit Account No. 18-1945 in the amount of $180.00 covering the fee set forth in 37 CFR § 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 (or with any paper hereafter filed in this application by this firm) to our Deposit Account No. 18-1945, under Order No. ALXN-P08-114.

Dated: January 22, 2013

Respectfully submitted,

Electronic signature: /Anita Varma/
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PTO/SB/06 (07-06)
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PATENT APPLICATION FEE DETERMINATION RECORD
Substitute for Form PTO-875

Application or Docket Number	Filing Date	☐ To be Mailed
13/426,973	03/22/2012	

APPLICATION AS FILED – PART I

	(Column 1)	(Column 2)	SMALL ENTITY ☐		OR	OTHER THAN SMALL ENTITY	
FOR	NUMBER FILED	NUMBER EXTRA	RATE ($)	FEE ($)		RATE ($)	FEE ($)
☐ BASIC FEE (37 CFR 1.16(a), (b), or (c))	N/A	N/A	N/A			N/A	
☐ SEARCH FEE (37 CFR 1.16(k), (i), or (m))	N/A	N/A	N/A			N/A	
☐ EXAMINATION FEE (37 CFR 1.16(o), (p), or (q))	N/A	N/A	N/A			N/A	
TOTAL CLAIMS (37 CFR 1.16(i))	minus 20 =	*	X $ =		OR	X $ =	
INDEPENDENT CLAIMS (37 CFR 1.16(h))	minus 3 =	*	X $ =			X $ =	
☐ APPLICATION SIZE FEE (37 CFR 1.16(s))	If the specification and drawings exceed 100 sheets of paper, the application size fee due is $250 ($125 for small entity) for each additional 50 sheets or fraction thereof. See 35 U.S.C. 41(a)(1)(G) and 37 CFR 1.16(s).						
☐ MULTIPLE DEPENDENT CLAIM PRESENT (37 CFR 1.16(j))							
* If the difference in column 1 is less than zero, enter "0" in column 2.			TOTAL			TOTAL	

APPLICATION AS AMENDED – PART II

		(Column 1)		(Column 2)	(Column 3)	SMALL ENTITY		OR	OTHER THAN SMALL ENTITY	
	01/22/2013	CLAIMS REMAINING AFTER AMENDMENT		HIGHEST NUMBER PREVIOUSLY PAID FOR	PRESENT EXTRA	RATE ($)	ADDITIONAL FEE ($)		RATE ($)	ADDITIONAL FEE ($)
AMENDMENT	Total (37 CFR 1.16(i))	* 15	Minus	** 25	= 0	X $ =		OR	X $62=	0
	Independent (37 CFR 1.16(h))	* 4	Minus	***4	= 0	X $ =		OR	X $250=	0
	☐ 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	0

		(Column 1)		(Column 2)	(Column 3)					
		CLAIMS REMAINING AFTER AMENDMENT		HIGHEST NUMBER PREVIOUSLY PAID FOR	PRESENT EXTRA	RATE ($)	ADDITIONAL FEE ($)		RATE ($)	ADDITIONAL FEE ($)
AMENDMENT	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 number found in the appropriate box in column 1.

Legal Instrument Examiner:
/TRINA STEPTOE/

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

If you need assistance in completing the form, call 1-800-PTO-9199 and select option 2.

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Page 9254

PTO/SB/08a (07-09)
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INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Use as many sheets as necessary)

Sheet 1 of 2

Complete if Known	
Application Number	13/426,973
Filing Date	March 22, 2012
First Named Inventor	Leonard Bell
Art Unit	1644
Examiner Name	J. L. Rogers
Attorney Docket Number	ALXN-P08-114

U.S. PATENT DOCUMENTS

Examiner Initials*	Cite No.[1]	Document Number Number-Kind Code[2] (if known)	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear

FOREIGN PATENT DOCUMENTS

Examiner Initials*	Cite No.[1]	Foreign Patent Document Country Code[3]-Number[4]-Kind Code[5] (if known)	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages Or Relevant Figures Appear	T[6]

Examiner Signature		Date Considered	

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant. [1] Applicant's unique citation designation number (optional). [2] See Kinds Codes of USPTO Patent Documents at www.uspto.gov or MPEP 901.04. [3] Enter Office that issued the document, by the two-letter code (WIPO Standard ST.3). [4] For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. [5] Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16 if possible. [6] Applicant is to place a check mark here if English language Translation is attached.

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INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Use as many sheets as necessary)

Sheet 2 of 2

Complete if Known	
Application Number	13/426,973
Filing Date	March 22, 2012
First Named Inventor	Leonard Bell
Art Unit	1644
Examiner Name	J. L. Rogers
Attorney Docket Number	ALXN-P08-114

NON PATENT LITERATURE DOCUMENTS

Examiner Initials*	Cite No.[1]	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, page(s), volume-issue number(s), publisher, city and/or country where published.	T[2]
		Clinics, Biotechnology News, Vol. 24(30): 10 (2004).	
		Hillmen et al., "Eculizumab, a C5 Complement-Blocking Antibody, Controls Hemolysis in Paroxysmal Nocturnal Hemoglobinuria (PNH) with Responses Maintained over prolonged Period of Therapy" Journal of The American Society of Hematology, Vol. 102(11), Abstract 1858 (2003).	
		Hillmen et al., "Eculizumab, a C5 complement-blocking antibody, controls haemolysis in paroxysmal nocturnal haemoglobinuria (PNH) with responses maintained over a prolonged period of therapy," British Journal of Haematology, Vol. 125 (Suppl. 1): 1-72, Abstract 5 (2004).	
		Notice of Opposition for EP Patent No. 1720571, dated 3/18/2013.	

Examiner Signature		Date Considered	

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

[1]Applicant's unique citation designation number (optional). [2]Applicant is to place a check mark here if English language Translation is attached.

Electronic Acknowledgement Receipt	
EFS ID:	15771020
Application Number:	13426973
International Application Number:	
Confirmation Number:	8851
Title of Invention:	TREATMENT OF PAROXYSMAL NOCTURNAL HEMOGLOBINURIA PATIENTS BY AN INHIBITOR OF COMPLEMENT
First Named Inventor/Applicant Name:	Leonard Bell
Customer Number:	28120
Filer:	Jason S. Cathelyn/ginny blundell
Filer Authorized By:	Jason S. Cathelyn
Attorney Docket Number:	ALXN-P08-114
Receipt Date:	14-MAY-2013
Filing Date:	22-MAR-2012
Time Stamp:	15:11:18
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	Transmittal Letter	ALEX-P08-114_SIDS.pdf	82191 8ac0f089fc36070af370e58976bdd81c9bff6173	no	2
Warnings:					
Information:					

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2	Non Patent Literature	ALEX-P08-114_Notice_Opposition.pdf	23779302 46324efb69054093bcf2571a8418b390e2c20773	no	22
Warnings:					
Information:					
3	Non Patent Literature	Cllinics_Biotechnology_News_24.pdf	6292303 14f2c4b63bd86f0344e4cda2e8514052f810f200	no	1
Warnings:					
Information:					
4	Non Patent Literature	HIllmen_Abstract_1858.pdf	2172732 753fbaefb022e2b5a82f0312690f0e8388aa34ef	no	3
Warnings:					
Information:					
5	Non Patent Literature	Hillmen_Abstract_5.pdf	127889 ec0fb79aa152978322 4f4335ea34e1c95de5ad1b	no	2
Warnings:					
Information:					
6	Information Disclosure Statement (IDS) Form (SB08)	ALEX-P08-114_SB08.pdf	127884 25872cd5f9954f277f6d677f6b8c53b7e46ad0b3	no	2
Warnings:					
Information:					
This is not an USPTO supplied IDS fillable form					
		Total Files Size (in bytes):	32582301		

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

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

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

Samsung Bioepis Exhibit No. 1002
Page 9258

Docket No.: ALXN-P08-114
(PATENT)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of:
Bell et al.

Application No.: 13/426,973 | Confirmation No.: 8851

Filed: March 22, 2012 | Art Unit: 1644

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

SUPPLEMENTAL INFORMATION DISCLOSURE STATEMENT (IDS)

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

Dear Madam:

In accordance with 37 C.F.R. § 1.97, Applicants hereby makes of record the following additional documents. A PTO Form SB/08 and a full copy of each of the documents required under 37 C.F.R. § 1.98(a)(2) accompany this statement.

Applicants have become aware of the following documents, cited in a Notice of Opposition to a European Patent issued March 18, 2013, during the prosecution of EP Application No. 1 720 571, which corresponds to the above referenced application, and in accordance with 37 C.F.R. § 1.97(c) and (e)(1) or (b)(3), hereby submit these documents for the Examiner's consideration. These documents are cited on the enclosed PTO Form SB/08, and a copy of the Notice Of Opposition and of each document required under 37 C.F.R. § 1.98(a)(2) cited thereon, which has not been submitted in a previous PTO Form SB/08, are enclosed as well.

35377574_1

Samsung Bioepis Exhibit No. 1002
Page 9259

This 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 document herein be construed *per se* as a representation that such document is prior art. Moreover, Applicants understand the Examiner will make an independent evaluation of the cited documents.

This Supplemental Information Disclosure Statement is filed more than three months after the U.S. filing date, and after the mailing date of the first Office Action on the merits, whichever occurs first, but before the mailing date of any of a Final Office Action, a Notice of Allowance (37 C.F.R. § 1.97(c)) or an action that otherwise closes prosecution in the application.

I hereby certify, pursuant to 37 C.F.R. § 1.97(e)(1), that each item of information contained in this Supplemental 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 this Supplemental Information Disclosure Statement.

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. 18-1945, under Order No. ALXN-P08-114.

Dated: May 14, 2013

Respectfully submitted,

By_/Jason S. Cathelyn/__
Jason S. Cathelyn, Ph.D.
Registration No.: 68,195
ROPES & GRAY LLP
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800 Boylston Street
Boston, Massachusetts 02199
(617) 951-7000
(617) 235-9492 (Fax)
Attorneys/Agents For Applicants

PTO/SB/08a (07-09)
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U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
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Substitute for form 1449/PTO

INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Use as many sheets as necessary)

Sheet 1 of 2

Complete if Known	
Application Number	13/426,973
Filing Date	March 22, 2012
First Named Inventor	Leonard Bell
Art Unit	1644
Examiner Name	J. L. Rogers
Attorney Docket Number	ALXN-P08-114

U.S. PATENT DOCUMENTS

Examiner Initials*	Cite No.[1]	Document Number Number-Kind Code[2] (if known)	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear

FOREIGN PATENT DOCUMENTS

Examiner Initials*	Cite No.[1]	Foreign Patent Document Country Code[3]-Number[4]-Kind Code[5] (if known)	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages Or Relevant Figures Appear	T[6]

Examiner Signature		Date Considered	

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Samsung Bioepis Exhibit No. 1002
Page 9261

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Sheet 2 of 2

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Application Number	13/426,973
Filing Date	March 22, 2012
First Named Inventor	Leonard Bell
Art Unit	1644
Examiner Name	J. L. Rogers
Attorney Docket Number	ALXN-P08-114

NON PATENT LITERATURE DOCUMENTS

Examiner Initials*	Cite No.[1]	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, page(s), volume-issue number(s), publisher, city and/or country where published.	T[2]
		Clinics, Biotechnology News, Vol. 24(30): 10 (2004).	
		Hillmen et al., "Eculizumab, a C5 Complement-Blocking Antibody, Controls Hemolysis in Paroxysmal Nocturnal Hemoglobinuria (PNH) with Responses Maintained over prolonged Period of Therapy" Journal of The American Society of Hematology, Vol. 102(11), Abstract 1858 (2003).	
		Hillmen et al., "Eculizumab, a C5 complement-blocking antibody, controls haemolysis in paroxysmal nocturnal haemoglobinuria (PNH) with responses maintained over a prolonged period of therapy," British Journal of Haematology, Vol. 125 (Suppl. 1): 1-72, Abstract 5 (2004).	
		Notice of Opposition for EP Patent No. 1720571, dated 3/18/2013.	

Examiner Signature		Date Considered	

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Docket No.: ALXN-P08-114
(PATENT)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of:
Bell et al.

Application No.: 13/426,973 Confirmation No.: 8851

Filed: March 22, 2012 Art Unit: 1644

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Commissioner for Patents
P.O. Box 1450
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Samsung Bioepis Exhibit No. 1002
Page 9263

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MAY 14 2013

Application No.: 13/426,973 Docket No.: ALXN-P08-114

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Dated: May 14, 2013

Respectfully submitted,

By_/Jason S. Cathelyn/__
Jason S. Cathelyn, Ph.D.
Registration No.: 68,195
ROPES & GRAY LLP
Prudential Tower
800 Boylston Street
Boston, Massachusetts 02199
(617) 951-7000
(617) 235-9492 (Fax)
Attorneys/Agents For Applicants

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INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Use as many sheets as necessary)

Sheet 1 of 2

Complete if Known	
Application Number	13/426,973
Filing Date	March 22, 2012
First Named Inventor	Leonard Bell
Art Unit	1644
Examiner Name	J. L. Rogers
Attorney Docket Number	ALXN-P08-114

U.S. PATENT DOCUMENTS

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Examiner Initials*	Cite No.[1]	Foreign Patent Document Country Code[3]-Number[4]-Kind Code[5] (if known)	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages Or Relevant Figures Appear	T[6]

Examiner Signature		Date Considered	

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Sheet 2 of 2

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Filing Date	March 22, 2012
First Named Inventor	Leonard Bell
Art Unit	1644
Examiner Name	J. L. Rogers
Attorney Docket Number	ALXN-P08-114

NON PATENT LITERATURE DOCUMENTS

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		Hillmen et al., "Eculizumab, a C5 Complement-Blocking Antibody, Controls Hemolysis in Paroxysmal Nocturnal Hemoglobinuria (PNH) with Responses Maintained over prolonged Period of Therapy" Journal of The American Society of Hematology, Vol. 102(11), Abstract 1858 (2003).	
		Hillmen et al., "Eculizumab, a C5 complement-blocking antibody, controls haemolysis in paroxysmal nocturnal haemoglobinuria (PNH) with responses maintained over a prolonged period of therapy," British Journal of Haematology, Vol. 125 (Suppl. 1): 1-72, Abstract 5 (2004).	
		Notice of Opposition for EP Patent No. 1720571, dated 3/18/2013.	

Examiner Signature		Date Considered	

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[1]Applicant's unique citation designation number (optional). [2]Applicant is to place a check mark here if English language Translation is attached.

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MAY 14 2013

FAX TRANSMISSION

DATE: May 14, 2013

PTO IDENTIFIER: **Application Number** 13/426,973
Patent Number
Inventor: Leonard Bell, et. al.

MESSAGE TO: Examiner J. L. Rogers

COMPANY: US Patent and Trademark Office

FAX NUMBER: ~~(570) 270-6374~~ 571-273-8300

FROM: ROPES & GRAY LLP
Jason S. Cathelyn, Ph.D.

PHONE: (617) 951-7725

Attorney Dkt. #: ALXN-P08-114

PAGES (Including Cover Sheet): 34

CONTENTS:

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ROPES & GRAY LLP
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PAGE 1/34 * RCVD AT 5/14/2013 6:22:14 PM [Eastern Daylight Time] * SVR:W-PTOFAX-002/30 * DNIS:2738300 * CSID:(617) 951-7050 * DURATION (mm-ss):18-09

Samsung Bioepis Exhibit No. 1002
Page 9267

Electronic Acknowledgement Receipt

EFS ID:	15771020
Application Number:	13426973
International Application Number:	
Confirmation Number:	8851
Title of Invention:	TREATMENT OF PAROXYSMAL NOCTURNAL HEMOGLOBINURIA PATIENTS BY AN INHIBITOR OF COMPLEMENT
First Named Inventor/Applicant Name:	Leonard Bell
Customer Number:	28120
Filer:	Jason S. Cathelyn/ginny blundell
Filer Authorized By:	Jason S. Cathelyn
Attorney Docket Number:	ALXN-P08-114
Receipt Date:	14-MAY-2013
Filing Date:	22-MAR-2012
Time Stamp:	15:11:18
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	Transmittal Letter	ALEX-P08-114_SIDS.pdf	82191	no	2

Warnings:	
Information:	

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2	Non Patent Literature	ALEX-P08-114_Notice_Opposition.pdf	23779302	no	22
Warnings:					
Information:					
3	Non Patent Literature	Clinics_Biotechnology_News_24.pdf	6292303	no	1
Warnings:					
Information:					
4	Non Patent Literature	Hillmen_Abstract_1858.pdf	2172732	no	3
Warnings:					
Information:					
5	Non Patent Literature	Hillmen_Abstract_5.pdf	127889	no	2
Warnings:					
Information:					
6	Information Disclosure Statement (IDS) Form (SB08)	ALEX-P08-114_SB08.pdf	127884	no	2
Warnings:					
Information:					
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UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
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Alexandria, Virginia 22313-1450
www.uspto.gov

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

ROPES & GRAY LLP
IPRM - Floor 43
PRUDENTIAL TOWER
800 BOYLSTON STREET
BOSTON, MA 02199-3600

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.

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).

May 20, 2013

/JAMES ROGERS/
Examiner, Art Unit 1644

/DANIEL E. KOLKER/
Supervisory Patent Examiner, Art Unit 1644
May 24, 2013

Notice of References Cited	Application/Control No. 13/426,973	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	Classification
*	A	US-6,355,245 B1	03-2002	Evans et al.	424/145.1
*	B	US-2005/0271660 A1	12-2005	Wang, Yi	424/144.1
	C	US-			
	D	US-			
	E	US-			
	F	US-			
	G	US-			
	H	US-			
	I	US-			
	J	US-			
	K	US-			
	L	US-			
	M	US-			

FOREIGN PATENT DOCUMENTS

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

NON-PATENT DOCUMENTS

*		Include as applicable: Author, Title Date, Publisher, Edition or Volume, Pertinent Pages)
	U	
	V	
	W	
	X	

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

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L48            4 FILE IPA
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Page 9280

supplemental STN search

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Page 9281

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INFORMATION DISCLOSURE STATEMENT BY APPLICANT

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Sheet 1 of 2

Complete if Known	
Application Number	13/426,973
Filing Date	March 22, 2012
First Named Inventor	Leonard Bell
Art Unit	1644
Examiner Name	J. L. Rogers
Attorney Docket Number	ALXN-P08-114

U.S. PATENT DOCUMENTS

Examiner Initials*	Cite No.[1]	Document Number Number-Kind Code[2] (*if known*)	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear

FOREIGN PATENT DOCUMENTS

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Examiner Signature		Date Considered	

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NON PATENT LITERATURE DOCUMENTS

Examiner Initials*	Cite No.[1]	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, page(s), volume-issue number(s), publisher, city and/or country where published.	T[2]
		Clinics, Biotechnology News, Vol. 24(30): 10 (2004).	
		Hillmen et al., "Eculizumab, a C5 Complement-Blocking Antibody, Controls Hemolysis in Paroxysmal Nocturnal Hemoglobinuria (PNH) with Responses Maintained over prolonged Period of Therapy" Journal of The American Society of Hematology, Vol. 102(11), Abstract 1858 (2003).	
		Hillmen et al., "Eculizumab, a C5 complement-blocking antibody, controls haemolysis in paroxysmal nocturnal haemoglobinuria (PNH) with responses maintained over a prolonged period of therapy," British Journal of Haematology, Vol. 125 (Suppl. 1): 1-72, Abstract 5 (2004).	
		Notice of Opposition for EP Patent No. 1720571, dated 3/18/2013.	

Examiner Signature	/James Rogers/	Date Considered	05/16/2013

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EAST Search History

EAST Search History (Prior Art)

Ref #	Hits	Search Query	DBs	Default Operator	Plurals	Time Stamp
L1	35	((hemolytic near3 disease) or hemolysis or hemoglobinuria) near20 (C5 near5 antibody)	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2013/05/09 15:07
L3	6	L1 and ("300" near3 mg)	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2013/05/09 15:37

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First Named Inventor	Leonard Bell
Art Unit	1644
Examiner Name	J. L. Rogers
Attorney Docket Number	ALXN-P08-114

NON PATENT LITERATURE DOCUMENTS

Examiner Initials*	Cite No.[1]	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, page(s), volume-issue number(s), publisher, city and/or country where published.	T[2]
		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).	

Examiner Signature	/James Rogers/	Date Considered	05/09/2013

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

[1]Applicant's unique citation designation number (optional). [2]Applicant is to place a check mark here if English language Translation is attached.

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

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Search Notes	Application/Control No.	Applicant(s)/Patent Under Reexamination
	13426973	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	7/30/2012	JR
EAST: PGPUB, USPAT, JPO, EPO, DRWNT, INVENTOR SEARCH	7/30/2012	JR
updated	5/8/2013	JR

INTERFERENCE SEARCH			
US Class/ CPC Symbol	US Subclass / CPC Group	Date	Examiner

Docket No.: ALXN-P08-114
(PATENT)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of:
Bell et al.

Application No.: 13/426,973 | Confirmation No.: 8851

Filed: March 22, 2012 | Art Unit: 1644

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

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

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

Dear Madam:

INTRODUCTORY COMMENTS

This submission responds to the Office Action dated May 31, 2013, in the above-identified U.S. patent application. Applicants' Petition for a two-month extension of time and a Supplemental Information Disclosure Statement are submitted concurrently herewith. Please enter the following:

Remarks/Arguments begin on page 2 of this paper.

REMARKS

Applicants respectfully request reconsideration in view of the following comments. Issues raised by the Examiner will be addressed in the order they appear in the Office Action.

Claims Rejected under 35 U.S.C. § 103(a) (Non-obviousness)

At pages 3 and 4 of the Office Action, claims 91, 98, 100-106, 112, and 113 were rejected under 35 U.S.C. § 103 as allegedly being unpatentable over Hillmen et al. [(2004) *N Engl J Med* 350:552-559] and Hill et al. [(2005) *Haematologica* 90:e111-e113], in view of Evans et al. [U.S. patent no. 6,355,245] and Wang et al. [U.S. patent application publication no. 20050271660]. Claims 91, 98, 100-106, 110, 112, and 113 were rejected under 35 U.S.C. § 103 as allegedly being unpatentable over Hillmen et al. (*supra*), Hill et al. (*supra*), Evans et al. (*supra*), and Wang et al. (*supra*), in further view of Garcia et al. [(2002) *Biologicals* 30:143-151]. In addition, claims 91, 98, 100-106, 111-113, and 115 were rejected under 35 U.S.C. § 103 as allegedly being unpatentable over Hillmen et al. (*supra*), Hill et al. (*supra*), Evans et al. (*supra*), and Wang et al. (*supra*), in further view of Rosse et al. [(2004) *Hematology Am Soc Hematol Educ Program* 48-62]. Applicants traverse.

The instant claims are drawn to methods for treating PNH patients who have been, or who are to be, vaccinated against *Neisseria meningitides*. The methods comprise administering to a PNH patient an effective amount of a novel pharmaceutical composition comprising a single unit dosage form of the antagonist anti-C5 antibody eculizumab. The single unit dosage form comprises: (i) 300 mg of the anti-C5 antibody and (ii) a 10 mg/mL solution of the anti-C5 antibody. The single unit dosage form also has a volume of 30 mL. According to the Examiner, it would have been *prima facie* obvious for a skilled artisan to arrive at the pharmaceutical unit dosage forms recited by the claims. *See, e.g.*, Office Action at page 5, sixth paragraph. It was not.

The law requires for a finding of obviousness that there be, at least, a reason for a skilled artisan to combine the cited references and arrive at the claimed invention. *KSR International Co. v. Teleflex Inc.*, 550 U.S. 398, 417, 418 (2007) (emphasis added). Furthermore, the Examination Guidelines Update (2010) promulgated by the U.S.P.T.O. state that "familiar lines of argument still apply, including teaching away from the claimed invention by the prior art…and unexpected results.

Indeed, they may have even taken on *added importance* in view of the recognition in *KSR* of a variety of possible rationales."[1]

As noted in Applicants' Amendment and Response filed 22 January 2013, out of a vast genus of potential dosage forms for eculizumab – e.g., varying widely in volume, concentration, and quantity – the instant claims are drawn to a distinct species of pharmaceutical composition in which volume, concentration, and quantity are defined. The Court of Appeals for the Federal Circuit [CAFC] has been quite clear that, in such a case, a finding that this species is obvious cannot be predicated merely on the existence of myriad hypothetical possibilities. *See*, e.g., *In re Baird*, 16 F.3d 380 (Fed. Cir. 1994). The prior art must provide some reason why a skilled artisan would have selected from the multitude of possibilities the particular species claimed. *Id.* at 382-383 (Judge Lourie stating that the "disclosure of millions of compounds does not render obvious a claim to three compounds, particularly when that disclosure indicates a preference leading away from the claimed compounds").[2] The Office bears the burden of proving that the cited prior art provides that requisite reason. *See*, e.g., *In re Bell*, 991 F.2d 781, 783 (Fed. Cir. 1993).

The Examiner acknowledges that 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….and comprises a 10 mg/mL solution.[3] Therefore, since the references do not themselves teach explicitly or inherently each and every element of the claims, Applicants understand that the Examiner has relied nearly exclusively on general knowledge to supply the requisite reason for the obviousness finding. And that reason is, in essence, *convenience*.[4]

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[1] Examination Guidelines Update: Developments in the Obviousness Inquiry After KSR v. Teleflex, *Federal Register* 75(169):53643, 53645, column 3 (emphasis added).
[2] *See also* M.P.E.P. § 2144.08.
[3] "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." Office Action at page 5.
[4] According to the remarks of the Office Action dated 20 August 2012 at page 9, "given that Hillmen teaches administration of a 600 mg and 900 mg doses [of eculizumab] which can both be obtained by simply administering two or three separate single unit dosage forms of 300 mg…respectively, the claimed dosage forms are simply a matter of convenience based upon the needs of the patients."

In further support of the convenience rationale, the Examiner now also cites to the '245 patent for its teaching that eculizumab "is effective at doses of 2.2, 3, or 5 mg per kg body weight; this corresponds to 154, 210, or 350 mg of antibody for a 70kg adult human". According to the present Office Action at page 5, given that "the '245 patent teaches that 210 or 350 mg of antibody would be expected to be therapeutically effective, arriving at the 300 mg dosage would have been routine, convenient and obvious." We disagree.

As an initial matter, Applicants respectfully point out that the instantly-claimed compositions not only feature limitations with respect to the *amount* of eculizumab (300 mg) in a dosage form, but also the concentration of the antibody (10 mg/mL) in, and the solution volume (30 mL) of, that dosage form. And neither the particular concentration nor volume limitations are disclosed or suggested by the cited prior art; nor could arriving at these novel features of the invention be accounted for solely by convenience. With respect to the dosage amount limitation, however, the Office appears to assert that a 300 mg formulation is *convenient* for treatment regimens involving 154, 210, or 350 mg of anti-C5 antibody. But, in fact, the opposite is true.

Weekly or biweekly injections of 154, 210, or 350 mg would require the use of multiple 300 mg vials of the instantly claimed formulation or multiple uses of the same vial. That is, doctors or nurses wishing to administer to a patient approximately 154 mg of an anti-C5 antibody formulated at 300 mg/vial would likely have had to either use the same vial: (a) more than once for the same patient or (b) for each of two patients or, otherwise, waste half of the vial's contents. To avoid the same product waste issue, the need to administer approximately 210 mg of an antibody to a patient would have necessitated the: (i) storage of a vial for potentially weeks (using only 210 mg of the 300 mg vial for the first dose and waiting for the second administration to use the remainder) or (ii) use of at least two vials for three patients. The same or similar practice conditions would result for a 350 mg dose regimen.

Yet skilled artisans (i.e., medical practitioners) would have been well aware that such approaches ran contrary to widely-accepted, best practices for safe injection in the U.S. – that "single-dose vials are intended for a single procedure or injection and should always be discarded at the end of the procedure/injection. They should never be stored for later use or subsequent

procedures, even if for the same patient." Pugliese et al. (2010) *Am J Infect Control* 38(10):789, 793 and Figure 1 referencing Guidelines promulgated by the Centers for Disease Control, U.S. Department of Health and Human Services (Exhibit A). *See also* Dolan et al. (2010) *Am J Infect Control* 38:167, 170 (the authors advocating strict adherence to established best practices including "discard[ing] single use vials after use [and n]ever use them again for another patient"), attached as Exhibit B. These best practices were and continue to be an easily-implemented way to reduce the potential risk for inadvertent nosocomial transmission of sexually-transmitted diseases (e.g., HIV), e.g., by using auto-disposable syringes and taking "the vaccine or medicine from a single-dose vial." Gisselquist et al. (2003) *International J STD & AIDS* 14:717, 719 (Exhibit C).

Thus, it appears that the teachings of '245 patent pointed to by the Examiner actually would have led a skilled artisan away from the instantly-claimed dosage forms. At a minimum, the teachings suggest that it would not have been *convenient* to use a 300 mg dosage form for 154 mg, 210 mg, or 350 mg dosages. And if it is not a matter of convenience to administer lower dosage amounts of eculizumab in a 300 mg format, convenience simply cannot be a reason, let alone *the reason*, for a skilled artisan to have arrived at the claimed pharmaceutical compositions and thereby render the compositions obvious. Accordingly, reconsideration and withdrawal of the rejection under 35 U.S.C. § 103 are respectfully requested.

CONCLUSION

In view of the above remarks, Applicants believe the pending application is in condition for allowance. The Examiner may address any questions raised by this submission to the undersigned at 617-951-7000.

Applicant believes no fee is due with this response other than those listed on the accompanying Fee Transmittal. However, if a fee is due, please charge our Deposit Account No. 18-1945, under Order No. ALXN-P08-114 from which the undersigned is authorized to draw.

Dated: October 23, 2013

Respectfully submitted,

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Electronic Patent Application Fee Transmittal

Application Number:	13426973
Filing Date:	22-Mar-2012
Title of Invention:	TREATMENT OF PAROXYSMAL NOCTURNAL HEMOGLOBINURIA PATIENTS BY AN INHIBITOR OF COMPLEMENT
First Named Inventor/Applicant Name:	Leonard Bell
Filer:	Gitanjali Chimalakonda/ginny blundell
Attorney Docket Number:	ALXN-P08-114

Filed as Large Entity

Utility under 35 USC 111(a) Filing Fees

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Basic Filing:				
Pages:				
Claims:				
Miscellaneous-Filing:				
Petition:				
Patent-Appeals-and-Interference:				
Post-Allowance-and-Post-Issuance:				
Extension-of-Time:				
Extension - 2 months with $0 paid	1252	1	600	600

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Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Miscellaneous:				
Submission- Information Disclosure Stmt	1806	1	180	180
		Total in USD ($)		**780**

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Electronic Acknowledgement Receipt	
EFS ID:	17208253
Application Number:	13426973
International Application Number:	
Confirmation Number:	8851
Title of Invention:	TREATMENT OF PAROXYSMAL NOCTURNAL HEMOGLOBINURIA PATIENTS BY AN INHIBITOR OF COMPLEMENT
First Named Inventor/Applicant Name:	Leonard Bell
Customer Number:	28120
Filer:	Gitanjali Chimalakonda/ginny blundell
Filer Authorized By:	Gitanjali Chimalakonda
Attorney Docket Number:	ALXN-P08-114
Receipt Date:	23-OCT-2013
Filing Date:	22-MAR-2012
Time Stamp:	16:49:52
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	yes
Payment Type	Deposit Account
Payment was successfully received in RAM	$780
RAM confirmation Number	4141
Deposit Account	181945
Authorized User	
The Director of the USPTO is hereby authorized to charge indicated fees and credit any overpayment as follows: Charge any Additional Fees required under 37 C.F.R. Section 1.21 (Miscellaneous fees and charges)	

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File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Miscellaneous Incoming Letter	Exhibit_A.pdf	179376 6e7e4681970aeeaf37557f4f65f25787c41e6c98	no	10
Warnings:					
Information:					
2	Miscellaneous Incoming Letter	Exhibit_B.pdf	3737601 c00cf1d5b1f15774de158dc6a57d3e383893d585	no	6
Warnings:					
Information:					
3	Miscellaneous Incoming Letter	Exhibit_C.pdf	139417 4353c83cde4147e93f75d0324ec4e15e41871f6e	no	6
Warnings:					
Information:					
4	Transmittal Letter	ALXN-P08-114_SIDS.pdf	70620 041f0ff0458d9646eeda9e406473f21e59be53d9	no	2
Warnings:					
Information:					
5	Information Disclosure Statement (IDS) Form (SB08)	ALXN-P08-114_SB08.pdf	126523 e663bb2f016a7f2caf5006ce8ece0c3af81d4d21	no	2
Warnings:					
Information:					
This is not an USPTO supplied IDS fillable form					
6	Extension of Time	ALXN-P08-114_EOT.pdf	92207 0915c47a1c4dcf3606555441aaeaebece770796a	no	1
Warnings:					
Information:					
7	Non Patent Literature	Lee.pdf	7408440 a6f2c866d5c205eedea1b00e6febec7f3f8ec16d	no	5
Warnings:					
Information:					
8	Foreign Reference	WO_2004029207.pdf	14936102 d7ed0aebdec52998eeb513c2533e5fbe7ef6b0fe	no	196
Warnings:					
Information:					

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9		ALXN-P08-114_Reply.pdf	149621 bbd8b438e1265b014a65ce4c6c1eaa4da90d799f	yes	6

	Multipart Description/PDF files in .zip description		
	Document Description	**Start**	**End**
	Amendment/Req. Reconsideration-After Non-Final Reject	1	1
	Applicant Arguments/Remarks Made in an Amendment	2	6

Warnings:					
Information:					
10	Fee Worksheet (SB06)	fee-info.pdf	32732 0b5faa84a1a6ecdb4826c8be1f89692985a5b460	no	2
Warnings:					
Information:					
		Total Files Size (in bytes):	26872639		

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.

<u>New Applications Under 35 U.S.C. 111</u>
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.

<u>National Stage of an International Application under 35 U.S.C. 371</u>
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.

<u>New International Application Filed with the USPTO as a Receiving Office</u>
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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Injection practices among clinicians in United States health care settings

Gina Pugliese, RN, MS,[a] Cathie Gosnell, RN, MS, MBA,[b] Judene M. Bartley, MS, MPH, CIC,[c] and Scott Robinson, MA, MPH[d]
Charlotte, North Carolina

Background: Improper use of syringes, needles, and medication vials has resulted in patient-to-patient transmission of bloodborne pathogens, including hepatitis C virus. This study examined the injection practices of health care providers to identify trends and target opportunities for education on safe practices.

Methods: An on-line survey was conducted in May and June 2010 of clinicians in US health care settings that prepare and/or administer parenteral medications.

Results: The majority of the 5446 eligible respondents reported injection practices consistent with current recommendations. However, the following unsafe practices were identified: 6.0% "sometimes or always" use single-dose/single-use vials for more than 1 patient; 0.9% "sometimes or always" reuse a syringe but change the needle for use on a second patient; 15.1% reuse a syringe to enter a multidose vial and then 6.5% save that vial for use on another patient (1.1% overall).

Conclusion: Unsafe injection practices represent an ongoing threat to patient safety. Ensuring safe injection practices in all health care settings will require a multifaceted approach that focuses on surveillance, oversight, enforcement, and continuing education.

Key Words: Injection safety; bloodborne pathogens; survey needlestick injuries; safety practices; reuse syringes; reuse vials; propofol.

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Increasing reports of outbreaks in health care settings in the United States involving transmission of hepatitis B virus (HBV) and hepatitis C virus (HCV) to patients associated with unsafe injection practices and breakdowns in basic infection control have uncovered an alarming trend. Recent reviews of HBV and HCV outbreaks showed that, from 1998 to 2009, there were 51 outbreaks involving the notification of more than 75,000 potentially exposed patients and identification of 620 who became infected with HBV or HCV.[1,2] These outbreaks occurred in a variety of health care settings including 9 hospitals; 9 hemodialysis facilities; 16 outpatient clinics and ambulatory surgery centers; and 17 long-term care facilities. The majority resulted from unsafe injection practices and lapses in basic infection control practices, including failure to maintain aseptic technique when preparing or administering parenteral medications (eg, overt syringe reuse or contamination of shared parenteral medications by reused syringes); contamination of equipment and supplies (eg, preparing medications in contaminated area); or improper use and handling of blood glucose monitoring equipment (eg, single patient use fingerstick devices used on multiple patients or blood glucose meters not cleaned between patients). These identified outbreaks may represent a wider problem. For example, 67% of recently surveyed ambulatory surgical centers in 3 states were found to have at least 1 lapse in basic infection control, including unsafe injection and medication practices.[3] It is also believed that identified outbreaks represent only a portion of the true burden of infection. Many outbreaks and sporadic transmission of health care-associated viral hepatitis go unrecognized because most patients with acute HBV or HCV infection are asymptomatic or have mild nonspecific symptoms.[4,5]

Studies in the mid-1990s indicated that 20% to 39% of anesthesia personnel were reusing syringes for multiple patients[6]; by 2002, this rate had dropped to 1% to 3% according to a telephone survey of 500 randomly selected providers, including anesthesiologists, other physicians, certified registered nurse anesthetists, other nurses, and oral surgeons.[7] Limited data in 2008 from an Anesthesia Patient Safety Foundation poll indicated that up to 27% of clinicians could be reusing propofol infusion syringes while changing only the tubing between patients.[8] To gain a full understanding about current injection practice patterns to assist with targeting outreach and education, the Premier

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Conflicts of interest: None to report.

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Safety Institute conducted a Web-based survey of clinicians that prepare and/or administer parenteral medications across a wide variety of US health care settings.

METHODS

During May and June 2010, we conducted an on-line survey of clinicians practicing in a variety of health care settings using a convenience sample. The survey was posted on the Safety Institute Web site, and an e-mail invitation with a link to the survey was sent to the 39,100 subscribers of Premier's *Safety Share* public newsletter that include clinicians and health care providers from hospital and non-hospital settings. The survey link was also shared via an e-mail invitation and in the newsletters of 10 collaborating organizations. These organizations included the American Academy of Anesthesiologist Assistants; Accreditation Association for Ambulatory Health Care; American Association of Critical-Care Nurses; American Society of Health-System Pharmacists; Association for Professionals in Infection Control and Epidemiology Infusion Nurses' Society; Pittsburgh Regional Health Initiative; Society for Healthcare Epidemiology of America; Society of Gastroenterology Nurses and Associates, and Innovatix (nonacute health care providers).

The survey contained questions about awareness of injection safety and respondents' primary source and method of receiving information on this topic and frequency of performing various injection practices. These practices included those generally considered acceptable if performed with aseptic technique according to current guidelines, as well as those not recommended, having been demonstrated to result in transmission of bloodborne pathogens.[2] The items in the survey that assessed specific injection practices were grouped according to the *type* of practice (eg, syringe use, single-dose vial use, or multidose vial use) and *not* according to recommended or unacceptable practices. Respondents were also asked to indicate their professional training, the type of health care organization, and the department in which they practice the majority of the time. Respondents had the ability to provide comments for each item in the survey. Examples of both the most frequently occurring and revealing comments on current practices are summarized in the results.

The exact number of individuals receiving the link to the survey provided by the Safety Institute and 10 collaborating organizations is not known; however, the combined membership of these organizations represents a wide variety of professions and practice settings. There were a total of 8,035 responses to the survey. All respondents were asked 3 general questions about their knowledge of injection safety and the source and format of this information. This information was analyzed separately.

We eliminated 492 respondents who identified themselves as pharmacists after learning from the open-ended responses that the majority of the pharmacists were working under a sterile pharmacy hood and not preparing or administering parenteral medications at the point of administration. An additional 2,097 responses were eliminated that answered "no" (1,678) or did not respond (419) to the question, "in your current practice do you prepare or administer parenteral medications," at which time the survey automatically closed, and participants were thanked for their participation. Thus, a total of 5,446 respondents was included in the final analysis.

RESULTS

The total number of individuals who actually received the link to the survey (eg, both opened and read the invitation) was not known, thus an overall response rate could not be determined. In the preliminary analysis of the 8,035 respondents, 79.6% answered "yes" to the first item in the survey "prior to receiving the survey, have you ever heard of injection safety?" The next 2 items asked about the source and format of this information. The professional organization was selected as the most frequent source (60.1%) and guidelines as the most common format (59.6%) (Table 1).

The fourth item asked them to indicate "yes or no" to the question, "in your current practice do you prepare or administer parenteral medications?" A total of 5,446 respondents answering yes to this question were included in the final analysis and represented a wide range of health care organizations (both hospital and non-hospital) and departments (Table 2). Of the 5,199 who indicated their health care organization, 66.0% (3,432) were from hospitals and 34.0% (1,767) were from non-hospital settings. The majority of respondents identified themselves as registered nurses (89.5%). Responses on specific injection practices are summarized in Table 3 and below.

Acceptable practices if performed with aseptic technique

Administering a medication in a syringe prepared by someone else. The majority of respondents (71.0%) indicated that they never administered a medication in a syringe that was prepared by someone else. Only 29.0% indicated that they "sometimes or always" administered medications prepared by someone else. The most frequent comments provided by this group described when they engaged in this practice, such as, "*only during a code or emergency, only in vaccine and*

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Table 1. Knowledge-awareness of injection safety

Source	n (%)
How did you hear about injection safety?	
Professional organizations	3568 (60.1)
Coworkers	2750 (45.9)
Centers for Disease Control and Prevention (CDC)	1854 (31.0)
Supervisor	1354 (22.6)
Media	898 (15.0)
Health department	780 (13.0)
Other	1108 (18.5)
How was information received?	
Guidelines	3536 (59.6)
Educational session - seminar	3278 (55.2)
Bulletins	2065 (34.8)
Brochures	1137 (19.2)
Textbook	1059 (17.8)
Other	727 (12.3)

NOTE. Total frequencies vary; multiple responses were possible; some respondents did not answer all questions.

flu clinics," and many pointed out that "*the syringe was always labeled*" or that they "*watched the person preparing the syringe.*"

Enter a single-dose vial more than once for the same patient. A total of 30.2% (1,599 respondents) reported that they "always or sometimes" enter a single-dose/single-use vial more than once for the same patient. However, we did not assess whether the respondents were using the same or a new sterile syringe to obtain the additional doses for that same patient. Comments included reasons such as, "*if it is done within 24 hours; only if a short time has passed; when giving heparin in dialysis lines; as a cost-cutting measure; we don't want to waste the drug; and during a code.*" Many of the respondents indicated that this was a practice for specific drugs, providing examples, such as the following: "*IV Dilaudid, insulin, lidocaine, Narcan, phenylephrine, Ativan, terbutaline, and fentanyl.*"

Use a multidose vial for more than 1 patient. A third of respondents (34.4%) never use a multidose vial on more than 1 patient, with the frequent comment: "*we don't use multidose vials at our organization.*" However, the majority (65.6%) is using multidose vials for more than 1 patient. Approximately half of the comments indicated they were using multidose vials for specific medications, and the most frequent examples were vaccines, tuberculin skin testing, vitamin B12, lidocaine, and insulin. The other half of the comments were about the techniques used, such as the following: "*I use a new syringe for each entry, and we date the vials after opening.*"

Practices not considered appropriate or consistent with current guidelines

Use of single-dose vial for more than 1 patient. A total of 318 respondents indicated that they "sometimes or always" use single-dose/single-use vials for more than 1 patient representing 6.0% of all respondents. Examples of frequent comments to explain this practice were the following: "*as a cost-saving measure, done only when obtaining all of the doses at the same time, always using a new syringe, it depends on*

Table 2. Characteristics of respondents on survey of injection practices

Category	n (%)
Professional training	
Anesthesiologist assistant (AA-C)	120 (2.4)
Anesthetist (CRNA)	49 (1.0)
Dentist (DDS)	9 (0.2)
Licensed nurse (LPN, LVN)	145 (2.8)
Laboratory technologist	13 (0.3)
Operating room technician (ORT)	10 (0.2)
Patient care technician (PCT)	35 (0.7)
Pharmacist	23 (0.5)
Physician (MD, DO, DPM)	120 (2.4)
Registered nurse (RN)	4570 (89.5)
Respiratory therapist	10 (0.2)
Health care organization	
Hospital setting (n = 3432)	
Hospital (<100 beds)	675 (13.0)
Hospital (100-250 beds)	1005 (19.3)
Hospital (251-500 beds)	1145 (22.0)
Hospital (>500 beds)	607 (11.7)
Non-hospital setting (n = 1767)	
Ambulatory surgery center	513 (9.9)
Ambulatory care center (1) (Hospital-based/affiliated)	244 (4.7)
Ambulatory care center (1) (stand alone)	456 (8.8)
Dialysis	10 (0.2)
Home care (2)	133 (2.6)
Long-term care (3)	110 (2.1)
Physician's office	243 (4.7)
Urgent care center (4) (stand alone)	22 (0.4)
Other (5)	36 (0.7)
Primary practice area/department	
Ambulatory (6)	185 (3.6)
Cardiac catheterization/electrophysiology (EP)	56 (1.1)
Emergency care	342 (6.6)
Endoscopy	321 (6.2)
General patient clinical care (7)	1276 (24.6)
Geriatrics/home care (8)	84 (1.6)
Infection control/employee health	233 (4.5)
Infusion therapy	214 (4.1)
Intensive (critical) care (9)	835 (16.1)
Maternal-child (10)	279 (5.4)
Oncology	147 (2.8)
Pain management	52 (1.00)
Radiology-radiation	90 (1.7)
Surgery or anesthesia services	927 (17.9)
Other (11)	146 (2.8)

NOTE. Total frequencies vary; some respondents did not answer all questions. (1) Clinics, public health, ambulatory infusion, behavioral health; (2) home health, home infusion, hospice; (3) assisted living, nursing homes; (4) emergency room (ER), trauma centers; (5) dental, laboratories, outpatient pharmacies, institutional settings; (6) clinics, offices, dialysis; (7) medical/surgical, telemetry, general care units; (8) long-term care, subacute, assisted living; (9) intensive care unit (ICU), coronary care unit (CCU), surgical intensive care unit (SICU); (10) Labor and delivery, mother baby, pediatrics, pediatric intensive care unit (PICU), neonatal intensive care unit (NICU); (11) administration, education, mental health.

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the size of the vial, only with sterile technique, when giving specific drugs (eg, vaccines or insulin), and when giving propofol during the shortage."

Reuse a syringe but change the needle for use on a second patient. Forty-five respondents representing 1.0% reported that they "sometimes or always" administer medication to more than 1 patient using the same syringe but a new sterile needle for each patient. Comments were provided by only 4 of the respondents, and 3 indicated they do this with insulin and 1 with propofol. Of the 37 individuals who provided information on the organization where they work, 24 (64.9%) worked in hospital settings, and 13 (35.1%) worked in non-hospital settings. Twelve of the 13 worked in ambulatory surgery centers, and the 1 remaining person worked in a long-term care facility.

Reuse syringe for additional doses from the same multidose vial. A total of 797 respondents (15.1%) indicated that they are "sometimes or always" reusing a syringe for additional doses from the same multidose vial for the same patient. Frequent comments made by those who reported this practice included the following: *"when giving insulin; for moderate sedation; for conscious sedation; for emergency situation; for critical care patients; for multiple IV medication doses, we use the vial as the cap for the needle if using the syringe more than once."* For those respondents who reported "always or sometimes" engaging in this practice, the survey prompted them to answer an additional question about what they did with the vial after re-entry with same syringe. The majority of those answering the follow-up question, 738 of 789 (93.5%), indicated that they discarded the vial. However, an alarming 51 of the 789 (6.5%) indicated that they *"saved that vial for use on another patient."* Four of the 51 clinicians provided comments: 2 indicated they did this with insulin, 1 stated *"only if there was medication left in the vial,"* and 1 explained *"only if the vial remained sterile."* A number of respondents—who indicated they *"always discard the vial"* after re-entry for the same patient—pointed out that they did observe this practice among other clinicians.

Of the 51 professionals who reported reusing a syringe to obtain an additional dose from a multidose vial and then leaving it for use on another patient, approximately half (52.0%) were from the hospital setting, and the other half (48.0%) were from the non-hospital setting.

Of the 47 who reported their department, 13 (27.7%) indicated they worked in surgery or anesthesia; 9 (19.0%) in general patient care; 3 (6.4%) in endoscopy; 3 (6.4%) in oncology; 3 (6.4%) in a physician office; 3 (6.4%) in emergency care; and the remaining 13 (27.7%) worked in a variety of other departments/locations, such as cardiac catheterization laboratory, employee health, dermatology, pain management clinic, and a travel clinic.

Use a bag or bottle of intravenous solution as a source of supply or medication diluent for more than 1 patient. A total of 448 respondents (9.0%) indicated that they "always or sometimes" use a bag or bottle of intravenous (IV) solution as a source of supply or medication diluent for more than 1 patient. The most frequent comments included the following: *"always use alcohol pad first; with one hour expiration; always a new needle and syringe; draw flushes with a spike; only for 24 hours; only in the med room; use a 500-mL bag of saline with stop-cock to dilute IV meds; only when we are out of single bottles of diluents."*

DISCUSSION

Our 2010 study aimed to identify the current injection practices of clinicians in US health care settings to assess the extent of acceptable and improper use of syringes, needles, and medication vials during preparation and administration of parenteral medications across multiple professions in both the hospital and the non-hospital settings. Although the majority of respondents indicated they were following recommended safe injection practices, even the small percentage of health care providers who were identified as not complying with recommended practices is alarming. Anything less than 100% compliance with infection control guidelines and aseptic technique contributes to risk of transmission of bloodborne viruses resulting in infections; both individual cases and outbreaks may go undetected for some time. In addition to increasing the potential for patient infections, unsafe injection practices put providers themselves at risk of needlestick injuries and potential infections, as well as licensing board actions and malpractice suits.[4]

Mistaken beliefs

There are a number of mistaken beliefs about the risks associated with syringe reuse and aseptic technique when handling injectable medications during preparation and administration that likely contribute to many of the outbreaks of health care-associated viral infections such as HBV and HCV infections.[4,6,7-13] For example, there is the belief that contamination is limited to the needle portion when a syringe and needle are used together as a unit. There is also an incorrect belief that the syringe does not become contaminated if the plunger is only "pushed" to inject medications and not "pulled" to aspirate or withdraw. However, decades old experimental studies have shown that contamination does in fact extend to the barrel of the syringe during intramuscular, subcutaneous,

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intradermal, and IV injections.[4,10-12] There is an additional risk of syringe contamination resulting from the negative pressure that occurs if a contaminated needle is removed from the syringe.

Another mistaken belief, in the case of IV administration, is that there is no risk of syringe contamination if the injection is given into the fluid path of IV tubing that is not visibly contaminated with blood.[4] To the contrary, the risk for syringe contamination is not eliminated by the length of IV tubing or the presence of heparin locks or valves.[13] When a contaminated needle or syringe is used to draw medication from a vial, the contamination can then be transferred to the vial. Professionals unfortunately often cite a need to reduce waste and costs as their rationale for reuse.

Aseptic technique is absolutely essential when handling, preparing, and administering parenteral medications (ie, injection or infusion) to prevent microbial contamination, protect the patient from infection, and prevent the spread of pathogens. Figure 1 summarizes the current recommendation for injection practices for patient safety.

Acceptable practices if performed with aseptic technique

There are a number of injection practices that are considered acceptable only if aseptic technique is strictly maintained. If these practices are not performed aseptically, they can lead to contamination of the injection equipment and supplies and disease transmission.

Administer a medication in a syringe prepared by someone else. Whereas this practice of administering a medication in a syringe prepared by someone else is not addressed in any guidelines, the person administering the injection must assume that aseptic technique was used to draw up the medication. We were glad to see that a common theme of the 1,557 respondents that indicated they always or sometimes engage in this practice was that they "*always watched the person preparing the syringe and ensured it was labeled*," suggesting that they understood the importance of aseptic technique.

Re-entry of single-dose vial for same patient. Approximately one third of our respondents indicated that they enter a *single-dose/single-use vial* more than once for an additional dose for the same patient; however, we did not assess whether they used the same syringe or a new sterile syringe for re-entry. The Centers for Disease Control and Prevention (CDC) guidelines emphasize that needles and syringes are single-use items and that any vial should *not* be entered with a used syringe or needle (Fig 1). First, re-entering a single-dose vial with the same needle is a risky practice because, if strict aseptic technique is not followed, there is a potential for contaminating the needle through inadvertent touch contamination from contact with organisms on the patient's skin, the IV tubing/access device if one is used (eg, heparin lock) that may be contaminated with the patient's blood, or during re-entry into the used vial. The risk of bacterial contamination is especially important for patients who may be immunocompromised. The use of a new sterile syringe and needle for re-entry into the vial does not eliminate the risk of compromising the sterility of single-dose vials of medications *if* strict aseptic technique is not used and the vial becomes contaminated. Once contaminated, the opportunities for bacterial growth are increased the longer the time elapsing between uses and the lack of bacteriostatic or preservative agents in many single-dose vials to inhibit bacterial growth (eg, vaccines). It is also important to note that single-dose vials are intended for a single procedure or injection and should always be discarded at the end of the procedure/injection. They should never be stored for later use or subsequent procedures, even if for the same patient.

Reuse of multidose vials. The majority of respondents (65.6%) reported using multidose vials for more than 1 patient. Although multidose vials contain more than 1 dose of medication because they contain a bacteriostatic agent, there is still a risk that a multidose vial may become contaminated. It is also important to note that bacteriostatic agents are not effective against viruses, such as HBV and HCV. It is for these reasons that the CDC recommends single-dose vials be used whenever possible and that medications packaged as multidose vials be assigned to a single patient whenever possible (Fig 1).

Practices not considered appropriate or consistent with current guidelines

There are certain inappropriate injection practices that have been associated with disease transmission and are dangerous and unacceptable.

Reuse of single-dose vials for multiple patients. The CDC explicitly recommends that single-dose vials or ampoules not be used for multiple patients (Fig 1). However, we found that 318 professionals, 6.0% of the respondents, reported this was their practice, and comments indicated this was often done with vaccines, insulin, and propofol. Another frequent comment was that reuse of the single-dose vial depended on the size of the vial. This comment reflects the confusion that many providers have about large volume vials that are labeled as single use (ie, single dose) believing that the large volume in the container makes it suitable for multiple patients and not to use it would be

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Injection safety is a set of measures taken to perform injections in an optimally safe manner for patients, health care personnel, and others.

Aseptic technique refers to the manner of handling medications and injection equipment to prevent microbial contamination; it applies to the handling, preparation, and storage of medications as well as the handling of all supplies used for injections and infusions, including syringes, needles, and IV tubing.

Recommendations	Practices You Must Know	CDC Category*
Use aseptic technique.	• Avoid contamination of sterile injection equipment.	1A
	• Do not administer medications from a syringe to multiple patients, even if the needle or cannula on the syringe is changed.	1A
Use syringes, needles and cannulae only once.	• Needles, cannulae and syringes are sterile, single-use items; they should not be reused for another patient nor to access a medication or solution that might be used for a subsequent patient.	1A
Use single-dose vials for parenteral medications *whenever possible.*	• Do not administer medications from single-dose vials or ampules to multiple patients or combine leftover contents for later use.	1A
If multi-dose vials are used, assign to a single patient *whenever possible.*	• If multi-dose vials must be used, both the needle or cannula and syringe used to access the multi-dose vial must be sterile.	1A
	• Do not keep multi-dose vials in the immediate patient treatment area and store in accordance with the manufacturer's recommendations; discard if sterility is compromised or questionable.	1A
Use fluid infusion and administration sets (i.e., intravenous bags, tubing and connectors) for one patient only and dispose appropriately after use.	• Do not use bags or bottles of intravenous solution as a common source of supply for more than one patient.	1B
	• Consider a syringe or needle/cannula contaminated once it has been used to enter or connect to a patient's intravenous infusion bag or administration set.	1B

*Category IA: Strongly recommended and supported by well-designed experimental, clinical or epidemiologic studies.
Category IB: Strongly recommended and supported by some experimental, clinical or epidemiologic studies and a strong theoretical rationale.
FROM: Centers for Disease Control and Prevention. Guideline for isolation precautions: preventing transmission of infectious agents in healthcare settings 2007. Atlanta (GA): U.S. Department of Health and Human Services, CDC; 2007. Available at: http://www.cdc.gov/ncidod/dhqp/gl_isolation.html.

Fig 1. Recommended injection practices for patient safety.

wasteful. A number of unsafe practices such as reuse of single-dose vials on multiple patients are done with the notion that they reduce costs without an appreciation of the risks involved. For example, in a Nevada endoscopy center outbreak investigated in 2008, it was discovered that syringes were routinely reused, after changing needles, to obtain additional doses of propofol from single-dose vials for patients who required additional sedation.[14,15] Although the syringe was discarded at the end of the procedure, any remaining medication in the single-dose propofol vial was used for subsequent patients. Over 63,000 patients who had undergone procedures were exposed to this long-standing practice and at risk of bloodborne pathogen transmission. Overall, 106 cases of hepatitis C were linked to this outbreak, costing the health department nearly $21 million for outbreak investigation, response, and testing of potentially exposed patients.[16]

Because propofol is formulated in a lipid emulsion that supports rapid bacterial growth even with inclusion of a bacteriostatic agent, there have also been numerous outbreaks from bacterial pathogens linked to reuse of single-dose vials of propofol.[17] The recent propofol shortage has prompted a number of providers to reuse single-dose vials of propofol, even though this is a very risky practice and has been implicated in numerous outbreaks of both viral and bacterial pathogens.[4,17]

Overt syringe reuse. Any form of syringe reuse is a dangerous practice. An alarming finding was that nearly 1.0% (45 out of 5,472 clinicians) responding to the question indicated that they use the *same* syringe for multiple patients but *change the needle* for each patient. Even 1% of clinician performing this unacceptable practice could translate into thousands of patients at risk and contribute to the burden of bloodborne pathogen transmission.

In an outbreak in Oklahoma, direct syringe reuse resulted in over 100 cases of HBV and HCV infections over a 3-year period.[16] Here, a professional in a pain remediation clinic routinely prepared a single needle and syringe at the beginning of each clinic session for 3 different medications. The 3 needles and syringes were used to administer the 3 medications sequentially to all patients treated in the individual clinic session through a peripheral IV catheter.

We were pleased to see that the majority (99.2%) of respondents indicated they never engaged in this practice and provided comments that reflected their awareness of this practice as egregious. These comments characterized the practice as "*appalling, horrifying, or gross.*"

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Table 3. Injection practices

	Never, n (%)	Combined always + sometimes, n (%)	Sometimes, n (%)	Always, n (%)	Total, n*
Acceptable practices if performed with aseptic technique					
How often do you administer a medication in a syringe that was prepared by someone else?	3813 (71.0)	1557 (29.0)	1482 (27.6)	75 (1.4)	5370
How often do you enter a single-dose/single-use vial more than once to obtain additional doses for the same patient?	3703 (69.8)	1599 (30.2)	1497 (28.2)	102 (1.9)	5302
How often do you use multidose vials for more than one patient?	1827 (34.4)	3484 (65.6)	2296 (43.2)	1188 (22.4)	5311
Practices not considered appropriate or consistent with current guidelines					
How often do you use single-dose/single-use vials for more than 1 patient?	4985 (94.0)	318 (6.0)	296 (5.6)	22 (0.4)	5303
How often do you administer medication to more than 1 patient using the *same syringe* but a *new sterile needle for each patient*?	5247 (99.2)	45 (0.9)	25 (0.5)	20 (0.4)	5292
How often do you use a bag or bottle of intravenous solution as a source of supply or medication diluent for more than 1 patient?	4817 (91.5)	448 (9.0)	403 (7.7)	45 (0.9)	5265
How often do you reuse a syringe to obtain additional doses from the *same multi-dose vial* for the *same patient*?	4492 (84.9)	797 (15.1)	714 (13.5)	83 (1.6)	5289
The disposition of the vial for 789 of the 797 who "always or sometimes" reuse a syringe to obtain additional doses from the *same multi-dose vial* for the *same patient*	Discard vial? 738 (93.5)	Leave for use on another patient? 51 (6.5)			789

*Total n = number of responses to each question. Frequencies vary; some respondents did not answer all questions.

Contamination of shared medications from reuse of syringes

Another deficient practice that has resulted in HBV and HCV transmission involves the reuse of a syringe to withdraw medications or solutions from containers of medication or solution that might be shared. This type of error does not typically involve overt reuse of a syringe for multiple patients. Instead, a syringe is reused to draw up additional medication for a single patient, thereby contaminating the medication vial or IV bag of solution that is subsequently used for multiple patients.[4]

For example, this practice led to the outbreak of HCV in the Nevada endoscopy center described above that involved routine reuse of syringes, after changing the needle, to obtain *additional doses of medication from a single-dose vial of propofol that was used for subsequent patients.*[15]

The current CDC guidelines specifically recommend that syringes, cannulas, and needles be used only once, and, if multidose vials are used, both the needle or cannula and syringe used to access the multidose vial must be sterile (Fig 1).[9] The CDC guidelines also recommend that needles and syringes should not be reused to access a medication or solution that might be used for a subsequent patient. Additionally, the CDC recommends limiting the use of multidose vials of medication to single patients, whenever possible, as an extra barrier of protection against unrecognized syringe reuse or other means of vial contamination.

In our study, the 797 respondents (15.1%) that indicated that they "sometimes or always" reuse a syringe for additional doses from the same multidose vial for the same patient were asked to indicate the disposition of the multidose vial. A total of 51 of the 789 (6.5%) who answered the question on disposition of the vial indicated that "*they saved the vial for reuse on another patient.*" Although only 4 of the 51 provided comments, they do provide some insight into the mistaken belief by some health care professionals that this practice is safe as long as good technique is used, for example, explaining this practice is done "*only if the vial remained sterile.*" A number of respondents who indicated they never engage in this practice did provide a comment that they have observed others doing this, suggesting that this practice may be more common than our data indicate.

Use a bag or bottle of IV solution for more than 1 patient. In another large outbreak, 99 patients treated at a hematology-oncology clinic in Nebraska were infected with HCV when a nurse reused syringes,

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after drawing blood from central venous catheters, to withdraw saline solution from 500-mL bags for flush procedures. Each bag of saline was routinely used as a common source of flush for 25 to 50 patients.[18] Our survey found that at least 448 health care professionals are using a bag or bottle of IV solution as a source of supply or medication diluent for more than 1 patient. There is little doubt that re-entering IV bags to obtain diluents for medications has the potential for outbreaks of significant size if large volume bags are used and aseptic technique is not followed as happened in the Nebraska outbreak. Some comments suggest that there is some awareness of potential risk and certain controls were being put into place that are believed to reduce the risk, for example: "*we limit use to 24 hours*" or "*we only do this in the medication room.*" However, even with limiting the use of IV bags as a common supply to 24 hours, this is still not an acceptable practice. Although it may shorten the duration of potential exposure, it will not prevent potential disease transmission if the IV bag becomes contaminated.

Insulin administration. "During insulin administration" was a common theme among the comments for many of the practices that are considered unsafe, for example, using single-dose vials for more than 1 patient, reusing a syringe on another patient after changing the needle, and reusing a syringe for the same multidose vial and then saving the vial for use on another patient. This finding is disturbing given the frequency of outbreaks of HBV infections from improper use and handling of blood glucose monitoring equipment, such as reusing fingerstick devices for multiple patients and sharing blood glucose meters between patients without disinfecting after each use.[19] Although many of the 15 reported outbreaks in the past decade have affected long-term care residents, the same conditions that facilitate transmission can be present in a wide variety of settings. A recent survey of infection control practices at 68 ambulatory surgical centers in 3 states found lapses in blood glucose monitoring in 46.3% of the centers.[3] Our survey data in combination with these reports suggest that lapses in infection control and aseptic technique for both glucose monitoring and insulin administration may be an under-recognized issue across other health care settings and worthy of increased attention.

Hospital versus non-hospital settings

Much of the recent focus has been on unsafe injection practices in the non-hospital setting[1,3] where it is thought that attention to infection prevention and control is lacking relative to hospital settings. However, our data trends indicate that unsafe injection practices are happening in both hospital and non-hospital settings. Of those who report reusing a syringe to obtain an additional dose from a multidose vial and then leaving it for use on another patient, approximately half were from the hospital setting and the other half were from the non-hospital setting. We also found that, for those who indicated they reused syringes and only changed the needle between patients, the majority (64.9%) of those providing information on their organization worked in hospital settings, and 35.1% (13 of 37) worked in non-hospital settings. Although the proportions of respondents varied by setting, our data suggest that unsafe injection practices likely resulting from mistaken beliefs may be occurring in the hospital setting more frequently than previously thought.

Limitations

Our study has several limitations. First, because our sample was only a convenience sample and not randomized, it may not be representative of all types of health care organizations and departments. Although the respondents represented many different health care professions, the majority was registered nurses. Second, respondents may be over-represented by those who were more interested in safe practices. Third, because it was not an observational study, it relied on self-reported practices that may not fully represent actual practice. We also did not assess the respondents' number of years in practice or the geographic location of their health care setting, which would have provided additional information on where to target outreach and education. As a result, our findings provide only conservative estimates of current injection practices.

Summary: Lessons learned

Our findings provide evidence that health care professionals continue to engage in unsafe injection practices, which represent an ongoing threat to patient safety in the United States and are devastating to all those patients who are impacted. A common theme among all the outbreaks was the failure of health care providers to adhere to the most basic concepts of infection control and injection safety.[9] Despite the availability of guidance on best practices from CDC and other groups, there remains a lack of awareness and implementation of these recommendations by many.

Although non-hospital settings have come under intense scrutiny in the past few years because of the frequency of reported outbreaks and breaches in infection control,[1,3] our data indicate that some of the most flagrant infractions (syringe reuse on multiple patients

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with only a needle change and re-entry into multidose vial leaving it for reuse on another patient) are being reported at least half of the time by professionals in hospital settings.

Preventing the spread of bloodborne pathogens such as HBV, HCV, and HIV is a basic expectation anywhere health care is provided.[2-5] This applies to protection of both the patient and the health care provider. Significant progress has been made in reducing risk of occupational infection with bloodborne pathogens such as HBV following widespread adoption of safer devices, safe work practices, and hepatitis B vaccination. We need to apply the same energy for reducing risks to patients from unsafe injection practices. This will require a multifaceted approach that focuses on surveillance, oversight, enforcement, and continuing educational efforts aimed at ensuring safe injection practices in all practice settings. It will also be important to get additional insight and address some of the incorrect beliefs about injection practices during educational programs. The source and format for receipt of information about injection safety (Table 1) should help guide educational efforts. The trends identified in this survey, including the range of locations and departments where unsafe practices are occurring, indicate the need for education in all settings where health care is provided. There is also a need for targeted educational initiatives, including curricula in nursing, medical, and other health care professional training and vocational programs. In addition to the CDC, a number of organizations and groups have educational resources, videos, guidelines, and position papers to assist in education and training.[20-23] Although there is clear need for more education, this may not necessarily eliminate all unsafe practices. Adopting principles from human factors engineering, we must consider redesigning devices, equipment, and processes to reduce or eliminate risk of bloodborne pathogen transmission. Just as we have seen sharps safety devices reduce risk of occupational needlesticks, we also need to look at engineering changes to reduce risks of unsafe injection practices, for example, redesigns of syringes that make it easy to comply with injection safety and consistent and clear labeling of medications vials to encourage intended usage.

Finally, each and every health care provider has a duty to carefully review their infection prevention and control practices and the practices of any staff peers as well as those they supervise, ensuring they are all following the recommended practices (Fig 1). We must create a safety culture whereby every provider is empowered to take responsibility to stop any colleague from engaging in unsafe practices and help ensure that safe practices are understood and followed by all. Patients must also be educated on safe practices and be empowered to question the practices of any health care provider that may impact the safety of a patient.

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AJIC special article

APIC position paper: Safe injection, infusion, and medication vial practices in health care

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Outbreaks involving the transmission of bloodborne pathogens or other microbial pathogens to patients in various types of health care settings due to unsafe injection, infusion, and medication vial practices are unacceptable. Each of the outbreaks could have been prevented by the use of proper aseptic technique in conjunction with basic infection prevention practices for handling parenteral medications, administration of injections, and procurement and sampling of blood. This document provides practice guidance for health care facilities on essential safe injection, infusion, and vial practices that should be consistently implemented in such settings.

Key Words: Bloodborne pathogens; injection; infusion; medication vial practices; aseptic technique; parenteral medications; administration of injections; procurement of blood.

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The transmission of bloodborne viruses and other microbial pathogens to patients during routine health care procedures continues to occur because of the use of unsafe and improper injection, infusion, and medication vial practices by health care professionals in various clinical settings throughout the United States.[1-13] Breaches in safe injection, infusion, and medication vial practices continue to result in unacceptable and devastating events for patients. More than 35 outbreaks of viral hepatitis have occurred in the United States over the past 10 years because of these unsafe practices and other breaches of infection prevention procedures. These outbreaks have resulted in the exposure of >100,000 individuals to viral hepatitis and the transmission of either hepatitis B virus (HBV) or hepatitis C virus (HCV) to more than 500 patients.[13] The unsafe practices used by health care personnel in these outbreaks can be categorized as (1) syringe reuse between patients during parenteral medication administration to multiple patients, (2) contamination of medication vials or intravenous (IV) bags after having been accessed with a used syringe and/or needle, (3) failure to follow basic injection safety practices when preparing and administering parenteral medications to multiple patients, and (4) inappropriate care/maintenance of finger stick devices and glucometer equipment between use on multiple patients.

In 2001, an anesthesiologist at a New York endoscopy clinic infected 19 patients with HCV by improperly reusing syringes and contaminating a multi-dose anesthesia medication vial subsequently used for multiple patients.[5] A similar HCV outbreak because of unsafe injection practices occurred in New York in 2002 and 2007, affecting a total of 102 patients.[13] In 2002, nearly 100 Nebraska hematology oncology clinic patients contracted HCV after a health care worker (HCW) responsible for medication infusions routinely used the same syringe and needle from a HCV-positive patient's blood draw to obtain saline flush solution from an IV bag. As a result, the patient's blood on the needle of the syringe was inoculated into the IV bag, which was then used as flushing solution for several other patients.[9] One of the most recent HCV

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outbreaks occurred at an endoscopy center in Nevada in 2008, again because of unsafe injection practices involving reusing syringes and sharing single-use medication vials between patients. This outbreak received significant media attention because, in part, of the fact that 63,000 persons were identified as being at potential risk for acquiring hepatitis. More than 12,000 patients have been tested to date, and at least 115 patients have been found to be infected with HCV. The investigation is ongoing.[12]

The Association for Professionals in Infection Control and Epidemiology (APIC) recognizes these outbreaks as unacceptable. Each of the outbreaks could have been prevented by the use of proper aseptic technique in conjunction with basic infection prevention practices for handling parenteral medications, administration of injections, and procurement and sampling of blood. Responsibility for the oversight and monitoring of patient safety must be clearly designated in health care settings to ensure that staff education is available for all health care professionals providing such services to patients. Furthermore, periodic monitoring for absolute adherence to safe injection practices in health care settings is vital to ensure effective engineering of and adherence to safe practices in everyday patient care.

In 2008, the United States Pharmacopeia (USP) published a revised USP General Chapter <797> Pharmaceutical Compounding—Sterile Preparations.[14] These standards apply to compounded sterile preparations (CSPs), which include compounded biologics, diagnostics, drugs, nutrients, and radiopharmaceuticals, including but not limited to the following dosage forms that must be sterile when they are administered to patients: aqueous bronchial and nasal inhalations, baths and soaks for live organs and tissues, injections (eg, colloidal dispersions, emulsions, solutions, suspensions, irrigations for wounds and body cavities, ophthalmic drops and ointments, and tissue implants). This includes manufactured bags or bottles of intravenous or irrigation fluid that may or may not contain additives and any solution drawn into a syringe for injection.

USP <797> applies to the pharmacy setting as well as to *all persons who prepare* medications that are administered and *all settings in which they are prepared* (eg, hospitals, other health care institutions, patient treatment clinics, physician's offices, and others). This chapter includes the standards for preparing, labeling, and time frames for discarding prepared medications. Pharmacies compound sterile preparations in an International Organization for Standardization (ISO) class 5 environment with primary engineering control devices, including laminar flow hoods, located in a "cleanroom" with stringent air quality, ventilation, personal protective equipment, and personnel and surface sanitation requirements to maintain the sterility of the preparation and safety of the compounding personnel. HCWs who prepare medications outside of ISO class 5 settings do so in environments with environmental particulates and microorganisms. Such settings and immediate-use preparation practices can potentially cause contamination of vials, IV solutions, and syringes from both airborne and direct contact sources. For example, clinicians who prepare injections and infusions may perform hand hygiene but not wear sterile gloves and a mask or contain their hair during preparation. When they remove the cap from the needle and insert it into the vial while breathing over the sterile needle and vial stopper, they create the potential for microbial contamination. Spiking a bag, vial, or bottle with a 1-way device and leaving it in place also increases the microbial contamination risk. The spike collects microorganism contamination from the environment, and the sterile solution is then poured out or withdrawn from a contaminated spout. For this reason, spiking any solution with a 1-way device and leaving it in place for multiple entries puts patients at risk for infection and is strongly discouraged.

According to USP <797>, immediate-use CSPs (prepared outside the ISO 5 environment) are exempted from the rigorous environmental purity standards and personnel cleansing and garbing practices that are required for all other categories of CSPs in USP <797>.[14] Immediate-use CSPs allow for certain sterile products to be prepared (compounded) without the need for special facilities (eg, clean room or ISO class 5 hood) and practices (eg, full cleansing or gowning). Dissolving, diluting, measuring, and mixing non-nutrient sterile injections using sterile devices (eg, ampuls, bags, needles, syringes, and vials) in clinical practice facilities (eg, patient care areas in hospitals, clinics, and physician offices) typify the conditions of what USP <797> calls "Immediate-use CSPs." USP <797> requires a 1-hour limit from completing preparation (eg, spiking an IV bag) until beginning administration of the immediate-use CSPs to patients. Their rationale is that the 1-hour limit is expected to preclude microbial population increase when accidental contamination of such drugs occurs with small quantities of microorganisms. Once microbial contamination occurs, the organism replication can begin within 1 to 4 hours with exponential growth occurring rapidly afterward.

For settings that prepare and use immediate-use CSPs (eg, operating rooms, ambulatory surgery centers, specialty clinics, and others), the cost of medication disposal, if administration has not begun 1-hour after preparation, can be daunting. USP recommends that these settings explore the possibility of having the pharmacy prepare the needed injectables and infusions in the ISO class 5 environment by properly trained, cleansed, and garbed personnel to prolong

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the usability of the CSPs. Most such CSPs according to USP <797> would then be classified "low risk level," for which the room temperature beyond-use date is 48 hours. This means that most CSPs prepared in a pharmacy ISO class 5 environment would be considered low risk level and could be stored for 48 hours, at which time the CSP would be discarded if not used. Another option is to locate a manufactured injectable product (eg, prepackaged syringe) that is discarded according to the manufacturer's expiration date.

However, it is important to recognize that many perioperative and clinical settings do not have ISO class 5 environments readily available. Clinicians spike IV solutions and prime IV tubing in operating rooms/departments and on patient care units in advance of their intended use so as to improve work flow and productivity. This advance preparation can occur at set time frames on the morning of or the evening prior to their intended use. USP <797> defines the time frame between preparation and initiating administration as 1 hour. This recommendation for immediate-use CSPs is a controversial unresolved issue and in actual practice difficult to comply with in certain settings. The APIC *does not support* the advance preparation (the night before or hours before administration) of immediate-use IV bags or syringes. The APIC *supports* the practice of preparing parenteral medications as close as possible to the time of administration and stresses the importance of educating designated staff, using tactile learning methods, verifying the competency of those performing the procedure, and periodic monitoring to assure compliance with aseptic technique and prevention of contamination. Proper technique is paramount to preventing accidental contamination during the process. Allowing only trained staff to prepare parenteral medications can decrease the risk of error/contamination. Preparation of parenteral medications must be performed in a clean, dry work space that is free of clutter and obvious contamination sources (eg, water, sinks). Prepared parenteral solutions should be stored in a controlled environment to limit the risk of tampering.

Another controversial and unresolved issue is the beyond-use date for opened multi-dose vials. The beyond-use date is the date after which an accessed product must be discarded. USP <797> requires medication multi-dose vials for injections be given a beyond-use date that is 28 days after initial stopper penetration (USP chapter <51>)[14] unless the product labeling (package insert) states otherwise. USP <797> requires that the vial be dated to reflect the date opened and/or beyond-use date. On the other hand, the Centers for Disease Control and Prevention (CDC) indicates that multi-dose vials can be used until the manufacturer's expiration date unless there are any concerns regarding the sterility of the product.[15] The US Food and Drug Administration defines an expiration date as "the date placed on the container/labels of a drug product designating the time during which a batch of the product is expected to remain within the approved shelf life specifications if stored under defined conditions and after which it may not be used."[16] Given the fact that this practice is variable and remains an unresolved issue at this time, the APIC recommends that facilities develop their policies and procedures based on either one of these recommendations. Rather than concentrate solely on beyond-use date or manufacturer expiration date, users of multi-dose vials must focus on the following: adhering to strict aseptic technique when accessing the vial; using a *new* sterile needle and a *new* sterile syringe for every access; removing all access devices from the vial; storing the vial in a clean, protected location according to the manufacturer's directions (eg, at room temperature or refrigerated); and ensuring that any vial whose sterility may be comprised is immediately discarded. Survey and accrediting agencies expect facilities to have written policies, based on the guidelines selected for use, that are consistently followed by staff.

The APIC strongly supports adherence to the following safe injection, infusion, and medication vial practices.[15-28]

ASEPTIC TECHNIQUE: IN LESS THAN AN ISO 5 ENVIRONMENT

- Perform hand hygiene (handwashing with soap and water or by application of a 60% or greater alcohol-based (In the United States, the alcohol component is predominantly ethyl alcohol (ethanol) or isopropyl alcohol.) hand sanitizer rub that is allowed to dry) before accessing supplies, handling vials and IV solutions, and preparing or administering medications.
- Use aseptic technique in all aspects of parenteral medication administration, medication vial use, injections, and glucose monitoring procedures.
- Store and prepare medications and supplies in a clean area on a clean surface.
- Never store needles and syringes unwrapped because sterility cannot be ensured.
- Discard all opened vials, IV solutions, and prepared or opened syringes that were involved in an emergency situation.
- Avoid contacting sterile drugs and sterile areas of devices and containers with non-sterile objects and/or secretions and particles shed from personnel.[27]

IV SOLUTIONS

- Never use IV solution containers (eg, bags, bottles) to obtain flush solutions or for any other purpose for more than 1 patient.

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- Never use infusion supplies, such as needles, syringes, flush solutions, administration sets, or IV fluids, on more than 1 patient.
- Prepare IV solutions and medications as close to administration as feasible. The time frame that can be allowed between the preparation and initiation of the administration of non-nutrient IV solutions that have been spiked or have had admixtures added in less than an ISO class 5 environment remains an *unresolved issue*. With limited data on actual contamination in real practice and linking contamination with patient infection, recommending a definitive time frame is not feasible at this time.
- Disinfect IV ports and vial stoppers by wiping and using friction with a sterile 70% isopropyl alcohol,[14,17] ethyl/ethanol alcohol, iodophor,[19] or other approved antiseptic swab. Allow the port to dry before accessing.
- Use a USP <797> primary engineering control with an ISO class 5 atmosphere to prepare admixtures of IV solutions when immediate use is not required. An admixture is defined as the addition of one or more concentrated drug injections from ampules and vials to larger volume bags and bottles of intravenous infusion fluids such as dextrose and sodium chloride injections.
- Do not use spiking devices, even if they have a 1-way valve, to remove fluid from IV bottles/bags for multiple uses or patients.

FLUSHING

- Use single-dose containers for flush solutions, whenever possible.
- If a multi-dose vial must be used, use it for only 1 patient and then discard it. Each entry into the multi-dose vial (dedicated to that patient) must be made with a new, unused sterile needle and new, unused sterile syringe.

SYRINGES

- Remove the sterile needle/cannulas and/or syringe from the package immediately before use.
- Never use a syringe for more than 1 patient even if the needle has been changed between patients. Changing the needle but not the syringe is unacceptable.
- Use a new syringe and a new needle for each entry into a vial or IV bag.
- Utilize sharps safety devices whenever possible.
- Discard syringes, needles, and cannulas after use directly on an individual patient or in an IV administration system.
- Dispose of used needles/syringes at the point of use in an approved sharps container.
- Do not prepare medication in one syringe to transfer to another syringe, ie, nurse draws up solution into syringe then transfers the solution to a syringe with plunger removed or injected into the bevel of the syringe to then be injected into the patient.
- Never store or transport syringes in clothing or pockets.
- Prepare syringes as close to administration as feasible.

VIALS

- Always follow the manufacturer's instructions for storage and use.
- Use single-use or single-dose vials whenever possible.
- Always use a new sterile syringe and new needle/cannula when entering a vial. Never enter a vial with a syringe or needle/cannula that has been previously used (eg, to inject a patient or access a medication vial).
- Cleanse the access diaphragm of vials using friction and a sterile 70% isopropyl alcohol,[14,17] ethyl alcohol, iodophor,[17] or other approved antiseptic swab. Allow the diaphragm to dry before inserting any device into the vial.
- Discard single-dose vials after use. Never use them again for another patient.
- Discard any vial that has been placed on a contaminated surface or a used procedure tray or that has been used during an emergency procedure.
- Use multi-dose medication vials for a single patient whenever possible and access all vials using a new sterile syringe and new needle/cannula adhering to aseptic technique. The risk of viral hepatitis transmission posed by multi-dose vials has been clearly demonstrated and mandates a practice of using 1 vial per 1 patient whenever possible. Infection transmission risk is reduced when multi-dose vials are dedicated to a single patient.
- Keep multi-dose vials away from the immediate patient environment.
- Never store or transport vials in clothing or pockets.
- Never pool or combine leftover contents of vials for later use.
- Never leave a needle, cannula, or spike device (even if it has a 1-way valve) inserted into a medication vial rubber stopper because it leaves the vial vulnerable to contamination.
- The beyond-use date and disposal of opened multi-dose medication vials for injection and/or IV administration remains an *unresolved issue* with differing opinions on the approach.
  - USP <797> requires a beyond-use date of 28 days after initial stopper penetration (USP chapter <51>)[14] unless the manufacturer's expiration date will be reached before 28 days or the product labeling (package insert) states otherwise. When

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following USP, date the vial to reflect the date opened and/or beyond use date. Discard the vial when the beyond-use date has been reached.
  - CDC indicates that the beyond-use date can be based on the manufacturer's expiration date.[15] When following CDC guidelines, date the vial to reflect the date opened.
  - Regardless of the beyond-use date or manufacturer's expiration date, a vial should be discarded sooner if the sterility of the product is in question.
  - The CDC Immunization Program recommends discarding of vaccines according to the manufacturer's expiration date.[27]
  - Facilities should develop a policy and procedure for their institution after reviewing and weighing these recommendations, implement an education and competency evaluation program for staff, and consider audits for adherence to the facility's policy/procedure.
- Inspect vials and discard if sterility is known or suspected to be compromised. Examine the vial for any particulate matter, discoloration, or turbidity; if present, do not use and discard immediately. All vials used during an emergency should be discarded because sterility cannot be guaranteed.

BLOOD GLUCOSE MONITORING DEVICES

- Assign a glucometer to each individual patient if possible. Clean and disinfect glucometers if they must be shared between multiple patients.
- Restrict the use of finger stick capillary blood sampling devices to individual patients.
- Maintain supplies and equipment, such as finger stick devices and glucometers, within individual inpatient rooms, if possible.
- Use single-use lancets that permanently retract after puncture.
- Never reuse finger stick devices and lancets. Dispose of them at the point of use in an approved sharps container. Lancets in a pen should be removed by mechanical means (hemostat) to avoid finger contact.
- Thoroughly clean all visible soil or organic material (eg, blood) from the glucometer before disinfection.
- Disinfect the exterior surfaces of the glucometer after each use following the manufacturer's directions. Use an Environmental Protection Agency-registered disinfectant effective against HBV, HCV, and HIV or a 1:10 bleach solution (1 part bleach to 9 parts water).

HCW

- Provide the HBV vaccination series to all previously unvaccinated health care personnel whose activities involve contact with blood or body fluids.[19]
- Check and document postvaccination titers 1 to 2 months after completion of the vaccination series.[19]
- Immediately report body fluid exposures and needlestick/sharps injuries.
- Ensure that staff preparing or administering injections or other parenteral medications are competent to perform these tasks aseptically.
- Periodically assess compliance with safe injection practices by observing and evaluating all personnel performing these procedures.

CONCLUSION

The use of safe injection practices is critical to prevent microbial contamination of products administered to patients. The ongoing reports of HBV and HCV transmission to patients and ongoing outbreaks of bacterial infections[29-31] indicate that much more is needed to ensure that these preventive practices are being scrupulously followed in all health care settings. HCWs and their managers must understand and practice these procedures safely. Administrators of medical facilities must be aware of safe injection practices and ensure that employees have the knowledge, training, and equipment to safely implement these procedures. It is critical that injectable medications, IV delivery systems, and blood glucose monitoring are used safely in all health care settings. As infection preventionists, we have an obligation to reiterate and ensure that safe injection, infusion, and medication vial practices are the absolute standard of care throughout various health care settings and across the continuum of care. We must take a lead role in promoting adherence by HCWs to these safe practices to protect the health and safety of our patients.

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REVIEW

Four policies to reduce HIV transmission through unsterile health care

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Summary: Residents of many developing countries face risks for themselves and their families to contract HIV and other bloodborne pathogens during unsterile health care. Helping people to understand and reduce these risks enlists their assistance to control the HIV/AIDS epidemic. To reduce HIV transmission through health care, we recommend four policies that international, foreign, and local public and private organizations can adopt and begin to implement even with little or no additional funds: (1) Educate the public about risks to contract HIV through unsterile health care. (2) Promote transparent practices for injections and other procedures that allow patients to see and know that care is safe (e.g., taking a new auto-disable syringe out of a sealed package and taking injecta from a single-dose vial). (3) Promote safe health care practices equally for clients and staff. (4) Establish a zero-tolerance policy for iatrogenic HIV infections, with publicly reported monitoring and investigations.

Keywords: HIV prevention, iatrogenic, injections, Africa

Informed opinion and active cooperation on the part of the public are of utmost importance in the improvement of the health of the people.

Constitution of the World Health Organization, 1946[1]

Introduction

Bloodborne pathogens known to be transmissible through unsterile health care include, among others, hepatitis B[2], HIV, and hepatitis C. Increasing international concern about transmission of bloodborne viruses during health care in developing countries[3–6] led to the formation of the Safe Injection Global Network (SIGN) in 1999, an independent organization with its secretariat currently at the World Health Organization (WHO). The SIGN secretariat and associates (individuals and organizations) have spearheaded major improvements in health care safety, including shifting United Nations Children's Fund (UNICEF)-supported immunization programmes to auto-disable (AD) syringes (that cannot be reused). However, this is only a beginning. Immunizations account for only 3% of injections outside rich countries[7]; and not all immunizations are in UNICEF-supported programmes.

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Unsterile health care remains common in many developing countries. According to estimates by WHO, health care providers — including informal providers — during the year 2000 reused syringes without sterilization for 6.6 billion injections (out of 16.7 billion injections, excluding rich countries) leading to an estimated 21 million hepatitis B, 2 million hepatitis C, and 260000 HIV infections[8] (a conservative figure which represents nevertheless about 5% of global HIV incidence; other estimates are higher[9]). Aside from syringes, evidence points to iatrogenic HIV infection via other common medical events such as antenatal care in Malawi and Zimbabwe[9] and collecting blood for tests in Malawi[10] and for plasma in Mexico[11], China[12], and other countries[13]. (Since people in developing countries receive health care from a wide range of formal and informal providers, we use the term 'iatrogenic' to refer to infections transmitted by all formal and informal providers, not only doctors.)

Large and explosive HIV outbreaks have occurred through unsterile health care in countries with better health care systems than are found in many developing countries. In 11 months, medical procedures at two hospitals in Elista, Russia, spread HIV from the index child to 90 children, during which time the number of infections doubled on average in less than two months[14,15]. In Romania in 1989–90, doctors found more than 1000 children infected through health care[16]. An investigation in Libya in 1998, found that

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procedures at a Benghazi hospital had spread HIV to more than 390 children[17]. Reports from China suggest that unsterile procedures during plasma collection in the 1990s infected several hundred thousand rural adults; some estimates indicate more than a million[12,18].

In these outbreaks, rapid HIV spread suggests that transmission through contaminated sharps is far more efficient than the one in 300 probability widely reported for needlestick injuries to health care workers[19]. Most needlestick injuries are superficial scratches; in a case–control study, average transmission through deep needlestick injuries — with the tip penetrating the skin as in an injection — was 2.3%, which is an improved but still uncertain approximation of transmission through contaminated injections[15,20].

In 1993, Mougdil and Daar reported that plasma from four of five HIV-infected volunteers remained infective after seven days at room temperature; decay, measured in tissue culture infective doses per mL, varied by patient but was slow for all in the first three days, ranging from $< 1/2$ to 1 log[21]. In 1987, the Centers for Disease Control and Prevention reported that drying HIV caused a 1–2 log reduction in concentration 'within several hours'[22]. Hence, in syringes, tubes, vials, and rinsing pans in medical settings, HIV may remain viable for delayed transmission hours to a week or more later.

Much of the public discussion about how to promote better health care in developing countries has focused on funding. While money helps, money alone — without a change in policies — will not ensure safe care. We recommend four policies for donors, governments, and non-governmental organizations (NGOs) to adopt to ensure sterile practices in most health care exposures in developing countries, no matter how poor. These policies can be introduced through ongoing programmes with little or no additional funding, e.g., by changing posters, clinic practices, content of professional courses, etc. Eventually, new programmes for safe care built around these policies may involve new spending. (These policies do not address continuing HIV transmission through untested blood, which calls for additional — and urgent — changes in policies and programmes.)

Four policies

Educate the public about risks for HIV in health care settings

Health care consumers need to know that unsterile care is a risk for HIV acquisition, and that large HIV outbreaks have been documented through unsafe care.

Rationale: Many people in developing countries do not know that injections may pose a risk for HIV. For example, in a 1996 survey, only 57% of Nigerian secondary students knew that HIV could be transmitted through unsterilized instruments[23]; in other recent surveys, 19% of Zimbabwean women[24] and 28% of South African military recruits[25] did not know that HIV could be contracted from sharing injection equipment.

In countries with generalized HIV epidemics (i.e., HIV prevalence of at least 1% in the general population), unsterile health care threatens everyone. Recognizing such risks, a 1999 UNAIDS booklet on HIV for UN employees gives equal space — two to three pages — to advice for preventing HIV acquisition through health care and sex[26]. Others in Africa and Asia need the same balanced attention to all risks.

Agencies and authorities that could be warning people about health care risks have not done so. For example, the US Agency for International Development estimates that only 0.01% of HIV transmission globally is attributable to health care exposures (aside from blood transfusions, estimated to account for 5%)[27]. The *Lancet* and the *British Medical Journal* have recently published articles presenting similar estimates[28,29].

In developing countries, health care systems comprise a range of sub-systems, including government and private clinics, traditional medicine, and informal providers. Since formal systems are limited by money and personnel, people — even poor people — choose and pay for much of their health care out of pocket[30]. Hence, choices about what safe practices to demand are in consumers' hands. While alternative and untrained providers are often maligned, some are thorough and careful. On the other hand, unsterile practices have been reported at many public and mission hospitals and clinics. Educating health care professionals is important, but decades of experience prove it is not enough to assure sterile care in many developing countries. An educated public can promote safe care — and protect themselves — in all health care settings.

Promote transparent practices for injections and other common health care procedures that allow patients to see and know that care is safe

For injections and other simple invasive procedures, practices can be identified and promoted that allow patients (and parents of young patients) to see that equipment is sterile and that injected substances are not contaminated (aside from fraud or product errors before packing). An acronym for all such transparent practices could be POST, for Patient Observed Sterile Treatment.

Rationale: With a shift to POST practices, health care consumers aware of risks in unsterile care can take an active role in monitoring and promoting safe care. While choice of procedures subject to POST — such as injections and vaginal examinations — and specific POST practices are best

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Table 1. Illustrative list of health care procedures and Patient Observed Sterile Treatment (POST) practices

Procedure	Average events per year	Potential risk	Current standard practices	Suggested POST practices	Higher cost with POST
Injection for immunization	0–5 or more, depending on age and country	Unsterile needle and syringe	Open a new AD syringe in front of the patient	Open a new AD syringe in front of the patient	–
		Contaminated injecta	Take injecta from multidose vials	Open a new single-dose vial in front of the patient	+$0.24 for hepatitis vaccine* Other vaccines?
Injection for treatment	1–10 or more, depending on age and country	Unsterile needle and syringe	Common reuse of unsterilized syringes	Open a new syringe in front of the patient	+$0.13–0.23 for a new AD syringe[32]
		Contaminated injecta	Take injecta from multidose vials	Open a new single-dose vial in front of the patient	?
Drawing venous blood for tests	?	Unsterile equipment		Single-use equipment	?
Drawing blood for transfusion	?	Unsterile equipment		Single-use equipment	?

*Calculated from $0.56 for a single-dose vial versus $0.32 per dose for a 10-dose vial[31]. AD = auto-disable

developed locally, one can anticipate common themes (Table 1). For example, to be sure that injections are safe, a patient could ask to see the provider remove a new AD syringe from a sealed package and take the vaccine or medicine from a single-dose vial. For dental care the solutions are not so obvious. Local research may be required to determine acceptability and reliability of some practices.

Some POST practices might have a cost, and the distribution of costs between consumer and provider may differ from one setting to another. However, these are secondary matters; with POST, consumers have the option to choose safe care and to pay for it if necessary. For many procedures, cost differences are minimal, and costs may be lower for some safe practices; for example, taking oral or no medication instead of injections for many common symptoms. From many studies, 70–90% of health care injections in developing countries are judged unnecessary[33].

Defining and implementing POST practices can begin at any level. A church, for example, may organize meetings between members and local health care providers to discuss and endorse POST practices. Promotion through government and donor programmes could accelerate adoption and acceptability among providers, but the key is that patients understand and appreciate that with POST practices they can ensure sterile care.

For some POST practices, donor and government collaboration — with or without added funding — may be essential. Avoiding use of multidose vials is one such practice. Donor-funded immunization programmes currently rely heavily on multidose vials, many with 10–20 vaccine doses per vial. A patient or parent who sees a nurse withdrawing vaccine from an already opened vial may wonder if previous withdrawals were performed with sterile needles. One option is for governments and donors to shift to single-dose vials and/or pre-loaded syringes, though cost and capacity may be limiting, at least in the short run. Alternatively, governments could supply single-dose vials at a premium, or allow private supply for those who want to pay. Other technical solutions may be found, such as redesigning multidose vials to dispense vaccines in a way that does not allow contamination. With current multidose vials, many patients in poor countries face the unpalatable choice between unsafe health care and no health care — when safe care is a viable third option.

With local initiative, people may extend POST practices to whatever exposures they are uneasy about and are able to change. For example, when a Ugandan patient enters a hospital, family and friends may bring 'a saucepan, cooking stove and fuel. . . . At the surgical ward where most patients are receiving over four injections daily, the[se] attendants would boil the equipment once in the morning and later in the evening'[34]. This is one solution in the POST spirit. Birungi suggests another, that 'People should be given a chance to witness the entire sterilization procedure and, where possible, to participate. The idea is that to restore people's trust in institutional things, they should be personally involved'[34].

Other than health care, parenteral exposure includes tattooing, body piercing, and shaving in the marketplace. For these and other non-medical procedures, POST practices can also be developed to allow consumers to be confident of sterile practices.

Promote safe health care practices equally for clients and staff

All aid agencies and multilateral organizations that fund or promote health care in developing countries should promote POST practices equally

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for clients and staff, so that for simple health care procedures, poor people in poor countries may be as certain as anyone in the world that delivery of medical services is sterile.

Rationale: For decades, foreign and international organizations funding and promoting health care in developing countries have advised their staff that local care is unsafe. For example, a 1999 UNAIDS publication encourages UN employees to 'carry sterile disposable needles and syringes for your personal use (as part of the WHO medical kit)' and to 'make sure that all equipment is properly sterilized. Do not be afraid to ask questions.... Parents should make sure that children know the facts about HIV transmission and... avoid any skin-piercing procedures... from unsterilized needles and other sharp instruments'[26]. Other foreign organizations routinely provide similar advice to employees travelling to Africa. This echoes POST, but only for staff.

Foreign organizations should ensure that the health care programmes they support warn (educate) clients about the risks of unsterile care, and that they implement POST for injections and other simple procedures, so that clients can see and know that the health care they receive is sterile. (Realistically, first and second-class care will continue for some complex procedures such as major surgery, even with diligent efforts to improve infection control in hospitals and clinics in poor countries.)

Establish a zero-tolerance policy for iatrogenic HIV infections, with accountability through publicly reported monitoring and investigations

A zero-tolerance policy means that national and/or sub-national governments monitor sterile conditions in health care settings and monitor and investigate iatrogenic infections (e.g., children with HIV who have HIV-negative mothers). For international and foreign organizations — including NGOs — zero-tolerance means that they cooperate with and support monitoring and investigations, and that their head offices report activities and findings to the foreign public that supports health aid.

Rationale: In many developing countries, monitoring health care safety has been weak, even for immunization programmes, where foreign aid is most influential. In 2001, only 53% of WHO member countries — and only 41% of African members — reported a system to monitor adverse events after immunizations[35].

Sterile conditions in health care settings could be monitored by sampling and testing instruments and partially-full multidose vials. Sampling could be done, for example, by inspectors or secret shoppers (persons posing as patients) collecting instruments and vials ready to use, exchanging new for old. Monitoring could cover all categories of formal and informal providers. Test results could be offered confidentially to individual providers, while composite results for all providers in a region should be reported to the public.

In countries with generalized epidemics, HIV transmission via health care procedures can be discovered by testing mothers of HIV-infected children. We expect that suspected iatrogenic HIV infections will continue to emerge in Africa and Asia in coming years as they have in the past. Over the past 18 years, scores of HIV-infected African children with HIV-negative mothers have been reported[9]. For example, a WHO-sponsored study of children 6–59 months old and their mothers in four African cities reported in 1993 that 61 (1.1%) of 5593 inpatient children were HIV-positive with HIV-negative mothers[36]. After this and many other similar reports, what has been strikingly absent, in sub-Saharan Africa especially, are the kinds of follow-up investigations conducted in Russia, Romania, Libya, and many other countries, where authorities sought out all linked cases, identified clinics and procedures involved in suspected HIV transmission, and terminated further iatrogenic transmission.

Lack of interest to investigate unexplained HIV infections is common among donors as well as many aid-receiving governments. For example, beginning in late 2000, one of us (DG) has presented public and private organizations involved in safe motherhood programmes detailed evidence suggestive of HIV transmission to women during antenatal care in Africa[9]. To our knowledge, no one has done what is necessary to figure out why African women seroconverted in high numbers during and after antenatal care; i.e., no one has collected and tested sharps and multidose vials for contamination or systematically tested husbands of seroconverting pregnant and postpartum women for HIV infections.

To promote appropriate investigations consistent with zero-tolerance, donor organizations with large health aid programmes could pre-commit a percent of their annual health aid budget in each country to investigate unexplained HIV infections. This could ensure that investigations take place when, for example, an HIV-negative mother comes forward with an HIV-infected child.

Conclusion

One common argument against public discussion of health care risks for HIV has been that people might not be able to understand accurate information and might avoid health care. This has led to decisions that endanger patients. For example, in 1990 donors in Uganda worried about 'mothers' refusal to have their children immunized because of resistance to the use of non-disposable injection equipment'. To allay such concerns 'radio messages about AIDS in Uganda [were] modified to ensure that parents are

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aware of the safety of immunizations'[37], even though risks continued[38]. Years later, donors including UNICEF shifted all immunizations in Uganda and throughout the world to AD syringes, implicitly acknowledging the wisdom and leadership of Ugandan mothers who feared injections with non-disposable equipment.

Fortunately, experts have been speaking up for public discussion of iatrogenic HIV risks. For example, in the mid-1990s, a WHO-sponsored study in 12 African countries reported that 'immunization injection practices . . . have not made any progress with regard to safety over the last 10 years', and that safety 'can no longer be ignored in the interests of quantity'. To improve safety, 'social mobilization teams should provide populations with adequate information about immunization so that consumer demand for safe injections can be created and the public receives appropriate information regarding AEFIs (adverse events following immunization)'[39].

During 1980–2000, the World Bank led efforts to reform health care systems in developing countries, urging decentralization, privatization, and fees. This was driven in part by economics, but also by an effort to improve accountability to patients as clients. These reforms have had strengths and weaknesses. On the one hand, they may increase accountability to clients, which is difficult to build into systems dominated by money and staff from national and international capitals. On the other hand, reforms have cut public health spending (which impacts health equity) and introduced fees for primary health services (which can block poor people's access to health services). But increases in funding for health systems must be accompanied by policy changes to ensure sterile care, so that more aid does not expose more people to unsafe health care.

The changes that are required to reduce health care risks are prefigured in the Constitution of the WHO, where member states recognize the importance of 'informed [public] opinion and active cooperation'[11]. We urge public education, transparent sterile procedures, equal advice to clients and staff, and zero-tolerance for iatrogenic HIV infections.

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Docket No.: ALXN-P08-114
(PATENT)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of:
Bell et al.

Application No.: 13/426,973 | Confirmation No.: 8851

Filed: March 22, 2012 | Art Unit: 1644

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

SUPPLEMENTAL INFORMATION DISCLOSURE STATEMENT (IDS)

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

Dear Madam:

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

This Supplemental Information Disclosure Statement is filed more than three months after the U.S. filing date, and after the mailing date of the first Office Action on the merits, whichever occurs first, but before the mailing date of any of a Final Office Action, a Notice of Allowance (37 C.F.R. § 1.97(c)) or an action that otherwise closes prosecution in the application.

Applicants submit herewith a copy of the foreign patent and non-patent literature in accordance with 37 C.F.R. § 1.98(a)(2).

In accordance with 37 C.F.R. § 1.97(g), the filing of this Supplemental Information Disclosure Statement shall not be construed to mean that a search has been made or that no other material information as defined in 37 C.F.R. § 1.56(a) exists. In accordance with 37 C.F.R. § 1.97(h), the filing of this Supplemental Information Disclosure Statement shall not be construed to be an admission that any patent, publication or other information referred to therein is "prior art" for this invention unless specifically designated as such.

It is submitted that the Supplemental Information Disclosure Statement is in compliance with 37 C.F.R. § 1.98 and the Examiner is respectfully requested to consider the listed references.

Please charge our Deposit Account No. 18-1945 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 (or with any paper hereafter filed in this application by this firm) to our Deposit Account No. 18-1945, under Order No. ALXN-P08-114.

Dated: October 23, 2013

Respectfully submitted,

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Sheet 1 of 2

Complete if Known	
Application Number	13/426,973
Filing Date	March 22, 2012
First Named Inventor	Leonard Bell
Art Unit	1644
Examiner Name	J. L. Rogers
Attorney Docket Number	ALXN-P08-114

U.S. PATENT DOCUMENTS

Examiner Initials*	Cite No.[1]	Document Number Number-Kind Code[2] (if known)	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear

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		WO 2004/029207 A2	04-08-2004	XENCOR		

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Sheet 2 of 2

Complete if Known	
Application Number	13/426,973
Filing Date	March 22, 2012
First Named Inventor	Leonard Bell
Art Unit	1644
Examiner Name	J. L. Rogers
Attorney Docket Number	ALXN-P08-114

NON PATENT LITERATURE DOCUMENTS

Examiner Initials*	Cite No.[1]	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, page(s), volume-issue number(s), publisher, city and/or country where published.	T[2]
		Lee et al., "Neisseria meningitidis Bacteremia in Association with Deficiency of the Sixth Component of Complement," Infection and Immunity, Vol. 24(3): 656-660 (1979).	

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PETITION FOR EXTENSION OF TIME UNDER 37 CFR 1.136(a)	Docket Number (Optional) ALXN-P08-114
Application Number 13/426,973	Filed March 22, 2012
For TREATMENT OF PAROXYSMAL NOCTURNAL HEMOGLOBINURIA PATIENTS BY AN INHIBITOR OF COMPLEMENT	
Art Unit 1644	Examiner J. L. Rogers

This is a request under the provisions of 37 CFR 1.136(a) to extend the period for filing a reply in the above-identified application.

The requested extension and fee are as follows (check time period desired and enter the appropriate fee below):

	Fee	Small Entity Fee	Micro Entity Fee	
☐ One month (37 CFR 1.17(a)(1))	$200	$100	$50	$
☒ Two months (37 CFR 1.17(a)(2))	$600	$300	$150	$ 600.00
☐ Three months (37 CFR 1.17(a)(3))	$1,400	$700	$350	$
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/Gitanjali Chimalakonda/	October 23, 2013
Signature	Date
Gitanjali Chimalakonda, Ph.D.	(617) 951-7000
Typed or printed name	Telephone Number

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(54) Title: OPTIMIZED FC VARIANTS AND METHODS FOR THEIR GENERATION

(57) Abstract: The present invention relates to optimized Fc variants, methods for their generation, and antibodies and Fc fusions comprising optimized Fc variants.

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OPTIMIZED Fc VARIANTS AND METHODS FOR THEIR GENERATION

[001] This application claims benefit under 35 U.S.C. §199(e) to USSNs 60/477,839 filed June 12, 2003; 60/467,606, filed May 2, 2003; 60/414,433 filed September 27, 2002; and 60/442,301 filed January 23, 2003, all of which are expressly incorporated by reference in their entirety.

FIELD OF THE INVENTION

[002] The present invention relates to novel optimized Fc variants, engineering methods for their generation, and their application, particularly for therapeutic purposes.

BACKGROUND OF THE INVENTION

[003] Antibodies are immunological proteins that bind a specific antigen. In most mammals, including humans and mice, antibodies are constructed from paired heavy and light polypeptide chains. Each chain is made up of individual immunoglobulin (Ig) domains, and thus the generic term immunoglobulin is used for such proteins. Each chain is made up of two distinct regions, referred to as the variable and constant regions. The light and heavy chain variable regions show significant sequence diversity between antibodies, and are responsible for binding the target antigen. The constant regions show less sequence diversity, and are responsible for binding a number of natural proteins to elicit important biochemical events. In humans there are five different classes of antibodies including IgA (which includes subclasses IgA1 and IgA2), IgD, IgE, IgG (which includes subclasses IgG1, IgG2, IgG3, and IgG4), and IgM. The distinguishing features between these antibody classes are their constant regions, although subtler differences may exist in the V region. Figure 1 shows an IgG1 antibody, used here as an example to describe the general structural features of immunoglobulins. IgG antibodies are tetrameric proteins composed of two heavy chains and two light chains. The IgG heavy chain is composed of four immunoglobulin domains linked from N- to C-terminus in the order V_H-Cγ1-Cγ2-Cγ3, referring to the heavy chain variable domain, constant gamma 1 domain, constant gamma 2 domain, and constant gamma 3 domain respectively. The IgG light chain is composed of two immunoglobulin domains linked from N- to C-terminus in the order V_L-C_L, referring to the light chain variable domain and the light chain constant domain respectively.

[004] The variable region of an antibody contains the antigen binding determinants of the molecule, and thus determines the specificity of an antibody for its target antigen. The variable region is so named because it is the most distinct in sequence from other antibodies within the same class. The majority of sequence variability occurs in the complementarity determining regions (CDRs). There are 6 CDRs total, three each per heavy and light chain, designated V_H CDR1, V_H CDR2, V_H CDR3, V_L

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CDR1, V_L CDR2, and V_L CDR3. The variable region outside of the CDRs is referred to as the framework (FR) region. Although not as diverse as the CDRs, sequence variability does occur in the FR region between different antibodies. Overall, this characteristic architecture of antibodies provides a stable scaffold (the FR region) upon which substantial antigen binding diversity (the CDRs) can be explored by the immune system to obtain specificity for a broad array of antigens. A number of high-resolution structures are available for a variety of variable region fragments from different organisms, some unbound and some in complex with antigen. The sequence and structural features of antibody variable regions are well characterized (Morea *et al.*, 1997, *Biophys Chem* 68:9-16; Morea *et al.*, 2000, *Methods* 20:267-279), and the conserved features of antibodies have enabled the development of a wealth of antibody engineering techniques (Maynard *et al.*, 2000, *Annu Rev Biomed Eng* 2:339-376). For example, it is possible to graft the CDRs from one antibody, for example a murine antibody, onto the framework region of another antibody, for example a human antibody. This process, referred to in the art as "humanization", enables generation of less immunogenic antibody therapeutics from nonhuman antibodies. Fragments comprising the variable region can exist in the absence of other regions of the antibody, including for example the antigen binding fragment (Fab) comprising V_H-Cγ1 and V_H-C_L, the variable fragment (Fv) comprising V_H and V_L, the single chain variable fragment (scFv) comprising V_H and V_L linked together in the same chain, as well as a variety of other variable region fragments (Little *et al.*, 2000, *Immunol Today* 21:364-370).

[005] The Fc region of an antibody interacts with a number of Fc receptors and ligands, imparting an array of important functional capabilities referred to as effector functions. For IgG the Fc region, as shown in Figure 1, comprises Ig domains Cγ2 and Cγ3 and the N-terminal hinge leading into Cγ2. An important family of Fc receptors for the IgG class are the Fc gamma receptors (FcγRs). These receptors mediate communication between antibodies and the cellular arm of the immune system (Raghavan *et al.*, 1996, *Annu Rev Cell Dev Biol* 12:181-220; Ravetch *et al.*, 2001, *Annu Rev Immunol* 19:275-290). In humans this protein family includes FcγRI (CD64), including isoforms FcγRIa, FcγRIb, and FcγRIc; FcγRII (CD32), including isoforms FcγRIIa (including allotypes H131 and R131), FcγRIIb (including FcγRIIb-1 and FcγRIIb-2), and FcγRIIc; and FcγRIII (CD16), including isoforms FcγRIIIa (including allotypes V158 and F158) and FcγRIIIb (including allotypes FcγRIIIb-NA1 and FcγRIIIb-NA2) (Jefferis *et al.*, 2002, *Immunol Lett* 82:57-65). These receptors typically have an extracellular domain that mediates binding to Fc, a membrane spanning region, and an intracellular domain that may mediate some signaling event within the cell. These receptors are expressed in a variety of immune cells including monocytes, macrophages, neutrophils, dendritic cells, eosinophils, mast cells, platelets, B cells, large granular lymphocytes, Langerhans' cells, natural killer (NK) cells, and $\gamma\gamma$ T cells. Formation of the Fc/FcγR complex recruits these effector cells to sites of bound antigen, typically resulting in signaling events within the cells and important subsequent immune responses such as release of inflammation mediators, B cell activation, endocytosis, phagocytosis, and cytotoxic attack. The ability to mediate cytotoxic and phagocytic effector functions is a potential mechanism by which antibodies destroy targeted cells. The cell-mediated reaction wherein nonspecific cytotoxic

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cells that express FcγRs recognize bound antibody on a target cell and subsequently cause lysis of the target cell is referred to as antibody dependent cell-mediated cytotoxicity (ADCC) (Raghavan *et al.*, 1996, *Annu Rev Cell Dev Biol* 12:181-220; Ghetie *et al.*, 2000, *Annu Rev Immunol* 18:739-766; Ravetch *et al.*, 2001, *Annu Rev Immunol* 19:275-290). The cell-mediated reaction wherein nonspecific cytotoxic cells that express FcγRs recognize bound antibody on a target cell and subsequently cause phagocytosis of the target cell is referred to as antibody dependent cell-mediated phagocytosis (ADCP). A number of structures have been solved of the extracellular domains of human FcγRs, including FcγRIIa (pdb accession code 1H9V)(Sondermann *et al.*, 2001, *J Mol Biol* 309:737-749) (pdb accession code 1FCG)(Maxwell *et al.*, 1999, *Nat Struct Biol* 6:437-442), FcγRIIb (pdb accession code 2FCB)(Sondermann *et al.*, 1999, *Embo J* 18:1095-1103); and FcγRIIIb (pdb accession code 1E4J)(Sondermann *et al.*, 2000, *Nature* 406:267-273.). All FcγRs bind the same region on Fc, at the N-terminal end of the Cγ2 domain and the preceding hinge, shown in Figure 2. This interaction is well characterized structurally (Sondermann *et al.*, 2001, *J Mol Biol* 309:737-749), and several structures of the human Fc bound to the extracellular domain of human FcγRIIIb have been solved (pdb accession code 1E4K)(Sondermann *et al.*, 2000, *Nature* 406:267-273.) (pdb accession codes 1IIS and 1IIX)(Radaev *et al.*, 2001, *J Biol Chem* 276:16469-16477), as well as has the structure of the human IgE Fc/FcεRIδ complex (pdb accession code 1F6A)(Garman *et al.*, 2000, *Nature* 406:259-266).

[006] The different IgG subclasses have different affinities for the FcγRs, with IgG1 and IgG3 typically binding substantially better to the receptors than IgG2 and IgG4 (Jefferis *et al.*, 2002, *Immunol Lett* 82:57-65). All FcγRs bind the same region on IgG Fc, yet with different affinities: the high affinity binder FcγRI has a Kd for IgG1 of 10^{-8} M^{-1}, whereas the low affinity receptors FcγRII and FcγRIII generally bind at 10^{-6} and 10^{-6} respectively. The extracellular domains of FcγRIIIa and FcγRIIIb are 96% identical, however FcγRIIIb does not have a intracellular signaling domain. Furthermore, whereas FcγRI, FcγRIIa/c, and FcγRIIIa are positive regulators of immune complex-triggered activation, characterized by having an intracellular domain that has an immunoreceptor tyrosine-based activation motif (ITAM), FcγRIIb has an immunoreceptor tyrosine-based inhibition motif (ITIM) and is therefore inhibitory. Thus the former are referred to as activation receptors, and FcγRIIb is referred to as an inhibitory receptor. The receptors also differ in expression pattern and levels on different immune cells. Yet another level of complexity is the existence of a number of FcγR polymorphisms in the human proteome. A particularly relevant polymorphism with clinical significance is V158/F158 FcγRIIIa. Human IgG1 binds with greater affinity to the V158 allotype than to the F158 allotype. This difference in affinity, and presumably its effect on ADCC and/or ADCP, has been shown to be a significant determinant of the efficacy of the anti-CD20 antibody rituximab (Rituxan®, a registered trademark of IDEC Pharmaceuticals Corporation). Patients with the V158 allotype respond favorably to rituximab treatment; however, patients with the lower affinity F158 allotype respond poorly (Cartron *et al.*, 2002, *Blood* 99:754-758). Approximately 10-20% of humans are V158/V158

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homozygous, 45% are V158/F158 heterozygous, and 35-45% of humans are F158/F158 homozygous (Lehrnbecher *et al.*, 1999, *Blood* 94:4220-4232; Cartron *et al.*, 2002, *Blood* 99:754-758). Thus 80-90% of humans are poor responders, that is they have at least one allele of the F158 FcγRIIIa.

[007] An overlapping but separate site on Fc, shown in Figure 1, serves as the interface for the complement protein C1q. In the same way that Fc/FcγR binding mediates ADCC, Fc/C1q binding mediates complement dependent cytotoxicity (CDC). C1q forms a complex with the serine proteases C1r and C1s to form the C1 complex. C1q is capable of binding six antibodies, although binding to two IgGs is sufficient to activate the complement cascade. Similar to Fc interaction with FcγRs, different IgG subclasses have different affinity for C1q, with IgG1 and IgG3 typically binding substantially better to the FcγRs than IgG2 and IgG4 (Jefferis *et al.*, 2002, *Immunol Lett* 82:57-65). There is currently no structure available for the Fc/C1q complex; however, mutagenesis studies have mapped the binding site on human IgG for C1q to a region involving residues D270, K322, K326, P329, and P331, and E333 (Idusogie *et al.*, 2000, *J Immunol* 164:4178-4184; Idusogie *et al.*, 2001, *J Immunol* 166:2571-2575).

[008] A site on Fc between the Cγ2 and Cγ3 domains, shown in Figure 1, mediates interaction with the neonatal receptor FcRn, the binding of which recycles endocytosed antibody from the endosome back to the bloodstream (Raghavan *et al.*, 1996, *Annu Rev Cell Dev Biol* 12:181-220; Ghetie *et al.*, 2000, *Annu Rev Immunol* 18:739-766). This process, coupled with preclusion of kidney filtration due to the large size of the full length molecule, results in favorable antibody serum half-lives ranging from one to three weeks. Binding of Fc to FcRn also plays a key role in antibody transport. The binding site for FcRn on Fc is also the site at which the bacterial proteins A and G bind. The tight binding by these proteins is typically exploited as a means to purify antibodies by employing protein A or protein G affinity chromatography during protein purification. Thus the fidelity of this region on Fc is important for both the clinical properties of antibodies and their purification. Available structures of the rat Fc/FcRn complex (Martin *et al.*, 2001, *Mol Cell* 7:867-877), and of the complexes of Fc with proteins A and G (Deisenhofer, 1981, *Biochemistry* 20:2361-2370; Sauer-Eriksson *et al.*, 1995, *Structure* 3:265-278; Tashiro *et al.*, 1995, *Curr Opin Struct Biol* 5:471-481) provide insight into the interaction of Fc with these proteins.

[009] A key feature of the Fc region is the conserved N-linked glycosylation that occurs at N297, shown in Figure 1. This carbohydrate, or oligosaccharide as it is sometimes referred, plays a critical structural and functional role for the antibody, and is one of the principle reasons that antibodies must be produced using mammalian expression systems. While not wanting to be limited to one theory, it is believed that the structural purpose of this carbohydrate may be to stabilize or solubilize Fc, determine a specific angle or level of flexibility between the Cγ3 and Cγ2 domains, keep the two Cγ2 domains from aggregating with one another across the central axis, or a combination of these.

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Efficient Fc binding to FcγR and C1q requires this modification, and alterations in the composition of the N297 carbohydrate or its elimination affect binding to these proteins (Umaña *et al.*, 1999, *Nat Biotechnol* 17:176-180; Davies *et al.*, 2001, *Biotechnol Bioeng* 74:288-294; Mimura *et al.*, 2001, *J Biol Chem* 276:45539-45547.; Radaev *et al.*, 2001, *J Biol Chem* 276:16478-16483; Shields *et al.*, 2001, *J Biol Chem* 276:6591-6604; Shields *et al.*, 2002, *J Biol Chem* 277:26733-26740; Simmons *et al.*, 2002, *J Immunol Methods* 263:133-147). Yet the carbohydrate makes little if any specific contact with FcγRs (Radaev *et al.*, 2001, *J Biol Chem* 276:16469-16477), indicating that the functional role of the N297 carbohydrate in mediating Fc/FcγR binding may be via the structural role it plays in determining the Fc conformation. This is supported by a collection of crystal structures of four different Fc glycoforms, which show that the composition of the oligosaccharide impacts the conformation of Cγ2 and as a result the Fc/FcγR interface (Krapp *et al.*, 2003, *J Mol Biol* 325:979-989).

[010] The features of antibodies discussed above - specificity for target, ability to mediate immune effector mechanisms, and long half-life in serum - make antibodies powerful therapeutics. Monoclonal antibodies are used therapeutically for the treatment of a variety of conditions including cancer, inflammation, and cardiovascular disease. There are currently over ten antibody products on the market and hundreds in development. In addition to antibodies, an antibody-like protein that is finding an expanding role in research and therapy is the Fc fusion (Chamow *et al.*, 1996, *Trends Biotechnol* 14:52-60; Ashkenazi *et al.*, 1997, *Curr Opin Immunol* 9:195-200). An Fc fusion is a protein wherein one or more polypeptides is operably linked to Fc. An Fc fusion combines the Fc region of an antibody, and thus its favorable effector functions and pharmacokinetics, with the target-binding region of a receptor, ligand, or some other protein or protein domain. The role of the latter is to mediate target recognition, and thus it is functionally analogous to the antibody variable region. Because of the structural and functional overlap of Fc fusions with antibodies, the discussion on antibodies in the present invention extends directly to Fc fusions.

[011] Despite such widespread use, antibodies are not optimized for clinical use. Two significant deficiencies of antibodies are their suboptimal anticancer potency and their demanding production requirements. These deficiencies are addressed by the present invention.

[012] There are a number of possible mechanisms by which antibodies destroy tumor cells, including anti-proliferation via blockage of needed growth pathways, intracellular signaling leading to apoptosis, enhanced down regulation and/or turnover of receptors, CDC, ADCC, ADCP, and promotion of an adaptive immune response (Cragg *et al.*, 1999, *Curr Opin Immunol* 11:541-547; Glennie *et al.*, 2000, *Immunol Today* 21:403-410). Anti-tumor efficacy may be due to a combination of these mechanisms, and their relative importance in clinical therapy appears to be cancer dependent. Despite this arsenal of anti-tumor weapons, the potency of antibodies as anti-cancer agents is unsatisfactory, particularly given their high cost. Patient tumor response data show that monoclonal

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antibodies provide only a small improvement in therapeutic success over normal single-agent cytotoxic chemotherapeutics. For example, just half of all relapsed low-grade non-Hodgkin's lymphoma patients respond to the anti-CD20 antibody rituximab (McLaughlin *et al.*, 1998, *J Clin Oncol* 16:2825-2833). Of 166 clinical patients, 6% showed a complete response and 42% showed a partial response, with median response duration of approximately 12 months. Trastuzumab (Herceptin®, a registered trademark of Genentech), an anti-HER2/neu antibody for treatment of metastatic breast cancer, has less efficacy. The overall response rate using trastuzumab for the 222 patients tested was only 15%, with 8 complete and 26 partial responses and a median response duration and survival of 9 to 13 months (Cobleigh *et al.*, 1999, *J Clin Oncol* 17:2639-2648). Currently for anticancer therapy, any small improvement in mortality rate defines success. Thus there is a significant need to enhance the capacity of antibodies to destroy targeted cancer cells.

[013] A promising means for enhancing the anti-tumor potency of antibodies is via enhancement of their ability to mediate cytotoxic effector functions such as ADCC, ADCP, and CDC. The importance of FcγR-mediated effector functions for the anti-cancer activity of antibodies has been demonstrated in mice (Clynes *et al.*, 1998, *Proc Natl Acad Sci U S A* 95:652-656; Clynes *et al.*, 2000, *Nat Med* 6:443-446), and the affinity of interaction between Fc and certain FcγRs correlates with targeted cytotoxicity in cell-based assays (Shields *et al.*, 2001, *J Biol Chem* 276:6591-6604; Presta *et al.*, 2002, *Biochem Soc Trans* 30:487-490; Shields *et al.*, 2002, *J Biol Chem* 277:26733-26740). Additionally, a correlation has been observed between clinical efficacy in humans and their allotype of high (V158) or low (F158) affinity polymorphic forms of FcγRIIIa (Cartron *et al.*, 2002, *Blood* 99:754-758). Together these data suggest that an antibody with an Fc region optimized for binding to certain FcγRs may better mediate effector functions and thereby destroy cancer cells more effectively in patients. The balance between activating and inhibiting receptors is an important consideration, and optimal effector function may result from an Fc with enhanced affinity for activation receptors, for example FcγRI, FcγRIIa/c, and FcγRIIIa, yet reduced affinity for the inhibitory receptor FcγRIIb. Furthermore, because FcγRs can mediate antigen uptake and processing by antigen presenting cells, enhanced Fc/FcγR affinity may also improve the capacity of antibody therapeutics to elicit an adaptive immune response.

[014] Mutagenesis studies have been carried out on Fc towards various goals, with substitutions typically made to alanine (referred to as alanine scanning) or guided by sequence homology substitutions (Duncan *et al.*, 1988, *Nature* 332:563-564; Lund *et al.*, 1991, *J Immunol* 147:2657-2662; Lund *et al.*, 1992, *Mol Immunol* 29:53-59; Jefferis *et al.*, 1995, *Immunol Lett* 44:111-117; Lund *et al.*, 1995, *Faseb J* 9:115-119; Jefferis *et al.*, 1996, *Immunol Lett* 54:101-104; Lund *et al.*, 1996, *J Immunol* 157:4963-4969; Armour *et al.*, 1999, *Eur J Immunol* 29:2613-2624; Shields *et al.*, 2001, *J Biol Chem* 276:6591-6604; Jefferis *et al.*, 2002, *Immunol Lett* 82:57-65) (US 5,624,821; US 5,885,573; PCT WO 00/42072; PCT WO 99/58572). The majority of substitutions reduce or ablate binding with FcγRs.

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However some success has been achieved at obtaining Fc variants with higher FcγR affinity. (See for example US 5,624,821, and PCT WO 00/42072). For example, Winter and colleagues substituted the human amino acid at position 235 of mouse IgG2b antibody (a glutamic acid to leucine mutation) that increased binding of the mouse antibody to human FcγRI by100-fold (Duncan *et al.*, 1988, *Nature* 332:563-564) (US 5,624,821). Shields *et al.* used alanine scanning mutagenesis to map Fc residues important to FcγR binding, followed by substitution of select residues with non-alanine mutations (Shields *et al.*, 2001, *J Biol Chem* 276:6591-6604; Presta *et al.*, 2002, *Biochem Soc Trans* 30:487-490) (PCT WO 00/42072). Several mutations disclosed in this study, including S298A, E333A, and K334A, show enhanced binding to the activating receptor FcγRIIIa and reduced binding to the inhibitory receptor FcγRIIb. These mutations were combined to obtain double and triple mutation variants that show additive improvements in binding. The best variant disclosed in this study is a S298A/E333A/K334A triple mutant with approximately a 1.7-fold increase in binding to F158 FcγRIIIa, a 5-fold decrease in binding to FcγRIIb, and a 2.1-fold enhancement in ADCC.

[015] Enhanced affinity of Fc for FcγR has also been achieved using engineered glycoforms generated by expression of antibodies in engineered or variant cell lines (Umaña *et al.*, 1999, *Nat Biotechnol* 17:176-180; Davies *et al.*, 2001, *Biotechnol Bioeng* 74:288-294; Shields *et al.*, 2002, *J Biol Chem* 277:26733-26740; Shinkawa *et al.*, 2003, *J Biol Chem* 278:3466-3473). This approach has generated substantial enhancements of the capacity of antibodies to bind FcγRIIIa and to mediate ADCC. Although there are practical limitations such as the growth efficiency of the expression strains under large scale production conditions, this approach for enhancing Fc/FcγR affinity and effector function is promising. Indeed, coupling of these alternate glycoform technologies with the Fc variants of the present invention may provide additive or synergistic effects for optimal effector function.

[016] Although there is a need for greater effector function, for some antibody therapeutics reduced or eliminated effector function may be desired. This is often the case for therapeutic antibodies whose mechanism of action involves blocking or antagonism but not killing of the cells bearing target antigen. In these cases depletion of target cells is undesirable and can be considered a side effect. For example, the ability of anti-CD4 antibodies to block CD4 receptors on T cells makes them effective anti-inflammatories, yet their ability to recruit FcγR receptors also directs immune attack against the target cells, resulting in T cell depletion (Reddy *et al.*, 2000, *J Immunol* 164:1925-1933). Effector function can also be a problem for radiolabeled antibodies, referred to as radioconjugates, and antibodies conjugated to toxins, referred to as immunotoxins. These drugs can be used to destroy cancer cells, but the recruitment of immune cells via Fc interaction with FcγRs brings healthy immune cells in proximity to the deadly payload (radiation or toxin), resulting in depletion of normal lymphoid tissue along with targeted cancer cells (Hutchins *et al.*, 1995, *Proc Natl Acad Sci U S A* 92:11980-11984; White *et al.*, 2001, *Annu Rev Med* 52:125-145). This problem can potentially be circumvented by using IgG isotypes that poorly recruit complement or effector cells, for example IgG2

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and IgG4. An alternate solution is to develop Fc variants that reduce or ablate binding (Alegre *et al.*, 1994, *Transplantation* 57:1537-1543; Hutchins *et al.*, 1995, *Proc Natl Acad Sci U S A* 92:11980-11984; Armour *et al.*, 1999, *Eur J Immunol* 29:2613-2624; Reddy *et al.*, 2000, *J Immunol* 164:1925-1933; Xu *et al.*, 2000, *Cell Immunol* 200:16-26; Shields *et al.*, 2001, *J Biol Chem* 276:6591-6604) (US 6,194,551; US 6,885,573; PCT WO 99/58572). A critical consideration for the reduction or elimination of effector function is that other important antibody properties not be perturbed. Fc variants should be engineered that not only ablate binding to FcγRs and/or C1q, but also maintain antibody stability, solubility, and structural integrity, as well as ability to interact with other important Fc ligands such as FcRn and proteins A and G.

[017] The present invention addresses another major shortcoming of antibodies, namely their demanding production requirements (Garber, 2001, *Nat Biotechnol* 19:184-185; Dove, 2002, *Nat Biotechnol* 20:777-779). Antibodies must be expressed in mammalian cells, and the currently marketed antibodies together with other high-demand biotherapeutics consume essentially all of the available manufacturing capacity. With hundreds of biologics in development, the majority of which are antibodies, there is an urgent need for more efficient and cheaper methods of production. The downstream effects of insufficient antibody manufacturing capacity are three-fold. First, it dramatically raises the cost of goods to the producer, a cost that is passed on to the patient. Second, it hinders industrial production of approved antibody products, limiting availability of high demand therapeutics to patients. Finally, because clinical trials require large amounts of a protein that is not yet profitable, the insufficient supply impedes progress of the growing antibody pipeline to market.

[018] Alternative production methods have been explored in attempts at alleviating this problem. Transgenic plants and animals are being pursued as potentially cheaper and higher capacity production systems (Chadd *et al.*, 2001, *Curr Opin Biotechnol* 12:188-194). Such expression systems, however, can generate glycosylation patterns significantly different from human glycoproteins. This may result in reduced or even lack of effector function because, as discussed above, the carbohydrate structure can significantly impact FcγR and complement binding. A potentially greater problem with nonhuman glycoforms may be immunogenicity; carbohydrates are a key source of antigenicity for the immune system, and the presence of nonhuman glycoforms has a significant chance of eliciting antibodies that neutralize the therapeutic, or worse cause adverse immune reactions. Thus the efficacy and safety of antibodies produced by transgenic plants and animals remains uncertain. Bacterial expression is another attractive solution to the antibody production problem. Expression in bacteria, for example *E. coli*, provides a cost-effective and high capacity method for producing proteins. For complex proteins such as antibodies there are a number of obstacles to bacterial expression, including folding and assembly of these complex molecules, proper disulfide formation, and solubility, stability, and functionality in the absence of glycosylation because proteins expressed in bacteria are not glycosylated. Full length unglycosylated antibodies that bind antigen have been successfully expressed in *E. coli* (Simmons *et al.*, 2002, *J Immunol*

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Methods 263:133-147), and thus, folding, assembly, and proper disulfide formation of bacterially expressed antibodies are possible in the absence of the eukaryotic chaperone machinery. However the ultimate utility of bacterially expressed antibodies as therapeutics remains hindered by the lack of glycosylation, which results in lack effector function and may result in poor stability and solubility. This will likely be more problematic for formulation at the high concentrations for the prolonged periods demanded by clinical use.

[019] An aglycosylated Fc with favorable solution properties and the capacity to mediate effector functions would be significantly enabling for the alternate production methods described above. By overcoming the structural and functional shortcomings of aglycosylated Fc, antibodies can be produced in bacteria and transgenic plants and animals with reduced risk of immunogenicity, and with effector function for clinical applications in which cytotoxicity is desired such as cancer. The present invention describes the utilization of protein engineering methods to develop stable, soluble Fc variants with effector function. Currently, such Fc variants do not exist in the art.

[020] In summary, there is a need for antibodies with enhanced therapeutic properties. Engineering of optimized or enhanced Fc variants is a promising approach to meeting this need. Yet a substantial obstacle to engineering Fc variants with the desired properties is the difficulty in predicting what amino acid modifications, out of the enormous number of possibilities, will achieve the desired goals, coupled with the inefficient production and screening methods for antibodies. Indeed one of the principle reasons for the incomplete success of the prior art is that approaches to Fc engineering have thus far involved hit-or-miss methods such as alanine scans or production of glycoforms using different expression strains. In these studies, the Fc modifications that were made were fully or partly random in hopes of obtaining variants with favorable properties. The present invention provides a variety of engineering methods, many of which are based on more sophisticated and efficient techniques, which may be used to overcome these obstacles in order to develop Fc variants that are optimized for the desired properties. The described engineering methods provide design strategies to guide Fc modification, computational screening methods to design favorable Fc variants, library generation approaches for determining promising variants for experimental investigation, and an array of experimental production and screening methods for determining the Fc variants with favorable properties.

SUMMARY OF THE INVENTION

[021] The present invention provides Fc variants that are optimized for a number of therapeutically relevant properties.

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[022] It is an object of the present invention to provide novel Fc positions at which amino acid modifications may be made to generate optimized Fc variants. Said Fc positions include 240, 244, 245, 247, 262, 263, 266, 299, 313, 325, 328, and 332, wherein the numbering of the residues in the Fc region is that of the EU index as in Kabat. The present invention describes any amino acid modification at any of said novel Fc positions in order to generate an optimized Fc variant.

[023] It is a further object of the present invention to provide Fc variants that have been screened computationally. A computationally screened Fc variant is one that is predicted by the computational screening calculations described herein as having a significantly greater potential than random for being optimized for a desired property. In this way, computational screening serves as a prelude to or surrogate for experimental screening, and thus said computationally screened Fc variants are considered novel.

[024] It is a further object of the present invention to provide Fc variants that have been characterized using one or more of the experimental methods described herein. In one embodiment, said Fc variants comprise at least one amino acid substitution at a position selected from the group consisting of: 234, 235, 239, 240, 241, 243, 244, 245, 247, 262, 263, 264, 265, 266, 267, 269, 296, 297, 298, 299, 313, 325, 327, 328, 329, 330, and 332, wherein the numbering of the residues in the Fc region is that of the EU index as in Kabat. In a preferred embodiment, said Fc variants comprise at least one substitution selected from the group consisting of L234D, L234E, L234N, L234Q, L234T, L234H, L234Y, L234I, L234V, L234F, L235D, L235S, L235N, L235Q, L235T, L235H, L235Y, L235I, L235V, L235F, S239D, S239E, S239N, S239Q, S239F, S239T, S239H, S239Y, V240I, V240A, V240T, V240M, F241W, F241L, F241Y, F241E, F241R, F243W, F243L F243Y, F243R, F243Q, P244H, P245A, P247V, P247G, V262I, V262A, V262T, V262E, V263I, V263A, V263T, V263M, V264L, V264I, V264W, V264T, V264R, V264F, V264M, V264Y, V264E, D265G, D265N, D265Q, D265Y, D265F, D265V, D265I, D265L, D265H, D265T, V266I, V266A, V266T, V266M, S267Q, S267L, E269H, E269Y, E269F, E269R, Y296E, Y296Q, Y296D, Y296N, Y296S, Y296T, Y296L, Y296I, Y296H, N297S, N297D, N297E, A298H, T299I, T299L, T299A, T299S, T299V, T299H, T299F, T299E, W313F, N325Q, N325L, N325I, N325D, N325E, N325A, N325T, N325V, N325H, A327N, A327L, L328M, L328D, L328E, L328N, L328Q, L328F, L328I, L328V, L328T, L328H, L328A, P329F, A330L, A330Y, A330V, A330I, A330F, A330R, A330H, I332D, I332E, I332N, I332Q, I332T, I332H, I332Y, and I332A, wherein the numbering of the residues in the Fc region is that of the EU index as in Kabat. In a mostly preferred embodiment, said Fc variants are selected from the group consisting of V264L, V264I, F241W, F241L, F243W, F243L, F241L/F243L/V262I/V264I, F241W/F243W, F241W/F243W/V262A/V264A, F241L/V262I, F243L/V264I, F243L/V262I/V264W, F241Y/F243Y/V262T/V264T, F241E/F243R/V262E/V264R, F241E/F243Q/V262T/V264E, F241R/F243Q/V262T/V264R, F241E/F243Y/V262T/V264R, L328M, L328E, L328F, I332E, L328M/I332E, P244H, P245A, P247V, W313F, P244H/P245A/P247V, P247G, V264I/I332E, F241E/F243R/V262E/V264R/I332E, F241E/F243Q/V262T/V264E/I332E,

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F241R/F243Q/V262T/V264R/I332E, F241E/F243Y/V262T/V264R/I332E, S298A/I332E, S239E/I332E, S239Q/I332E, S239E, D265G, D265N, S239E/D265G, S239E/D265N, S239E/D265Q, Y296E, Y296Q, T299I, A327N, S267Q/A327S, S267L/A327S , A327L, P329F, A330L, A330Y, I332D, N297S, N297D, N297S/I332E, N297D/I332E, N297E/I332E, D265Y/N297D/I332E, D265Y/N297D/T299L/I332E, D265F/N297E/I332E, L328I/I332E, L328Q/I332E, I332N, I332Q, V264T, V264F, V240I, V263I, V266I, T299A, T299S, T299V, N325Q, N325L, N325I, S239D, S239N, S239F, S239D/I332D, S239D/I332E, S239D/I332N, S239D/I332Q, S239E/I332D, S239E/I332N, S239E/I332Q, S239N/I332D, S239N/I332E, S239N/I332N, S239N/I332Q, S239Q/I332D, S239Q/I332N, S239Q/I332Q, Y296D, Y296N, F241Y/F243Y/V262T/V264T/N297D/I332E, A330Y/I332E, V264I/A330Y/I332E, A330L/I332E, V264I/A330L/I332E, L234D, L234E, L234N, L234Q, L234T, L234H, L234Y, L234I, L234V, L234F, L235D, L235S, L235N, L235Q, L235T, L235H, L235Y, L235I, L235V, L235F, S239T, S239H, S239Y, V240A, V240T, V240M, V263A, V263T, V263M, V264M, V264Y, V266A, V266T, V266M, E269H, E269Y, E269F, E269R, Y296S, Y296T, Y296L, Y296I, A298H, T299H, A330V, A330I, A330F, A330R, A330H, N325D, N325E, N325A, N325T, N325V, N325H, L328D/I332E, L328E/I332E, L328N/I332E, L328Q/I332E, L328V/I332E, L328T/I332E, L328H/I332E, L328I/I332E, L328A, I332T, I332H, I332Y, I332A, S239E/V264I/I332E, S239Q/V264I/I332E, S239E/V264I/A330Y/I332E, S239E/V264I/S298A/A330Y/I332E, S239D/N297D/I332E, S239E/N297D/I332E, S239D/D265V/N297D/I332E, S239D/D265I/N297D/I332E, S239D/D265L/N297D/I332E, S239D/D265F/N297D/I332E, S239D/D265Y/N297D/I332E, S239D/D265H/N297D/I332E, S239D/D265T/N297D/I332E, V264E/N297D/I332E, Y296D/N297D/I332E, Y296E/N297D/I332E, Y296N/N297D/I332E, Y296Q/N297D/I332E, Y296H/N297D/I332E, Y296T/N297D/I332E, N297D/T299V/I332E, N297D/T299I/I332E, N297D/T299L/I332E, N297D/T299F/I332E, N297D/T299H/I332E, N297D/T299E/I332E, N297D/A330Y/I332E, N297D/S298A/A330Y/I332E, S239D/A330Y/I332E, S239N/A330Y/I332E, S239D/A330L/I332E, S239N/A330L/I332E, V264I/S298A/I332E, S239D/S298A/I332E, S239N/S298A/I332E, S239D/V264I/I332E, S239D/V264I/S298A/I332E, and S239D/V264I/A330L/I332E, wherein the numbering of the residues in the Fc region is that of the EU index as in Kabat.

[025] It is a further object of the present invention to provide an Fc variant that binds with greater affinity to one or more FcγRs. In one embodiment, said Fc variants have affinity for an FcγR that is more than 1-fold greater than that of the parent Fc polypeptide. In an alternate embodiment, said Fc variants have affinity for an FcγR that is more than 5-fold greater than that of the parent Fc polypeptide. In a preferred embodiment, said Fc variants have affinity for an FcγR that is between 5-fold and 300-fold greater than that of the parent Fc polypeptide. In one embodiment, said Fc variants comprise at least one amino acid substitution at a position selected from the group consisting of: 234, 235, 239, 240, 243, 264, 266, 328, 330, 332, and 325, wherein the numbering of the residues in the Fc region is that of the EU index as in Kabat. In a preferred embodiment, said Fc variants comprise at least one amino acid substitution selected from the group consisting of: L234E, L234Y, L234I, L235D,

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L235S, L235Y, L235I, S239D, S239E, S239N, S239Q, S239T, V240I, V240M, F243L, V264I, V264T, V264Y, V266I, L328M, L328I, L328Q, L328D, L328V, L328T, A330Y, A330L, A330I, I332D, I332E, I332N, I332Q, and N325T, wherein the numbering of the residues in the Fc region is that of the EU index as in Kabat. In a mostly preferred embodiment, said Fc variants are selected from the group consisting of V264I, F243L/V264I, L328M, I332E, L328M/I332E, V264I/I332E, S298A/I332E, S239E/I332E, S239Q/I332E, S239E, A330Y, I332D, L328I/I332E, L328Q/I332E, V264T, V240I, V266I, S239D, S239D/I332D, S239D/I332E, S239D/I332N, S239D/I332Q, S239E/I332D, S239E/I332N, S239E/I332Q, S239N/I332D, S239N/I332E, S239Q/I332D, A330Y/I332E, V264I/A330Y/I332E, A330L/I332E, V264I/A330L/I332E, L234E, L234Y, L234I, L235D, L235S, L235Y, L235I, S239T, V240M, V264Y, A330I, N325T, L328D/I332E, L328V/I332E, L328T/I332E, L328I/I332E, S239E/V264I/I332E, S239Q/V264I/I332E, S239E/V264I/A330Y/I332E, S239D/A330Y/I332E, S239N/A330Y/I332E, S239D/A330L/I332E, S239N/A330L/I332E, V264I/S298A/I332E, S239D/S298A/I332E, S239N/S298A/I332E, S239D/V264I/I332E, S239D/V264I/S298A/I332E, and S239D/V264I/A330L/I332E, wherein the numbering of the residues in the Fc region is that of the EU index as in Kabat.

[026] It is a further object of the present invention to provide Fc variantd that have a FcγRIIIa-fold:FcγRIIb-fold ratio greater than 1:1. In one embodiment, said Fc variants have a FcγRIIIa-fold:FcγRIIb-fold ratio greater than 11:1. In a preferred embodiment, said Fc variants have a FcγRIIIa-fold:FcγRIIb-fold ratio between 11:1 and 86:1. In one embodiment, said Fc variants comprise at least one amino acid substitution at a position selected from the group consisting of: 234, 235, 239, 240, 264, 296, 330, and I332, wherein the numbering of the residues in the Fc region is that of the EU index as in Kabat. In a preferred embodiment, said Fc variants comprise at least one amino acid substitution selected from the group consisting of: L234Y, L234I, L235I, S239D, S239E, S239N, S239Q, V240A, V240M, V264I, V264Y, Y296Q, A330L, A330Y, A330I, I332D, and I332E, wherein the numbering of the residues in the Fc region is that of the EU index as in Kabat. In a mostly preferred embodiment, said Fc variants are selected from the group consisting of: I332E, V264I/I332E, S239E/I332E, S239Q/I332E, Y296Q, A330L, A330Y, I332D, S239D, S239D/I332E, A330Y/I332E, V264I/A330Y/I332E, A330L/I332E, V264I/A330L/I332E, L234Y, L234I, L235I, V240A, V240M, V264Y, A330I, S239D/A330L/I332E, S239D/S298A/I332E, S239N/S298A/I332E, S239D/V264I/I332E, S239D/V264I/S298A/I332E, and S239D/V264I/A330L/I332E, wherein the numbering of the residues in the Fc region is that of the EU index as in Kabat.

[027] It is a further object of the present invention to provide Fc variants that mediate effector function more effectively in the presence of effector cells. In one embodiment, said Fc variants mediate ADCC that is greater than that mediated by the parent Fc polypeptide. In a preferred embodiment, said Fc variants mediate ADCC that is more than 5-fold greater than that mediated by the parent Fc polypeptide. In a mostly preferred embodiment, said Fc variants mediate ADCC that is between 5-fold and 50-fold greater than that mediated by the parent Fc polypeptide. In one

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embodiment, said Fc variants comprise at least one amino acid substitution at a position selected from the group consisting of: 234, 235, 239, 240, 243, 264, 266, 328, 330, 332, and 325, wherein the numbering of the residues in the Fc region is that of the EU index as in Kabat. In a preferred embodiment, said Fc variants comprise at least one amino acid substitutions selected from the group consisting of: L234E, L234Y, L234I, L235D, L235S, L235Y, L235I, S239D, S239E, S239N, S239Q, S239T, V240I, V240M, F243L, V264I, V264T, V264Y, V266I, L328M, L328I, L328Q, L328D, L328V, L328T, A330Y, A330L, A330I, I332D, I332E, I332N, I332Q, and N325T, wherein the numbering of the residues in the Fc region is that of the EU index as in Kabat. In a mostly preferred embodiment, said Fc variants are selected from the group consisting of: V264I, F243L/V264I, L328M, I332E, L328M/I332E, V264I/I332E, S298A/I332E, S239E/I332E, S239Q/I332E, S239E, A330Y, I332D, L328I/I332E, L328Q/I332E, V264T, V240I, V266I, S239D, S239D/I332D, S239D/I332E, S239D/I332N, S239D/I332Q, S239E/I332D, S239E/I332N, S239E/I332Q, S239N/I332D, S239N/I332E, S239Q/I332D, A330Y/I332E, V264I/A330Y/I332E, A330L/I332E, V264I/A330L/I332E, L234E, L234Y, L234I, L235D, L235S, L235Y, L235I, S239T, V240M, V264Y, A330I, N325T, L328D/I332E, L328V/I332E, L328T/I332E, L328I/I332E, S239E/V264I/I332E, S239Q/V264I/I332E, S239E/V264I/A330Y/I332E, S239D/A330Y/I332E, S239N/A330Y/I332E, S239D/A330L/I332E, S239N/A330L/I332E, V264I/S298A/I332E, S239D/S298A/I332E, S239N/S298A/I332E, S239D/V264I/I332E, S239D/V264I/S298A/I332E, and S239D/V264I/A330L/I332E, wherein the numbering of the residues in the Fc region is that of the EU index as in Kabat.

[028] It is a further object of the present invention to provide Fc variants that bind with weaker affinity to one or more FcγRs. In one embodiment, said Fc variants comprise at least one amino acid substitution at a position selected from the group consisting of: 234, 235, 239, 240, 241, 243, 244, 245, 247, 262, 263, 264, 265, 266, 267, 269, 296, 297, 298, 299, 313, 325, 327, 328, 329, 330, and 332, wherein the numbering of the residues in the Fc region is that of the EU index as in Kabat. In a preferred embodiment, said Fc variants comprise an amino acid substitution at a position selected from the group consisting of: L234D, L234N, L234Q, L234T, L234H, L234V, L234F, L235N, L235Q, L235T, L235H, L235V, L235F, S239E, S239N, S239Q, S239F, S239H, S239Y, V240A, V240T, F241W, F241L, F241Y, F241E, F241R, F243W, F243L F243Y, F243R, F243Q, P244H, P245A, P247V, P247G, V262I, V262A, V262T, V262E, V263I, V263A, V263T, V263M, V264L, V264I, V264W, V264T, V264R, V264F, V264M, V264E, D265G, D265N, D265Q, D265Y, D265F, D265V, D265I, D265L, D265H, D265T, V266A, V266T, V266M, S267Q, S267L, E269H, E269Y, E269F, E269R, Y296E, Y296Q, Y296D, Y296N, Y296S, Y296T, Y296L, Y296I, Y296H, N297S, N297D, N297E, A298H, T299I, T299L, T299A, T299S, T299V, T299H, T299F, T299E, W313F, N325Q, N325L, N325I, N325D, N325E, N325A, N325V, N325H, A327N, A327L, L328M, 328E, L328N, L328Q, L328F, L328H, L328A, P329F, A330L, A330V, A330F, A330R, A330H, I332N, I332Q, I332T, I332H, I332Y, and I332A, wherein the numbering of the residues in the Fc region is that of the EU index as in Kabat. In a mostly preferred embodiment, said Fc variants are selected from the group consisting of: V264L, F241W, F241L, F243W, F243L, F241L/F243L/V262I/V264I, F241W/F243W, F241W/F243W/V262A/V264A, F241L/V262I, F243L/V262I/V264W, F241Y/F243Y/V262T/V264T,

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F241E/F243R/V262E/V264R, F241E/F243Q/V262T/V264E, F241R/F243Q/V262T/V264R, F241E/F243Y/V262T/V264R, L328M, L328E, L328F, P244H, P245A, P247V, W313F, P244H/P245A/P247V, P247G, F241E/F243R/V262E/V264R/I332E, F241E/F243Y/V262T/V264R/I332E, D265G, D265N, S239E/D265G, S239E/D265N, S239E/D265Q, Y296E, Y296Q, T299I, A327N, S267Q/A327S, S267L/A327S , A327L, P329F, A330L, N297S, N297D, N297S/I332E, I332N, I332Q, V264F, V263I, T299A, T299S, T299V, N325Q, N325L, N325I, S239N, S239F, S239N/I332N, S239N/I332Q, S239Q/I332N, S239Q/I332Q, Y296D, Y296N, L234D, L234N, L234Q, L234T, L234H, L234V, L234F, L235N, L235Q, L235T, L235H, L235V, L235F, S239H, S239Y, V240A, V263T, V263M, V264M, V266A, V266T, V266M, E269H, E269Y, E269F, E269R, Y296S, Y296T, Y296L, Y296I, A298H, T299H, A330V, A330F, A330R, A330H, N325D, N325E, N325A, N325V, N325H, L328E/I332E, L328N/I332E, L328Q/I332E, L328H/I332E, L328A, I332T, I332H, I332Y, and I332A, wherein the numbering of the residues in the Fc region is that of the EU index as in Kabat.

[029] It is a further object of the present invention to provide Fc variants that mediate ADCC in the presence of effector cells less effectively. In one embodiment, said Fc variants comprise at least one amino acid substitution at a position selected from the group consisting of: 234, 235, 239, 240, 241, 243, 244, 245, 247, 262, 263, 264, 265, 266, 267, 269, 296, 297, 298, 299, 313, 325, 327, 328, 329, 330, and 332, wherein the numbering of the residues in the Fc region is that of the EU index as in Kabat. In a preferred embodiment, said Fc variants comprise at least one amino acid substitution at a position selected from the group consisting of: L234D, L234N, L234Q, L234T, L234H, L234V, L234F, L235N, L235Q, L235T, L235H, L235V, L235F, S239E, S239N, S239Q, S239F, S239H, S239Y, V240A, V240T, F241W, F241L, F241Y, F241E, F241R, F243W, F243L F243Y, F243R, F243Q, P244H, P245A, P247V, P247G, V262I, V262A, V262T, V262E, V263I, V263A, V263T, V263M, V264L, V264I, V264W, V264T, V264R, V264F, V264M, V264E, D265G, D265N, D265Q, D265Y, D265F, D265V, D265I, D265L, D265H, D265T, V266A, V266T, V266M, S267Q, S267L, E269H, E269Y, E269F, E269R, Y296E, Y296Q, Y296D, Y296N, Y296S, Y296T, Y296L, Y296I, Y296H, N297S, N297D, N297E, A298H, T299I, T299L, T299A, T299S, T299V, T299H, T299F, T299E, W313F, N325Q, N325L, N325I, N325D, N325E, N325A, N325V, N325H, A327N, A327L, L328M, L328E, L328N, L328Q, L328F, L328H, L328A, P329F, A330L, A330V, A330F, A330R, A330H, I332N, I332Q, I332T, I332H, I332Y, and I332A, wherein the numbering of the residues in the Fc region is that of the EU index as in Kabat. In a mostly preferred embodiment, said Fc variants are selected from the group consisting of: V264L, F241W, F241L, F243W, F243L, F241L/F243L/V262I/V264I, F241W/F243W, F241W/F243W/V262A/V264A, F241L/V262I, F243L/V262I/V264W, F241Y/F243Y/V262T/V264T, F241E/F243R/V262E/V264R, F241E/F243Q/V262T/V264E, F241R/F243Q/V262T/V264R, F241E/F243Y/V262T/V264R, L328M, L328E, L328F, P244H, P245A, P247V, W313F, P244H/P245A/P247V, P247G, F241E/F243R/V262E/V264R/I332E, F241E/F243Y/V262T/V264R/I332E, D265G, D265N, S239E/D265G, S239E/D265N, S239E/D265Q, Y296E, Y296Q, T299I, A327N, S267Q/A327S, S267L/A327S , A327L, P329F, A330L, N297S, N297D, N297S/I332E, I332N, I332Q, V264F, V263I, T299A, T299S, T299V, N325Q, N325L, N325I,

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S239N, S239F, S239N/I332N, S239N/I332Q, S239Q/I332N, S239Q/I332Q, Y296D, Y296N, L234D, L234N, L234Q, L234T, L234H, L234V, L234F, L235N, L235Q, L235T, L235H, L235V, L235F, S239H, S239Y, V240A, V263T, V263M, V264M, V266A, V266T, V266M, E269H, E269Y, E269F, E269R, Y296S, Y296T, Y296L, Y296I, A298H, T299H, A330V, A330F, A330R, A330H, N325D, N325E, N325A, N325V, N325H, L328E/I332E, L328N/I332E, L328Q/I332E, L328H/I332E, L328A, I332T, I332H, I332Y, and I332A, wherein the numbering of the residues in the Fc region is that of the EU index as in Kabat.

[030] It is a further object of the present invention to provide Fc variants that have improved function and/or solution properties as compared to the aglycosylated form of the parent Fc polypeptide. Improved functionality herein includes but is not limited to binding affinity to an Fc ligand. Improved solution properties herein includes but is not limited to stability and solubility. In one embodiment, said aglycosylated Fc variants bind to an FcγR with an affinity that is comparable to or better than the glycosylated parent Fc polypeptide. In an alternate embodiment, said Fc variants bind to an FcγR with an affinity that is within 0.4-fold of the glycosylated form of the parent Fc polypeptide. In one embodiment, said Fc variants comprise at least one amino acid substitution at a position selected from the group consisting of: 239, 241, 243, 262, 264, 265, 296, 297, 330, and 332, wherein the numbering of the residues in the Fc region is that of the EU index as in Kabat. In a preferred embodiment, said Fc variants comprise an amino acid substitution selected from the group consisting of: S239D, S239E, F241Y, F243Y, V262T, V264T, V264E, D265Y, D265H, Y296N, N297D, A330Y, and I332E, wherein the numbering of the residues in the Fc region is that of the EU index as in Kabat. In a mostly preferred embodiment, said Fc variants are selected from the group consisting of: N297D/I332E, F241Y/F243Y/V262T/V264T/N297D/I332E, S239D/N297D/I332E, S239E/N297D/I332E, S239D/D265Y/N297D/I332E, S239D/D265H/N297D/I332E, V264E/N297D/I332E, Y296N/N297D/I332E, and N297D/A330Y/I332E, wherein the numbering of the residues in the Fc region is that of the EU index as in Kabat.

[031] The present invention also provides methods for engineering optimized Fc variants. It is an object of the present invention to provide design strategies that may be used to guide Fc optimization. It is a further object of the present invention to provide computational screening methods that may be used to design Fc variants. It is a further object of the present invention to provide methods for generating libraries for experimental testing. It is a further object of the present invention to provide experimental production and screening methods for obtaining optimized Fc variants.

[032] The present invention provides isolated nucleic acids encoding the Fc variants described herein. The present invention provides vectors comprising said nucleic acids, optionally, operably linked to control sequences. The present invention provides host cells containing the vectors, and methods for producing and optionally recovering the Fc variants.

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[033] The present invention provides novel antibodies and Fc fusions that comprise the Fc variants disclosed herein. Said novel antibodies and Fc fusions may find use in a therapeutic product.

[034] The present invention provides compositions comprising antibodies and Fc fusions that comprise the Fc variants described herein, and a physiologically or pharmaceutically acceptable carrier or diluent.

[035] The present invention contemplates therapeutic and diagnostic uses for antibodies and Fc fusions that comprise the Fc variants disclosed herein.

BRIEF DESCRIPTION OF THE DRAWINGS

[036] Figure 1. Antibody structure and function. Shown is a model of a full length human IgG1 antibody, modeled using a humanized Fab structure from pdb accession code 1CE1 (James *et al.*, 1999, *J Mol Biol* 289:293-301) and a human IgG1 Fc structure from pdb accession code 1DN2 (DeLano *et al.*, 2000, *Science* 287:1279-1283). The flexible hinge that links the Feb and Fc regions is not shown. IgG1 is a homodimer of heterodimers, made up of two light chains and two heavy chains. The Ig domains that comprise the antibody are labeled, and include V_L and C_L for the light chain, and V_H, Cgamma1 ($C\gamma1$), Cgamma2 ($C\gamma2$), and Cgamma3 ($C\gamma3$) for the heavy chain. The Fc region is labeled. Binding sites for relevant proteins are labeled, including the antigen binding site in the variable region, and the binding sites for FcγRs, FcRn, C1q, and proteins A and G in the Fc region.

[037] Figure 2. The Fc/FcγRIIIb complex structure 1IIS. Fc is shown as a gray ribbon diagram, and FcγRIIIb is shown as a black ribbon. The N297 carbohydrate is shown as black sticks.

[038] Figure 3. The amino acid sequence of the heavy chain of the antibody alemtuzumab (Campath®, a registered trademark of Ilex Pharmaceuticals LP), illustrating positions numbered sequentially (2 lines above the amino acid sequence) and positions numbered according to the EU index as in Kabat (2 lines below the amino acid sequence. The approximate beginnings of Ig domains VH1, Cγ1, the hinge, Cγ2, and Cγ3 are also labeled above the sequential numbering. Polymorphisms have been observed at a number of Fc positions, including but not limited to Kabat 270, 272, 312, 315, 356, and 358, and thus slight differences between the presented sequence and sequences in the prior art may exist.

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[039] Figure 4. Experimental library residues mapped onto the Fc/FcγRIIIb complex structure 1IIS. Fc is shown as a gray ribbon diagram, and FcγRIIIb is shown as a black ribbon. Experimental library residues are shown as black ball and sticks. The N297 carbohydrate is shown as black sticks.

[040] Figure 5. The human IgG1 Fc sequence showing positions relevant to the design of the Fc variant experimental library. The sequence includes the hinge region, domain Cγ2, and domain Cγ3. Residue numbers are according to the EU index as in Kabat. Positions relevant to the experimental library are underlined. Because of observed polymorphic mutations at a number of Fc positions, slight differences between the presented sequence and sequences in the literature may exist.

[041] Figure 6. Expression of Fc variant and wild type (WT) proteins of alemtuzumab in 293T cells. Plasmids containing alemtuzumab heavy chain genes (WT or variants) were co-transfected with plasmid containing the alemtuzumab light chain gene. Media were harvested 5 days after transfection. For each transfected sample, 10ul medium was loaded on a SDS-PAGE gel for Western analysis. The probe for Western was peroxidase-conjugated goat-anti human IgG (Jackson Immuno-Research, catalog # 109-035-088). WT: wild type alemtuzumab; 1-10: alemtuzumab variants. H and L indicate antibody heavy chain and light chain, respectively.

[042] Figure 7. Purification of alemtuzumab using protein A chromatography. WT alemtuzumab proteins was expressed in 293T cells and the media was harvested 5 days after transfection. The media were diluted 1:1 with PBS and purified with protein A (Pierce, Catalog # 20334). O: original sample before purification; FT: flow through; E: elution; C: concentrated final sample. The left picture shows a Simple Blue-stained SDS-PAGE gel, and the right shows a western blot labeled using peroxidase-conjugated goat-anti human IgG.

[043] Figure 8. Production of deglycosylated antibodies. Wild type and variants of alemtuzumab were expressed in 293T cells and purified with protein A chromatography. Antibodies were incubated with peptide-N-glycosidase (PNGase F) at 37°C for 24h. For each antibody, a mock treated sample (- PNGase F) was done in parallel. WT: wild-type alemtuzumab; #15, #16, #17, #18, #22: alemtuzumab variants F241E/F243R/V262E/V264R, F241E/F243Q/V262T/V264E, F241R/F243Q/V262T/V264R, F241E/F243Y/V262T/V264R, and I332E respectively. The faster migration of the PNGase F treated versus the mock treated samples represents the deglycosylated heavy chains.

[044] Figure 9. Alemtuzumab expressed from 293T cells binds its antigen. The antigenic CD52 peptide, fused to GST, was expressed in *E. coli* BL21 (DE3) under IPTG induction. Both uninduced and induced samples were run on a SDS-PAGE gel, and transferred to PVDF membrane. For western analysis, either alemtuzumab from Sotec (□-CD52, Sotec) (final concentration 2.5ng/ul) or

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media of transfected 293T cells (Campath, Xencor) (final alemtuzumab concentration approximately 0.1-0.2ng/ul) were used as primary antibody, and peroxidase-conjugated goat-anti human IgG was used as secondary antibody. M: pre-stained marker; U: un-induced sample for GST-CD52; I: induced sample for GST-CD52.

[045] Figure 10. Expression and purification of extracellular region of human V158 FcγRIIIa. Tagged FcγRIIIa was transfected in 293T cells, and media containing secreted FcγRIIIa were harvested 3 days later and purified using affinity chromatography. 1: media; 2: flow through; 3: wash; 4-8: serial elutions. Both simple blue-stained SDS-PAGE gel and western result are shown. For the western blot, membrane was probed with anti-GST antibody.

[046] Figure 11. Binding to human V158 FcγRIIIa by select alemtuzumab Fc variants from the experimental library as determined by the AlphaScreen™ assay, described in Example 2. In the presence of competitor antibody (Fc variant or WT alemtuzumab) a characteristic inhibition curve is observed as a decrease in luminescence signal. Phosphate buffer saline (PBS) alone was used as the negative control. These data were normalized to the maximum and minimum luminescence signal provided by the baselines at low and high concentrations of competitor antibody respectively. The curves represent the fits of the data to a one site competition model using nonlinear regression. These fits provide IC50s for each antibody, illustrated for WT and S239D by the dotted lines.

[047] Figures 12. AlphaScreen™ assay showing binding of select alemtuzumab Fc variants to human FcγRIIb. The data were normalized, and the curves represent the fits of the data to a one site competition model. PBS was used as a negative control.

[048] Figures 13. AlphaScreen™ assay showing binding of select alemtuzumab Fc variants to human Val158 FcγRIIIa. The data were normalized, and the curves represent the fits of the data to a one site competition model. PBS was used as a negative control.

[049] Figure 14. AlphaScreen™ assay measuring binding to human V158 FcγRIIIa by select Fc variants in the context of rituximab. The data were normalized, and the curves represent the fits of the data to a one site competition model. PBS was used as a negative control.

[050] Figure 15. AlphaScreen™ assay measuring binding to human V158 FcγRIIIa by select Fc variants in the context of trastuzumab. The data were normalized, and the curves represent the fits of the data to a one site competition model. PBS was used as a negative control.

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[051] Figures 16a – 16b. AlphaScreen™ assay comparing binding of select alemtuzumab Fc variants to human V158 FcγRIIIa (Figure 16a) and human FcγRIIb (Figure 16b). The data were normalized, and the curves represent the fits of the data to a one site competition model. PBS was used as a negative control.

[052] Figure 17. AlphaScreen™ assay measuring binding to human V158 FcγRIIIa by select Fc variants in the context of trastuzumab. The data were normalized, and the curves represent the fits of the data to a one site competition model.

[053] Figures 18. AlphaScreen™ assay showing binding of select alemtuzumab Fc variants to human R131 FcγRIIa. The data were normalized, and the curves represent the fits of the data to a one site competition model.

[054] Figures 19a and 19b. AlphaScreen™ assay showing binding of select alemtuzumab Fc variants to human V158 FcγRIIIa. The data were normalized, and the curves represent the fits of the data to a one site competition model. PBS was used as a negative control.

[055] Figure 20. AlphaScreen™ assay showing binding of agiycosylated alemtuzumab Fc variants to human V158 FcγRIIIa. The data were normalized, and the curves represent the fits of the data to a one site competition model. PBS was used as a negative control.

[056] Figure 21. AlphaScreen™ assay comparing human V158 FcγRIIIa binding by select alemtuzumab Fc variants in glycosylated (solid symbols, solid lines) and deglycosylated (open symbols, dotted lines). The data were normalized, and the curves represent the fits of the data to a one site competition model.

[057] Figures 22a – 22b. AlphaScreen™ assay showing binding of select alemtuzumab Fc variants to the V158 (Figure 22a) and F158 (Figure 22b) allotypes of human FcγRIIIa. The data were normalized, and the curves represent the fits of the data to a one site competition model. PBS was used as a negative control.

[058] Figures 23a – 23d. Figures 23a and 23b show the correlation between SPR Kd's and AlphaScreen™ IC50's from binding of select alemtuzumab Fc variants to V158 FcγRIIIa (Figure 23a)

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and F158 FcγRIIIa (Figure 23b). Figures 23c and 23d show the correlation between SPR and AlphaScreen™ fold-improvements over WT for binding of select alemtuzumab Fc variants to V158 FcγRIIIa (Figure 23c) and F158 FcγRIIIa (Figure 23d). Binding data are presented in Table 62. The lines through the data represent the linear fits of the data, and the r^2 values indicate the significance of these fits.

[059] Figures 24a – 24b. Cell-based ADCC assays of select Fc variants in the context of alemtuzumab. ADCC was measured using the DELFIA® EuTDA-based cytotoxicity assay (Perkin Elmer, MA), as described in Example 7, using DoHH-2 lymphoma target cells and 50-fold excess human PBMCs. Figure 24a is a bar graph showing the raw fluorescence data for the indicated alemtuzumab antibodies at 10 ng/ml. The PBMC bar indicates basal levels of cytotoxicity in the absence of antibody. Figure 24b shows the dose-dependence of ADCC on antibody concentration for the indicated alemtuzumab antibodies, normalized to the minimum and maximum fluorescence signal provided by the baselines at low and high concentrations of antibody respectively. The curves represent the fits of the data to a sigmoidal dose-response model using nonlinear regression.

[060] Figures 25a – 25b. Cell-based ADCC assays of select Fc variants in the context of rituximab. ADCC was measured using the DELFIA® EuTDA-based cytotoxicity assay, as described in Example 7, using WIL2-S lymphoma target cells and 50-fold excess human PBMCs. Figure 25a is a bar graph showing the raw fluorescence data for the indicated rituximab antibodies at 1 ng/ml. The PBMC bar indicates basal levels of cytotoxicity in the absence of antibody. Figure 25b shows the dose-dependence of ADCC on antibody concentration for the indicated rituximab antibodies, normalized to the minimum and maximum fluorescence signal provided by the baselines at low and high concentrations of antibody respectively. The curves represent the fits of the data to a sigmoidal dose-response model using nonlinear regression.

[061] Figures 26a – 26c. Cell-based ADCC assays of select Fc variants in the context of trastuzumab. ADCC was measured using the DELFIA® EuTDA-based cytotoxicity assay, as described in Example 7, using BT474 and Sk-Br-3 breast carcinoma target cells and 50-fold excess human PBMCs. Figure 26a is a bar graph showing the raw fluorescence data for the indicated trastuzumab antibodies at 1 ng/ml. The PBMC bar indicates basal levels of cytotoxicity in the absence of antibody. Figures 26b and 26c show the dose-dependence of ADCC on antibody concentration for the indicated trastuzumab antibodies, normalized to the minimum and maximum fluorescence signal provided by the baselines at low and high concentrations of antibody respectively. The curves represent the fits of the data to a sigmoidal dose-response model using nonlinear regression.

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[062] Figures 27a – 27b. Capacity of select Fc variants to mediate binding and activation of complement. Figure 27a shows an AlphaScreen™ assay measuring binding of select alemtuzumab Fc variants to C1q. The data were normalized to the maximum and minimum luminescence signal provided by the baselines at low and high concentrations of competitor antibody respectively. The curves represent the fits of the data to a one site competition model using nonlinear regression. Figure 27b shows a cell-based assay measuring capacity of select rituximab Fc variants to mediate CDC. CDC assays were performed using Amar Blue to monitor lysis of Fc variant and WT rituximab - opsonized WIL2-S lymphoma cells by human serum complement (Quidel, San Diego, CA). The dose-dependence on antibody concentration of complement-mediated lysis is shown for the indicated rituximab antibodies, normalized to the minimum and maximum fluorescence signal provided by the baselines at low and high concentrations of antibody respectively. The curves represent the fits of the data to a sigmoidal dose-response model using nonlinear regression.

[063] Figure 28. AlphaScreen™ assay measuring binding of select alemtuzumab Fc variants to bacterial protein A, as described in Example 9. The data were normalized, and the curves represent the fits of the data to a one site competition modal. PBS was used as a negative control.

[064] Figure 29. AlphaScreen™ assay measuring binding of select alemtuzumab Fc variants to mouse FcγRIII, as described in Example 10. The data were normalized, and the curves represent the fits of the data to a one site competition model. PBS was used as a negative control.

[065] Figure 30. AlphaScreen™ assay measuring binding to human V158 FcγRIIIa by select trastuzumab Fc variants expressed in 293T and CHO cells, as described in Example 11. The data were normalized, and the curves represent the fits of the data to a one site competition model. PBS was used as a negative control.

[066] Figures 31a – 31c. Sequences showing improved anti-CD20 antibodies. The light and heavy chain sequences of rituximab are presented in Figure 31a and Figure 31b respectively, and are taken from translated Sequence 3 of US 5,736,137. Relevant positions in Figure 31b are bolded, including S239, V240, V264I, N297, S298, A330, and I332. Figure 31c shows the improved anti-CD20 antibody heavy chain sequences, with variable positions designated in bold as X_1, X_2, X_3, X_4, X_5, X_6 and Z_1. The table below the sequence provides possible substitutions for these positions. The improved anti-CD20 antibody sequences comprise at least one non-WT amino acid selected from the group of possible substitutions for X_1, X_2, X_3, X_4, X_5, and X_6. These improved anti-CD20 antibody sequences may also comprise a substitution Z_1. These positions are numbered according to the EU index as in Kabat, and thus do not correspond to the sequential order in the sequence.

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DETAILED DESCRIPTION OF THE INVENTION

[067] In order that the invention may be more completely understood, several definitions are set forth below. Such definitions are meant to encompass grammatical equivalents.

[068] By "ADCC" or "antibody dependent cell-mediated cytotoxicity" as used herein is meant the cell-mediated reaction wherein nonspecific cytotoxic cells that express FcγRs recognize bound antibody on a target cell and subsequently cause lysis of the target cell.

[069] By "ADCP" or antibody dependent cell-mediated phagocytosis as used herein is meant the cell-mediated reaction wherein nonspecific cytotoxic cells that express FcγRs recognize bound antibody on a target cell and subsequently cause phagocytosis of the target cell.

[070] By "amino acid modification" herein is meant an amino acid substitution, insertion, and/or deletion in a polypeptide sequence. The preferred amino acid modification herein is a substitution. **TT

[071] By "antibody" herein is meant a protein consisting of one or more polypeptides substantially encoded by all or part of the recognized immunoglobulin genes. The recognized immunoglobulin genes, for example in humans, include the kappa (□), lambda (□), and heavy chain genetic loci, which together comprise the myriad variable region genes, and the constant region genes mu (□), delta (□), gamma (γ), sigma (□), and alpha (□) which encode the IgM, IgD, IgG, IgE, and IgA isotypes respectively. Antibody herein is meant to include full length antibodies and antibody fragments, and may refer to a natural antibody from any organism, an engineered antibody, or an antibody generated recombinantly for experimental, therapeutic, or other purposes as further defined below. Thus, "antibody" includes both polyclonal and monoclonal antibody (mAb). Methods of preparation and purification of monoclonal and polyclonal antibodies are known in the art and e.g., are described in Harlow and Lane, Antibodies: A Laboratory Manual (New York: Cold Spring Harbor Laboratory Press, 1988). As outlined herein, "antibody" specifically includes Fc variants described herein, "full length" antibodies including the Fc variant fragments described herein, and Fc variant fusions to other proteins as described herein.

[072] n some embodiments, antibodies can be neutralizing or inhibitory, or stimulatory, and in preferred embodiments, as described herein, the stimulatory activity is measured by an increase in affinity of a variant antibody to a receptor, as compared to either the parent antibody (e.g. when a non-naturally occuring variant is used as the starting point for the computation analysis herein), or to the original wild-type antibody. Accordingly, by "neutralization," "neutralize," "neutralizing" and grammatical equivalents herein is meant to inhibit or lessen the biological effect of the antibody, in some cases by binding (e.g. competitively) to a antigen and avoiding or decreasing the biological effect of binding, or by binding that results in decreasing the biological effect of binding.

[073] The term "antibody" include antibody fragments, as are known in the art, such as Fab, Fab', F(ab')2, Fcs or other antigen-binding subsequences of antibodies, such as, single chain antibodies (Fv for example), chimeric antibodies, etc., either produced by the modification of whole antibodies or those synthesized de novo using recombinant DNA technologies. Particularly preferred are Fc variants as described herein. The term "antibody" further comprises polyclonal antibodies and mAbs which can be agonist or antagonist antibodies.

[074] The antibodies of the invention specifically bind to Fc receptors, as outlined herein. By "specifically bind" herein is meant that the LC antibodies have a binding constant in the range of at least 10^{-4} - 10^{-9} M^{-1}, with a preferred range being 10^{-7} - 10^{-9} M^{-1}.

In a preferred embodiment, the antibodies of the invention are humanized. Using current monoclonal antibody technology one can produce a humanized antibody to virtually any target antigen that can be identified [Stein, Trends Biotechnol. 15:88-90 (1997)]. Humanized forms of non-human (e.g., murine) antibodies are chimeric molecules of immunoglobulins, immunoglobulin chains or fragments thereof (such as Fv, Fc, Fab, Fab', F(ab')2 or other antigen-binding subsequences of antibodies) which contain minimal sequence derived from non-human immunoglobulin. Humanized antibodies include human immunoglobulins (recipient antibody) in which residues form a complementary determining region (CDR) of the recipient are replaced by residues from a CDR of a non-human species (donor antibody) such as mouse, rat or rabbit having the desired specificity, affinity and capacity. In some instances, Fv framework residues of the human immunoglobulin are replaced by corresponding non-human residues. Humanized antibodies may also comprise residues which are found neither in the recipient antibody nor in the imported CDR or framework sequences. In general, the humanized antibody will comprise substantially all of at least one, and typically two, variable domains, in which all or substantially all of the CDR regions correspond to those of a non-human immunoglobulin and all or substantially all of the FR regions are those of a human immunoglobulin consensus sequence. The humanized antibody optimally also will comprise at least a portion of an immunoglobulin constant region (Fc), typically that of a human immunoglobulin [Jones et al., Nature 321:522-525 (1986); Riechmann et al., Nature 332:323-329 (1988); and Presta, Curr. Op. Struct. Biol. 2:593-596 (1992)]. Methods for humanizing non-human antibodies are well known in the art. Generally, a humanized antibody has one or more amino acid residues introduced into it from a source which is non-human. These non-human amino acid residues are often referred to as import residues, which are typically taken from an import variable domain. Humanization can be essentially performed following the method of Winter and co-workers [Jones et al., supra; Riechmann et al., supra; and Verhoeyen et al., Science, 239:1534-1536 (1988)], by substituting rodent CDRs or CDR sequences for the corresponding sequences of a human antibody. Additional examples of humanized murine monoclonal antibodies are also known in the art, e.g., antibodies binding human protein C [O'Connor et al., Protein Eng. 11:321-8 (1998)], interleukin 2 receptor [Queen et al., Proc. Natl. Acad. Sci., U.S.A. 86:10029-33 (1989)], and human epidermal growth factor receptor 2 [Carter et al., Proc. Natl. Acad. Sci. U.S.A. 89:4285-9 (1992)]. Accordingly, such humanized antibodies are chimeric antibodies (U.S. Patent No. 4,816,567), wherein substantially less than an intact human variable domain has

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been substituted by the corresponding sequence from a non-human species. In practice, humanized antibodies are typically human antibodies in which some CDR residues and possibly some FR residues are substituted by residues from analogous sites in rodent antibodies.

[075] In a preferred embodiment, the antibodies of the invention are based on human sequences, and are thus human sequences are used as the "base" sequences, against which other sequences, such as rat, mouse and monkey sequences. In order to establish homology to primary sequence or structure, the amino acid sequence of a precursor or parent Fc is directly compared to the human Fc sequence outlined herein. After aligning the sequences, using one or more of the homology alignment programs described herein (for example using conserved residues as between species), allowing for necessary insertions and deletions in order to maintain alignment (i.e., avoiding the elimination of conserved residues through arbitrary deletion and insertion), the residues equivalent to particular amino acids in the primary sequence of human Fc are defined. Alignment of conserved residues preferably should conserve 100% of such residues. However, alignment of greater than 75% or as little as 50% of conserved residues is also adequate to define equivalent residues (sometimes referred to herein as "corresponding residues").

[076] Equivalent residues may also be defined by determining homology at the level of tertiary structure for an Fc fragment whose tertiary structure has been determined by x-ray crystallography. Equivalent residues are defined as those for which the atomic coordinates of two or more of the main chain atoms of a particular amino acid residue of the parent or precursor (N on N, CA on CA, C on C and O on O) are within 0.13 nm and preferably 0.1 nm after alignment. Alignment is achieved after the best model has been oriented and positioned to give the maximum overlap of atomic coordinates of non-hydrogen protein atoms of the Fc variant fragment.

[077] Specifically included within the definition of "antibody" are aglycosylated antibodies. By "aglycosylated antibody" as used herein is meant an antibody that lacks carbohydrate attached at position 297 of the Fc region, wherein numbering is according to the EU system as in Kabat. The aglycosylated antibody may be a deglycosylated antibody, that is an antibody for which the Fc carbohydrate has been removed, for example chemically or enzymatically. Alternatively, the aglycosylated antibody may be a nonglycosylated or unglycosylated antibody, that is an antibody that was expressed without Fc carbohydrate, for example by mutation of one or residues that encode the glycosylation pattern or by expression in an organism that does not attach carbohydrates to proteins, for example bacteria.

[078] Specifically included within the definition of "antibody" are full-length antibodies that contain an Fc variant portion. .By "full length antibody" herein is meant the structure that constitutes the natural biological form of an antibody, including variable and constant regions. For example, in most mammals, including humans and mice, the full length antibody of the IgG class is a tetramer and consists of two identical pairs of two immunoglobulin chains, each pair having one light and one heavy

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chain, each light chain comprising immunoglobulin domains V_L and C_L, and each heavy chain comprising immunoglobulin domains V_H, Cγ1, Cγ2, and Cγ3. In some mammals, for example in camels and llamas, IgG antibodies may consist of only two heavy chains, each heavy chain comprising a variable domain attached to the Fc region. By "IgG" as used herein is meant a polypeptide belonging to the class of antibodies that are substantially encoded by a recognized immunoglobulin gamma gene. In humans this class comprises IgG1, IgG2, IgG3, and IgG4. In mice this class comprises IgG1, IgG2a, IgG2b, IgG3.

[079] By "amino acid" and "amino acid identity" as used herein is meant one of the 20 naturally occurring amino acids or any non-natural analogues that may be present at a specific, defined position. By "protein" herein is meant at least two covalently attached amino acids, which includes proteins, polypeptides, oligopeptides and peptides. The protein may be made up of naturally occurring amino acids and peptide bonds, or synthetic peptidomimetic structures, i.e. "analogs", such as peptoids (see Simon et al., PNAS USA 89(20):9367 (1992)) particularly when LC peptides are to be administered to a patient. Thus "amino acid", or "peptide residue", as used herein means both naturally occurring and synthetic amino acids. For example, homophenylalanine, citrulline and norleucine are considered amino acids for the purposes of the invention. "Amino acid" also includes imino acid residues such as proline and hydroxyproline. The side chain may be in either the (R) or the (S) configuration. In the preferred embodiment, the amino acids are in the (S) or L-configuration. If non-naturally occurring side chains are used, non-amino acid substituents may be used, for example to prevent or retard in vivo degradation.

[080] By "computational screening method" herein is meant any method for designing one or more mutations in a protein, wherein said method utilizes a computer to evaluate the energies of the interactions of potential amino acid side chain substitutions with each other and/or with the rest of the protein. As will be appreciated by those skilled in the art, evaluation of energies, referred to as energy calculation, refers to some method of scoring one or more amino acid modifications. Said method may involve a physical or chemical energy term, or may involve knowledge-, statistical-, sequence-based energy terms, and the like. The calculations that compose a computational screening method are herein referred to as "computational screening calculations".

[081] By "effector function" as used herein is meant a biochemical event that results from the interaction of an antibody Fc region with an Fc receptor or ligand. Effector functions include but are not limited to ADCC, ADCP, and CDC. By "effector cell" as used herein is meant a cell of the immune system that expresses one or more Fc receptors and mediates one or more effector functions. Effector cells include but are not limited to monocytes, macrophages, neutrophils, dendritic cells, eosinophils, mast cells, platelets, B cells, large granular lymphocytes, Langerhans' cells, natural killer (NK) cells, and γγ T cells, and may be from any organism including but not limited to humans, mice,

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rats, rabbits, and monkeys. By "library" herein is meant a set of Fc variants in any form, including but not limited to a list of nucleic acid or amino acid sequences, a list of nucleic acid or amino acid substitutions at variable positions, a physical library comprising nucleic acids that encode the library sequences, or a physical library comprising the Fc variant proteins, either in purified or unpurified form.

[082] By "Fc", "Fc region", FC polypeptide", etc. as used herein is meant an antibody as defined herein that includes the polypeptides comprising the constant region of an antibody excluding the first constant region immunoglobulin domain. Thus Fc refers to the last two constant region immunoglobulin domains of IgA, IgD, and IgG, and the last three constant region immunoglobulin domains of IgE and IgM, and the flexible hinge N-terminal to these domains. For IgA and IgM Fc may include the J chain. For IgG, as illustrated in Figure 1, Fc comprises immunoglobulin domains Cgamma2 and Cgamma3 (Cγ2 and Cγ3) and the hinge between Cgamma1 (Cγ1) and Cgamma2 (Cγ2). Although the boundaries of the Fc region may vary, the human IgG heavy chain Fc region is usually defined to comprise residues C226 or P230 to its carboxyl-terminus, wherein the numbering is according to the EU index as in Kabat. Fc may refer to this region in isolation, or this region in the context of an antibody, antibody fragment, or Fc fusion. An Fc may be an antibody, Fc fusion, or an protein or protein domain that comprises Fc. Particularly preferred are Fc variants, which are non-naturally occurring variants of an Fc.

[083] By "Fc fusion" as used herein is meant a protein wherein one or more polypeptides is operably linked to Fc. Fc fusion is herein meant to be synonymous with the terms "immunoadhesin", "Ig fusion", "Ig chimera", and "receptor globulin" (sometimes with dashes) as used in the prior art (Chamow *et al.*, 1996, *Trends Biotechnol* 14:52-60; Ashkenazi *et al.*, 1997, *Curr Opin Immunol* 9:195-200). An Fc fusion combines the Fc region of an immunoglobulin with a fusion partner, which in general can be any protein, including, but not limited to, the target-binding region of a receptor, an adhesion molecule, a ligand, an enzyme, or some other protein or protein domain. The role of the non-Fc part of an Fc fusion is to mediate target binding, and thus it is functionally analogous to the variable regions of an antibody.

[084] By "Fc gamma receptor" or "FcγR" as used herein is meant any member of the family of proteins that bind the IgG antibody Fc region and are substantially encoded by the FcγR genes. In humans this family includes but is not limited to FcγRI (CD64), including isoforms FcγRIa, FcγRIb, and FcγRIc; FcγRII (CD32), including isoforms FcγRIIa (including allotypes H131 and R131), FcγRIIb (including FcγRIIb-1 and FcγRIIb-2), and FcγRIIc; and FcγRIII (CD16), including isoforms FcγRIIIa (including allotypes V158 and F158) and FcγRIIIb (including allotypes FcγRIIIb-NA1 and FcγRIIIb-NA2) (Jefferis *et al.*, 2002, *Immunol Lett* 82:57-65), as well as any undiscovered human FcγRs or FcγR isoforms or allotypes. An FcγR may be from any organism, including but not limited to humans,

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mice, rats, rabbits, and monkeys. Mouse FcγRs include but are not limited to FcγRI (CD64), FcγRII (CD32), FcγRIII (CD16), and FcγRIII-2 (CD16-2), as well as any undiscovered mouse FcγRs or FcγR isoforms or allotypes.

[085] By "Fc ligand" as used herein is meant a molecule, preferably a polypeptide, from any organism that binds to the Fc region of an antibody to form an Fc-ligand complex. Fc ligands include but are not limited to FcγRs, FcγRs, FcγRs, FcRn, C1q, C3, mannan binding lectin, mannose receptor, *staphylococcal* protein A, *streptococcal* protein G, and viral FcγR. Fc ligands may include undiscovered molecules that bind Fc

[086] By "IgG" as used herein is meant a polypeptide belonging to the class of antibodies that are substantially encoded by a recognized immunoglobulin gamma gene. In humans this class comprises IgG1, IgG2, IgG3, and IgG4. In mice this class comprises IgG1, IgG2a, IgG2b, IgG3. By "immunoglobulin (Ig)" herein is meant a protein consisting of one or more polypeptides substantially encoded by immunoglobulin genes. Immunoglobulins include but are not limited to antibodies. Immunoglobulins may have a number of structural forms, including but not limited to full length antibodies, antibody fragments, and individual immunoglobulin domains. By "immunoglobulin (Ig) domain" herein is meant a region of an immunoglobulin that exists as a distinct structural entity as ascertained by one skilled in the art of protein structure. Ig domains typically have a characteristic β-sandwich folding topology. The known Ig domains in the IgG class of antibodies are V_H, Cγ1, Cγ2, Cγ3, V_L, and C_L.

[087] By "parent polypeptide" or "precursor polypeptide" (including Fc parent or precursors) as used herein is meant a polypeptide that is subsequently modified to generate a variant. Said parent polypeptide may be a naturally occurring polypeptide, or a variant or engineered version of a naturally occurring polypeptide. Parent polypeptide may refer to the polypeptide itself, compositions that comprise the parent polypeptide, or the amino acid sequence that encodes it. Accordingly, by "parent Fc polypeptide" as used herein is meant an unmodified Fc polypeptide that is modified to generate a variant, and by "parent antibody" as used herein is meant an unmodified antibody that is modified to generate a variant antibody.

[088] As outlined above, certain positions of the Fc molecule can be altered. By "position" as used herein is meant a location in the sequence of a protein. Positions may be numbered sequentially, or according to an established format, for example the EU index as in Kabat. For example, position 297 is a position in the human antibody IgG1. Corresponding positions are determined as outlined above, generally through alignment with other parent sequences.

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[089] By "residue" as used herein is meant a position in a protein and its associated amino acid identity. For example, Asparagine 297 (also referred to as N297, also referred to as N297) is a residue in the human antibody IgG1.

[090] By "target antigen" as used herein is meant the molecule that is bound specifically by the variable region of a given antibody. A target antigen may be a protein, carbohydrate, lipid, or other chemical compound.

[091] By "target cell" as used herein is meant a cell that expresses a target antigen.

[092] By "variable region" as used herein is meant the region of an immunoglobulin that comprises one or more Ig domains substantially encoded by any of the VΚ, VΛ, and/or V_H genes that make up the kappa, lambda, and heavy chain immunoglobulin genetic loci respectively.

[093] By "variant polypeptide" as used herein is meant a polypeptide sequence that differs from that of a parent polypeptide sequence by virtue of at least one amino acid modification. Variant polypeptide may refer to the polypeptide itself, a composition comprising the polypeptide, or the amino sequence that encodes it. Preferably, the variant polypeptide has at least one amino acid modification compared to the parent polypeptide, e.g. from about one to about ten amino acid modifications, and preferably from about one to about five amino acid modifications compared to the parent. The variant polypeptide sequence herein will preferably possess at least about 80% homology with a parent polypeptide sequence, and most preferably at least about 90% homology, more preferably at least about 95% homology. Accordingly, by "Fc variant" as used herein is meant an Fc sequence that differs from that of a parent Fc sequence by virtue of at least one amino acid modification. An Fc variant may only encompass an Fc region, or may exist in the context of an antibody, Fc fusion, or other polypeptide that is substantially encoded by Fc. Fc variant may refer to the Fc polypeptide itself, compositions comprising the Fc variant polypeptide, or the amino acid sequence that encodes it.

[094] For all positions discussed in the present invention, numbering of an immunoglobulin heavy chain is according to the EU index (Kabat et al., 1991, Sequences of Proteins of Immunological Interest, 5th Ed., United States Public Health Svice, National Institutes of Health, Bethesda). The "EU index as in Kabat" refers to the residue numbering of the human IgG1 EU antibody.

[095] The Fc variants of the present invention may be optimized for a variety of properties. Properties that may be optimized include but are not limited to enhanced or reduced affinity for an

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FcγR. In a preferred embodiment, the Fc variants of the present invention are optimized to possess enhanced affinity for a human activating FcγR, preferably FcγRI, FcγRIIa, FcγRIIc, FcγRIIIa, and FcγRIIIb, most preferably FcγRIIIa. In an alternately preferred embodiment, the Fc variants are optimized to possess reduced affinity for the human inhibitory receptor FcγRIIb. These preferred embodiments are anticipated to provide antibodies and Fc fusions with enhanced therapeutic properties in humans, for example enhanced effector function and greater anti-cancer potency. In an alternate embodiment, the Fc variants of the present invention are optimized to have reduced or ablated affinity for a human FcγR, including but not limited to FcγRI, FcγRIIa, FcγRIIb, FcγRIIc, FcγRIIIa, and FcγRIIIb. These embodiments are anticipated to provide antibodies and Fc fusions with enhanced therapeutic properties in humans, for example reduced effector function and reduced toxicity. Preferred embodiments comprise optimization of Fc binding to a human FcγR, however in alternate embodiments the Fc variants of the present invention possess enhanced or reduced affinity for FcγRs from nonhuman organisms, including but not limited to mice, rats, rabbits, and monkeys. Fc variants that are optimized for binding to a nonhuman FcγR may find use in experimentation. For example, mouse models are available for a variety of diseases that enable testing of properties such as efficacy, toxicity, and pharmacokinetics for a given drug candidate. As is known in the art, cancer cells can be grafted or injected into mice to mimic a human cancer, a process referred to as xenografting. Testing of antibodies or Fc fusions that comprise Fc variants that are optimized for one or more mouse FcγRs, may provide valuable information with regard to the efficacy of the antibody or Fc fusion, its mechanism of action, and the like. The Fc variants of the present invention may also be optimized for enhanced functionality and/or solution properties in aglycosylated form. In a preferred embodiment, the aglycosylated Fc variants of the present invention bind an Fc ligand with greater affinity than the aglycosylated form of the parent Fc polypeptide. Said Fc ligands include but are not limited to FcγRs, C1q, FcRn, and proteins A and G, and may be from any source including but not limited to human, mouse, rat, rabbit, or monkey, preferably human. In an alternately preferred embodiment, the Fc variants are optimized to be more stable and/or more soluble than the aglycosylated form of the parent Fc polypeptide. An Fc variant that is engineered or predicted to display any of the aforementioned optimized properties is herein referred to as an "optimized Fc variant".

[096] The Fc variants of the present invention may be derived from parent Fc polypeptides that are themselves from a wide range of sources. The parent Fc polypeptide may be substantially encoded by one or more Fc genes from any organism, including but not limited to humans, mice, rats, rabbits, camels, llamas, dromedaries, monkeys, preferably mammals and most preferably humans and mice. In a preferred embodiment, the parent Fc polypeptide composes an antibody, referred to as the parent antibody. The parent antibody may be fully human, obtained for example using transgenic mice (Bruggemann *et al.*, 1997, *Curr Opin Biotechnol* 8:455-458) or human antibody libraries coupled with selection methods (Griffiths *et al.*, 1998, *Curr Opin Biotechnol* 9:102-108). The parent antibody need not be naturally occurring. For example, the parent antibody may be an engineered antibody,

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including but not limited to chimeric antibodies and humanized antibodies (Clark, 2000, *Immunol Today* 21:397-402). The parent antibody may be an engineered variant of an antibody that is substantially encoded by one or more natural antibody genes. In one embodiment, the parent antibody has been affinity matured, as is known in the art. Alternatively, the antibody has been modified in some other way, for example as described in USSN 10/339788, filed on March 3, 2003.

[097] The Fc variants of the present invention may be substantially encoded by immunoglobulin genes belonging to any of the antibody classes. In a preferred embodiment, the Fc variants of the present invention find use in antibodies or Fc fusions that comprise sequences belonging to the IgG class of antibodies, including IgG1, IgG2, IgG3, or IgG4. In an alternate embodiment the Fc variants of the present invention find use in antibodies or Fc fusions that comprise sequences belonging to the IgA (including subclasses IgA1 and IgA2), IgD, IgE, IgG, or IgM classes of antibodies. The Fc variants of the present invention may comprise more than one protein chain. That is, the present invention may find use in an antibody or Fc fusion that is a monomer or an oligomer, including a homo- or hetero-oligomer.

[098] The Fc variants of the present invention may be combined with other Fc modifications, including but not limited to modifications that alter effector function. Such combination may provide additive, synergistic, or novel properties in antibodies or Fc fusions. In one embodiment, the Fc variants of the present invention may be combined with other known Fc variants (Duncan *et al.*, 1988, *Nature* 332:563-564; Lund *et al.*, 1991, *J Immunol* 147:2657-2662; Lund *et al.*, 1992, *Mol Immunol* 29:53-59; Alegre *et al.*, 1994, *Transplantation* 57:1537-1543; Hutchins *et al.*, 1995, *Proc Natl Acad Sci U S A* 92:11980-11984; Jefferis *et al.*, 1995, *Immunol Lett* 44:111-117; Lund *et al.*, 1995, *Faseb J* 9:115-119; Jefferis *et al.*, 1996, *Immunol Lett* 54:101-104; Lund *et al.*, 1996, *J Immunol* 157:4963-4969; Armour *et al.*, 1999, *Eur J Immunol* 29:2613-2624; Idusogie *et al.*, 2000, *J Immunol* 164:4178-4184; Reddy *et al.*, 2000, *J Immunol* 164:1925-1933; Xu *et al.*, 2000, *Cell Immunol* 200:16-26; Idusogie *et al.*, 2001, *J Immunol* 166:2571-2575; Shields *et al.*, 2001, *J Biol Chem* 276:6591-6604; Jefferis *et al.*, 2002, *Immunol Lett* 82:57-65; Presta *et al.*, 2002, *Biochem Soc Trans* 30:487-490) (US 5,624,821; US 5,885,573; US 6,194,551; PCT WO 00/42072; PCT WO 99/58572). In an alternate embodiment, the Fc variants of the present invention are incorporated into an antibody or Fc fusion that comprises one or more engineered glycoforms. By "engineered glycoform" as used herein is meant a carbohydrate composition that is covalently attached to an Fc polypeptide, wherein said carbohydrate composition differs chemically from that of a parent Fc polypeptide. Engineered glycoforms may be useful for a variety of purposes, including but not limited to enhancing or reducing effector function. Engineered glycoforms may be generated by any method, for example by using engineered or variant expression strains, by co-expression with one or more enzymes, for example β1–4- N-acetylglucosaminyltransferase III (GnTIII), by expressing an Fc polypeptide in various organisms or cell lines from various organisms, or by modifying carbohydrate(s) after the Fc polypeptide has been expressed. Methods for generating engineered glycoforms are known in the

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art, and include but are not limited to (Umaña *et al.*, 1999, *Nat Biotechnol* 17:176-180; Davies *et al.*, 2001, *Biotechnol Bioeng* 74:288-294; Shields *et al.*, 2002, *J Biol Chem* 277:26733-26740; Shinkawa *et al.*, 2003, *J Biol Chem* 278:3466-3473) US 6,602,684; USSN 10/277,370; USSN 10/113,929; PCT WO 00/61739A1; PCT WO 01/29246A1; PCT WO 02/31140A1; PCT WO 02/30954A1; Potelligent™ technology (Biowa, Inc., Princeton, N.J.); GlycoMAb™ glycosylation engineering technology (GLYCART biotechnology AG, Zürich, Switzerland)). Engineered glycoform typically refers to the different carbohydrate or oligosaccharide; thus an Fc polypeptide, for example an antibody or Fc fusion, may comprise an engineered glycoform. Alternatively, engineered glycoform may refer to the Fc polypeptide that comprises the different carbohydrate or oligosaccharide. Thus combinations of the Fc variants of the present invention with other Fc modifications, as well as undiscovered Fc modifications, are contemplated with the goal of generating novel antibodies or Fc fusions with optimized properties.

[099] The Fc variants of the present invention may find use in an antibody. By "antibody of the present invention" as used herein is meant an antibody that comprises an Fc variant of the present invention. The present invention may, in fact, find use in any protein that comprises Fc, and thus application of the Fc variants of the present invention is not limited to antibodies. The Fc variants of the present invention may find use in an Fc fusion. By "Fc fusion of the present invention" as used herein refers to an Fc fusion that comprises an Fc variant of the present invention. Fc fusions may comprise an Fc variant of the present invention operably linked to a cytokine, soluble receptor domain, adhesion molecule, ligand, enzyme, peptide, or other protein or protein domain, and include but are not limited to Fc fusions described in US 5,843,725; US 6,018,026; US 6,291,212; US 6,291,646; US 6,300,099; US 6,323,323; PCT WO 00/24782; and in (Chamow *et al.*, 1996, *Trends Biotechnol* 14:52-60; Ashkenazi *et al.*, 1997, *Curr Opin Immunol* 9:195-200).

[100] Virtually any antigen may be targeted by the antibodies and fusions of the present invention, including but are not limited to the following list of proteins, subunits, domains, motifs, and epitopes belonging to the following list of proteins: CD2; CD3, CD3E, CD4, CD11, CD11a, CD14, CD16, CD18, CD19, CD20, CD22, CD23, CD25, CD28, CD29, CD30, CD32, CD33 (p67 proisin), CD38, CD40, CD40L, CD52, CD54, CD56, CD80, CD147, GD3, IL-1, IL-1R, IL-2, IL-2R, IL-4, IL-5, IL-6, IL-6R, IL-8, IL-12, IL-15, IL-18, IL-23, interferon alpha, interferon beta, interferon gamma; TNF-alpha, TNFbeta2, TNFc, TNFalphabeta, TNF-RI, TNF-RII, FasL, CD27L, CD30L, 4-1BBL, TRAIL, RANKL, TWEAK, APRIL, BAFF, LIGHT, VEGI, OX40L, TRAIL Receptor-1, A1 Adenosine Receptor, Lymphotoxin Beta Receptor, TACI, BAFF-R, EPO; LFA-3, ICAM-1, ICAM-3, EpCAM, integrin beta1, integrin beta2, integrin alpha4/beta7, integrin alpha2, integrin alpha3, integrin alpha4, integrin alpha5, integrin alpha6, integrin alphav, alphaVbeta3 integrin, FGFR-3, Keratinocyte Growth Factor, VLA-1, VLA-4, L-selectin, anti-Id, E-selectin, HLA, HLA-DR, CTLA-4, T cell receptor, B7-1, B7-2, VNRintegrin, TGFbeta1, TGFbeta2, eotaxin1, BLyS (B-lymphocyte Stimulator), complement C5, IgE, factor VII, CD64, CBL, NCA 90, EGFR (ErbB-1), Her2/neu (ErbB-2), Her3 (ErbB-3), Her4 (ErbB-4), Tissue

Factor, VEGF, VEGFR, endothelin receptor, VLA-4, Hapten NP-cap or NIP-cap, T cell receptor alpha/beta, E-selectin, digoxin, placental alkaline phosphatase (PLAP) and testicular PLAP-like alkaline phosphatase, transferrin receptor, Carcinoembryonic antigen (CEA), CEACAM5, HMFG PEM, mucin MUC1, MUC18, Heparanase I, human cardiac myosin, tumor-associated glycoprotein-72 (TAG-72), tumor-associated antigen CA 125, Prostate specific membrane antigen (PSMA), High molecular weight melanoma-associated antigen (HMW-MAA), carcinoma-associated antigen, Gcoprotein IIb/IIIa (GPIIb/IIIa), tumor-associated antigen expressing Lewis Y related carbohydrate, human cytomegalovirus (HCMV) gH envelope glycoprotein, HIV gp120, HCMV, respiratory syncitial virus RSV F, RSVF Fgp, VNRintegrin, IL-8, cytokeratin tumor-associated antigen, Hep B gp120, CMV, gpIIbIIIa, HIV IIIB gp120 V3 loop, respiratory syncytial virus (RSV) Fgp, Herpes simplex virus (HSV) gD glycoprotein, HSV gB glycoprotein, HCMV gB envelope glycoprotein, and *Clostridium perfringens* toxin.

[101] One skilled in the art will appreciate that the aforementioned list of targets refers not only to specific proteins and biomolecules, but the biochemical pathway or pathways that comprise them. For example, reference to CTLA-4 as a target antigen implies that the ligands and receptors that make up the T cell co-stimulatory pathway, including CTLA-4, B7-1, B7-2, CD28, and any other undiscovered ligands or receptors that bind these proteins, are also targets. Thus target as used herein refers not only to a specific biomolecule, but the set of proteins that interact with said target and the members of the biochemical pathway to which said target belongs. One skilled in the art will further appreciate that any of the aforementioned target antigens, the ligands or receptors that bind them, or other members of their corresponding biochemical pathway, may be operably linked to the Fc variants of the present invention in order to generate an Fc fusion. Thus for example, an Fc fusion that targets EGFR could be constructed by operably linking an Fc variant to EGF, TGF□, or any other ligand, discovered or undiscovered, that binds EGFR. Accordingly, an Fc variant of the present invention could be operably linked to EGFR in order to generate an Fc fusion that binds EGF, TGF□, or any other ligand, discovered or undiscovered, that binds EGFR. Thus virtually any polypeptide, whether a ligand, receptor, or some other protein or protein domain, including but not limited to the aforementioned targets and the proteins that compose their corresponding biochemical pathways, may be operably linked to the Fc variants of the present invention to develop an Fc fusion.

[102] A number of antibodies and Fc fusions that are approved for use, in clinical trials, or in development may benefit from the Fc variants of the present invention. Said antibodies and Fc fusions are herein referred to as "clinical products and candidates". Thus in a preferred embodiment, the Fc variants of the present invention may find use in a range of clinical products and candidates. For example, a number of antibodies that target CD20 may benefit from the Fc variants of the present invention. For example the Fc variants of the present invention may find use in an antibody that is substantially similar to rituximab (Rituxan®, IDEC/Genentech/Roche) (see for example US 5,736,137), a chimeric anti-CD20 antibody approved to treat Non-Hodgkin's lymphoma; HuMax-

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CD20, an anti-CD20 currently being developed by Genmab, an anti-CD20 antibody described in US 5,500,362, AME-133 (Applied Molecular Evolution), hA20 (Immunomedics, Inc.), and HumaLYM (Intracel). A number of antibodies that target members of the family of epidermal growth factor receptors, including EGFR (ErbB-1), Her2/neu (ErbB-2), Her3 (ErbB-3), Her4 (ErbB-4), may benefit from the Fc variants of the present invention. For example the Fc variants of the present invention may find use in an antibody that is substantially similar to trastuzumab (Herceptin®, Genentech) (see for example US 5,877,171), a humanized anti-Her2/neu antibody approved to treat breast cancer; pertuzumab (rhuMab-2C4, Omnitarg™), currently being developed by Genentech; an anti-Her2 antibody described in US 4,753,894; cetuximab (Erbitux®, Imclone) (US 4,943,533; PCT WO 96/40210), a chimeric anti-EGFR antibody in clinical trials for a variety of cancers; ABX-EGF (US 6,235,883), currently being developed by Abgenix/Immunex/Amgen; HuMax-EGFr (USSN 10/172,317), currently being developed by Genmab; 425, EMD55900, EMD62000, and EMD72000 (Merck KGaA) (US 5558864; Murthy et al. 1987, *Arch Biochem Biophys.* 252(2):549-60; Rodeck et al., 1987, *J Cell Biochem.* 35(4):315-20; Kettleborough et al., 1991, *Protein Eng.* 4(7):773-83); ICR62 (Institute of Cancer Research) (PCT WO 95/20045; Modjtahedi et al., 1993, *J. Cell Biophys.* 1993, 22(1-3):129-46; Modjtahedi et al., 1993, *Br J Cancer.* 1993, 67(2):247-53; Modjtahedi et al, 1996, *Br J Cancer*, 73(2):228-35; Modjtahedi et al, 2003, *Int J Cancer*, 105(2):273-80); TheraCIM hR3 (YM Biosciences, Canada and Centro de Immunologia Molecular, Cuba (US 5,891,996; US 6, 506,883; Mateo et al, 1997, *Immunotechnology*, 3(1):71-81); mAb-806 (Ludwig Institue for Cancer Research, Memorial Sloan-Kettering) (Jungbluth et al. 2003, *Proc Natl Acad Sci U S A.* 100(2):639-44); KSB-102 (KS Biomedix); MR1-1 (IVAX, National Cancer Institute) (PCT WO 0162931A2); and SC100 (Scancell) (PCT WO 01/88138). In another preferred embodiment, the Fc variants of the present invention may find use in alemtuzumab (Campath®, Millenium), a humanized monoclonal antibody currently approved for treatment of B-cell chronic lymphocytic leukemia. The Fc variants of the present invention may find use in a variety of antibodies or Fc fusions that are substantially similar to other clinical products and candidates, including but not limited to muromonab-CD3 (Orthoclone OKT3®), an anti-CD3 antibody developed by Ortho Biotech/Johnson & Johnson, ibritumomab tiuxetan (Zevalin®), an anti-CD20 antibody developed by IDEC/Schering AG, gemtuzumab ozogamicin (Mylotarg®), an anti-CD33 (p67 protein) antibody developed by Celltech/Wyeth, alefacept (Amevive®), an anti-LFA-3 Fc fusion developed by Biogen), abciximab (ReoPro®), developed by Centocor/Lilly, basiliximab (Simulect®), developed by Novartis, palivizumab (Synagis®), developed by MedImmune, infliximab (Remicade®), an anti-TNFalpha antibody developed by Centocor, adalimumab (Humira®, an anti-TNFalpha antibody developed by Abbott, Humicade™, an anti-TNFalpha antibody developed by Celltech, etanercept (Enbrel®), an anti-TNFalpha Fc fusion developed by Immunex/Amgen, ABX-CBL, an anti-CD147 antibody being developed by Abgenix, ABX-IL8, an anti-IL8 antibody being developed by Abgenix, ABX-MA1, an anti-MUC18 antibody being developed by Abgenix, Pemtumomab (R1549, ^{90}Y-muHMFG1), an anti-MUC1 in development by Antisoma, Therex (R1550), an anti-MUC1 antibody being developed by Antisoma, AngioMab (AS1405), being developed by Antisoma, HuBC-1, being developed by Antisoma, Thioplatin (AS1407) being developed by Antisoma, Antegren® (natalizumab), an anti-alpha-4-beta-1 (VLA-4) and alpha-4-

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beta-7 antibody being developed by Biogen, VLA-1 mAb, an anti-VLA-1 integrin antibody being developed by Biogen, LTBR mAb, an anti-lymphotoxin beta receptor (LTBR) antibody being developed by Biogen, CAT-152, an anti-TGF□2 antibody being developed by Cambridge Antibody Technology, J695, an anti-IL-12 antibody being developed by Cambridge Antibody Technology and Abbott, CAT-192, an anti-TGF□1 antibody being developed by Cambridge Antibody Technology and Genzyme, CAT-213, an anti-Eotaxin1 antibody being developed by Cambridge Antibody Technology, LymphoStat-B™ an anti-Blys antibody being developed by Cambridge Antibody Technology and Human Genome Sciences Inc., TRAIL-R1mAb, an anti-TRAIL-R1 antibody being developed by Cambridge Antibody Technology and Human Genome Sciences, Inc., Avastin™ (bevacizumab, rhuMAb-VEGF), an anti-VEGF antibody being developed by Genentech, an anti-HER receptor family antibody being developed by Genentech, Anti-Tissue Factor (ATF), an anti-Tissue Factor antibody being developed by Genentech, Xolair™ (Omalizumab), an anti-IgE antibody being developed by Genentech, Raptiva™ (Efalizumab), an anti-CD11a antibody being developed by Genentech and Xoma, MLN-02 Antibody (formerly LDP-02), being developed by Genentech and Millenium Pharmaceuticals, HuMax CD4, an anti-CD4 antibody being developed by Genmab, HuMax-IL15, an anti-IL15 antibody being developed by Genmab and Amgen, HuMax-Inflam, being developed by Genmab and Medarex, HuMax-Cancer, an anti-Heparanase I antibody being developed by Genmab and Medarex and Oxford GcoSciences, HuMax-Lymphoma, being developed by Genmab and Amgen, HuMax-TAC, being developed by Genmab, IDEC-131, and anti-CD40L antibody being developed by IDEC Pharmaceuticals, IDEC-151 (Clenoliximab), an anti-CD4 antibody being developed by IDEC Pharmaceuticals, IDEC-114, an anti-CD80 antibody being developed by IDEC Pharmaceuticals, IDEC-152, an anti-CD23 being developed by IDEC Pharmaceuticals, anti-macrophage migration factor (MIF) antibodies being developed by IDEC Pharmaceuticals, BEC2, an anti-idiotypic antibody being developed by Imclone, IMC-1C11, an anti-KDR antibody being developed by Imclone, DC101, an anti-flk-1 antibody being developed by Imclone, anti-VE cadherin antibodies being developed by Imclone, CEA-Cide™ (labetuzumab), an anti-carcinoembryonic antigen (CEA) antibody being developed by Immunomedics, LymphoCide™ (Epratuzumab), an anti-CD22 antibody being developed by Immunomedics, AFP-Cide, being developed by Immunomedics, MyelomaCide, being developed by Immunomedics, LkoCide, being developed by Immunomedics, ProstaCide, being developed by Immunomedics, MDX-010, an anti-CTLA4 antibody being developed by Medarex, MDX-060, an anti-CD30 antibody being developed by Medarex, MDX-070 being developed by Medarex, MDX-018 being developed by Medarex, Osidem™ (IDM-1), and anti-Her2 antibody being developed by Medarex and Immuno-Designed Molecules, HuMax™-CD4, an anti-CD4 antibody being developed by Medarex and Genmab, HuMax-IL15, an anti-IL15 antibody being developed by Medarex and Genmab, CNTO 148, an anti-TNF□ antibody being developed by Medarex and Centocor/J&J, CNTO 1275, an anti-cytokine antibody being developed by Centocor/J&J, MOR101 and MOR102, anti-intercellular adhesion molecule-1 (ICAM-1) (CD54) antibodies being developed by MorphoSys, MOR201, an anti-fibroblast growth factor receptor 3 (FGFR-3) antibody being developed by MorphoSys, Nuvion® (visilizumab), an anti-CD3 antibody being developed by Protein Design Labs, HuZAF™, an anti-gamma interferon antibody being developed by Protein Design Labs, Anti-□5□1

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integrin, being developed by Protein Design Labs, anti-IL-12, being developed by Protein Design Labs, ING-1, an anti-Ep-CAM antibody being developed by Xoma, and MLN01, an anti-Beta2 integrin antibody being developed by Xoma.

[103] Application of the Fc variants to the aforementioned antibody and Fc fusion clinical products and candidates is not meant to be constrained to their precise composition. The Fc variants of the present invention may be incorporated into the aforementioned clinical candidates and products, or into antibodies and Fc fusions that are substantially similar to them. The Fc variants of the present invention may be incorporated into versions of the aforementioned clinical candidates and products that are humanized, affinity matured, engineered, or modified in some other way. Furthermore, the entire polypeptide of the aforementioned clinical products and candidates need not be used to construct a new antibody or Fc fusion that incorporates the Fc variants of the present invention; for example only the variable region of a clinical product or candidate antibody, a substantially similar variable region, or a humanized, affinity matured, engineered, or modified version of the variable region may be used. In another embodiment, the Fc variants of the present invention may find use in an antibody or Fc fusion that binds to the same epitope, antigen, ligand, or receptor as one of the aforementioned clinical products and candidates.

[104] The Fc variants of the present invention may find use in a wide range of antibody and Fc fusion products. In one embodiment the antibody or Fc fusion of the present invention is a therapeutic, a diagnostic, or a research reagent, preferably a therapeutic. Alternatively, the antibodies and Fc fusions of the present invention may be used for agricultural or industrial uses. In an alternate embodiment, the Fc variants of the present invention compose a library that may be screened experimentally. This library may be a list of nucleic acid or amino acid sequences, or may be a physical composition of nucleic acids or polypeptides that encode the library sequences. The Fc variant may find use in an antibody composition that is monoclonal or polyclonal. In a preferred embodiment, the antibodies and Fc fusions of the present invention are used to kill target cells that bear the target antigen, for example cancer cells. In an alternate embodiment, the antibodies and Fc fusions of the present invention are used to block, antagonize, or agonize the target antigen, for example for antagonizing a cytokine or cytokine receptor. In an alternately preferred embodiment, the antibodies and Fc fusions of the present invention are used to block, antagonize, or agonize the target antigen and kill the target cells that bear the target antigen.

[105] The Fc variants of the present invention may be used for various therapeutic purposes. In a preferred embodiment, the Fc variant proteins are administered to a patient to treat an antibody-related disorder. A "patient" for the purposes of the present invention includes both humans and other animals, preferably mammals and most preferably humans. Thus the antibodies and Fc fusions of the present invention have both human therapy and veterinary applications. In the preferred embodiment

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the patient is a mammal, and in the most preferred embodiment the patient is human. The term "treatment" in the present invention is meant to include therapeutic treatment, as well as prophylactic, or suppressive measures for a disease or disorder. Thus, for example, successful administration of an antibody or Fc fusion prior to onset of the disease results in treatment of the disease. As another example, successful administration of an optimized antibody or Fc fusion after clinical manifestation of the disease to combat the symptoms of the disease comprises treatment of the disease. "Treatment" also encompasses administration of an optimized antibody or Fc fusion protein after the appearance of the disease in order to eradicate the disease. Successful administration of an agent after onset and after clinical symptoms have developed, with possible abatement of clinical symptoms and perhaps amelioration of the disease, comprises treatment of the disease. Those "in need of treatment" include mammals already having the disease or disorder, as well as those prone to having the disease or disorder, including those in which the disease or disorder is to be prevented. By "antibody related disorder" or "antibody responsive disorder" or "condition" or "disease" herein are meant a disorder that may be ameliorated by the administration of a pharmaceutical composition comprising an antibody or Fc fusion of the present invention. Antibody related disorders include but are not limited to autoimmune diseases, immunological diseases, infectious diseases, inflammatory diseases, neurological diseases, and oncological and neoplastic diseases including cancer. By "cancer" and "cancerous" herein refer to or describe the physiological condition in mammals that is typically characterized by unregulated cell growth. Examples of cancer include but are not limited to carcinoma, lymphoma, blastoma, sarcoma (including liposarcoma), neuroendocrine tumors, mesothelioma, schwanoma, meningioma, adenocarcinoma, melanoma, and leukemia or lymphoid malignancies. More particular examples of such cancers include squamous cell cancer (e.g. epithelial squamous cell cancer), lung cancer including small-cell lung cancer, non-small cell lung cancer, adenocarcinoma of the lung and squamous carcinoma of the lung, cancer of the peritoneum, hepatocellular cancer, gastric or stomach cancer including gastrointestinal cancer, pancreatic cancer, glioblastoma, cervical cancer, ovarian cancer, liver cancer, bladder cancer, hepatoma, breast cancer, colon cancer, rectal cancer, colorectal cancer, endometrial or uterine carcinoma, salivary gland carcinoma, kidney or renal cancer, prostate cancer, vulval cancer, thyroid cancer, hepatic carcinoma, anal carcinoma, penile carcinoma, testicular cancer, esophageal cancer, tumors of the biliary tract, as well as head and neck cancer. Furthermore, the Fc variants of the present invention may be used to treat conditions including but not limited to congestive heart failure (CHF), vasculitis, rosecea, acne, eczema, myocarditis and other conditions of the myocardium, systemic lupus erythematosus, diabetes, spondylopathies, synovial fibroblasts, and bone marrow stroma; bone loss; Paget's disease, osteoclastoma; multiple myeloma; breast cancer; disuse osteopenia; malnutrition, periodontal disease, Gaucher's disease, Langerhans' cell histiocytosis, spinal cord injury, acute septic arthritis, osteomalacia, Cushing's syndrome, monoostotic fibrous dysplasia, polyostotic fibrous dysplasia, periodontal reconstruction, and bone fractures; sarcoidosis; multiple myeloma; osteolytic bone cancers, breast cancer, lung cancer, kidney cancer and rectal cancer; bone metastasis, bone pain management, and humoral malignant hypercalcemia, ankylosing spondylitisa and other spondyloarthropathies; transplantation rejection, viral infections, hematologic neoplasisas and

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neoplastic-like conditions for example, Hodgkin's lymphoma; non-Hodgkin's lymphomas (Burkitt's lymphoma, small lymphocytic lymphoma/chronic lymphocytic leukemia, mycosis fungoides, mantle cell lymphoma, follicular lymphoma, diffuse large B-cell lymphoma, marginal zone lymphoma, hairy cell leukemia and lymphoplasmacytic leukemia), tumors of lymphocyte precursor cells, including B-cell acute lymphoblastic leukemia/lymphoma, and T-cell acute lymphoblastic leukemia/lymphoma, thymoma, tumors of the mature T and NK cells, including peripheral T-cell leukemias, adult T-cell leukemia/T-cell lymphomas and large granular lymphocytic leukemia, Langerhans cell histocytosis, myeloid neoplasias such as acute myelogenous leukemias, including AML with maturation, AML without differentiation, acute promyelocytic leukemia, acute myelomonocytic leukemia, and acute monocytic leukemias, myelodysplastic syndromes, and chronic myeloproliferative disorders, including chronic myelogenous leukemia, tumors of the central nervous system, e.g., brain tumors (glioma, neuroblastoma, astrocytoma, medulloblastoma, ependymoma, and retinoblastoma), solid tumors (nasopharyngeal cancer, basal cell carcinoma, pancreatic cancer, cancer of the bile duct, Kaposi's sarcoma, testicular cancer, uterine, vaginal or cervical cancers, ovarian cancer, primary liver cancer or endometrial cancer, and tumors of the vascular system (angiosarcoma and hemagiopericytoma), osteoporosis, hepatitis, HIV, AIDS, spondylearthritis, rheumatoid arthritis, inflammatory bowel diseases (IBD), sepsis and septic shock, Crohn's Disease, psoriasis, schleraderma, graft versus host disease (GVHD), allogenic islet graft rejection, hematologic malignancies, such as multiple myeloma (MM), myelodysplastic syndrome (MDS) and acute myelogenous leukemia (AML), inflammation associated with tumors, peripheral nerve injury or demyelinating diseases.

[106] In one embodiment, an antibody or Fc fusion of the present invention is administered to a patient having a disease involving inappropriate expression of a protein. Within the scope of the present invention this is meant to include diseases and disorders characterized by aberrant proteins, due for example to alterations in the amount of a protein present, the presence of a mutant protein, or both. An overabundance may be due to any cause, including but not limited to overexpression at the molecular level, prolonged or accumulated appearance at the site of action, or increased activity of a protein relative to normal. Included within this definition are diseases and disorders characterized by a reduction of a protein. This reduction may be due to any cause, including but not limited to reduced expression at the molecular level, shortened or reduced appearance at the site of action, mutant forms of a protein, or decreased activity of a protein relative to normal. Such an overabundance or reduction of a protein can be measured relative to normal expression, appearance, or activity of a protein, and said measurement may play an important role in the development and/or clinical testing of the antibodies and Fc fusions of the present invention.

[107] In one embodiment, an antibody or Fc fusion of the present invention is the only therapeutically active agent administered to a patient. Alternatively, the antibody or Fc fusion of the present invention is administered in combination with one or more other therapeutic agents, including but not limited to cytotoxic agents, chemotherapeutic agents, cytokines, growth inhibitory agents, anti-

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hormonal agents, kinase inhibitors, anti-angiogenic agents, cardioprotectants, or other therapeutic agents. Such molecules are suitably present in combination in amounts that are effective for the purpose intended. The skilled medical practitioner can determine empirically the appropriate dose or doses of other therapeutic agents useful herein. The antibodies and Fc fusions of the present invention may be administered concomitantly with one or more other therapeutic regimens. For example, an antibody or Fc fusion of the present invention may be administered to the patient along with chemotherapy, radiation therapy, or both chemotherapy and radiation therapy. In one embodiment, the antibody or Fc fusion of the present invention may be administered in conjunction with one or more antibodies or Fc fusions, which may or may not comprise an Fc variant of the present invention.

[108] In one embodiment, the antibodies and Fc fusions of the present invention are administered with a chemotherapeutic agent. By "chemotherapeutic agent" as used herein is meant a chemical compound useful in the treatment of cancer. Examples of chemotherapeutic agents include but are not limited to alkylating agents such as thiotepa and cyclosphosphamide (CYTOXAN™); alkyl sulfonates such as busulfan, improsulfan and piposulfan; aziridines such as benzodopa, carboquone, meturedopa, and uredopa; ethylenimines and methylamelamines including altretamine, triethylenemelamine, trietylenephosphoramide, triethylenethiophosphaoramide and trimethylolomelamine; nitrogen mustards such as chlorambucil, chlornaphazine, cholophosphamide, estramustine, ifosfamide, mechlorethamine, mechlorethamine oxide hydrochloride, melphalan, novembichin, phenesterine, prednimustine, trofosfamide, uracil mustard; nitrosureas such as carmustine, chlorozotocin, fotemustine, lomustine, nimustine, ranimustine; antibiotics such as aclacinomysins, actinomycin, authramycin, azaserine, bleomycins, cactinomycin, calicheamicin, carabicin, caminomycin, carzinophilin, chromomycins, dactinomycin, daunorubicin, detorubicin, 6-diazo-5-oxo-L-norleucine, doxorubicin, epirubicin, esorubicin, idarubicin, marcellomycin, mitomycins, mycophenolic acid, nogalamycin, olivomycins, peplomycin, potfiromycin, puromycin, quelamycin, rodorubicin, streptonigrin, streptozocin, tubercidin, ubenimex, zinostatin, zorubicin; anti-metabolites such as methotrexate and 5-fluorouracil (5-FU); folic acid analogues such as denopterin, methotrexate, pteropterin, trimetrexate; purine analogs such as fludarabine, 6-mercaptopurine, thiamiprine, thioguanine; pyrimidine analogs such as ancitabine, azacitidine, 6-azauridine, carmofur, cytarabine, dideoxyuridine, doxifluridine, enocitabine, floxuridine, 5-FU; androgens such as calusterone, dromostanolone propionate, epitiostanol, mepitiostane, testolactone; anti-adrenals such as aminoglutethimide, mitotane, trilostane; folic acid replenisher such as frolinic acid; aceglatone; aldophosphamide glycoside; aminolevulinic acid; amsacrine; bestrabucil; bisantrene; edatraxate; defofamine; demecolcine; diaziquone; elformithine; elliptinium acetate; etoglucid; gallium nitrate; hydroxyurea; lentinan; lonidamine; mitoguazone; mitoxantrone; mopidemol; nitracrine; pentostatin; phenamet; pirarubicin; podophyllinic acid; 2-ethylhydrazide; procarbazine; PSK®; razoxane; sizofuran; spirogermanium; tenuazonic acid; triaziquone; 2, 2',2"-trichlorotriethylamine; urethan; vindesine; dacarbazine; mannomustine; mitobronitol; mitolactol; pipobroman; gacytosine; arabinoside ("Ara-C"); cyclophosphamide; thiotepa; taxanes, e.g. paclitaxel (TAXOL®, Bristol-Myers Squibb

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Oncology, Princeton, N.J.) and docetaxel (TAXOTERE®, Rhne-Poulenc Rorer, Antony, France); chlorambucil; gemcitabine; 6-thioguanine; mercaptopurine; methotrexate; platinum analogs such as cisplatin and carboplatin; vinblastine; platinum; etoposide (VP-16); ifosfamide; mitomycin C; mitoxantrone; vincristine; vinorelbine; navelbine; novantrone; teniposide; daunomycin; aminopterin; xeloda; ibandronate; CPT-11; topoisomerase inhibitor RFS 2000; difluoromethylornithine (DMFO); retinoic acid; asparamicins; capecitabine; thymidylate synthase inhibitor (such as Tomudex); cox-2 inhibitors, such as celicoxib (CELEBREX®) or MK-0966 (VIOXX®); and pharmaceutically acceptable salts, acids or derivatives of any of the above. Also included in this definition are anti-hormonal agents that act to regulate or inhibit hormone action on tumors such as anti estrogens including for example tamoxifen, raloxifene, aromatase inhibiting 4(5)-imidazoles, 4-hydroxytamoxifen, trioxifene, keoxifene, LY 117018, onapristone, and toremifene (Fareston); and anti-androgens such as flutamide, nilutamide, bicalutamide, leuprolide, and goserelin; and pharmaceutically acceptable salts, acids or derivatives of any of the above.

[109] A chemotherapeutic or other cytotoxic agent may be administered as a prodrug. By "prodrug" as used herein is meant a precursor or derivative form of a pharmaceutically active substance that is less cytotoxic to tumor cells compared to the parent drug and is capable of being enzymatically activated or converted into the more active parent form. See, for example Wilman, 1986, Biochemical Society Transactions, 615th Meeting Belfast, 14:375-382; and Stella *et al.*, "Prodrugs: A Chemical Approach to Targeted Drug Delivery," Directed Drug Delivery, Borchardt *et al.*, (ed.): 247-267, Humana Press, 1985. The prodrugs that may find use with the present invention include but are not limited to phosphate-containing prodrugs, thiophosphate-containing prodrugs, sulfate-containing prodrugs, peptide-containing prodrugs, D-amino acid-modified prodrugs, glycosylated prodrugs, beta-lactam-containing prodrugs, optionally substituted phenoxyacetamide-containing prodrugs or optionally substituted phenylacetamide-containing prodrugs, 5-fluorocytosine and other 5-fluorouridine prodrugs which can be converted into the more active cytotoxic free drug. Examples of cytotoxic drugs that can be derivatized into a prodrug form for use with the antibodies and Fc fusions of the present invention include but are not limited to any of the aforementioned chemotherapeutic agents.

[110] The antibodies and Fc fusions of the present invention may be combined with other therapeutic regimens. For example, in one embodiment, the patient to be treated with the antibody or Fc fusion may also receive radiation therapy. Radiation therapy can be administered according to protocols commonly employed in the art and known to the skilled artisan. Such therapy includes but is not limited to cesium, iridium, iodine, or cobalt radiation. The radiation therapy may be whole body irradiation, or may be directed locally to a specific site or tissue in or on the body, such as the lung, bladder, or prostate. Typically, radiation therapy is administered in pulses over a period of time from about 1 to 2 weeks. The radiation therapy may, however, be administered over longer periods of time. For instance, radiation therapy may be administered to patients having head and neck cancer for about 6 to about 7 weeks. Optionally, the radiation therapy may be administered as a single dose

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or as multiple, sequential doses. The skilled medical practitioner can determine empirically the appropriate dose or doses of radiation therapy useful herein. In accordance with another embodiment of the invention, the antibody or Fc fusion of the present invention and one or more other anti-cancer therapies are employed to treat cancer cells *ex vivo*. It is contemplated that such *ex vivo* treatment may be useful in bone marrow transplantation and particularly, autologous bone marrow transplantation. For instance, treatment of cells or tissue(s) containing cancer cells with antibody or Fc fusion and one or more other anti-cancer therapies, such as described above, can be employed to deplete or substantially deplete the cancer cells prior to transplantation in a recipient patient. It is of course contemplated that the antibodies and Fc fusions of the invention can be employed in combination with still other therapeutic techniques such as surgery.

[111] In an alternate embodiment, the antibodies and Fc fusions of the present invention are administered with a cytokine. By "cytokine" as used herein is meant a generic term for proteins released by one cell population that act on another cell as intercellular mediators. Examples of such cytokines are lymphokines, monokines, and traditional polypeptide hormones. Included among the cytokines are growth hormone such as human growth hormone, N-methionyl human growth hormone, and bovine growth hormone; parathyroid hormone; thyroxine; insulin; proinsulin; relaxin; prorelaxin; glycoprotein hormones such as follicle stimulating hormone (FSH), thyroid stimulating hormone (TSH), and luteinizing hormone (LH); hepatic growth factor; fibroblast growth factor; prolactin; placental lactogen; tumor necrosis factor-alpha and -beta; mullerian-inhibiting substance; mouse gonadotropin-associated peptide; inhibin; activin; vascular endothelial growth factor; integrin; thrombopoietin (TPO); nerve growth factors such as NGF-beta; platelet-growth factor; transforming growth factors (TGFs) such as TGF-alpha and TGF-beta; insulin-like growth factor-I and -II; erythropoietin (EPO); osteoinductive factors; interferons such as interferon-alpha, beta, and -gamma; colony stimulating factors (CSFs) such as macrophage-CSF (M-CSF); granulocyte-macrophage-CSF (GM-CSF); and granulocyte-CSF (G-CSF); interleukins (ILs) such as IL-1, IL-1alpha, IL-2, IL-3, IL-4, IL-5, IL-6, IL-7, IL-8, IL-9, IL-10, IL-11, IL-12; IL-18, a tumor necrosis factor such as TNF-alpha or TNF-beta; and other polypeptide factors including LIF and kit ligand (KL). As used herein, the term cytokine includes proteins from natural sources or from recombinant cell culture, and biologically active equivalents of the native sequence cytokines.

[112] A variety of other therapeutic agents may find use for administration with the antibodies and Fc fusions of the present invention. In one embodiment, the antibody or Fc fusion is administered with an anti-angiogenic agent. By "anti-angiogenic agent" as used herein is meant a compound that blocks, or interferes to some degree, the development of blood vessels. The anti-angiogenic factor may, for instance, be a small molecule or a protein, for example an antibody, Fc fusion, or cytokine, that binds to a growth factor or growth factor receptor involved in promoting angiogenesis. The preferred anti-angiogenic factor herein is an antibody that binds to Vascular Endothelial Growth Factor (VEGF). In an alternate embodiment, the antibody or Fc fusion is administered with a therapeutic

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agent that induces or enhances adaptive immune response, for example an antibody that targets CTLA-4. In an alternate embodiment, the antibody or Fc fusion is administered with a tyrosine kinase inhibitor. By "tyrosine kinase inhibitor" as used herein is meant a molecule that inhibits to some extent tyrosine kinase activity of a tyrosine kinase. Examples of such inhibitors include but are not limited to quinazolines, such as PD 153035, 4-(3-chloroanilino) quinazoline; pyridopyrimidines; pyrimidopyrimidines; pyrrolopyrimidines, such as CGP 59326, CGP 60261 and CGP 62706; pyrazolopyrimidines, 4-(phenylamino)-7H-pyrrolo(2,3-d) pyrimidines; curcumin (diferuloyl methane, 4,5-bis (4-fluoroanilino)phthalimide); tyrphostines containing nitrothiophene moieties; PD-0183805 (Warner-Lambert); antisense molecules (e.g. those that bind to ErbB-encoding nucleic acid); quinoxalines (US 5,804,396); tryphostins (US 5,804,396); ZD6474 (Astra Zeneca); PTK-787 (Novartis/Schering A G); pan-ErbB inhibitors such as C1-1033 (Pfizer); Affinitac (ISIS 3521; Isis/Lilly); Imatinib mesylate (STI571,Gleevec®; Novartis); PKI 166 (Novartis); GW2016 (Glaxo SmithKline); C1-1033 (Pfizer); EKB-569 (Wyeth); Semaxinib (Sugen); ZD6474 (AstraZeneca); PTK-787 (Novartis/Schering AG); INC-1C11 (Imclone); or as described in any of the following patent publications: US 5,804,396; PCT WO 99/09016 (American Cyanimid); PCT WO 98/43960 (American Cyanamid); PCT WO 97/38983 (Warner-Lambert); PCT WO 99/06378 (Warner-Lambert); PCT WO 99/06396 (Warner-Lambert); PCT WO 96/30347 (Pfizer, Inc); PCT WO 96/33978 (AstraZeneca); PCT WO96/3397 (AstraZeneca); PCT WO 96/33980 (AstraZeneca), gefitinib (IRESSA™, ZD1839, AstraZeneca), and OSI-774 (Tarceva™, OSI Pharmaceuticals/Genentech).

[113] In an alternate embodiment, the antibody or Fc fusion of the present invention is conjugated or operably linked to another therapeutic compound. The therapeutic compound may be a cytotoxic agent, a chemotherapeutic agent, a toxin, a radioisotope, a cytokine, or other therapeutically active agent. Conjugates of the antibody or Fc fusion and cytotoxic agent may be made using a variety of bifunctional protein coupling agents such as N-succinimidyl-3-(2-pyridyldithiol) propionate (SPDP), succinimidyl-4-(N-maleimidomethyl) cyclohexane-1-carboxylate, iminothiolane (IT), bifunctional derivatives of imidoesters (such as dimethyl adipimidate HCL), active esters (such as disuccinimidyl suberate), aldehydes (such as glutareldehyde), bis-azido compounds (such as bis (p-azidobenzoyl) hexanediamine), bis-diazonium derivatives (such as bis-(p-diazoniumbenzoyl)-ethylenediamine), diisocyanates (such as tolyene 2,6-diisocyanate), and bis-active fluorine compounds (such as 1,5-difluoro-2,4-dinitrobenzene). For example, a ricin immunotoxin can be prepared as described in Vitetta et al., 1971, Science 238:1098. Carbon-14-labeled 1-isothiocyanatobenzyl-3-methyldiethylene triaminepentaacetic acid (MX-DTPA) is an exemplary chelating agent for conjugation of radionucleotide to the antibody. See PCT WO 94/11026. The linker may be a cleavable linker facilitating release of the cytotoxic drug in the cell. For example, an acid-labile linker, peptidase-sensitive linker, dimethyl linker or disulfide-containing linker (Chari et al., 1992, Cancer Research 52: 127-131) may be used. Alternatively, the antibody or Fc fusion is operably linked to the therapeutic agent, e.g. by recombinant techniques or peptide synthesis.

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[114] Chemotherapeutic agents that may be useful for conjugation to the antibodies and Fc fusions of the present invention have been described above. In an alternate embodiment, the antibody or Fc fusion is conjugated or operably linked to a toxin, including but not limited to small molecule toxins and enzymatically active toxins of bacterial, fungal, plant or animal origin, including fragments and/or variants thereof. Small molecule toxins include but are not limited to calicheamicin, maytansine (US 5,208,020), trichothene, and CC1065. In one embodiment of the invention, the antibody or Fc fusion is conjugated to one or more maytansine molecules (e.g. about 1 to about 10 maytansine molecules per antibody molecule). Maytansine may, for example, be converted to May-SS-Me which may be reduced to May-SH3 and reacted with modified antibody or Fc fusion (Chari *et al.*, 1992, *Cancer Research* 52: 127-131) to generate a maytansinoid-antibody or maytansinoid-Fc fusion conjugate. Another conjugate of interest comprises an antibody or Fc fusion conjugated to one or more calicheamicin molecules. The calicheamicin family of antibiotics are capable of producing double-stranded DNA breaks at sub-picomolar concentrations. Structural analogues of calicheamicin that may be used include but are not limited to γ_1^1, α_2^1, α_3, N-acetyl-γ_1^1, PSAG, and θ^1_1, (Hinman *et al.*, 1993, *Cancer Research* 53:3336-3342; Lode *et al.*, 1998, *Cancer Research* 58:2925-2928) (US 5,714,586; US 5,712,374; US 5,264,586; US 5,773,001). Dolastatin 10 analogs such as auristatin E (AE) and monomethylauristatin E (MMAE) may find use as conjugates for the Fc variants of the present invention (Doronina *et al.*, 2003, *Nat Biotechnol* 21(7):778-84; Francisco *et al.*, 2003 *Blood* 102(4):1458-65). Useful enyzmatically active toxins include but are not limited to diphtheria A chain, nonbinding active fragments of diphtheria toxin, exotoxin A chain (from *Pseudomonas aeruginosa*), ricin A chain, abrin A chain, modeccin A chain, alpha-sarcin, Aleurites fordii proteins, dianthin proteins, Phytolaca americana proteins (PAPI, PAPII, and PAP-S), momordica charantia inhibitor, curcin, crotin, sapaonaria officinalis inhibitor, gelonin, mitogellin, restrictocin, phenomycin, enomycin and the tricothecenes. See, for example, PCT WO 93/21232. The present invention further contemplates a conjugate or fusion formed between an antibody or Fc fusion of the present invention and a compound with nucleolytic activity, for example a ribonuclease or DNA endonuclease such as a deoxyribonuclease (DNase).

[115] In an alternate embodiment, an antibody or Fc fusion of the present invention may be conjugated or operably linked to a radioisotope to form a radioconjugate. A variety of radioactive isotopes are available for the production of radioconjugate antibodies and Fc fusions. Examples include, but are not limited to, At^{211}, I^{131}, I^{125}, Y^{90}, Re^{186}, Re^{188}, Sm^{153}, Bi^{212}, P^{32}, and radioactive isotopes of Lu.

[116] In yet another embodiment, an antibody or Fc fusion of the present invention may be conjugated to a "receptor" (such streptavidin) for utilization in tumor pretargeting wherein the antibody-receptor or Fc fusion-receptor conjugate is administered to the patient, followed by removal of unbound conjugate from the circulation using a clearing agent and then administration of a "ligand" (e.g. avidin) which is conjugated to a cytotoxic agent (e.g. a radionucleotide). In an alternate

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embodiment, the antibody or Fc fusion is conjugated or operably linked to an enzyme in order to employ Antibody Dependent Enzyme Mediated Prodrug Therapy (ADEPT). ADEPT may be used by conjugating or operably linking the antibody or Fc fusion to a prodrug-activating enzyme that converts a prodrug (e.g. a peptidyl chemotherapeutic agent, see PCT WO 81/01145) to an active anti-cancer drug. See, for example, PCT WO 88/07378 and US 4,975,278. The enzyme component of the immunoconjugate useful for ADEPT includes any enzyme capable of acting on a prodrug in such a way so as to covert it into its more active, cytotoxic form. Enzymes that are useful in the method of this invention include but are not limited to alkaline phosphatase useful for converting phosphate-containing prodrugs into free drugs; arylsulfatase useful for converting sulfate-containing prodrugs into free drugs; cytosine deaminase useful for converting non-toxic 5-fluorocytosine into the anti-cancer drug, 5-fluorouracil; proteases, such as serratia protease, thermolysin, subtilisin, carboxypeptidases and cathepsins (such as cathepsins B and L), that are useful for converting peptide-containing prodrugs into free drugs; D-alanylcarboxypeptidases, useful for converting prodrugs that contain D-amino acid substituents; carbohydrate-cleaving enzymes such as .beta.-galactosidase and neuraminidase useful for converting glycosylated prodrugs into free drugs; beta-lactamase useful for converting drugs derivatized,with .alpha.-lactams into free drugs; and penicillin amidases, such as penicillin V amidase or penicillin G amidase, useful for converting drugs derivatized at their amine nitrogens with phenoxyacetyl or phenylacetyl groups, respectively, into free drugs. Alternatively, antibodies with enzymatic activity, also known in the art as "abzymes", can be used to convert the prodrugs of the invention into free active drugs (see, for example, Massey, 1987, *Nature* 328: 457-458). Antibody-abzyme and Fc fusion-abzyme conjugates can be prepared for delivery of the abzyme to a tumor cell population. Other modifications of the antibodies and Fc fusions of the present invention are contemplated herein. For example, the antibody or Fc fusion may be linked to one of a variety of nonproteinaceous polymers, e.g., polyethylene glycol, polypropylene glycol, polyoxyalkylenes, or copolymers of polyethylene glycol and polypropylene glycol.

[117] Pharmaceutical compositions are contemplated wherein an antibody or Fc fusion of the present invention and and one or more therapeutically active agents are formulated. Formulations of the antibodies and Fc fusions of the present invention are prepared for storage by mixing said antibody or Fc fusion having the desired degree of purity with optional pharmaceutically acceptable carriers, excipients or stabilizers (Remington's Pharmaceutical Sciences 16th edition, Osol, A. Ed.,1980), in the form of lyophilized formulations or aqueous solutions. Acceptable carriers, excipients, or stabilizers are nontoxic to recipients at the dosages and concentrations employed, and include buffers such as phosphate, citrate, acetate, and other organic acids; antioxidants including ascorbic acid and methionine; preservatives (such as octadecyldimethylbenzyl ammonium chloride; hexamethonium chloride; benzalkonium chloride, benzethonium chloride; phenol, butyl orbenzyl alcohol; alkyl parabens such as methyl or propyl paraben; catechol; resorcinol; cyclohexanol; 3-pentanol; and m-cresol); low molecular weight (less than about 10 residues) polypeptides; proteins, such as serum albumin, gelatin, or immunoglobulins; hydrophilic polymers such as polyvinylpyrrolidone; amino acids such as glycine, glutamine, asparagine, histidine, arginine, or lysine;

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monosaccharides, disaccharides, and other carbohydrates including glucose, mannose, or dextrins; chelating agents such as EDTA; sugars such as sucrose, mannitol, trehalose or sorbitol; sweeteners and other flavoring agents; fillers such as microcrystalline cellulose, lactose, corn and other starches; binding agents; additives; coloring agents; salt-forming counter-ions such as sodium; metal complexes (e.g. Zn-protein complexes); and/or non-ionic surfactants such as TWEEN™, PLURONICS™ or polyethylene glycol (PEG). In a preferred embodiment, the pharmaceutical composition that comprises the antibody or Fc fusion of the present invention is in a water-soluble form, such as being present as pharmaceutically acceptable salts, which is meant to include both acid and base addition salts. "Pharmaceutically acceptable acid addition salt" refers to those salts that retain the biological effectiveness of the free bases and that are not biologically or otherwise undesirable, formed with inorganic acids such as hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid and the like, and organic acids such as acetic acid, propionic acid, glycolic acid, pyruvic acid, oxalic acid, maleic acid, malonic acid, succinic acid, fumaric acid, tartaric acid, citric acid, benzoic acid, cinnamic acid, mandelic acid, methanesulfonic acid, ethanesulfonic acid, p-toluenesulfonic acid, salicylic acid and the like. "Pharmaceutically acceptable base addition salts" include those derived from inorganic bases such as sodium, potassium, lithium, ammonium, calcium, magnesium, iron, zinc, copper, manganese, aluminum salts and the like. Particularly preferred are the ammonium, potassium, sodium, calcium, and magnesium salts. Salts derived from pharmaceutically acceptable organic non-toxic bases include salts of primary, secondary, and tertiary amines, substituted amines including naturally occurring substituted amines, cyclic amines and basic ion exchange resins, such as isopropylamine, trimethylamine, diethylamine, triethylamine, tripropylamine, and ethanolamine. The formulations to be used for *in vivo* administration are preferrably sterile. This is readily accomplished by filtration through sterile filtration membranes or other methods.

[118] The antibodies and Fc fusions disclosed herein may also be formulated as immunoliposomes. A liposome is a small vesicle comprising various types of lipids, phospholipids and/or surfactant that is useful for delivery of a therapeutic agent to a mammal. Liposomes containing the antibody or Fc fusion are prepared by methods known in the art, such as described in Epstein *et al.*, 1985, *Proc Natl Acad Sci USA*, 82:3688; Hwang *et al.*, 1980, *Proc Natl Acad Sci USA*, 77:4030; US 4,485,045; US 4,544,545; and PCT WO 97/38731. Liposomes with enhanced circulation time are disclosed in US 5,013,556. The components of the liposome are commonly arranged in a bilayer formation, similar to the lipid arrangement of biological membranes. Particularly useful liposomes can be generated by the reverse phase evaporation method with a lipid composition comprising phosphatidylcholine, cholesterol and PEG-derivatized phosphatidylethanolamine (PEG-PE). Liposomes are extruded through filters of defined pore size to yield liposomes with the desired diameter. A chemotherapeutic agent or other therapeutically active agent is optionally contained within the liposome (Gabizon *et al.*, 1989, *J National Cancer Inst* 81:1484).

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[119] The antibodies, Fc fusions, and other therapeutically active agents may also be entrapped in microcapsules prepared by methods including but not limited to coacervation techniques, interfacial polymerization (for example using hydroxymethylcellulose or gelatin-microcapsules, or poly-(methylmethacylate) microcapsules), colloidal drug delivery systems (for example, liposomes, albumin microspheres, microemulsions, nano-particles and nanocapsules), and macroemulsions. Such techniques are disclosed in Remington's Pharmaceutical Sciences 16th edition, Osol, A. Ed., 1980. Sustained-release preparations may be prepared. Suitable examples of sustained-release preparations include semipermeable matrices of solid hydrophobic polymer, which matrices are in the form of shaped articles, e.g. films, or microcapsules. Examples of sustained-release matrices include polyesters, hydrogels (for example poly(2-hydroxyethyl-methacrylate), or poly(vinylalcohol)), polylactides (US 3,773,919), copolymers of L-glutamic acid and gamma ethyl-L-glutamate, non-degradable ethylene-vinyl acetate, degradable lactic acid-glycolic acid copolymers such as the LUPRON DEPOT™ (which are injectable microspheres composed of lactic acid-glycolic acid copolymer and leuprolide acetate), poly-D-(-)-3-hydroxybutyric acid, and ProLease® (commercially available from Alkermes), which is a microsphere-based delivery system composed of the desired bioactive molecule incorporated into a matrix of poly-DL-lactide-co-glycolide (PLG).

[120] The concentration of the therapeutically active antibody or Fc fusion of the present invention in the formulation may vary from about 0.1 to 100 weight %. In a preferred embodiment, the concentration of the antibody or Fc fusion is in the range of 0.003 to 1.0 molar. In order to treat a patient, a therapeutically effective dose of the antibody or Fc fusion of the present invention may be administered. By "therapeutically effective dose" herein is meant a dose that produces the effects for which it is administered. The exact dose will depend on the purpose of the treatment, and will be ascertainable by one skilled in the art using known techniques. Dosages may range from 0.01 to 100 mg/kg of body weight or greater, for example 0.1, 1, 10, or 50 mg/kg of body weight, with 1 to 10mg/kg being preferred. As is known in the art, adjustments for antibody or Fc fusion degradation, systemic versus localized delivery, and rate of new protease synthesis, as well as the age, body weight, general health, sex, diet, time of administration, drug interaction and the severity of the condition may be necessary, and will be ascertainable with routine experimentation by those skilled in the art.

[121] Administration of the pharmaceutical composition comprising an antibody or Fc fusion of the present invention, preferably in the form of a sterile aqueous solution, may be done in a variety of ways, including, but not limited to, orally, subcutaneously, intravenously, intranasally, intraotically, transdermally, topically (e.g., gels, salves, lotions, creams, etc.), intraperitoneally, intramuscularly, intrapulmonary (e.g., AERx® inhalable technology commercially available from Aradigm, or Inhance™ pulmonary delivery system commercially available from Inhale Therapeutics), vaginally, parenterally, rectally, or intraocularly. In some instances, for example for the treatment of wounds, inflammation, etc., the antibody or Fc fusion may be directly applied as a solution or spray. As is known in the art,

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the pharmaceutical composition may be formulated accordingly depending upon the manner of introduction.

Engineering Methods

[122] The present invention provides engineering methods that may be used to generate Fc variants. A principal obstacle that has hindered previous attempts at Fc engineering is that only random attempts at modification have been possible, due in part to the inefficiency of engineering strategies and methods, and to the low-throughput nature of antibody production and screening. The present invention describes engineering methods that overcome these shortcomings. A variety of design strategies, computational screening methods, library generation methods, and experimental production and screening methods are contemplated. These strategies, approaches, techniques, and methods may be applied individually or in various combinations to engineer optimized Fc variants.

Design Strategies

[123] The most efficient approach to generating Fc variants that are optimized for a desired property is to direct the engineering efforts toward that goal. Accordingly, the present invention teaches design strategies that may be used to engineer optimized Fc variants. The use of a design strategy is meant to guide Fc engineering, but is not meant to constrain an Fc variant to a particular optimized property based on the design strategy that was used to engineer it. At first thought this may seem counterintuitive; however its validity is derived from the enormous complexity of subtle interactions that determine the structure, stability, solubility, and function of proteins and protein-protein complexes. Although efforts can be made to predict which protein positions, residues, interactions, etc. are important for a design goal, often times critical ones are not predictable. Effects on protein structure, stability, solubility, and function, whether favorable or unfavorable, are often unforeseen. Yet there are innumerable amino acid modifications that are detrimental or deleterious to proteins. Thus often times the best approach to engineering comes from generation of protein variants that are focused generally towards a design goal but do not cause detrimental effects. In this way, a principal objective of a design strategy may be the generation of quality diversity. At a simplistic level this can be thought of as stacking the odds in one's favor. As an example, perturbation of the Fc carbohydrate or a particular domain-domain angle, as described below, are valid design strategies for generating optimized Fc variants, despite the fact that how carbohydrate and domain-domain angles determine the properties of Fc is not well understood. By reducing the number of detrimental amino acid modifications that are screened, i.e. by screening quality diversity, these design strategies become practical. Thus the true value of the design strategies taught in the present invention is their ability to direct engineering efforts towards the generation of valuable Fc variants. The specific value of any one resulting variant is determined after experimentation.

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[124] One design strategy for engineering Fc variants is provided in which interaction of Fc with some Fc ligand is altered by engineering amino acid modifications at the interface between Fc and said Fc ligand. Fc ligands herein may include but are not limited to FcγRs, C1q, FcRn, protein A or G, and the like. By exploring energetically favorable substitutions at Fc positions that impact the binding interface, variants can be engineered that sample new interface conformations, some of which may improve binding to the Fc ligand, some of which may reduce Fc ligand binding, and some of which may have other favorable properties. Such new interface conformations could be the result of, for example, direct interaction with Fc ligand residues that form the interface, or indirect effects caused by the amino acid modifications such as perturbation of side chain or backbone conformations. Variable positions may be chosen as any positions that are believed to play an important role in determining the conformation of the interface. For example, variable positions may be chosen as the set of residues that are within a certain distance, for example 5 Angstroms (Å), preferrably between 1 and 10 Å, of any residue that makes direct contact with the Fc ligand.

[125] An additional design strategy for generating Fc variants is provided in which the conformation of the Fc carbohydrate at N297 is optimized. Optimization as used in this context is meant to includes conformational and compositional changes in the N297 carbohydrate that result in a desired property, for example increased or reduced affinity for an FcγR. Such a strategy is supported by the observation that the carbohydrate structure and conformation dramatically affect Fc/FcγR and Fc/C1q binding (Umaña *et al.*, 1999, *Nat Biotechnol* 17:176-180; Davies *et al.*, 2001, *Biotechnol Bioeng* 74:288-294; Mimura *et al.*, 2001, *J Biol Chem* 276:45539-45547.; Radaev *et al.*, 2001, *J Biol Chem* 276:16478-16483; Shields *et al.*, 2002, *J Biol Chem* 277:26733-26740; Shinkawa *et al.*, 2003, *J Biol Chem* 278:3466-3473). However the carbohydrate makes no specific contacts with FcγRs. By exploring energetically favorable substitutions at positions that interact with carbohydrate, a quality diversity of variants can be engineered that sample new carbohydrate conformations, some of which may improve and some of which may reduce binding to one or more Fc ligands. While the majority of mutations near the Fc/carbohydrate interface appear to alter carbohydrate conformation, some mutations have been shown to alter the glycosylation composition (Lund *et al.*, 1996, *J Immunol* 157:4963-4969; Jefferis *et al.*, 2002, *Immunol Lett* 82:57-65).

[126] Another design strategy for generating Fc variants is provided in which the angle between the Cγ2 and Cγ3 domains is optimized. Optimization as used in this context is meant to describe conformational changes in the Cγ2-Cγ3 domain angle that result in a desired property, for example increased or reduced affinity for an FcγR. This angle is an important determinant of Fc/FcγR affinity (Radaev *et al.*, 2001, *J Biol Chem* 276:16478-16483), and a number of mutations distal to the Fc/FcγR interface affect binding potentially by modulating it (Shields *et al.*, 2001, *J Biol Chem* 276:6591-6604). By exploring energetically favorable substitutions positions that appear to play a key role in determining the Cγ2-Cγ3 angle and the flexibility of the domains relative to one another, a

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quality diversity of variants can be designed that sample new angles and levels of flexibility, some of which may be optimized for a desired Fc property.

[127] Another design strategy for generating Fc variants is provided in which Fc is reengineered to eliminate the structural and functional dependence on glycosylation. This design strategy involves the optimization of Fc structure, stability, solubility, and/or Fc function (for example affinity of Fc for one or more Fc ligands) in the absence of the N297 carbohydrate. In one approach, positions that are exposed to solvent in the absence of glycosylation are engineered such that they are stable, structurally consistent with Fc structure, and have no tendency to aggregate. The Cγ2 is the only unpaired Ig domain in the antibody (see Figure 1). Thus the N297 carbohydrate covers up the exposed hydrophobic patch that would normally be the interface for a protein-protein interaction with another Ig domain, maintaining the stability and structural integrity of Fc and keeping the Cγ2 domains from aggregating across the central axis. Approaches for optimizing aglycosylated Fc may involve but are not limited to designing amino acid modifications that enhance aglycosiated Fc stability and/or solubility by incorporating polar and/or charged residues that face inward towards the Cγ2-Cγ2 dimer axis, and by designing amino acid modifications that directly enhance the aglycosylated Fc/FcγR interface or the interface of aglycosylated Fc with some other Fc ligand.

[128] An additional design strategy for engineering Fc variants is provided in which the conformation of the Cγ2 domain is optimized. Optimization as used in this context is meant to describe conformational changes in the Cγ2 domain angle that result in a desired property, for example increased or reduced affinity for an FcγR. By exploring energetically favorable substitutions at Cγ2 positions that impact the Cγ2 conformation, a quality diversity of variants can be engineered that sample new Cγ2 conformations, some of which may achieve the design goal. Such new Cγ2 conformations could be the result of, for example, alternate backbone conformations that are sampled by the variant. Variable positions may be chosen as any positions that are believed to play an important role in determining C□2 structure, stability, solubility, flexibility, function, and the like. For example, Cγ2 hydrophobic core residues, that is Cγ2 residues that are partially or fully sequestered from solvent, may be reengineered. Alternatively, noncore residues may be considered, or residues that are deemed important for determining backbone structure, stability, or flexibility.

[129] An additional design strategy for Fc optimization is provided in which binding to an FcγR, complement, or some other Fc ligand is altered by modifications that modulate the electrostatic interaction between Fc and said Fc ligand. Such modifications may be thought of as optimization of the global electrostatic character of Fc, and include replacement of neutral amino acids with a charged amino acid, replacement of a charged amino acid with a neutral amino acid, or replacement of a charged amino acid with an amino acid of opposite charge (i.e. charge reversal). Such

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modifications may be used to effect changes in binding affinity between an Fc and one or more Fc ligands, for example FcγRs. In a preferred embodiment, positions at which electrostatic substitutions might affect binding are selected using one of a variety of well known methods for calculation of electrostatic potentials. In the simplest embodiment, Coulomb's law is used to generate electrostatic potentials as a function of the position in the protein. Additional embodiments include the use of Debye-Huckel scaling to account for ionic strength effects, and more sophisticated embodiments such as Poisson-Boltzmann calculations. Such electrostatic calculations may highlight positions and suggest specific amino acid modifications to achieve the design goal. In some cases, these substitutions may be anticipated to variably affect binding to different Fc ligands, for example to enhance binding to activating FcγRs while decreasing binding affinity to inhibitory FcγRs.

Computational Screening

[130] A principal obstacle to obtaining valuable Fc variants is the difficulty in predicting what amino acid modifications, out of the enormous number of possibilities, will achieve the desired goals. Indeed one of the principle reasons that previous attempts at Fc engineering have failed to produce Fc variants of significant clinical value is that approaches to Fc engineering have thus far involved hit-or-miss approaches. The present invention provides computational screening methods that enable quantitative and systematic engineering of Fc variants. These methods typically use atomic level scoring functions, side chain rotamer sampling, and advanced optimization methods to accurately capture the relationships between protein sequence, structure, and function. Computational screening enables exploration of the entire sequence space of possibilities at target positions by filtering the enormous diversity which results. Variant libraries that are screened computationally are effectively enriched for stable, properly folded, and functional sequences, allowing active optimization of Fc for a desired goal. Because of the overlapping sequence constraints on protein structure, stability, solubility, and function, a large number of the candidates in a library occupy "wasted" sequence space. For example, a large fraction of sequence space encodes unfolded, misfolded, incompletely folded, partially folded, or aggregated proteins. This is particularly relevant for Fc engineering because Ig domains are small beta sheet structures, the engineering of which has proven extremely demanding (Quinn *et al.*, 1994, *Proc Natl Acad Sci U S A* 91:8747-8751; Richardson *et al.*, 2002, *Proc Natl Acad Sci U S A* 99:2754-2759). Even seemingly harmless substitutions on the surface of a beta sheet can cause severe packing conflicts, dramatically disrupting folding equilibrium (Smith *et al.*, 1995, *Science* 270:980-982); incidentally, alanine is one of the worst beta sheet formers (Minor *et al.*, 1994, *Nature* 371:264-267). The determinants of beta sheet stability and specificity are a delicate balance between an extremely large number of subtle interactions. Computational screening enables the generation of libraries that are composed primarily of productive sequence space, and as a result increases the chances of identifying proteins that are optimized for the design goal. In effect, computational screening yields an increased hit-rate, thereby decreasing the number of variants that must be screened experimentally. An additional obstacle to Fc engineering is the need for active design of correlated or coupled mutations. For example, the greatest Fc/FcγR affinity

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enhancement observed thus far is S298A/E333A/K334A, obtained by combining three better binders obtained separately in an alanine scan (Shields *et al.*, 2001, *J Biol Chem* 276:6591-6604). Computational screening is capable of generating such a three-fold variant in one experiment instead of three separate ones, and furthermore is able to test the functionality of all 20 amino acids at those positions instead of just alanine. Computational screening deals with such complexity by reducing the combinatorial problem to an experimentally tractable size.

[131] Computational screening, viewed broadly, has four steps: 1) selection and preparation of the protein template structure or structures, 2) selection of variable positions, amino acids to be considered at those positions, and/or selection of rotamers to model considered amino acids, 3) energy calculation, and 4) combinatorial optimization. In more detail, the process of computational screening can be described as follows. A three-dimensional structure of a protein is used as the starting point. The positions to be optimized are identified, which may be the entire protein sequence or subset(s) thereof. Amino acids that will be considered at each position are selected. In a preferred embodiment, each considered amino acid may be represented by a discrete set of allowed conformations, called rotamers. Interaction energies are calculated between each considered amino acid and each other considered amino acid, and the rest of the protein, including the protein backbone and invariable residues. In a preferred embodiment, interaction energies are calculated between each considered amino acid side chain rotamer and each other considered amino acid side chain rotamer and the rest of the protein, including the protein backbone and invariable residues. One or more combinatorial search algorithms are then used to identify the lowest energy sequence and/or low energy sequences.

[132] In a preferred embodiment, the computational screening method used is substantially similar to Protein Design Automation® (PDA®) technology, as is described in US 6,188,965; US 6,269,312; US 6,403,312; USSN 09/782,004; USSN 09/927,790; USSN 10/218,102; PCT WO 98/07254; PCT WO 01/40091; and PCT WO 02/25588. In another preferred embodiment, a computational screening method substantially similar to Sequence Prediction Algorithm™ (SPA™) technology is used, as is described in (Raha *et al.*, 2000, *Protein Sci* 9:1106-1119), USSN 09/877,695, and USSN 10/071,859. In another preferred embodiment, the computational screening methods described in USSN 10/339788, filed on March 3, 2003, entitled "ANTIBODY OPTIMIZATION", are used. In some embodiments, combinations of different computational screening methods are used, including combinations of PDA® technology and SPA™ technology, as well as combinations of these computational methods in combination with other design tools. Similarly, these computational methods can be used simultaneously or sequentially, in any order.

[133] A template structure is used as input into the computational screening calculations. By "template structure" herein is meant the structural coordinates of part or all of a protein to be

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optimized. The template structure may be any protein for which a three dimensional structure (that is, three dimensional coordinates for a set of the protein's atoms) is known or may be calculated, estimated, modeled, generated, or determined. The three dimensional structures of proteins may be determined using methods including but not limited to X-ray crystallographic techniques, nuclear magnetic resonance (NMR) techniques, *de novo* modeling, and homology modeling. If optimization is desired for a protein for which the structure has not been solved experimentally, a suitable structural model may be generated that may serve as the template for computational screening calculations. Methods for generating homology models of proteins are known in the art, and these methods find use in the present invention. See for example, Luo, *et al.* 2002, *Protein Sci* 11: 1218-1226, Lehmann & Wyss, 2001, *Curr Opin Biotechnol* 12(4):371-5.; Lehmann *et al.*, 2000, Biochim Biophys Acta 1543(2):408-415; Rath & Davidson, 2000, *Protein Sci*, 9(12):2457-69; Lehmann *et al.*, 2000, *Protein Eng* 13(1):49-57; Desjarlais & Berg, 1993, *Proc Natl Acad Sci USA* 90(6):2256-60; Desjarlais & Berg, 1992, *Proteins* 12(2):101-4; Henikoff & Henikoff, 2000, *Adv Protein Chem* 54:73-97; Henikoff & Henikoff, 1994, *J Mol Biol* 243(4):574-8; Morea *et al.*, 2000, *Methods* 20:267-269. Protein/protein complexes may also be obtained using docking methods. Suitable protein structures that may serve as template structures include, but are not limited to, all of those found in the Protein Data Base compiled and serviced by the Research Collaboratory for Structural Bioinformatics (RCSB, formerly the Brookhaven National Lab).

[134] The template structure may be of a protein that occurs naturally or is engineered. The template structure may be of a protein that is substantially encoded by a protein from any organism, with human, mouse, rat, rabbit, and monkey preferred. The template structure may comprise any of a number of protein structural forms. In a preferred embodiment the template structure comprises an Fc region or a domain or fragment of Fc. In an alternately preferred embodiment the template structure comprises Fc or a domain or fragment of Fc bound to one or more Fc ligands, with an Fc/FcγR complex being preferred. The Fc in the template structure may be glycosylated or unglycosylated. The template structure may comprise more than one protein chain. The template structure may additionally contain nonprotein components, including but not limited to small molecules, substrates, cofactors, metals, water molecules, prosthetic groups, polymers and carbohydrates. In a preferred embodiment, the template structure is a plurality or set of template proteins, for example an ensemble of structures such as those obtained from NMR. Alternatively, the set of template structures is generated from a set of related proteins or structures, or artificially created ensembles. The composition and source of the template structure depends on the engineering goal. For example, for enhancement of human Fc/FcγR affinity, a human Fc/FcγR complex structure or derivative thereof may be used as the template structure. Alternatively, the uncomplexed Fc structure may be used as the template structure. If the goal is to enhance affinity of a human Fc for a mouse FcγR, the template structure may be a structure or model of a human Fc bound to a mouse FcγR.

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[135] The template structure may be modified or altered prior to design calculations. A variety of methods for template structure preparation are described in US 6,188,965; US 6,269,312; US 6,403,312; USSN 09/782,004; USSN 09/927,790; USSN 09/877,695; USSN 10/071,869, USSN 10/218,102; PCT WO 98/07254; PCT WO 01/40091; and PCT WO 02/26588. For example, in a preferred embodiment, explicit hydrogens may be added if not included within the structure. In an alternate embodiment, energy minimization of the structure is run to relax strain, including strain due to van der Waals clashes, unfavorable bond angles, and unfavorable bond lengths. Alternatively, the template structure is altered using other methods, such as manually, including directed or random perturbations. It is also possible to modify the template structure during later steps of computational screening, including during the energy calculation and combinatorial optimization steps. In an alternate embodiment, the template structure is not modified before or during computational screening calculations.

[136] Once a template structure has been obtained, variable positions are chosen. By "variable position" herein is meant a position at which the amino acid identity is allowed to be altered in a computational screening calculation. As is known in the art, allowing amino acid modifications to be considered only at certain variable positions reduces the complexity of a calculation and enables computational screening to be more directly tailored for the design goal. One or more residues may be variable positions in computational screening calculations. Positions that are chosen as variable positions may be those that contribute to or are hypothesized to contribute to the protein property to be optimized, for example Fc affinity for an FcγR, Fc stability, Fc solubility, and so forth. Residues at variable positions may contribute favorably or unfavorably to a specific protein property. For example, a residue at an Fc/FcγR interface may be involved in mediating binding, and thus this position may be varied in design calculations aimed at improving Fc/FcγR affinity. As another example, a residue that has an exposed hydrophobic side chain may be responsible for causing unfavorable aggregation, and thus this position may be varied in design calculations aimed at improving solubility. Variable positions may be those positions that are directly involved in interactions that are determinants of a particular protein property. For example, the FcγR binding site of Fc may be defined to include all residues that contact that particular FcγR. By "contact" herein is meant some chemical interaction between at least one atom of an Fc residue with at least one atom of the bound FcγR, with chemical interaction including, but not limited to van der Waals interactions, hydrogen bond interactions, electrostatic interactions, and hydrophobic interactions. In an alternative embodiment, variable positions may include those positions that are indirectly involved in a protein property, i.e. such positions may be proximal to residues that are known to or hypothesized to contribute to an Fc property. For example, the FcγR binding site of an Fc may be defined to include all Fc residues within a certain distance, for example 4 - 10 Å, of any Fc residue that is in van der Waals contact with the FcγR. Thus variable positions in this case may be chosen not only as residues that directly contact the FcγR, but also those that contact residues that contact the FcγR and thus influence binding indirectly. The specific positions chosen are dependent on the design strategy being employed.

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[137] One or more positions in the template structure that are not variable may be floated. By "floated position" herein is meant a position at which the amino acid conformation but not the amino acid identity is allowed to vary in a computational screening calculation. In one embodiment, the floated position may have the parent amino acid identity. For example, floated positions may be positions that are within a small distance, for example 5 Å, of a variable position residue. In an alternate embodiment, a floated position may have a non-parent amino acid identity. Such an embodiment may find use in the present invention, for example, when the goal is to evaluate the energetic or structural outcome of a specific mutation.

[138] Positions that are not variable or floated are fixed. By "fixed position" herein is meant a position at which the amino acid identity and the conformation are held constant in a computational screening calculation. Positions that may be fixed include residues that are not known to be or hypothesized to be involved in the property to be optimized. In this case the assumption is that there is little or nothing to be gained by varying these positions. Positions that are fixed may also include positions whose residues are known or hypothesized to be important for maintaining proper folding, structure, stability, solubility, and/or biological function. For example, positions may be fixed for residues that interact with a particular Fc ligand or residues that encode a glycosylation site in order to ensure that binding to the Fc ligand and proper glycosylation respectively are not perturbed. Likewise, if stability is being optimized, it may be beneficial to fix positions that directly or indirectly interact with an Fc ligand, for example an FcγR, so that binding is not perturbed. Fixed positions may also include structurally important residues such as cysteines participating in disulfide bridges, residues critical for determining backbone conformation such as proline or glycine, critical hydrogen bonding residues, and residues that form favorable packing interactions.

[139] The next step in computational screening is to select a set of possible amino acid identities that will be considered at each particular variable position. This set of possible amino acids is herein referred to as "considered amino acids" at a variable position. "Amino acids" as used herein refers to the set of natural 20 amino acids and any nonnatural or synthetic analogues. In one embodiment, all 20 natural amino acids are considered. Alternatively, a subset of amino acids, or even only one amino acid is considered at a given variable position. As will be appreciated by those skilled in the art, there is a computational benefit to considering only certain amino acid identities at variable positions, as it decreases the combinatorial complexity of the search. Furthermore, considering only certain amino acids at variable positions may be used to tailor calculations toward specific design strategies. For example, for solubility optimization of aglycosylated Fc, it may be beneficial to allow only polar amino acids to be considered at nonpolar Fc residues that are exposed to solvent in the absence of carbohydrate. Nonnatural amino acids, including synthetic amino acids and analogues of natural amino acids, may also be considered amino acids. For example see Chin *et al.*, 2003, *Science*, 301(5635):964-7; and Chin *et al.*, 2003, *Chem Biol.*10(6):511-9.

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[140] A wide variety of methods may be used, alone or in combination, to select which amino acids will be considered at each position. For example, the set of considered amino acids at a given variable position may be chosen based on the degree of exposure to solvent. Hydrophobic or nonpolar amino acids typically reside in the interior or core of a protein, which are inaccessible or nearly inaccessible to solvent. Thus at variable core positions it may be beneficial to consider only or mostly nonpolar amino acids such as alanine, valine, isoleucine, leucine, phenylalanine, tyrosine, tryptophan, and methionine. Hydrophilic or polar amino acids typically reside on the exterior or surface of proteins, which have a significant degree of solvent accessibility. Thus at variable surface positions it may be beneficial to consider only or mostly polar amino acids such as alanine, serine, threonine, aspartic acid, asparagine, glutamine, glutamic acid, arginine, lysine and histidine. Some positions are partly exposed and partly buried, and are not clearly protein core or surface positions, in a sense serving as boundary residues between core and surface residues. Thus at such variable boundary positions it may be beneficial to consider both nonpolar and polar amino acids such as alanine, serine, threonine, aspartic acid, asparagine, glutamine, glutamic acid, arginine, lysine histidine, valine, isoleucine, leucine, phenylalanine, tyrosine, tryptophan, and methionine. Determination of the degree of solvent exposure at variable positions may be by subjective evaluation or visual inspection of the template structure by one skilled in the art of protein structural biology, or by using a variety of algorithms that are known in the art. Selection of amino acid types to be considered at variable positions may be aided or determined wholly by computational methods, such as calculation of solvent accessible surface area, or using algorithms that assess the orientation of the C□-C□ vectors relative to a solvent accessible surface, as outlined in US 6,188,965; 6,269,312; US 6,403,312; USSN 09/782,004; USSN 09/927,790; USSN 10/218,102; PCT WO 98/07254; PCT WO 01/40091; and PCT WO 02/25588. In one embodiment, each variable position may be classified explicitly as a core, surface, or boundary position or a classification substantially similar to core, surface, or boundary.

[141] In an alternate embodiment, selection of the set of amino acids allowed at variable positions may be hypothesis-driven. Hypotheses for which amino acid types should be considered at variable positions may be derived by a subjective evaluation or visual inspection of the template structure by one skilled in the art of protein structural biology. For example, if it is suspected that a hydrogen bonding interaction may be favorable at a variable position, polar residues that have the capacity to form hydrogen bonds may be considered, even if the position is in the core. Likewise, if it is suspected that a hydrophobic packing interaction may be favorable at a variable position, nonpolar residues that have the capacity to form favorable packing interactions may be considered, even if the position is on the surface. Other examples of hypothesis-driven approaches may involve issues of backbone flexibility or protein fold. As is known in the art, certain residues, for example proline, glycine, and cysteine, play important roles in protein structure and stability. Glycine enables greater backbone flexibility than all other amino acids, proline constrains the backbone more than all other

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amino acids, and cysteines may form disulfide bonds. It may therefore be beneficial to include one or more of these amino acid types to achieve a desired design goal. Alternatively, it may be beneficial to exclude one or more of these amino acid types from the list of considered amino acids.

[142] In an alternate embodiment, subsets of amino acids may be chosen to maximize coverage. In this case, additional amino acids with properties similar to that in the template structure may be considered at variable positions. For example, if the residue at a variable position in the template structure is a large hydrophobic residue, additional large hydrophobic amino acids may be considered at that position. Alternatively, subsets of amino acids may be chosen to maximize diversity. In this case, amino acids with properties dissimilar to those in the template structure may be considered at variable positions. For example, if the residue at a variable position in the template is a large hydrophobic residue, amino acids that are small, polar, etc. may be considered.

[143] As is known in the art, some computational screening methods require only the identity of considered amino acids to be determined during design calculations. That is, no information is required concerning the conformations or possible conformations of the amino acid side chains. Other preferred methods utilize a set of discrete side chain conformations, called rotamers, which are considered for each amino acid. Thus, a set of rotamers may be considered at each variable and floated position. Rotamers may be obtained from published rotamer libraries (see for example, Lovel *et al.*, 2000, *Proteins: Structure Function and Genetics* 40:389-408; Dunbrack & Cohen, 1997, *Protein Science* 6:1661-1681; DeMaeyer *et al.*, 1997, *Folding and Design* 2:53-66; Tuffery *et al.*, 1991, *J Biomol Struct Dyn* 8:1267-1289, Ponder & Richards, 1987, *J Mol Biol* 193:775-791). As is known in the art, rotamer libraries may be backbone-independent or backbone-dependent. Rotamers may also be obtained from molecular mechanics or *ab initio* calculations, and using other methods. In a preferred embodiment, a flexible rotamer model is used (see Mendes *et al.*, 1999, *Proteins: Structure, Function, and Genetics* 37:530-543). Similarly, artificially generated rotamers may be used, or augment the set chosen for each amino acid and/or variable position. In one embodiment, at least one conformation that is not low in energy is included in the list of rotamers. In an alternate embodiment, the rotamer of the variable position residue in the template structure is included in the list of rotamers allowed for that variable position. In an alternate embodiment, only the identity of each amino acid considered at variable positions is provided, and no specific conformational states of each amino acid are used during design calculations. That is, use of rotamers is not essential for computational screening.

[144] Experimental information may be used to guide the choice of variable positions and/or the choice of considered amino acids at variable positions. As is known in the art, mutagenesis experiments are often carried out to determine the role of certain residues in protein structure and function, for example, which protein residues play a role in determining stability, or which residues

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make up the interface of a protein-protein interaction. Data obtained from such experiments are useful in the present invention. For example, variable positions for Fc/FcγR affinity enhancement could involve varying all positions at which mutation has been shown to affect binding. Similarly, the results from such an experiment may be used to guide the choice of allowed amino acid types at variable positions. For example, if certain types of amino acid substitutions are found to be favorable, similar types of those amino acids may be considered. In one embodiment, additional amino acids with properties similar to those that were found to be favorable experimentally may be considered at variable positions. For example, if experimental mutation of a variable position at an Fc/FcγR interface to a large hydrophobic residue was found to be favorable, the user may choose to include additional large hydrophobic amino acids at that position in the computational screen. As is known in the art, display and other selection technologies may be coupled with random mutagenesis to generate a list or lists of amino acid substitutions that are favorable for the selected property. Such a list or lists obtained from such experimental work find use in the present invention. For example, positions that are found to be invariable in such an experiment may be excluded as variable positions in computational screening calculations, whereas positions that are found to be more acceptable to mutation or respond favorably to mutation may be chosen as variable positions. Similarly, the results from such experiments may be used to guide the choice of allowed amino acid types at variable positions. For example, if certain types of amino acids arise more frequently in an experimental selection, similar types of those amino acids may be considered. In one embodiment, additional amino acids with properties similar to those that were found to be favorable experimentally may be considered at variable positions. For example, if selected mutations at a variable position that resides at an Fc/FcγR interface are found to be uncharged polar amino acids, the user may choose to include additional uncharged polar amino acids, or perhaps charged polar amino acids, at that position.

[145] Sequence information may also be used to guide choice of variable positions and/or the choice of amino acids considered at variable positions. As is known in the art, some proteins share a common structural scaffold and are homologous in sequence. This information may be used to gain insight into particular positions in the protein family. As is known in the art, sequence alignments are often carried out to determine which protein residues are conserved and which are not conserved. That is to say, by comparing and contrasting alignments of protein sequences, the degree of variability at a position may be observed, and the types of amino acids that occur naturally at positions may be observed. Data obtained from such analyses are useful in the present invention. The benefit of using sequence information to choose variable positions and considered amino acids at variable positions are several fold. For choice of variable positions, the primary advantage of using sequence information is that insight may be gained into which positions are more tolerant and which are less tolerant to mutation. Thus sequence information may aid in ensuring that quality diversity, i.e. mutations that are not deleterious to protein structure, stability, etc., is sampled computationally. The same advantage applies to use of sequence information to select amino acid types considered at variable positions. That is, the set of amino acids that occur in a protein sequence alignment may be

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thought of as being pre-screened by evolution to have a higher chance than random for being compatible with a protein's structure, stability, solubility, function, etc. Thus higher quality diversity is sampled computationally. A second benefit of using sequence information to select amino acid types considered at variable positions is that certain alignments may represent sequences that may be less immunogenic than random sequences. For example, if the amino acids considered at a given variable position are the set of amino acids which occur at that position in an alignment of human protein sequences, those amino acids may be thought of as being pre-screened by nature for generating no or low immune response if the optimized protein is used as a human therapeutic.

[146] The source of the sequences may vary widely, and include one or more of the known databases, including but not limited to the Kabat database (Johnson & Wu, 2001, *Nucleic Acids Res* 29:205-206; Johnson & Wu, 2000, *Nucleic Acids Res* 28:214-218), the IMGT database (IMGT, the international ImMunoGeneTics information system®; Lefranc *et al.*, 1999, *Nucleic Acids Res* 27:209-212; Ruiz *et al.*, 2000 *Nucleic Acids Re.* 28:219-221; Lefranc *et al.*, 2001, *Nucleic Acids Res* 29:207-209; Lefranc *et al.*, 2003, *Nucleic Acids Res* 31:307-310), and VBASE, SwissProt, GenBank and Entrez, and EMBL Nucleotide Sequence Database. Protein sequence information can be obtained, compiled, and/or generated from sequence alignments of naturally occurring proteins from any organism, including but not limited to mammals. Protein sequence information can be obtained from a database that is compiled privately. There are numerous sequence-based alignment programs and methods known in the art, and all of these find use in the present invention for generation of sequence alignments of proteins that comprise Fc and Fc ligands.

[147] Once alignments are made, sequence information can be used to guide choice of variable positions. Such sequence information can relate the variability, natural or otherwise, of a given position. Variability herein should be distinguished from variable position. Variability refers to the degree to which a given position in a sequence alignment shows variation in the types of amino acids that occur there. Variable position, to reiterate, is a position chosen by the user to vary in amino acid identity during a computational screening calculation. Variability may be determined qualitatively by one skilled in the art of bioinformatics. There are also methods known in the art to quantitatively determine variability that may find use in the present invention. The most preferred embodiment measures Information Entropy or Shannon Entropy. Variable positions can be chosen based on sequence information obtained from closely related protein sequences, or sequences that are less closely related.

[148] The use of sequence information to choose variable positions finds broad use in the present invention. For example, if an Fc/FcγR interface position in the template structure is tryptophan, and tryptophan is observed at that position in greater than 90% of the sequences in an alignment, it may be beneficial to leave that position fixed. In contrast, if another interface position is found to have a

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greater level of variability, for example if five different amino acids are observed at that position with frequencies of approximately 20% each, that position may be chosen as a variable position. In another embodiment, visual inspection of aligned protein sequences may substitute for or aid visual inspection of a protein structure. Sequence information can also be used to guide the choice of amino acids considered at variable positions. Such sequence information can relate to how frequently an amino acid, amino acids, or amino acid types (for example polar or nonpolar, charged or uncharged) occur, naturally or otherwise, at a given position. In one embodiment, the set of amino acids considered at a variable position may comprise the set of amino acids that is observed at that position in the alignment. Thus, the position-specific alignment information is used directly to generate the list of considered amino acids at a variable position in a computational screening calculation. Such a strategy is well known in the art; see for example Lehmann & Wyss, 2001, *Curr Opin Biotechnol* 12(4):371-5; Lehmann *et al.*, 2000, *Biochim Biophys Acta* 1543(2):408-415; Rath & Davidson, 2000, *Protein Sci*, 9(12):2457-69; Lehmann *et al.*, 2000, *Protein Eng* 13(1):49-57; Desjarlais & Berg, 1993, *Proc Natl Acad Sci USA* 90(6):2256-60; Desjarlais & Berg, 1992, *Proteins* 12(2):101-4; Henikoff & Henikoff, 2000, *Adv Protein Chem* 54:73-97; Henikoff & Henikoff, 1994, *J Mol Biol* 243(4):574-8. In an alternate embodiment, the set of amino acids considered at a variable position or positions may comprise a set of amino acids that is observed most frequently in the alignment. Thus, a certain criteria is applied to determine whether the frequency of an amino acid or amino acid type warrants its inclusion in the set of amino acids that are considered at a variable position. As is known in the art, sequence alignments may be analyzed using statistical methods to calculate the sequence diversity at any position in the alignment and the occurrence frequency or probability of each amino acid at a position. Such data may then be used to determine which amino acids types to consider. In the simplest embodiment, these occurrence frequencies are calculated by counting the number of times an amino acid is observed at an alignment position, then dividing by the total number of sequences in the alignment. In other embodiments, the contribution of each sequence, position or amino acid to the counting procedure is weighted by a variety of possible mechanisms. In a preferred embodiment, the contribution of each aligned sequence to the frequency statistics is weighted according to its diversity weighting relative to other sequences in the alignment. A common strategy for accomplishing this is the sequence weighting system recommended by Henikoff and Henikoff (Henikoff & Henikoff, 2000, *Adv Protein Chem* 54:73-97; Henikoff & Henikoff, 1994, *J Mol Biol* 243:574-8. In a preferred embodiment, the contribution of each sequence to the statistics is dependant on its extent of similarity to the target sequence, i.e. the template structure used, such that sequences with higher similarity to the target sequence are weighted more highly. Examples of similarity measures include, but are not limited to, sequence identity, BLOSUM similarity score, PAM matrix similarity score, and BLAST score. In an alternate embodiment, the contribution of each sequence to the statistics is dependent on its known physical or functional properties. These properties include, but are not limited to, thermal and chemical stability, contribution to activity, and solubility. For example, when optimizing aglycosylated Fc for solubility, those sequences in an alignment that are known to be most soluble (for example see Ewert *et al.*, 2003, *J Mol Biol* 325:531-553), will contribute more heavily to the calculated frequencies.

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[149] Regardless of what criteria are applied for choosing the set of amino acids in a sequence alignment to be considered at variable positions, use of sequence information to choose considered amino acids finds broad use in the present invention. For example, to optimize Fc solubility by replacing exposed nonpolar surface residues, considered amino acids may be chosen as the set of amino acids, or a subset of those amino acids which meet some criteria, that are observed at that position in an alignment of protein sequences. As another example, one or more amino acids may be added or subtracted subjectively from a list of amino acids derived from a sequence alignment in order to maximize coverage. For example, additional amino acids with properties similar to those that are found in a sequence alignment may be considered at variable positions. For example, if an Fc position that is known to or hypothesized to bind an FcγR is observed to have uncharged polar amino acids in a sequence alignment, the user may choose to include additional uncharged polar amino acids in a computational screening calculation, or perhaps charged polar amino acids, at that position.

[150] In one embodiment, sequence alignment information is combined with energy calculation, as discussed below. For example, pseudo energies can be derived from sequence information to generate a scoring function. The use of a sequence-based scoring function may assist in significantly reducing the complexity of a calculation. However, as is appreciated by those skilled in the art, the use of a sequence-based scoring function alone may be inadequate because sequence information can often indicate misleading correlations between mutations that may in reality be structurally conflicting. Thus, in a preferred embodiment, a structure-based method of energy calculation is used, either alone or in combination with a sequence-based scoring function. That is, preferred embodiments do not rely on sequence alignment information alone as the analysis step.

[151] Energy calculation refers to the process by which amino acid modifications are scored. The energies of interaction are measured by one or more scoring functions. A variety of scoring functions find use in the present invention for calculating energies. Scoring functions may include any number of potentials, herein referred to as the energy terms of a scoring function, including but not limited to a van der Waals potential, a hydrogen bond potential, an atomic solvation potential or other solvation models, a secondary structure propensity potential, an electrostatic potential, a torsional potential, and an entropy potential. At least one energy term is used to score each variable or floated position, although the energy terms may differ depending on the position, considered amino acids, and other considerations. In one embodiment, a scoring function using one energy term is used. In the most preferred embodiment, energies are calculated using a scoring function that contains more than one energy term, for example describing van der Waals, solvation, electrostatic, and hydrogen bond interactions, and combinations thereof. In additional embodiments, additional energy terms include but are not limited to entropic terms, torsional energies, and knowledge-based energies.

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[152] A variety of scoring functions are described in US 6,188,965; US 6,269,312; US 6,403,312; USSN 09/782,004; USSN 09/927,790; USSN 09/877,695; USSN 10/071,859, USSN 10/216,102; PCT WO 98/07254; PCT WO 01/40091; and PCT WO 02/25588. As will be appreciated by those skilled in the art, scoring functions need not be limited to physico-chemical energy terms. For example, knowledge-based potentials may find use in the computational screening methodology of the present invention. Such knowledge-based potentials may be derived from protein sequence and/or structure statistics including but not limited to threading potentials, reference energies, pseudo energies, homology-based energies, and sequence biases derived from sequence alignments. In a preferred embodiment, a scoring function is modified to include models for immunogenicity, such as functions derived from data on binding of peptides to MHC (Major Histocompatability Complex), that may be used to identify potentially immunogenic sequences (see for example USSN 09/903,378; USSN 10/039,170; USSN 60/222,697; USSN 10/339788; PCT WO 01/21823; and PCT WO 02/00165). In one embodiment, sequence alignment information can be used to score amino acid substitutions. For example, comparison of protein sequences, regardless of whether the source of said proteins is human, monkey, mouse, or otherwise, may be used to suggest or score amino acid mutations in the computational screening methodology of the present invention. In one embodiment, as is known in the art, one or more scoring functions may be optimized or "trained" during the computational analysis, and then the analysis re-run using the optimized system. Such altered scoring functions may be obtained for example, by training a scoring function using experimental data. As will be appreciated by those skilled in the art, a number of force fields, which are comprised of one or more energy terms, may serve as scoring functions. Force fields include but are not limited to *ab initio* or quantum mechanical force fields, semi-empirical force fields, and molecular mechanics force fields. Scoring functions that are knowledge-based or that use statistical methods may find use in the present invention. These methods may be used to assess the match between a sequence and a three-dimensional protein structure, and hence may be used to score amino acid substitutions for fidelity to the protein structure. In one embodiment, molecular dynamics calculations may be used to computationally screen sequences by individually calculating mutant sequence scores.

[153] There are a variety of ways to represent amino acids in order to enable efficient energy calculation. In a preferred embodiment, considered amino acids are represented as rotamers, as described previously, and the energy (or score) of interaction of each possible rotamer at each variable and floated position with the other variable and floated rotamers, with fixed position residues, and with the backbone structure and any non-protein atoms, is calculated. In a preferred embodiment, two sets of interaction energies are calculated for each side chain rotamer at every variable and floated position: the interaction energy between the rotamer and the fixed atoms (the "singles" energy), and the interaction energy between the variable and floated positions rotamer and all other possible rotamers at every other variable and floated position (the "doubles" energy). In an alternate embodiment, singles and doubles energies are calculated for fixed positions as well as for variable and floated positions. In an alternate embodiment, considered amino acids are not represented as rotamers.

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[154] An important component of computational screening is the identification of one or more sequences that have a favorable score, i.e. are low in energy. Determining a set of low energy sequences from an extremely large number of possibilities is nontrivial, and to solve this problem a combinatorial optimization algorithm is employed. The need for a combinatorial optimization algorithm is illustrated by examining the number of possibilities that are considered in a typical computational screening calculation. The discrete nature of rotamer sets allows a simple calculation of the number of possible rotameric sequences for a given design problem. A backbone of length n with m possible rotamers per position will have m^n possible rotamer sequences, a number that grows exponentially with sequence length. For very simple calculations, it is possible to examine each possible sequence in order to identify the optimal sequence and/or one or more favorable sequences. However, for a typical design problem, the number of possible sequences (up to 10^{30} or more) is sufficiently large that examination of each possible sequence is intractable. A variety of combinatorial optimization algorithms may then be used to identify the optimum sequence and/or one or more favorable sequences. Combinatorial optimization algorithms may be divided into two classes: (1) those that are guaranteed to return the global minimum energy configuration if they converge, and (2) those that are not guaranteed to return the global minimum energy configuration, but which will always return a solution. Examples of the first class of algorithms include but are not limited to Dead-End Elimination (DEE) and Branch & Bound (B&B) (including Branch and Terminate) (Gordon & Mayo, 1999, *Structure Fold Des* 7:1089-98). Examples of the second class of algorithms include, but are not limited to, Monte Carlo (MC), self-consistent mean field (SCMF), Boltzmann sampling (Metropolis *et al.*, 1953, *J Chem Phys* 21:1087), simulated annealing (Kirkpatrick *et al.*, 1983, *Science*, 220:671-680), genetic algorithm (GA), and Fast and Accurate Side-Chain Topology and Energy Refinement (FASTER) (Desmet, et al., 2002, Proteins, 48:31-43). A combinatorial optimization algorithm may be used alone or in conjunction with another combinatorial optimization algorithm.

[155] In one embodiment of the present invention, the strategy for applying a combinatorial optimization algorithm is to find the global minimum energy configuration. In an alternate embodiment, the strategy is to find one or more low energy or favorable sequences. In an alternate embodiment, the strategy is to find the global minimum energy configuration and then find one or more low energy or favorable sequences. For example, as outlined in USSN 6,269,312, preferred embodiments utilize a Dead End Elimination (DEE) step and a Monte Carlo step. In other embodiments, tabu search algorithms are used or combined with DEE and/or Monte Carlo, among other search methods (see Modern Heuristic Search Methods, edited by V.J. Rayward-Smith *et al.*, 1996, John Wiley & Sons Ltd.; USSN 10/218,102; and PCT WO 02/25588). In another preferred embodiment, a genetic algorithm may be used; see for example USSN 09/877,695 and USSN 10/071,859. As another example, as is more fully described in US 6,188,965; US 6,269,312; US 6,403,312; USSN 09/782,004; USSN 09/927,790; USSN 10/218,102; PCT WO 98/07254; PCT WO 01/40091; and PCT WO 02/25588, the global optimum may be reached, and then further

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computational processing may occur, which generates additional optimized sequences. In the simplest embodiment, design calculations are not combinatorial. That is, energy calculations are used to evaluate amino acid substitutions individually at single variable positions. For other calculations it is preferred to evaluate amino acid substitutions at more than one variable position. In a preferred embodiment, all possible interaction energies are calculated prior to combinatorial optimization. In an alternatively preferred embodiment, energies may be calculated as needed during combinatorial optimization.

Library generation

[156] The present invention provides methods for generating libraries that may subsequently be screened experimentally to single out optimized Fc variants. By "library" as used herein is meant a set of one or more Fc variants. Library may refer to the set of variants in any form. In one embodiment, the library is a list of nucleic acid or amino acid sequences, or a list of nucleic acid or amino acid substitutions at variable positions. For example, the examples used to illustrate the present invention below provide libraries as amino acid substitutions at variable positions. In one embodiment, a library is a list of at least one sequence that are Fc variants optimized for a desired property. For example see, Filikov *et al.*, 2002, *Protein Sci* 11:1452-1461 and Luo *et al.*, 2002, *Protein Sci* 11:1218-1226. In an alternate embodiment, a library may be defined as a combinatorial list, meaning that a list of amino acid substitutions is generated for each variable position, with the implication that each substitution is to be combined with all other designed substitutions at all other variable positions. In this case, expansion of the combination of all possibilities at all variable positions results in a large explicitly defined library. A library may refer to a physical composition of polypeptides that comprise the Fc region or some domain or fragment of the Fc region. Thus a library may refer to a physical composition of antibodies or Fc fusions, either in purified or unpurified form. A library may refer to a physical composition of nucleic acids that encode the library sequences. Said nucleic acids may be the genes encoding the library members, the genes encoding the library members with any operably linked nucleic acids, or expression vectors encoding the library members together with any other operably linked regulatory sequences, selectable markers, fusion constructs, and/or other elements. For example, the library may be a set of mammalian expression vectors that encode Fc library members, the protein products of which may be subsequently expressed, purified, and screened experimentally. As another example, the library may be a display library. Such a library could, for example, comprise a set of expression vectors that encode library members operably linked to some fusion partner that enables phage display, ribosome display, yeast display, bacterial surface display, and the like.

[157] The library may be generated using the output sequence or sequences from computational screening. As discussed above, computationally generated libraries are significantly enriched in stable, properly folded, and functional sequences relative to randomly generated libraries. As a result, computational screening increases the chances of identifying proteins that are optimized for the

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design goal. The set of sequences in a library is generally, but not always, significantly different from the parent sequence, although in some cases the library preferably contains the parent sequence. As is known in the art, there are a variety of ways that a library may be derived from the output of computational screening calculations. For example, methods of library generation described in US 6,403,312; USSN 09/782,004; USSN 09/927,790; USSN 10/218,102; PCT WO 01/40091; and PCT WO 02/25588 find use in the present invention. In one embodiment, sequences scoring within a certain range of the global optimum sequence may be included in the library. For example, all sequences within 10 kcal/mol of the lowest energy sequence could be used as the library. In an alternate embodiment, sequences scoring within a certain range of one or more local minima sequences may be used. In a preferred embodiment, the library sequences are obtained from a filtered set. Such a list or set may be generated by a variety of methods, as is known in the art, for example using an algorithm such as Monte Carlo, B&B, or SCMF. For example, the top 10^3 or the top 10^6 sequences in the filtered set may comprise the library. Alternatively, the total number of sequences defined by the combination of all mutations may be used as a cutoff criterion for the library. Preferred values for the total number of recombined sequences range from 10 to 10^{20}, particularly preferred values range from 100 to 10^9. Alternatively, a cutoff may be enforced when a predetermined number of mutations per position is reached. In some embodiments, sequences that do not make the cutoff are included in the library. This may be desirable in some situations, for instance to evaluate the approach to library generation, to provide controls or comparisons, or to sample additional sequence space. For example, the parent sequence may be included in the library, even if it does not make the cutoff.

[158] Clustering algorithms may be useful for classifying sequences derived by computational screening methods into representative groups. For example, the methods of clustering and their application described in USSN 10/218,102 and PCT WO 02/25588, find use in the present invention. Representative groups may be defined, for example, by similarity. Measures of similarity include, but are not limited to sequence similarity and energetic similarity. Thus the output sequences from computational screening may be clustered around local minima, referred to herein as clustered sets of sequences. For example, sets of sequences that are close in sequence space may be distinguished from other sets. In one embodiment, coverage within one or a subset of clustered sets may be maximized by including in the library some, most, or all of the sequences that make up one or more clustered sets of sequences. For example, it may be advantageous to maximize coverage within the one, two, or three lowest energy clustered sets by including the majority of sequences within these sets in the library. In an alternate embodiment, diversity across clustered sets of sequences may be sampled by including within a library only a subset of sequences within each clustered set. For example, all or most of the clustered sets could be broadly sampled by including the lowest energy sequence from each clustered set in the library.

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[159] Sequence information may be used to guide or filter computationally screening results for generation of a library. As discussed, by comparing and contrasting alignments of protein sequences, the degree of variability at a position and the types of amino acids which occur naturally at that position may be observed. Data obtained from such analyses are useful in the present invention. The benefits of using sequence information have been discussed, and those benefits apply equally to use of sequence information to guide library generation. The set of amino acids that occur in a sequence alignment may be thought of as being pre-screened by evolution to have a higher chance than random at being compatible with a protein's structure, stability, solubility, function, and immunogenicity. The variety of sequence sources, as well as the methods for generating sequence alignments that have been discussed, find use in the application of sequence information to guiding library generation. Likewise, as discussed above, various criteria may be applied to determine the importance or weight of certain residues in an alignment. These methods also find use in the application of sequence information to guide library generation. Using sequence information to guide library generation from the results of computational screening finds broad use in the present invention. In one embodiment, sequence information is used to filter sequences from computational screening output. That is to say, some substitutions are subtracted from the computational output to generate the library. For example the resulting output of a computational screening calculation or calculations may be filtered so that the library includes only those amino acids, or a subset of those amino acids that meet some criteria, for example that are observed at that position in an alignment of sequences. In an alternate embodiment, sequence information is used to add sequences to the computational screening output. That is to say, sequence information is used to guide the choice of additional amino acids that are added to the computational output to generate the library. For example, the output set of amino acids for a given position from a computational screening calculation may be augmented to include one or more amino acids that are observed at that position in an alignment of protein sequences. In an alternate embodiment, based on sequence alignment information, one or more amino acids may be added to or subtracted from the computational screening sequence output in order to maximize coverage or diversity. For example, additional amino acids with properties similar to those that are found in a sequence alignment may be added to the library. For example, if a position is observed to have uncharged polar amino acids in a sequence alignment, additional uncharged polar amino acids may be included in the library at that position.

[160] Libraries may be processed further to generate subsequent libraries. In this way, the output from a computational screening calculation or calculations may be thought of as a primary library. This primary library may be combined with other primary libraries from other calculations or other libraries, processed using subsequent calculations, sequence information, or other analyses, or processed experimentally to generate a subsequent library, herein referred to as a secondary library. As will be appreciated from this description, the use of sequence information to guide or filter libraries, discussed above, is itself one method of generating secondary libraries from primary libraries. Generation of secondary libraries gives the user greater control of the parameters within a library.

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This enables more efficient experimental screening, and may allow feedback from experimental results to be interpreted more easily, providing a more efficient design/experimentation cycle.

[161] There are a wide variety of methods to generate secondary libraries from primary libraries. For example, USSN 10/218,102 and PCT WO 02/25588, describes methods for secondary library generation that find use in the present invention. Typically some selection step occurs in which a primary library is processed in some way. For example, in one embodiment a selection step occurs wherein some set of primary sequences are chosen to form the secondary library. In an alternate embodiment, a selection step is a computational step, again generally including a selection step, wherein some subset of the primary library is chosen and then subjected to further computational analysis, including both further computational screening as well as techniques such as "*in silico*" shuffling or recombination (see, for example US 5,830,721; US 5,811,238; US 5,605,793; and US 5,837,458, error-prone PCR, for example using modified nucleotides; known mutagenesis techniques including the use of multi-cassettes; and DNA shuffling (Crameri *et al.*, 1998, *Nature* 391:288-291; Coco *et al.*, 2001, *Nat Biotechnol* 19:354-9; Coco *et al.*, 2002, *Nat Biotechnol*, 20:1246-50), heterogeneous DNA samples (US 5,939,250); ITCHY (Ostermeier *et al.*, 1999, *Nat Biotechnol* 17:1205-1209); StEP (Zhao *et al.*, 1998, *Nat Biotechnol* 16:258-261), GSSM (US 6,171,820 and US 5,965,408); *in vivo* homologous recombination, ligase assisted gene assembly, end-complementary PCR, profusion (Roberts & Szostak, 1997, *Proc Natl Acad Sci USA* 94:12297-12302); yeast/bacteria surface display (Lu *et al.*, 1995, *Biotechnology* 13:366-372); Seed & Aruffo, 1987, *Proc Natl Acad Sci USA* 84(10):3365-3369; Boder & Wittrup, 1997, *Nat Biotechnol* 15:553-557). In an alternate embodiment, a selection step occurs that is an experimental step, for example any of the library screening steps below, wherein some subset of the primary library is chosen and then recombined experimentally, for example using one of the directed evolution methods discussed below, to form a secondary library. In a preferred embodiment, the primary library is generated and processed as outlined in US 6,403,312.

[162] Generation of secondary and subsequent libraries finds broad use in the present invention. In one embodiment, different primary libraries may be combined to generate a secondary or subsequent library. In another embodiment, secondary libraries may be generated by sampling sequence diversity at highly mutatable or highly conserved positions. The primary library may be analyzed to determine which amino acid positions in the template protein have high mutational frequency, and which positions have low mutational frequency. For example, positions in a protein that show a great deal of mutational diversity in computational screening may be fixed in a subsequent round of design calculations. A filtered set of the same size as the first would now show diversity at positions that were largely conserved in the first library. Alternatively, the secondary library may be generated by varying the amino acids at the positions that have high numbers of mutations, while keeping constant the positions that do not have mutations above a certain frequency.

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[163] This discussion is not meant to constrain generation of libraries subsequent to primary libraries to secondary libraries. As will be appreciated, primary and secondary libraries may be processed further to generate tertiary libraries, quaternary libraries, and so on. In this way, library generation is an iterative process. For example, tertiary libraries may be constructed using a variety of additional steps applied to one or more secondary libraries; for example, further computational processing may occur, secondary libraries may be recombined, or subsets of different secondary libraries may be combined. In a preferred embodiment, a tertiary library may be generated by combining secondary libraries. For example, primary and/or secondary libraries that analyzed different parts of a protein may be combined to generate a tertiary library that treats the combined parts of the protein. In an alternate embodiment, the variants from a primary library may be combined with the variants from another primary library to provide a combined tertiary library at lower computational cost than creating a very long filtered set. These combinations may be used, for example, to analyze large proteins, especially large multi-domain proteins, of which Fc is an example. Thus the above description of secondary library generation applies to generating any library subsequent to a primary library, the end result being a final library that may screened experimentally to obtain protein variants optimized for a design goal. These examples are not meant to constrain generation of secondary libraries to any particular application or theory of operation for the present invention. Rather, these examples are meant to illustrate that generation of secondary libraries, and subsequent libraries such as tertiary libraries and so on, is broadly useful in computational screening methodology for library generation.

Experimental Production and Screening

[164] The present invention provides methods for producing and screening libraries of Fc variants. The described methods are not meant to constrain the present invention to any particular application or theory of operation. Rather, the provided methods are meant to illustrate generally that one or more Fc variants or one or more libraries of Fc variants may be produced and screened experimentally to obtain optimized Fc variants. Fc variants may be produced and screened in any context, whether as an Fc region as precisely defined herein, a domain or fragment thereof, or a larger polypeptide that comprises Fc such as an antibody or Fc fusion. General methods for antibody molecular biology, expression, purification, and screening are described in Antibody Engineering, edited by Duebel & Kontermann, Springer-Verlag, Heidelberg, 2001; and Hayhurst & Georgiou, 2001, *Curr Opin Chem Biol* 5:683-689; Maynard & Georgiou, 2000, *Annu Rev Biomed Eng* 2:339-76.

[165] In one embodiment of the present invention, the library sequences are used to create nucleic acids that encode the member sequences, and that may then be cloned into host cells, expressed and assayed, if desired. Thus, nucleic acids, and particularly DNA, may be made that encode each member protein sequence. These practices are carried out using well-known procedures. For example, a variety of methods that may find use in the present invention are described in Molecular Cloning - A Laboratory Manual, 3rd Ed. (Maniatis, Cold Spring Harbor Laboratory Press, New York,

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2001), and Current Protocols in Molecular Biology (John Wiley & Sons). As will be appreciated by those skilled in the art, the generation of exact sequences for a library comprising a large number of sequences is potentially expensive and time consuming. Accordingly, there are a variety of techniques that may be used to efficiently generate libraries of the present invention. Such methods that may find use in the present invention are described or referenced in US 6,403,312; USSN 09/782,004; USSN 09/927,790; USSN 10/218,102; PCT WO 01/40091; and PCT WO 02/25588. Such methods include but are not limited to gene assembly methods, PCR-based method and methods which use variations of PCR, ligase chain reaction-based methods, pooled oligo methods such as those used in synthetic shuffling, error-prone amplification methods and methods which use oligos with random mutations, classical site-directed mutagenesis methods, cassette mutagenesis, and other amplification and gene synthesis methods. As is known in the art, there are a variety of commercially available kits and methods for gene assembly, mutagenesis, vector subcloning, and the like, and such commercial products find use in the present invention for generating nucleic acids that encode Fc variant members of a library.

[166] The Fc variants of the present invention may be produced by culturing a host cell transformed with nucleic acid, preferably an expression vector, containing nucleic acid encoding the Fc variants, under the appropriate conditions to induce or cause expression of the protein. The conditions appropriate for expression will vary with the choice of the expression vector and the host cell, and will be easily ascertained by one skilled in the art through routine experimentation. A wide variety of appropriate host cells may be used, including but not limited to mammalian cells, bacteria, insect cells, and yeast. For example, a variety of cell lines that may find use in the present invention are described in the ATCC® cell line catalog, available from the American Type Culture Collection.

[167] In a preferred embodiment, the Fc variants are expressed in mammalian expression systems, including systems in which the expression constructs are introduced into the mammalian cells using virus such as retrovirus or adenovirus. Any mammalian cells may be used, with human, mouse, rat, hamster, and primate cells being particularly preferred. Suitable cells also include known research cells, including but not limited to Jurkat T cells, NIH3T3, CHO, COS, and 293 cells. In an alternately preferred embodiment, library proteins are expressed in bacterial cells. Bacterial expression systems are well known in the art, and include *Escherichia coli* (*E. coli*), *Bacillus subtilis*, *Streptococcus cremoris*, and *Streptococcus lividans*. In alternate embodiments, Fc variants are produced in insect cells or yeast cells. In an alternate embodiment, Fc variants are expressed *in vitro* using cell free translation systems. In vitro translation systems derived from both prokaryotic (e.g. *E. coli*) and eukaryotic (e.g. wheat germ, rabbit reticulocytes) cells are available and may be chosen based on the expression levels and functional properties of the protein of interest. For example, as appreciated by those skilled in the art, *in vitro* translation is required for some display technologies, for example ribosome display. In addition, the Fc variants may be produced by chemical synthesis methods.

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[168] The nucleic acids that encode the Fc variants of the present invention may be incorporated into an expression vector in order to express the protein. A variety of expression vectors may be utilized for protein expression. Expression vectors may comprise self-replicating extra-chromosomal vectors or vectors which integrate into a host genome. Expression vectors are constructed to be compatible with the host cell type. Thus expression vectors which find use in the present invention include but are not limited to those which enable protein expression in mammalian cells, bacteria, insect cells, yeast, and in *in vitro* systems. As is known in the art, a variety of expression vectors are available, commercially or otherwise, that may find use in the present invention for expressing Fc variant proteins.

[169] Expression vectors typically comprise a protein operably linked with control or regulatory sequences, selectable markers, any fusion partners, and/or additional elements. By "operably linked" herein is meant that the nucleic acid is placed into a functional relationship with another nucleic acid sequence. Generally, these expression vectors include transcriptional and translational regulatory nucleic acid operably linked to the nucleic acid encoding the Fc variant, and are typically appropriate to the host cell used to express the protein. In general, the transcriptional and translational regulatory sequences may include promoter sequences, ribosomal binding sites, transcriptional start and stop sequences, translational start and stop sequences, and enhancer or activator sequences. As is also known in the art, expression vectors typically contain a selection gene or marker to allow the selection of transformed host cells containing the expression vector. Selection genes are well known in the art and will vary with the host cell used.

[170] Fc variants may be operably linked to a fusion partner to enable targeting of the expressed protein, purification, screening, display, and the like. Fusion partners may be linked to the Fc variant sequence via a linker sequences. The linker sequence will generally comprise a small number of amino acids, typically less than ten, although longer linkers may also be used. Typically, linker sequences are selected to be flexible and resistant to degradation. As will be appreciated by those skilled in the art, any of a wide variety of sequences may be used as linkers. For example, a common linker sequence comprises the amino acid sequence GGGGS. A fusion partner may be a targeting or signal sequence that directs Fc variant protein and any associated fusion partners to a desired cellular location or to the extracellular media. As is known in the art, certain signaling sequences may target a protein to be either secreted into the growth media, or into the periplasmic space, located between the inner and outer membrane of the cell. A fusion partner may also be a sequence that encodes a peptide or protein that enables purification and/or screening. Such fusion partners include but are not limited to polyhistidine tags (His-tags) (for example H_6 and H_{10} or other tags for use with Immobilized Metal Affinity Chromatography (IMAC) systems (e.g. Ni^{+2} affinity columns)), GST fusions, MBP fusions, Strep-tag, the BSP biotinylation target sequence of the bacterial enzyme BirA, and epitope tags which are targeted by antibodies (for example c-myc tags, flag-tags, and the like). As will be appreciated by those skilled in the art, such tags may be useful for purification, for screening, or both.

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For example, an Fc variant may be purified using a His-tag by immobilizing it to a Ni^{+2} affinity column, and then after purification the same His-tag may be used to immobilize the antibody to a Ni^{+2} coated plate to perform an ELISA or other binding assay (as described below). A fusion partner may enable the use of a selection method to screen Fc variants (see below). Fusion partners that enable a variety of selection methods are well-known in the art, and all of these find use in the present invention. For example, by fusing the members of an Fc variant library to the gene III protein, phage display can be employed (Kay *et al.*, Phage display of peptides and proteins: a laboratory manual, Academic Press, San Diego, CA, 1996; Lowman *et al.*, 1991, *Biochemistry* 30:10832-10838; Smith, 1985, *Science* 228:1315-1317). Fusion partners may enable Fc variants to be labeled. Alternatively, a fusion partner may bind to a specific sequence on the expression vector, enabling the fusion partner and associated Fc variant to be linked covalently or noncovalently with the nucleic acid that encodes them. For example, USSN 09/642,574; USSN 10/080,376; USSN 09/792,630; USSN 10/023,208; USSN 09/792,626; USSN 10/082,671; USSN 09/953,351; USSN 10/097,100; USSN 60/366,658; PCT WO 00/22906; PCT WO 01/49058; PCT WO 02/04852; PCT WO 02/04853; PCT WO 02/08023; PCT WO 01/28702; and PCT WO 02/07466 describe such a fusion partner and technique that may find use in the present invention.

[171] The methods of introducing exogenous nucleic acid into host cells are well known in the art, and will vary with the host cell used. Techniques include but are not limited to dextran-mediated transfection, calcium phosphate precipitation, calcium chloride treatment, polybrene mediated transfection, protoplast fusion, electroporation, viral or phage infection, encapsulation of the polynucleotide(s) in liposomes, and direct microinjection of the DNA into nuclei. In the case of mammalian cells, transfection may be either transient or stable.

[172] In a preferred embodiment, Fc variant proteins are purified or isolated after expression. Proteins may be isolated or purified in a variety of ways known to those skilled in the art. Standard purification methods include chromatographic techniques, including ion exchange, hydrophobic interaction, affinity, sizing or gel filtration, and reversed-phase, carried out at atmospheric pressure or at high pressure using systems such as FPLC and HPLC. Purification methods also include electrophoretic, immunological, precipitation, dialysis, and chromatofocusing techniques. Ultrafiltration and diafiltration techniques, in conjunction with protein concentration, are also useful. As is well known in the art, a variety of natural proteins bind Fc and antibodies, and these proteins can find use in the present invention for purification of Fc variants. For example, the bacterial proteins A and G bind to the Fc region. Likewise, the bacterial protein L binds to the Fab region of some antibodies, as of course does the antibody's target antigen. Purification can often be enabled by a particular fusion partner. For example, Fc variant proteins may be purified using glutathione resin if a GST fusion is employed, Ni^{+2} affinity chromatography if a His-tag is employed, or immobilized anti-flag antibody if a flag-tag is used. For general guidance in suitable purification techniques, see Protein Purification: Principles and Practice, 3rd Ed., Scopes, Springer-Verlag, NY, 1994. The degree of

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purification necessary will vary depending on the screen or use of the Fc variants. In some instances no purification is necessary. For example in one embodiment, if the Fc variants are secreted, screening may take place directly from the media. As is well known in the art, some methods of selection do not involve purification of proteins. Thus, for example, if a library of Fc variants is made into a phage display library, protein purification may not be performed.

[173] Fc variants may be screened using a variety of methods, including but not limited to those that use *in vitro* assays, *in vivo* and cell-based assays, and selection technologies. Automation and high-throughput screening technologies may be utilized in the screening procedures. Screening may employ the use of a fusion partner or label. The use of fusion partners has been discussed above. By "labeled" herein is meant that the Fc variants of the invention have one or more elements, isotopes, or chemical compounds attached to enable the detection in a screen. In general, labels fall into three classes: a) immune labels, which may be an epitope incorporated as a fusion partner that is recognized by an antibody, b) isotopic labels, which may be radioactive or heavy isotopes, and c) small molecule labels, which may include fluorescent and colorimetric dyes, or molecules such as biotin that enable other labeling methods. Labels may be incorporated into the compound at any position and may be incorporated *in vitro* or *in vivo* during protein expression.

[174] In a preferred embodiment, the functional and/or biophysical properties of Fc variants are screened in an *in vitro* assay. *In vitro* assays may allow a broad dynamic range for screening properties of interest. Properties of Fc variants that may be screened include but are not limited to stability, solubility, and affinity for Fc ligands, for example Fc□Rs. Multiple properties may be screened simultaneously or individually. Proteins may be purified or unpurified, depending on the requirements of the assay. In one embodiment, the screen is a qualitative or quantitative binding assay for binding of Fc variants to a protein or nonprotein molecule that is known or thought to bind the Fc variant. In a preferred embodiment, the screen is a binding assay for measuring binding to the antibody's or Fc fusions' target antigen. In an alternately preferred embodiment, the screen is an assay for binding of Fc variants to an Fc ligand, including but are not limited to the family of Fc□Rs, the neonatal receptor FcRn, the complement protein C1q, and the bacterial proteins A and G. Said Fc ligands may be from any organism, with humans, mice, rats, rabbits, and monkeys preferred. Binding assays can be carried out using a variety of methods known in the art, including but not limited to FRET (Fluorescence Resonance Energy Transfer) and BRET (Bioluminescence Resonance Energy Transfer) -based assays, AlphaScreen™ (Amplified Luminescent Proximity Homogeneous Assay), Scintillation Proximity Assay, ELISA (Enzyme-Linked Immunosorbent Assay), SPR (Surface Plasmon Resonance, also known as BIACORE®), isothermal titration calorimetry, differential scanning calorimetry, gel electrophoresis, and chromatography including gel filtration. These and other methods may take advantage of some fusion partner or label of the Fc variant. Assays may employ a variety of detection methods including but not limited to chromogenic, fluorescent, luminescent, or isotopic labels.

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[175] The biophysical properties of Fc variant proteins, for example stability and solubility, may be screened using a variety of methods known in the art. Protein stability may be determined by measuring the thermodynamic equilibrium between folded and unfolded states. For example, Fc variant proteins of the present invention may be unfolded using chemical denaturant, heat, or pH, and this transition may be monitored using methods including but not limited to circular dichroism spectroscopy, fluorescence spectroscopy, absorbance spectroscopy, NMR spectroscopy, calorimetry, and proteolysis. As will be appreciated by those skilled in the art, the kinetic parameters of the folding and unfolding transitions may also be monitored using these and other techniques. The solubility and overall structural integrity of an Fc variant protein may be quantitatively or qualitatively determined using a wide range of methods that are known in the art. Methods which may find use in the present invention for characterizing the biophysical properties of Fc variant proteins include gel electrophoresis, chromatography such as size exclusion chromatography and reversed-phase high performance liquid chromatography, mass spectrometry, ultraviolet absorbance spectroscopy, fluorescence spectroscopy, circular dichroism spectroscopy, isothermal titration calorimetry, differential scanning calorimetry, analytical ultra-centrifugation, dynamic light scattering, proteolysis, and cross-linking, turbidity measurement, filter retardation assays, immunological assays, fluorescent dye binding assays, protein-staining assays, microscopy, and detection of aggregates via ELISA or other binding assay. Structural analysis employing X-ray crystallographic techniques and NMR spectroscopy may also find use. In one embodiment, stability and/or solubility may be measured by determining the amount of protein solution after some defined period of time. In this assay, the protein may or may not be exposed to some extreme condition, for example elevated temperature, low pH, or the presence of denaturant. Because function typically requires a stable, soluble, and/or well-folded/structured protein, the aforementioned functional and binding assays also provide ways to perform such a measurement. For example, a solution comprising an Fc variant could be assayed for its ability to bind target antigen, then exposed to elevated temperature for one or more defined periods of time, then assayed for antigen binding again. Because unfolded and aggregated protein is not expected to be capable of binding antigen, the amount of activity remaining provides a measure of the Fc variant's stability and solubility.

[176] In a preferred embodiment, the library is screened using one or more cell-based or *in vivo* assays. For such assays, Fc variant proteins, purified or unpurified, are typically added exogenously such that cells are exposed to individual variants or pools of variants belonging to a library. These assays are typically, but not always, based on the function of an antibody or Fc fusion that comprises the Fc variant; that is, the ability of the antibody or Fc fusion to bind a target antigen and mediate some biochemical event, for example effector function, ligand/receptor binding inhibition, apoptosis, and the like. Such assays often involve monitoring the response of cells to antibody or Fc fusion, for example cell survival, cell death, change in cellular morphology, or transcriptional activation such as cellular expression of a natural gene or reporter gene. For example, such assays may measure the

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ability of Fc variants to elicit ADCC, ADCP, or CDC. For some assays additional cells or components, that is in addition to the target cells, may need to be added, for example example serum complement, or effector cells such as peripheral blood monocytes (PBMCs), NK cells, macrophages, and the like. Such additional cells may be from any organism, preferably humans, mice, rat, rabbit, and monkey. Antibodies and Fc fusions may cause apoptosis of certain cell lines expressing the antibody's target antigen, or they may mediate attack on target cells by immune cells which have been added to the assay. Methods for monitoring cell death or viability are known in the art, and include the use of dyes, immunochemical, cytochemical, and radioactive reagents. For example, caspase staining assays may enable apoptosis to be measured, and uptake or release of radioactive substrates or fluorescent dyes such as alamar blue may enable cell growth or activation to be monitored. In a preferred embodiment, the DELFIA® EuTDA-based cytotoxicity assay (Perkin Elmer, MA) is used. Alternatively, dead or damaged target cells may be monitored by measuring the release of one or more natural intracellular proteins, for example lactate dehydrogenase. Transcriptional activation may also serve as a method for assaying function in cell-based assays. In this case, response may be monitored by assaying for natural genes or proteins which may be upregulated, for example the release of certain interleukins may be measured, or alternatively readout may be via a reporter construct. Cell-based assays may also involve the measure of morphological changes of cells as a response to the presence of an Fc variant. Cell types for such assays may be prokaryotic or eukaryotic, and a variety of cell lines that are known in the art may be employed.

[177] Alternatively, cell-based screens are performed using cells that have been transformed or transfected with nucleic acids encoding the Fc variants. That is, Fc variant proteins are not added exogenously to the cells. For example, in one embodiment, the cell-based screen utilizes cell surface display. A fusion partner can be employed that enables display of Fc variants on the surface of cells (Wittrup, 2001, *Curr Opin Biotechnol*, 12:395-399). Cell surface display methods that may find use in the present invention include but are not limited to display on bacteria (Georgiou *et al.*, 1997, *Nat Biotechnol* 15:29-34; Georgiou *et al.*, 1993, *Trends Biotechnol* 11:6-10; Lee *et al.*, 2000, *Nat Biotechnol* 18:645-648; Jun *et al.*, 1998, *Nat Biotechnol* 16:576-80), yeast (Boder & Wittrup, 2000, *Methods Enzymol* 328:430-44; Boder & Wittrup, 1997, *Nat Biotechnol* 15:553-557), and mammalian cells (Whitehorn *et al.*, 1995, *Biotechnology* 13:1215-1219). In an alternate embodiment, Fc variant proteins are not displayed on the surface of cells, but rather are screened intracellularly or in some other cellular compartment. For example, periplasmic expression and cytometric screening (Chen *et al.*, 2001, *Nat Biotechnol* 19: 537-542), the protein fragment complementation assay (Johnsson & Varshavsky, 1994, *Proc Natl Acad Sci USA* 91:10340-10344.; Pelletier *et al.*, 1998, *Proc Natl Acad Sci USA* 95:12141-12146), and the yeast two hybrid screen (Fields & Song, 1989, Nature 340:245-246) may find use in the present invention. Alternatively, if a polypeptide that comprises the Fc variants, for example an antibody or Fc fusion, imparts some selectable growth advantage to a cell, this property may be used to screen or select for Fc variants.

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[178] As is known in the art, a subset of screening methods are those that select for favorable members of a library. Said methods are herein referred to as "selection methods", and these methods find use in the present invention for screening Fc variant libraries. When libraries are screened using a selection method, only those members of a library that are favorable, that is which meet some selection criteria, are propagated, isolated, and/or observed. As will be appreciated, because only the most fit variants are observed, such methods enable the screening of libraries that are larger than those screenable by methods that assay the fitness of library members individually. Selection is enabled by any method, technique, or fusion partner that links, covalently or noncovalently, the phenotype of an Fc variant with its genotype, that is the function of an Fc variant with the nucleic acid that encodes it. For example the use of phage display as a selection method is enabled by the fusion of library members to the gene III protein. In this way, selection or isolation of variant proteins that meet some criteria, for example binding affinity for an FcγR, also selects for or isolates the nucleic acid that encodes it. Once isolated, the gene or genes encoding Fc variants may then be amplified. This process of isolation and amplification, referred to as panning, may be repeated, allowing favorable Fc variants in the library to be enriched. Nucleic acid sequencing of the attached nucleic acid ultimately allows for gene identification.

[179] A variety of selection methods are known in the art that may find use in the present invention for screening Fc variant libraries. These include but are not limited to phage display (Phage display of peptides and proteins: a laboratory manual, Kay *et al.*, 1996, Academic Press, San Diego, CA, 1996; Lowman *et al.*, 1991, *Biochemistry* 30:10832-10838; Smith, 1985, *Science* 228:1315-1317) and its derivatives such as selective phage infection (Malmborg *et al.*, 1997, J Mol Biol 273:544-551), selectively infective phage (Krebber *et al.*, 1997, *J Mol Biol* 268:619-630), and delayed infectivity panning (Benhar *et al.*, 2000, *J Mol Biol* 301:893-904), cell surface display (Wittrup, 2001, *Curr Opin Biotechnol*, 12:395-399) such as display on bacteria (Georgiou *et al.*, 1997, *Nat Biotechnol* 15:29-34; Georgiou *et al.*, 1993, *Trends Biotechnol* 11:6-10; Lee *et al.*, 2000, *Nat Biotechnol* 18:645-648; Jun *et al.*, 1998, *Nat Biotechnol* 16:576-80), yeast (Boder & Wittrup, 2000, *Methods Enzymol* 328:430-44; Boder & Wittrup, 1997, *Nat Biotechnol* 15:553-557), and mammalian cells (Whitehorn *et al.*, 1995, *Bio/technology* 13:1215-1219), as well as *in vitro* display technologies (Amstutz *et al.*, 2001, *Curr Opin Biotechnol* 12:400-405) such as polysome display (Mattheakis *et al.*, 1994, *Proc Natl Acad Sci USA* 91:9022-9026), ribosome display (Hanes *et al.*, 1997, *Proc Natl Acad Sci USA* 94:4937-4942), mRNA display (Roberts & Szostak, 1997, *Proc Natl Acad Sci USA* 94:12297-12302; Nemoto *et al.*, 1997, *FEBS Lett* 414:405-408), and ribosome-inactivation display system (Zhou *et al.*, 2002, *J Am Chem Soc* 124, 538-543)

[180] Other selection methods that may find use in the present invention include methods that do not rely on display, such as *in vivo* methods including but not limited to periplasmic expression and cytometric screening (Chen *et al.*, 2001, *Nat Biotechnol* 19:537-542), the protein fragment complementation assay (Johnsson & Varshavsky, 1994, *Proc Natl Acad Sci USA* 91:10340-10344;

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Pelletier *et al.*, 1998, *Proc Natl Acad Sci USA* 95:12141-12146), and the yeast two hybrid screen (Fields & Song, 1989, *Nature* 340:245-246) used in selection mode (Visintin *et al.*, 1999, *Proc Natl Acad Sci USA* 96:11723-11728). In an alternate embodiment, selection is enabled by a fusion partner that binds to a specific sequence on the expression vector, thus linking covalently or noncovalently the fusion partner and associated Fc variant library member with the nucleic acid that encodes them. For example, USSN 09/642,574; USSN 10/080,376; USSN 09/792,630; USSN 10/023,208; USSN 09/792,626; USSN 10/082,671; USSN 09/953,351; USSN 10/097,100; USSN 60/366,658; PCT WO 00/22906; PCT WO 01/49058; PCT WO 02/04852; PCT WO 02/04853; PCT WO 02/08023; PCT WO 01/28702; and PCT WO 02/07466 describe such a fusion partner and technique that may find use in the present invention. In an alternative embodiment, *in vivo* selection can occur if expression of a polypeptide that comprises the Fc variant, such as an antibody or Fc fusion, imparts some growth, reproduction, or survival advantage to the cell.

[181] A subset of selection methods referred to as "directed evolution" methods are those that include the mating or breading of favorable sequences during selection, sometimes with the incorporation of new mutations. As will be appreciated by those skilled in the art, directed evolution methods can facilitate identification of the most favorable sequences in a library, and can increase the diversity of sequences that are screened. A variety of directed evolution methods are known in the art that may find use in the present invention for screening Fc variant libraries, including but not limited to DNA shuffling (PCT WO 00/42561 A3; PCT WO 01/70947 A3), exon shuffling (US 6,365,377; Kolkman & Stemmer, 2001, *Nat Biotechnol* 19:423-428), family shuffling (Crameri *et al.*, 1998, *Nature* 391:288-291; US 6,376,246), RACHITT™ (Coco *et al.*, 2001, *Nat Biotechnol* 19:354- 359; PCT WO 02/06469), STEP and random priming of *in vitro* recombination (Zhao *et al.*, 1998, *Nat Biotechnol* 16:258-261; Shao *et al.*, 1998, *Nucleic Acids Res* 26:681-683), exonuclease mediated gene assembly (US 6,352,842; US 6,361,974), Gene Site Saturation Mutagenesis™ (US 6,358,709), Gene Reassembly™ (US 6,358,709), SCRATCHY (Lutz et al., 2001, *Proc Natl Acad Sci USA* 98:11248-11253), DNA fragmentation methods (Kikuchi *et al.*, *Gene* 236:159-167), single-stranded DNA shuffling (Kikuchi *et al.*, 2000, *Gene* 243:133-137), and AMEsystem™ directed evolution protein engineering technology (Applied Molecular Evolution) (US US 6,824,514; US 5,817,483; US 5,814,476; US 5,763,192; US 5,723,323).

[182] The biological properties of the antibodies and Fc fusions that comprise the Fc variants of the present invention may be characterized in cell, tissue, and whole organism experiments. As is know in the art, drugs are often tested in animals, including but not limited to mice, rats, rabbits, dogs, cats, pigs, and monkeys, in order to measure a drug's efficacy for treatment against a disease or disease model, or to measure a drug's pharmacokinetics, toxicity, and other properties. Said animals may be referred to as disease models. Therapeutics are often tested in mice, including but not limited to nude mice, SCID mice, xenograft mice, and transgenic mice (including knockins and knockouts). For example, an antibody or Fc fusion of the present invention that is intended as an anti-cancer

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therapeutic may be tested in a mouse cancer model, for example a xenograft mouse. In this method, a tumor or tumor cell line is grafted onto or injected into a mouse, and subsequently the mouse is treated with the therapeutic to determine the ability of the antibody or Fc fusion to reduce or inhibit cancer growth. Such experimentation may provide meaningful data for determination of the potential of said antibody or Fc fusion to be used as a therapeutic. Any organism, preferably mammals, may be used for testing. For example because of their genetic similarity to humans, monkeys can be suitable therapeutic models, and thus may be used to test the efficacy, toxicity, pharmacokinetics, or other property of the antibodies and Fc fusions of the present invention. Tests of the antibodies and Fc fusions of the present invention in humans are ultimately required for approval as drugs, and thus of course these experiments are contemplated. Thus the antibodies and Fc fusions of the present invention may be tested in humans to determine their therapeutic efficacy, toxicity, pharmacokinetics, and/or other clinical properties.

EXAMPLES

[183] Examples are provided below to illustrate the present invention. These examples are not meant to constrain the present invention to any particular application or theory of operation.

[184] For all positions discussed in the present invention, numbering is according to the EU index as in Kabat (Kabat *et al.*, 1991, *Sequences of Proteins of Immunological Interest,* 5th Ed., United States Public Health Svice, National Institutes of Health, Bethesda). Those skilled in the art of antibodies will appreciate that this convention consists of nonsequential numbering in specific regions of an immunoglobulin sequence, enabling a normalized reference to conserved positions in immunoglobulin families. Accordingly, the positions of any given immunoglobulin as defined by the EU index will not necessarily correspond to its sequential sequence. Figure 3 shows the sequential and EU index numbering schemes for the antibody alemtuzumab in order to illustrate this principal more clearly. It should also be noted that polymorphisms have been observed at a number of Fc positions, including but not limited to Kabat 270, 272, 312, 315, 356, and 358, and thus slight differences between the presented sequence and sequences in the scientific literature may exist.

[185] Example 1. Computational Screening and Design of Fc Libraries

Computational screening calculations were carried out to design optimized Fc variants. Fc variants were computationally screened, constructed, and experimentally investigated over several computation/experimention cycles. For each successive cycle, experimental data provided feedback into the next set of computational screening calculations and library design. All computational screening calculations and library design are presented in Example 1. For each set of calculations, a table is provided that presents the results and provides relevant information and parameters.

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[186] Several different structures of Fc bound bound to the extracellular domain of FcRs served as template structures for the computational screening calculations. Publicly available Fc/FcγR complex structures included pdb accession code 1E4K (Sondermann *et al.*, 2000, *Nature* 406:267-273.), and pdb accession codes 1IIS and 1IIX (Radaev *et al.*, 2001, *J Biol Chem* 276:16469-16477). The extracellular regions of FcRIIIb and FcγRIIIa are 99% identical, and therefore the use of the Fc/FcγRIIIb structure is essentially equivalent to use of FcγRIIIa. Nonetheless, for some calculations, a more precise Fc/FcRIIIa template structure was constructed by modeling a D129G mutation in the 1IIS and 1E4K structures (referred to as D129G 1IIS and D129G 1E4K template structures). In addition, the structures for human Fc bound to the extracellular domains of human FcγRIIb, human F158 FcRIIIa, and mouse FcγRIII were modeled using standard methods, the available FcR sequence information, the aforementioned Fc/FcγR structures, as well as structural information for unbound complexes (pdb accession code 1HSV)(Sondermann *et al.*, 2001, *J Mol Biol* 309:737-749) (pdb accession code 1FCG)(Maxwell *et al.*, 1999, *Nat Struct Biol* 6:437-442), FcRIIb (pdb accession code 2FCB)(Sondermann *et al.*, 1999, *Embo J* 18:1095-1103), and FcRIIIb (pdb accession code 1E4J)(Sondermann *et al.*, 2000, *Nature* 406:267-273.).

[187] Variable positions and amino acids to be considered at those positions were chosen by visual inspection of the aforementioned Fc/FcγR and FcγR structures, and using solvent accessibility information and sequence information. Sequence information of Fcs and FcγRs was particularly useful for determining variable positions at which substitutions may provide distinguishing affinities between activating and inhibitory receptors. Virtually all Cγ2 positions were screened computationally. The Fc structure is a homodimer of two heavy chains (labeled chains A and B in the 1IIS, 1IIX, and 1E4K structures) that each include the hinge and C2-C3 domains (shown in Figure 2). Because the FcR (labeled chain C in the 1IIS, 1IIX, and 1E4K structures) binds asymmetrically to the Fc homodimer, each chain was often considered separately in design calculations. For some calculations, Fc and/or FcR residues proximal to variable position residues were floated, that is the amino acid conformation but not the amino acid identity was allowed to vary in a protein design calculation to allow for conformational adjustments. These are indicated below the table for each set of calculations when relevant. Considered amino acids typically belonged to either the Core, Core XM, Surface, Boundary, Boundary XM, or All 20 classifications, unless noted otherwise. These classifications are defined as follows: Core = alanine, valine, isoleucine, leucine, phenylalanine, tyrosine, tryptophan, and methionine; Core XM = alanine, valine, isoleucine, leucine, phenylalanine, tyrosine, and tryptophan; Surface = alanine, serine, threonine, aspartic acid, asparagine, glutamine, glutamic acid, arginine, lysine and histidine; Boundary = alanine, serine, threonine, aspartic acid, asparagine, glutamine, glutamic acid, arginine, lysine, histidine, valine, isoleucine, leucine, phenylalanine, tyrosine, tryptophan, and methionine; Boundary XM = Boundary = alanine, serine, threonine, aspartic acid, asparagine, glutamine, glutamic acid, arginine, lysine, histidine, valine, isoleucine, leucine, phenylalanine, tyrosine, and tryptophan; All 20 = all 20 naturally occurring amino acids.

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[188] The majority of calculations followed one of two general types of computational screening methods. In one method, the conformations of amino acids at variable positions were represented as a set of backbone-independent side chain rotamers derived from the rotamer library of Dunbrack & Cohen (Dunbrack *et al.*, 1997, *Protein Sci* 6:1661-1681). The energies of all possible combinations of the considered amino acids at the chosen variable positions were calculated using a force field containing terms describing van der Waals, solvation, electrostatic, and hydrogen bond interactions, and the optimal (ground state) sequence was determined using a Dead End Elimination (DEE) algorithm. As will be appreciated by those in the art, the predicted lowest energy sequence is not necessarily the true lowest energy sequence because of errors primarily in the scoring function, coupled with the fact that subtle conformational differences in proteins can result in dramatic differences in stability. However, the predicted ground state sequence is likely to be close to the true ground state, and thus additional favorable diversity can be explored by evaluating the energy of sequences that are close in sequence space and energy around the predicted ground state. To accomplish this, as well as to generate a diversity of sequences for a library, a Monte Carlo (MC) algorithm was used to evaluate the energies of 1000 similar sequences around the predicted ground state. The number of sequences out of the 1000 sequence set that contain that amino acid at that variable position is referred to as the occupancy for that substitution, and this value may reflect how favorable that substitution is. This computational screening method is substantially similar to Protein Design Automation® (PDA®) technology, as described in US 6,188,965; US 6,269,312; US 6,403,312; USSN 09/782,004; USSN 09/927,790; USSN 10/218,102; PCT WO 98/07254; PCT WO 01/40091; and PCT WO 02/25588, and for ease of description, is referred to as PDA® technology throughout the examples. Tables that present the results of these calculations provide for each variable position on the designated chain (column 1) the amino acids considered at each variable position (column 2), the WT Fc amino acid identity at each variable position (column 3), the amino acid identity at each variable position in the DEE ground state sequence (column 4), and the set of amino acids and corresponding occupancy that are observed in the Monte Carlo output (column 5).

[189] Other calculations utilized a genetic algorithm (GA) to screen for low energy sequences, with energies being calculated during each round of "evolution" for those sequences being sampled. The conformations of amino acids at variable and floated positions were represented as a set of side chain rotamers derived from a backbone-independent rotamer library using a flexible rotamer model (Mendes *et al.*, 1999, *Proteins* 37:530-543). Energies were calculated using a force field containing terms describing van der Waals, solvation, electrostatic, and hydrogen bond interactions. This calculation generated a list of 300 sequences which are predicted to be low in energy. To facilitate analysis of the results and library generation, the 300 output sequences were clustered computationally into 10 groups of similar sequences using a nearest neighbor single linkage hierarchical clustering algorithm to assign sequences to related groups based on similarity scores (Diamond, 1995, *Acta Cryst* D51:127-135). That is, all sequences within a group are most similar to

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all other sequences within the same group and less similar to sequences in other groups. The lowest energy sequence from each of these ten clusters are used as a representative of each group, and are presented as results. This computational screening method is substantially similar to Sequence Prediction Algorithm™ (SPA™) technology, as described in (Raha *et al.*, 2000, *Protein Sci* 9:1106-1119); USSN 09/877,695; and USSN 10/071,869, and for ease of description, is referred to as SPA™ technology throughout the examples.

[190] Computational screening was applied to design energetically favorable interactions at the Fc/Fc□R interface at groups of variable positions that mediate or potentially mediate binding with Fc□R. Because the binding interface involves a large number of Fc residues on the two different chains, and because Fc□Rs bind asymmetrically to Fc, residues were grouped in different sets of interacting variable positions, and designed in separate sets of calculations. In many cases these sets were chosen as groups of residues that were deemed to be coupled, that is the energy of one or more residues is dependent on the identity of one or more other residues. Various template structures were used, and in many cases calculations explored substitutions on both chains. For many of the variable position sets, calculations were carried out using both the PDA® and SPA™ technology computational screening methods described. The results of these calculations and relevant parameters and information are presented in Tables 1 – 30 below.

[191] Tables that present the results of these calculations provide for each variable position on the designated chain (column 1) the amino acids considered at each variable position (column 2), the WT Fc amino acid identity at each variable position (column 3), and the amino acid identity at the variable positions for the lowest energy sequence from each cluster group (columns 4-13). Tables 1-59 are broken down into two sets, as labeled below, PDA® and SPA™ technology. Column 4 of the PDA® tables show the frequency of each residue that occurs in the top 1000 sequences during that PDA® run. Thus, in the first row of Table 1, at position 328, when run using boundary amino acids as the set of variable residues for that position, L occurred 330 times in the top 1000 sequence, M occurred 302 times, etc.

[192] In addition, included within the compositions of the invention are antibodies that have any of the listed amino acid residues in the listed positions, either alone or in any combination (note preferred combinations are listed in the claims, the summary and the figures). One preferred combination is the listed amino acids residues in the listed positions in a ground state (sometimes referred to herein as the "global solution", as distinguished from the wild-type). Similarly, residue positions and particular amino acids at those residue positions may be combined between tables.

[193] For SPA™ technology tables, such as Table 4, column 4 is a SPA™ run that results in a protein with the six listed amino acids at the six listed positions (e.g. column 4 is a single protein with

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a wild-type sequence except for 239E, 265G, 267S, 269Y, 270T and 299S. Thus, each of these individual proteins are included within the invention. In addition, combinations between SPA™ proteins, both within tables and between tables, are also included.

[194] In addition, each table shows the presence or absence of carbohydrate, but specifically included are the reverse sequences; e.g. Table 1 is listed for an aglycosylated variant, but these same amino acid changes can be done on a glycosylated variant.

[195] Furthermore, each table lists the template structure used, as well as "floated" residues; for example, Table 2 used a PDA® run that floated C120, C132 and C134.

Table 1

Position	Considered Amino Acids	WT	Ground State	Sequences Around Ground State
328 A	Boundary	L	L	L:330 M:302 E:111 K:62 A:45 Q:39 D:36 S:30 T:28 N:10 R:7
332 A	Surface	I	R	R:247 K:209 Q:130 H:95 E:92 T:59 D:51 N:51 S:42 A:24
328 B	Boundary	L	L	L:321 M:237 T:166 K:73 R:72 S:55 Q:20 D:17 E:13 A:12 V:10 N:4
332 B	Surface	I	E	E:269 Q:180 R:145 K:111 D:97 T:78 N:65 S:28 A:14 H:13

PDA® technology, 1IIS template structure; - carbohydrate

Table 2

Position	Considered Amino Acids	WT	Ground State	Sequences Around Ground State
239 A	Surface	S	K	E:349 D:203 K:196 A:95 Q:83 S:63 N:10 R:1
265 A	Boundary XM	D	D	D:616 N:113 L:110 E:104 S:25 A:23 Q:9
299 A	Boundary XM	T	I	I:669 H:196 V:135
327 A	Boundary XM	A	S	A:518 S:389 N:67 D:26
265 B	Boundary XM	D	Q	Q:314 R:247 N:116 I:115 A:63 E:55 D:34 S:22 K:21 V:11

PDA® technology; 1IIS template structure; + carbohydrate; floated 120 C, 132 C, 134 C

Table 3

Position	Considered Amino Acids	WT	Ground State	Sequences Around Ground State
239 A	Surface	S	E	E:872 Q:69 D:39 K:16 A:4
265 A	Boundary XM	D	Y	Y:693 H:111 E:69 D:62 F:29 K:19 R:14 W:2 Q:1
267 A	Boundary XM	S	S	S:991 A:9
269 A	Core XM	E	F	F:938 E:59 Y:3
270 A	Surface	D	E	E:267 T:218 K:186 D:89 Q:88 R:46 S:34 N:29 H:23 A:20
299 A	Boundary XM	T	H	H:486 T:245 K:130 E:40 S:39 D:27 Q:27 A:4 N:2

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PDA® technology; 1IIS template structure; - carbohydrate; floated 120 C, 122 C, 132 C, 133 C, 134 C

Table 4

Position	Considered Amino Acids	WT	1	2	3	4	5	6	7	8	9	10
239 A	Surface	S	E	Q	Q	Q	E	E	E	Q	E	E
265 A	All 20	D	G	G	G	G	G	G	G	G	G	G
267 A	All 20	S	S	S	S	S	S	S	S	S	S	S
269 A	Core	E	Y	Y	A	A	V	Y	A	A	A	A
270 A	Surface	D	T	S	A	S	T	T	T	A	A	A
299 A	All 20	T	S	S	S	S	S	S	S	S	S	S

SPA™ technology; 1IIS template structure; + carbohydrate; floated 120 C, 122 C, 132 C, 133 C, 134 C

Table 5

Position	Considered Amino Acids	WT	Ground State	Sequences Around Ground State
236 A	Boundary XM	L	T	T:195 V:131 L:112 W:107 K:86 F:66 Y:56 E:52 Q:38 S:37 I:34 R:29 H:26 N:23 D:9
296 A	Surface	Y	N	N:322 D:181 R:172 K:76 Y:70 Q:59 E:48 S:40 H:20 T:11 A:1
298 A	Surface	S	T	T:370 R:343 K:193 A:55 S:39
235 B	Boundary XM	L	L	L:922 I:78

PDA® technology; 1IIS template structure; - carbohydrate; floated 119 C, 128 C, 157 C

Table 6

Position	Considered Amino Acids	WT	1	2	3	4	5	6	7	8	9	10
235 A	All 20	L	S	S	P	S	S	S	S	S	S	S
296 A	Surface	Y	Q	Q	Q	E	E	Q	E	Q	Q	N
298 A	Surface	S	S	K	K	K	K	S	S	S	K	S
235 B	All 20	L	K	K	K	L	L	L	L	L	L	K

SPA™ technology; 1IIS template structure; + carbohydrate; floated 119 C, 128 C, 157 C

Table 7

Position	Considered Amino Acids	WT	Ground State	Sequences Around Ground State
239 B	Surface	S	E	K:402 E:282 H:116 T:67 R:47 Q:39 D:26 A:11 S:7 N:3
265 B	Boundary XM	D	W	Y:341 W:283 I:236 V:77 F:36 H:9 T:7 E:4 K:4 A:2 D:1
327 B	Boundary XM	A	R	R:938 K: 86 H:35 E:12 T:10 Q:7 A:6 D:3 N:3
328 B	Core XM	L	L	L:1000
329 B	Core XM	P	P	P:801 A:199
330 B	Core XM	A	Y	Y:918 F:42 L:22 A:18
332 B	Surface	I	I	I:792 E:202 Q:5 K:1

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PDA® technology; 1IIS template structure; - carbohydrate; floated 88 C, 90 C, 113 C, 114 C, 116 C, 160 C, 161 C

Table 8

Position	Considered Amino Acids	WT	1	2	3	4	5	6	7	8	9	10
239 B	Surface	S	D	T	E	E	E	E	E	E	E	E
265 B	All 20	D	G	G	K	G	K	G	G	K	K	G
327 B	All 20	A	K	M	L	L	N	L	K	L	L	L
328 B	Core	L	M	M	M	L	A	M	L	M	L	L
329 B	Core	P	P	P	P	P	P	P	P	P	P	P
330 B	Core	A	L	A	A	A	A	A	A	A	A	A
332 B	Surface	I	I	Q	I	I	Q	Q	E	D	I	I

SPA™ technology; 1IIS template structure; + carbohydrate; floated 88 C, 90 C, 113 C, 114 C, 116 C, 160 C, 161 C

Table 9

Position	Considered Amino Acids	WT	1	2	3	4	5	6	7	8	9	10
239 A	Surface	S	Q	Q	Q	E	Q	E	Q	E	Q	Q
265 A	All 20	D	G	G	G	G	G	G	G	G	G	G
299 A	All 20	T	S	S	A	S	S	S	S	S	S	S
327 A	All 20	A	A	S	S	S	S	S	S	S	A	S
265 B	All 20	D	N	G	G	G	G	G	G	G	G	G

SPA™ technology; 1IIS template structure; - carbohydrate; floated 120 C, 132 C, 134 C

Table 10

Position	Considered Amino Acids	WT	Ground State	Sequences Around Ground State
234 A	Boundary XM	L	K	Y:401 L:260 F:151 I:82 K:63 H:17 Q:11 W:7 R:3 T:2 E:2 V:1
235 A	Boundary XM	L	L	W:777 L:200 K:12 Y:5 I:3 F:2 V:1
234 B	Boundary XM	L	W	W:427 Y:203 L:143 F:74 I:59 E:32 K:23 V:14 D:10 T:7 H:4 R:4
235 B	Boundary XM	L	W	W:380 Y:380 F:135 K:38 L:26 E:15 Q:12 H:8 R:4 T:2

PDA® technology; D129G 1E4K template structure; - carbohydrate; floated 113 C, 116 C, 132 C, 155 C, 157 C

Table 11

Position	Considered Amino Acids	WT	1	2	3	4	5	6	7	8	9	10
234 A	All 20	L	G	G	G	G	G	G	G	G	G	G
235 A	All 20	L	T	L	L	L	L	L	L	L	T	L
234 B	All 20	L	G	G	G	G	G	G	G	G	G	G
235 B	All 20	L	S	A	S	A	A	S	S	S	A	A

SPA™ technology; D129G 1E4K template structure; + carbohydrate; floated 113 C, 116 C, 132 C, 155 C, 157 C

Table 12

Position	Considered Amino Acids	WT	Ground State	Sequences Around Ground State
239 A	Boundary XM	S	E	E:235 S:122 D:94 Q:93 A:74 K:70 L:67 T:63 N:57 R:51 I:29 V:18 W:15 H:12
328 A	Boundary XM	L	L	L:688 E:121 K:43 Q:41 A:33 D:26 S:14 T:14 N:12 R:8
332 A	Boundary XM	I	W	I:155 W:96 L:82 K:79 E:74 Q:69 H:67 V:63 R:57 T:57 D:45 S:43 N:42 A:35 F:19 Y:18

PDA® technology; D129G 1IIS template structure; - carbohydrate; floated 120 C

Table 13

Position	Considered Amino Acids	WT	1	2	3	4	5	6	7	8	9	10
239 A	All 20	S	L	E	E	Q	E	E	K	K	K	K
328 A	All 20	L	L	Q	L	Q	K	L	L	Q	K	L
332 A	All 20	I	K	K	L	Q	A	K	L	Q	A	Q

SPA™ technology; D129G 1IIS template structure; + carbohydrate; floated 120 C

Table 14

Position	Considered Amino Acids	WT	Ground State	Sequences Around Ground State
239 B	Boundary XM	S	I	R:195 I:169 L:126 V:91 K:89 E:61 H:52 T:50 Q:42 N:35 S:34 D:30 A:26
328 B	Boundary XM	L	L	L:671 T:165 K:40 S:38 E:28 R:17 Q:17 V:11 A:8 D:5
332 B	Boundary XM	I	I	I:387 E:157 L:151 V:78 Q:63 K:50 R:33 T:29 D:25 A:12 N:8 S:6 W:1

PDA® technology; D129G 1IIS template structure; - carbohydrate; floated 90 C, 160 C, 161 C

Table 15

Position	Considered Amino Acids	WT	1	2	3	4	5	6	7	8	9	10
239 B	All 20	S	T	L	L	L	L	L	L	L	L	L
328 B	All 20	L	M	R	M	D	T	M	L	Q	D	L
332 B	All 20	I	I	D	Q	Q	Q	L	L	T	Q	L

SPA™ technology; D129G 1IIS template structure; + carbohydrate; floated 90 C, 160 C, 161 C

Table 16

Position	Considered Amino Acids	WT	Ground State	Sequences Around Ground State
239 B	Boundary XM	S	T	T:164 S:159 L:156 E:86 W:76 K:71 D:65 A:52 R:43 H:38 Q:38 N:31 I:14 V:7
328 B	Boundary XM	L	L	L:656 E:114 T:84 K:80 S:69 Q:36 A:31 D:15 R:11 N:4
332 B	Boundary XM	I	W	I:188 W:177 E:97 L:94 T:89 Q:57 V:54 K:52 F:51 D:34 H:33 S:27 R:26 N:18 A:17 Y:16

PDA® technology; D129G 1E4K template structure; - carbohydrate; floated 117 C

Table 17

Position	Considered Amino Acids	WT	1	2	3	4	5	6	7	8	9	10
239 S	All 20	S	P	S	P	E	L	L	L	L	L	L
328 S	All 20	L	K	K	K	K	K	L	K	K	K	L
332 S	All 20	I	S	S	E	L	L	L	E	L	L	L

SPA™ technology; D129G 1E4K template structure; + carbohydrate; floated 117 C

Table 18

Position	Considered Amino Acids	WT	Ground State	Sequences Around Ground State
239 A	Boundary XM	S	L	K:196 L:171 I:146 E:88 V:76 R:75 T:50 H:46 D:43 Q:39 S:30 N:22 A:19
328 A	Boundary XM	L	W	L:517 F:230 W:164 H:40 K:29 E:11 R:5 T:4
332 A	Boundary XM	I	E	I:283 L:217 E:178 Q:81 V:64 D:47 T:35 K:27 W:18 R:12 A:10 Y:7 N:7 F:6 S:5 H:3

PDA® technology; D129G 1E4K template structure; - carbohydrate; floated 87 C, 157 C, 158 C

Table 19

Position	Considered Amino Acids	WT	1	2	3	4	5	6	7	8	9	10
239 A	All 20	S	F	Q	E	T	P	P	T	P	P	P
328 A	All 20	L	K	R	R	K	K	M	R	K	M	R
332 A	All 20	I	L	L	I	I	E	I	E	E	I	I

SPA™ technology; D129G 1E4K template structure; + carbohydrate atoms; floated 87 C, 157 C, 158 C

Table 20

Position	Considered Amino Acids	WT	Ground State	Sequences Around Ground State
240 A	Core + Thr	V	V	V:698 M:162 T:140
263 A	Core + Thr	V	V	V:966 T:34
266 A	Core + Thr	V	V	V:983 T:17
325 A	Boundary	N	N	N:943 T:40 A:17
328 A	Boundary	L	L	L:610 M:363 K:27
332 A	Glu	I	E	E:1000

PDA® technology; D129G 1IIS template structure; - carbohydrate; floated 273 A, 275 A, 302 A, 323 A, 134 C

Table 21

Position	Considered Amino Acids	WT	1	2	3	4	5	6	7	8	9	10
240 A	All 20	V	V	A	V	V	V	V	V	V	V	V
263 A	All 20	V	V	V	V	V	V	V	V	V	V	V
266 A	All 20	V	I	V	I	I	T	V	V	V	V	I
325 A	All 20	N	A	N	N	N	Q	T	T	Q	N	T

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328 A	All 20	L	K	K	L	K	L	K	L	L	L	L
332 A	Glu	I	D	D	D	D	D	D	D	D	D	D

SPA™ technology; D129G 1IIS template structure; + carbohydrate; floated 273 A, 275 A, 302 A, 323 A, 134 C

Table 22

Position	Considered Amino Acids	WT	Ground State	Sequences Around Ground State
240 B	Core + Thr	V	V	V:713 T:287
263 B	Core + Thr	V	V	V:992 T:8
266 B	Core + Thr	V	V	V:976 T:24
325 B	Boundary	N	N	N:453 T:296 A:116 D:96 S:30 V:9
328 B	Boundary	L	L	L:623 M:194 T:100 R:72 K:11
332 B	Glu	I	E	E:1000

PDA® technology; D129G 1IIS template structure; - carbohydrate; floated 273 B, 275 B, 302 B, 323 B, 161 C

Table 23

Position	Considered Amino Acids	WT	1	2	3	4	5	6	7	8	9	10
240 B	All 20	V	A	T	A	T	T	A	A	T	T	T
263 B	All 20	V	V	A	A	T	T	V	V	T	A	T
266 B	All 20	V	V	V	V	V	V	V	V	V	I	V
325 B	All 20	N	N	K	K	N	K	K	N	N	N	N
328 B	All 20	L	R	L	L	L	L	L	L	L	L	L
332 A	Glu	I	D	D	D	D	D	D	D	D	D	D

SPA™ technology; D129G 1IIS template structure; + carbohydrate; floated 273 B, 275 B, 302 B, 323 B, 161 C

Table 24

Position	Considered Amino Acids	WT	Ground State	Sequences Around Ground State
240 B	Core + Thr	V	M	V:715 M:271 T:12 I:2
263 B	Core + Thr	V	V	V:992 T:8
266 B	Core + Thr	V	V	V:996 T:4
325 B	Boundary	N	N	N:651 T:232 D:64 A:53
328 B	Boundary	L	M	M:566 L:407 K:37
332 B	Glu	I	E	E:1000

PDA® technology; D129G 1E4K template structure; - carbohydrate; floated 273 B, 275 B, 302 B, 323 B, 131 C

Table 25

Position	Considered Amino Acids	WT	1	2	3	4	5	6	7	8	9	10
240 B	All 20	V	T	A	T	A	A	A	A	T	A	A
263 B	All 20	V	T	W	T	T	A	T	T	T	L	L
266 B	All 20	V	L	A	T	T	V	L	T	T	L	V
325 B	All 20	N	A	N	A	A	N	A	A	A	A	A
328 B	All 20	L	L	K	L	L	L	L	L	L	L	L

332 A	Glu	I	D	D	D	D	D	D	D	D	D	D

SPA™ technology; D129G 1E4K template structure; + carbohydrate; floated 273 B, 275 B, 302 B, 323 B, 131 C

Table 26

Position	Considered Amino Acids	WT	Ground State	Sequences Around Ground State
240 A	Core + Thr	V	V	V:876 T:109 M:15
263 A	Core + Thr	V	V	V:913 T:87
266 A	Core + Thr	V	V	V:969 T:31
325 A	Boundary	N	V	V:491 N:236 T:187 A:35 D:32 S:19
328 A	Boundary	L	L	L:321 W:290 M:271 F:49 K:46 R:23
332 A	Glu	I	E	E:1000

PDA® technology; D129G 1E4K template structure; - carbohydrate; floated 273 A, 275 A, 302 A, 323 A, 158 C

Table 27

Position	Considered Amino Acids	WT	1	2	3	4	5	6	7	8	9	10
240 A	All 20	V	A	T	A	A	T	T	A	A	A	T
263 A	All 20	V	T	T	V	V	T	V	L	L	V	T
266 A	All 20	V	V	V	V	V	V	V	V	V	V	V
325 A	All 20	N	Q	N	Q	Q	Q	Q	Q	Q	N	N
328 A	All 20	L	K	M	K	K	K	K	K	K	K	K
332 A	Glu	I	D	D	D	D	D	D	D	D	D	D

SPA™ technology; D129G 1E4K template structure; + carbohydrate; floated 273 A, 275 A, 302 A, 323 A, 158 C

[196] Computational screening calculations were aimed at designing Fc variants to optimize the conformation of the N297 carbohydrate and the Cγ2 domain. By exploring energetically favorable substitutions at positions that interact with carbohydrate, variants can be engineered that sample new, potentially favorable carbohydrate conformations. Fc residues F241, F243, V262, and V264 mediate the Fc/carbohydrate interaction and thus are target positions. The results of these design calculations are presented in Table 28.

Table 28

Position	Considered Amino Acids	WT	Ground State	Sequences Around Ground State
241 A	Core	F	Y	Y:172 M:162 L:144 F:140 W:110 I:97 A:91 V:84
243 A	Core	F	Y	Y:211 L:204 W:199 F:160 M:141 A:85
262 A	Core	V	M	M:302 I:253 V:243 A:202
264 A	Core	V	F	I:159 M:152 V:142 L:140 W:136 F:120 Y:104 A:47

PDA® technology; 1IIS template structure; - carbohydrate

[197] Computational screening calculations were aimed at designing Fc variants to optimize the angle between the Cγ3 and Cγ2 domains. Residues P244, P245, P247, and W313, which reside at the Cγ2/Cγ3 interface, appear to play a key role in determining the Cγ2-Cγ3 angle and the flexibility of the domains relative to one another. By exploring energetically favorable substitutions at these positions, variants can be designed that sample new, potentially favorable angles and levels of flexibility. The results of these design calculations are presented in Table 29.

Table 29

Position	Considered Amino Acids	WT	Ground State	Sequences Around Ground State
244 A	Boundary	P	H	K:164 H:152 R:110 M:100 S:92 N:57 A:54 D:50 Q:49 T:46 E:37 V:30 L:27 W:23 F:9
245 A	Boundary	P	A	A:491 S:378 N:131
247 A	Boundary	P	V	V:156 T:125 K:101 E:87 Q:79 R:78 S:76 A:72 D:72 H:60 M:47 N:47
313 A	Boundary	W	W	W:359 F:255 Y:128 M:114 H:48 K:29 T:24 A:11 E:10 V:10 S:9 Q:3

PDA® technology; 1IIS template structure; - carbohydrate

[198] In addition to the above calculations using PDA® and SPA™ computational screening methods, additional calculations using solely an electrostatic potential were used to computationally screen Fc variants. Calculations with Coulomb's law and Debye-Huckel scaling highlighted a number of positions in the Fc for which amino acid substitutions would favorably affect binding to one or more FcγRs, including positions for which replacement of a neutral amino acid with a negatively charged amino acid may enhance binding to FcγRIIIa, and for which replacement of a positively charged amino acid with a neutral or negatively charged amino acid may enhance binding to FcγRIIIa. These results are presented in Table 30.

Table 30

Replacement of a + residue with a - residue	Replacement of a neutral residue with a - residue
H268	S239
K326	Y296
K334	A327
	I332

Coulomb's law and Debye-Huckel scaling; 1IIS template structure; + carbohydrate

[199] Computational screening calculations were carried out to optimize aglycosylated Fc, that is to optimize Fc structure, stability, solubility, and Fc/FcγR affinity in the absence of the N297 carbohydrate. Design calculations were aimed at designing favorable substitutions in the context of

the aglycosylated Fc template structure at residue 297, residues proximal to it, residues at the Fc/FcγR interface, and residues at the Fc/carbohydrate interface. Variable positions were grouped in different sets of interacting variable positions and designed in separate sets of calculations, and various template structures were used. For many of the variable position sets, calculations were carried out using both the PDA® and SPA™ computational screening methods. The results of these calculations and relevant information are presented in Tables 31 - 53 below.

Table 31

Position	Considered Amino Acids	WT	Ground State	Sequences Around Ground State
265 A	Boundary XM	D	Y	Y:531 F:226 W:105 H:62 K:21 D:16 E:6 T:3
297 A	Boundary XM	N	D	A:235 S:229 D:166 E:114 N:92 Y:57 F:55 Q:25 H:10 T:7 K:6 L:3 R:1
299 A	Boundary XM	T	L	L:482 Y:186 F:131 T:55 S:51 K:31 H:22 A:18 E:14 Q:10
297 B	Boundary XM	N	I	I:299 K:147 V:85 R:82 W:71 N:65 D:35 E:35 Q:34 S:32 L:31 H:30 T:28 A:26

PDA® technology; 1IIS template structure; - carbohydrate; floated 122 C, 129 C, 132 C, 155 C

Table 32

Position	Considered Amino Acids	WT	1	2	3	4	5	6	7	8	9	10
265 A	All 20	D	G	G	G	G	G	G	G	G	G	G
297 A	All 20	N	A	T	A	E	K	K	A	A	N	N
299 A	All 20	T	S	K	S	K	F	F	F	F	F	S
297 B	All 20	N	K	K	K	K	K	K	K	K	K	K

SPA™ technology; 1IIS template structure; - carbohydrate; floated 122 C, 129 C, 132 C, 155 C

Table 33

Position	Considered Amino Acids	WT	Ground State	Sequences Around Ground State
239 A	Surface	S	E	E:928 Q:65 D:7
265 A	Boundary XM	D	W	W:709 Y:248 F:43
296 A	Surface	Y	H	H:449 Y:146 E:137 D:89 K:64 N:32 T:30 R:25 Q:23 S:5
297 A	Surface	N	E	E:471 H:189 D:102 T:97 K:96 R:22 Q:15 S:8
298 A	Boundary XM	S	R	R:353 T:275 K:269 A:58 S:38 E:5 Q:2 H:2
299 A	Boundary XM	T	F	Y:395 F:366 L:217 H:15 K:4

PDA® technology; D129G 1IIS template structure; - carbohydrate; floated 120 C, 122 C, 128 C, 132 C, 155 C

Table 34

Position	Considered Amino Acids	WT	1	2	3	4	5	6	7	8	9	10
239 A	All 20	S	E	Q	Q	E	Q	Q	Q	Q	Q	Q
265 A	All 20	D	G	G	G	G	G	G	G	G	G	G
296 A	All 20	Y	D	Q	N	N	Q	N	N	N	Q	N

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297 A	All 20	N	A	A	N	A	D	D	E	N	N	E
298 A	All 20	S	K	K	K	S	K	K	K	K	S	K
299 A	All 20	T	S	Y	F	S	Y	F	K	F	S	K

SPA™ technology; D129G 1IIS template structure; - carbohydrate; floated 120 C, 122 C, 128 C, 132 C, 155 C

Table 35

Position	Considered Amino Acids	WT	Ground State	Sequences Around Ground State
239 B	Surface	S	E	E:417 T:122 D:117 Q:94 R:84 S:63 K:47 H:29 N:19 A:8
265 B	Boundary XM	D	W	W:865 Y:79 F:55 K:1
296 B	Surface	Y	Y	Y:549 H:97 D:80 S:75 N:48 E:45 K:32 R:30 Q:28 A:16
297 B	Surface	N	R	R:265 H:224 E:157 K:154 Q:75 D:47 T:34 N:24 S:13 A:7
298 B	Boundary XM	S	V	V:966 D:10 T:8 A:8 N:4 S:4
299 B	Boundary XM	T	Y	Y:667 F:330 H:3

PDA® technology; D129G 1E4K template structure; - carbohydrate; floated 117 C, 119 C, 125 C, 129 C, 152 C

Table 36

Position	Considered Amino Acids	WT	1	2	3	4	5	6	7	8	9	10
239 B	All 20	S	S	R	E	K	S	S	E	E	E	K
265 B	All 20	D	A	D	K	Y	A	A	F	F	K	Y
296 B	All 20	Y	A	A	A	A	A	A	A	A	A	A
297 B	All 20	N	T	S	T	T	E	E	E	S	E	E
298 B	All 20	S	G	G	G	G	G	G	G	G	G	G
299 B	All 20	T	L	F	E	E	Y	F	Y	F	Y	Y

SPA™ technology; D129G 1E4K template structure; - carbohydrate; floated 117 C, 119 C, 125 C, 129 C, 152 C

Table 37

Position	Considered Amino Acids	WT	Ground State	Sequences Around Ground State
239 A	Surface	S	E	E:868 Q:92 D:38 K:1 N:1
265 A	Boundary XM	D	W	W:575 Y:343 F:66 H:15 K:1
296 A	Surface	Y	H	H:489 Y:103 R:98 K:97 Q:64 D:63 T:41 N:38 E:7
297 A	Asp	N	D	D:1000
298 A	Boundary XM	S	R	R:340 K:262 T:255 A:59 S:57 E:11 Q:10 H:6
299 A	Boundary XM	T	F	Y:375 F:323 L:260 H:24 K:18

PDA® technology; D129G 1IIS template structure; - carbohydrate; floated 120 C, 122 C, 128 C, 132 C, 155 C

Table 38

Position	Considered Amino Acids	WT	1	2	3	4	5	6	7	8	9	10
239 A	All 20	S	E	Q	E	E	E	E	E	E	Q	E

265 A	All 20	D	G	G	G	G	G	G	G	G	G	G
296 A	All 20	Y	E	N	Q	E	N	Q	Q	Q	Q	N
297 A	Asp	N	D	D	D	D	D	D	D	D	D	D
298 A	All 20	S	K	S	K	S	K	K	K	S	K	K
299 A	All 20	T	S	K	Y	S	F	F	F	F	F	K

SPA™ technology; D129G 1IIS template structure; - carbohydrate; floated 120 C, 122 C, 128 C, 132 C, 155 C

Table 39

Position	Considered Amino Acids	WT	Ground State	Sequences Around Ground State
239 B	Surface	S	E	E:318 Q:123 T:109 D:108 R:93 S:89 K:69 N:40 H:38 A:13
265 B	Boundary XM	D	W	W:745 Y:158 F:85 K:9 E:1 R:1 H:1
296 B	Surface	Y	Y	Y:390 H:127 S:83 R:81 K:78 N:65 D:55 E:49 Q:44 A:28 T:2
297 B	Asp	N	D	D:1000
298 B	Boundary XM	S	V	V:890 T:35 A:29 D:19 S:16 N:10 E:1
299 B	Boundary XM	T	Y	Y:627 F:363 H:10

PDA® technology; D129G 1E4K template structure; - carbohydrate; floated 117 C, 119 C, 125 C, 129 C, 152 C

Table 40

Position	Considered Amino Acids	WT	1	2	3	4	5	6	7	8	9	10
239 B	All 20	S	K	E	E	Q	E	K	Q	E	K	Q
265 B	All 20	D	F	K	K	A	K	Y	W	K	L	F
296 B	All 20	Y	A	A	A	A	A	A	A	A	A	A
297 B	Asp	N	D	D	D	D	D	D	D	D	D	D
298 B	All 20	S	G	G	G	G	G	G	G	G	G	G
299 B	All 20	T	Y	Y	Y	Y	Y	Y	F	F	Y	Y

SPA™ technology; D129G 1E4K template structure; - carbohydrate; floated 117 C, 119 C, 125 C, 129 C, 152 C

Table 41

Position	Considered Amino Acids	WT	Ground State	Sequences Around Ground State
239 A	Boundary XM	S	E	E:312 L:148 D:102 Q:98 K:64 I:61 S:57 A:44 T:39 N:29 R:23 V:18 W:5
265 A	Boundary XM	D	W	W:363 Y:352 F:139 H:77 K:39 R:14 D:11 E:4 Q:1
297 A	Asp	N	D	D:1000
299 A	Boundary XM	T	Y	Y:309 F:224 L:212 H:96 K:92 E:28 Q:20 R:16 T:2 S:1

PDA® technology; D129G 1IIS template structure; - carbohydrate; floated 120 C, 122 C, 132 C, 155 C

Table 42

Position	Considered	WT	1	2	3	4	5	6	7	8	9	10

	Amino Acids											
239 A	All 20	S	E	L	L	L	E	E	E	Q	L	E
265 A	All 20	D	G	G	G	G	G	G	G	G	G	G
297 B	Asp	N	D	D	D	D	D	D	D	D	D	D
299 A	All 20	T	S	K	K	F	F	F	K	F	K	F

SPA™ technology; D129G 1IIS template structure; - carbohydrate; floated 120 C, 122 C, 132 C, 155 C

Table 43

Position	Considered Amino Acids	WT	Ground State	Sequences Around Ground State
239 B	Boundary XM	S	L	L:194 T:122 S:120 E:111 D:79 K:71 A:62 Q:57 R:43 H:43 N:37 I:24 W:24 V:13
265 B	Boundary XM	D	W	Y:248 W:233 F:198 K:84 D:57 E:55 H:42 R:28 Q:20 A:10 T:10 N:8 S:7
297 B	Asp	N	D	D:1000
299 B	Boundary XM	T	Y	Y:483 F:380 H:76 T:31 E:10 D:4 A:3 S:3

PDA® technology; D129G 1E4K template structure; - carbohydrate; floated 117 C, 119 C, 129 C, 152 C

Table 44

Position	Considered Amino Acids	WT	1	2	3	4	5	6	7	8	9	10
239 B	All 20	S	R	E	P	L	L	F	P	P	L	L
265 B	All 20	D	D	K	S	F	S	Y	A	M	A	D
297 B	Asp	N	D	D	D	D	D	D	D	D	D	D
299 B	All 20	T	Y	Y	Y	Y	E	Y	Y	Y	Y	Y

SPA™ technology; D129G 1E4K template structure; - carbohydrate; floated 117 C, 119 C, 129 C, 152 C

Table 45

Position	Considered Amino Acids	WT	Ground State	Sequences Around Ground State
239 A	Boundary XM	S	E	E:251 L:125 D:120 Q:112 S:73 K:65 I:61 A:58 T:45 N:35 R:28 V:23 W:4
265 A	Boundary XM	D	Y	Y:216 H:153 K:135 D:109 W:104 F:86 R:54 T:38 E:29 Q:22 A:21 N:17 S:13 L:3
297 A	Asp	N	D	D:1000

PDA® technology; D129G 1IIS template structure; - carbohydrate; floated 299 A, 120 C, 122 C, 132 C, 155 C

Table 46

Position	Considered Amino Acids	WT	1	2	3	4	5	6	7	8	9	10
239 A	All 20	S	S	L	E	L	Q	Q	E	Q	Q	E
265 A	All 20	D	G	G	G	G	G	G	G	G	G	G
297 A	Asp	N	D	D	D	D	D	D	D	D	D	D

SPA™ technology; D129G 1IIS template structure; - carbohydrate; floated 299 A, 120 C, 122 C, 132 C, 155 C

Table 47

Position	Considered Amino Acids	WT	Ground State	Sequences Around Ground State
239 B	Boundary XM	S	L	L:158 S:137 T:125 E:116 D:86 K:75 A:62 Q:56 H:43 R:39 N:35 W:30 I:24 V:15
265 B	Boundary XM	D	Y	Y:188 W:159 F:156 D:122 K:77 E:71 H:61 Q:44 R:39 A:24 S:22 N:19 T:18
297 B	Asp	N	D	D:1000

PDA® technology; D129G 1E4K template structure; - carbohydrate; floated 299 B, 117 C, 119 C, 129 C, 152 C

Table 48

Position	Considered Amino Acids	WT	1	2	3	4	5	6	7	8	9	10
239 B	All 20	S	S	E	P	P	E	S	P	L	F	L
265 B	All 20	D	A	K	A	M	K	F	Y	D	F	F
297 B	Asp	N	D	D	D	D	D	D	D	D	D	D

SPA™ technology; D129G 1E4K template structure; - carbohydrate; floated 299 B, 117 C, 119 C, 129 C, 152 C

Table 49

Position	Considered Amino Acids	WT	Ground State	Sequences Around Ground State
297 A	Asp	N	D	D:1000
299 A	Boundary XM	T	Y	T:123 Y:64 H:64 K:64 Q:64 F:64 R:63 D:63 E:63 S:63 L:63 N:62 I:57 A:54 V:62 W:17

PDA® technology; D129G 1IIS template structure; - carbohydrate; floated 239 A, 265 A, 120 C, 122 C, 132 C, 155 C

Table 50

Position	Considered Amino Acids	WT	1	2	3	4	5	6	7	8	9	10
297 A	Asp	N	D	D	D	D	D	D	D	D	D	D
299 A	All 20	T	K	K	K	K	F	F	K	K	K	K

SPA™ technology; D129G 1IIS template structure; - carbohydrate; floated 239 A, 265 A, 120 C, 122 C, 132 C, 155 C

Table 51

Position	Considered Amino Acids	WT	Ground State	Sequences Around Ground State
297 B	Asp	N	D	D:1000
299 B	Boundary XM	T	Y	T:123 F:64 Y:64 H:64 S:63 N:61 Q:61 D:61 E:60 K:58 V:57 A:57 R:54 I:52 L:51 W:50

PDA® technology; D129G 1E4K template structure; - carbohydrate; floated 239 B, 265 B, 117 C, 119 C, 129 C, 152 C

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Table 52

Position	Considered Amino Acids	WT	1	2	3	4	5	6	7	8	9	10
297 B	Asp	N	D	D	D	D	D	D	D	D	D	D
299 B	All 20	T	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y

SPA™ technology; D129G 1E4K template structure; - carbohydrate; floated 239 B, 265 B, 117 C, 119 C, 129 C, 152 C

[200] Computational screening calculations were carried out to optimize aglycosylated Fc by designing favorable substitutions at residues that are exposed to solvent in the absence of glycosylation such that they are stable, maintain Fc structure, and have no tendency to aggregate. The N297 carbohydrate covers up the exposed hydrophobic patch that would normally be the interface for a protein-protein interaction with another Ig domain, maintaining the stability and structural integrity of Fc and keeping the Cγ2 domains from aggregating across the central axis. Key residues for design are F241, F243, V262, and V264, which reside behind the carbohydrate on Cγ2, in addition to residues such as L328, I332, and I336, which are exposed nonpolar residues facing inward towards the opposed Cγ2 domain, that were considered in previously presented calculations. The importance of these Cγ2 residues is supported by noting that the corresponding residues in the Cγ3 domain by sequence alignment either mediate the nonpolar interaction between the two Cγ3 domains or are buried in the Cγ3 core. The results of these design calculations are presented in Table 53.

Table 53

Position	Considered Amino Acids	WT	Ground State	Sequences Around Ground State
241 A	Surface	F	E	E:190 R:172 K:138 H:117 T:93 Q:91 D:85 S:49 N:49 A:16
243 A	Surface	F	R	R:190 H:164 Q:152 E:149 K:92 T:71 D:64 N:58 S:42 A:18
262 A	Surface	V	D	D:416 E:164 N:138 Q:87 T:83 R:44 S:32 K:24 A:11 H:1
264 A	Surface	V	H	R:368 H:196 K:147 E:108 Q:66 T:34 N:33 D:25 S:15 A:6

PDA® technology; 1IIS template structure; - carbohydrate

[201] In a final set of calculations, a SPA™ computational screening method was applied to evaluate the replacement of all chosen variable positions with all 20 amino acids. The lowest energy rotamer conformation for all 20 amino acids was determined, and this energy was defined as the energy of substitution for that amino acid at that variable position. These calculations thus provided an energy of substitution for each of the 20 amino acids at each variable position. These data were

useful for a variety of design goals aimed at both glycosylated and aglycosylated Fc, including optimization of Fc/FcγR affinity, Fc stability, Fc solubility, carbohydrate conformation, and hinge conformation. Furthermore, because these calculations provide energies for both favorable and unfavorable substitutions, they guide substitutions that may enable differential binding to activating versus inhibitory FcγRs. Various template structures were used, and calculations explored substitutions on both chains. The results of these calculations and relevant parameters and information are presented in Tables 54 - 59 below. Column 1 lists the variable positions on chain A and B of the 1IIS template structure. Column 2 lists the wild-type amino acid identity at each variable position. The remaining 20 columns provide the energy for each of the natural 20 amino acids (shown in the top row). All substitutions were normalized with respect to the lowest energy substitution, which was set to 0 energy. For example in Table 54, for L235 on chain A, serine is the lowest energy substitution, and L235A is 0.9 kcal/mol less stable than L235S. Extremely high energies were set to 20 kcal/mol for energies between 20 – 50 kcal/mol, and 50 kcal/mold for energies greater than 50 kcal/mol. Favorable substitutions may be considered to be the lowest energy substitution for each position, and substitutions that have small energy differences from the lowest energy substitution, for example substitutions within 1-2, 1-3, 1-5, or 1-10 kcal/mol.

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Table 54

Pos	WT	A	C	D	E	F	G	H	I	K	L	M	N	P	Q	R	S	T	V	W	Y
235 A	L	0.9	2.8	2.8	1.5	3.2	3.2	3.4	4.9	1.6	2.1	3.2	0.9	0.3	1.3	0.7	0.0	1.7	4.3	6.5	3.2
236 A	G	0.0	1.9	5.1	6.7	10.0	2.3	4.3	17.2	5.7	20.0	4.6	3.2	12.6	5.6	6.1	0.6	6.2	12.0	6.7	20.0
237 A	G	20.0	20.0	20.0	50.0	50.0	0.0	50.0	50.0	20.0	50.0	20.0	20.0	50.0	50.0	50.0	20.0	20.0	50.0	50.0	50.0
239 A	S	0.2	4.3	2.6	0.0	12.8	4.5	6.9	11.3	1.7	0.1	2.1	1.7	7.9	1.2	2.6	0.3	5.7	11.0	20.0	20.0
265 A	D	9.0	8.1	6.3	7.8	5.1	0.0	7.3	50.0	8.2	9.9	7.7	6.0	50.0	9.0	8.5	7.8	20.0	50.0	30.0	5.8
267 A	S	2.1	3.3	7.3	1.4	50.0	7.3	20.0	20.0	0.9	2.2	5.0	4.8	0.0	2.2	3.1	2.9	20.0	20.0	50.0	50.0
269 A	E	0.5	2.1	1.3	0.6	1.6	3.9	2.0	1.2	1.1	1.3	2.7	0.0	50.0	0.6	1.1	0.3	0.8	1.0	5.6	1.2
270 A	D	0.3	2.8	2.3	2.0	4.0	4.0	3.4	2.4	1.2	0.0	2.3	2.1	20.0	2.0	2.3	1.4	1.8	4.2	5.4	6.0
296 A	Y	2.7	2.0	1.4	0.0	50.0	0.0	50.0	4.6	2.1	2.4	3.3	1.2	50.0	0.2	1.5	1.3	4.6	4.4	16.3	18.2
298 A	S	0.7	2.4	6.7	3.4	20.0	3.9	20.0	6.7	0.0	4.1	1.4	4.1	50.0	1.8	1.1	0.2	2.2	6.3	17.8	20.0
299 A	T	0.6	2.8	11.5	10.1	20.0	6.1	20.0	10.7	7.1	20.0	4.3	6.8	50.0	6.3	12.0	0.0	3.0	7.1	14.8	20.0
234 B	L	2.1	3.2	4.1	4.2	1.6	5.3	0.1	0.7	0.6	1.0	2.0	1.7	50.0	2.8	0.3	2.3	1.7	2.6	13.0	0.0
235 B	L	0.8	2.3	2.5	0.7	5.4	4.8	1.4	3.6	0.1	0.0	2.0	1.7	16.6	0.5	1.2	0.7	0.7	5.3	6.8	5.5
236 B	G	3.1	1.3	4.4	8.2	5.2	0.0	1.9	20.0	3.1	20.0	4.1	2.7	50.0	3.7	16.0	1.2	20.0	20.0	20.0	11.3
237 B	G	20.0	50.0	50.0	50.0	50.0	0.0	50.0	50.0	50.0	50.0	50.0	50.0	50.0	50.0	50.0	50.0	50.0	50.0	50.0	50.0
239 B	S	0.9	2.4	3.4	1.8	5.4	5.6	2.7	3.0	0.9	0.0	2.0	1.6	50.0	1.8	1.8	1.4	1.4	5.1	20.0	5.3
265 B	D	4.5	5.1	4.6	4.6	4.9	0.0	3.8	9.0	2.0	2.5	4.1	2.1	50.0	4.5	5.1	4.4	5.9	9.2	11.4	5.8
327 B	A	1.8	3.4	4.7	3.9	20.	7.0	20.	20.	0.8	0.0	1.9	1.5	20.	3.0	2.6	3.2	20.	20.	20.	20.

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328 B	L	3.7	3.6	4.0	3.7	50.0	8.4	6.8	50.0	3.8	0.0	2.1	4.1	50.0	3.6	8.1	4.9	3.0	12.5	50.0	50.0
329 B	P	3.4	8.6	20.0	20.0	50.0	8.0	16.8	50.0	20.0	20.0	16.9	20.0	0.0	20.0	20.0	1.3	17.1	16.5	50.0	50.0
330 B	A	0.5	2.0	2.6	0.5	2.4	3.8	1.4	4.2	0.0	2.0	2.2	0.8	20.0	0.1	0.6	0.9	0.3	5.1	6.0	2.7
332 B	I	1.5	2.7	1.2	1.6	11.9	6.8	12.9	1.2	2.9	0.0	1.4	1.7	50.0	1.3	4.9	1.8	1.7	3.0	20.0	20.0

SPA™ technology; 1IIS template structure; + carbohydrate atoms, no floated positions

Table 55

Pos	WT	A	C	D	E	F	G	H	I	K	L	M	N	P	Q	R	S	T	V	W	Y
235 A	L	0.9	2.8	2.6	1.7	3.3	3.3	3.4	5.0	1.6	2.1	3.3	1.0	0.3	1.4	1.8	0.0	1.9	3.6	6.6	3.3
236 A	G	0.0	1.7	5.2	6.0	11.3	2.3	4.4	17.2	5.8	19.0	4.9	3.3	8.2	5.6	6.0	0.8	5.6	11.8	6.6	20.0
237 A	G	20.0	20.0	20.0	50.0	50.0	0.0	50.0	50.0	20.0	50.0	20.0	20.0	50.0	50.0	50.0	20.0	20.0	50.0	50.0	50.0
238 A	P	8.6	8.0	10.5	13.4	6.4	0.0	5.0	50.0	12.4	11.3	9.7	9.3	3.2	12.4	20.0	8.6	50.0	50.0	20.0	8.4
239 A	S	0.1	4.2	2.5	0.0	20.0	4.5	9.0	10.8	1.8	0.2	2.1	1.8	9.1	1.3	2.5	0.3	5.7	10.7	20.0	19.7
240 A	V	1.3	2.4	2.3	6.3	20.0	7.2	20.0	5.1	10.8	6.2	5.7	2.0	1.1	9.5	13.1	2.5	0.5	0.0	20.0	20.0
241 A	F	0.1	1.6	1.2	0.3	0.2	4.1	1.2	10.0	1.3	0.1	2.1	0.4	14.7	0.5	1.1	0.1	0.0	8.3	3.6	0.4
242 A	L	3.0	3.4	5.5	8.3	14.4	8.5	11.1	3.3	13.9	2.2	2.7	5.5	0.9	7.9	17.1	3.8	2.3	0.0	20.0	17.5
243 A	F	1.6	2.2	2.7	0.2	1.4	5.6	2.5	0.0	2.2	2.0	3.0	2.3	10.2	0.5	1.6	1.3	0.9	1.2	5.3	1.6
244 A	P	1.2	1.8	3.8	0.8	10.2	3.8	4.6	20.0	0.2	2.9	2.0	2.8	2.0	0.9	1.7	0.0	19.3	20.0	7.6	12.2
245 A	P	3.9	20.0	20.0	20.0	20.0	9.1	20.0	20.0	20.0	20.0	20.0	20.0	0.0	20.0	20.0	8.0	20.0	50.0	20.0	20.0
246 A	K	1.3	2.7	2.0	2.0	2.9	5.7	2.9	1.4	1.4	1.5	3.1	0.2	0.0	1.2	1.5	1.7	1.4	1.2	5.4	3.0
247 A	P	1.2	2.1	0.3	0.7	4.0	3.9	3.7	1.8	1.6	1.7	3.3	0.0	0.5	0.9	1.5	0.7	1.1	1.3	6.9	3.7
248 A	K	0.9	2.7	1.5	0.8	3.1	4.7	3.4	3.3	2.0	1.9	2.6	1.2	3.6	1.5	2.3	0.7	0.0	2.5	5.6	2.7
249 A	D	1.2	3.7	1.6	0.0	20.0	7.3	19.7	50.0	1.7	20.0	2.2	1.4	20.0	1.5	3.4	2.5	18.3	50.0	20.0	20.0
250 A	T	0.0	1.8	3.8	5.8	50.0	6.0	20.0	4.5	6.3	6.3	0.3	3.2	50.0	8.7	9.3	1.8	1.3	1.9	20.0	50.0
251 A	L	1.1	1.9	1.2	0.5	5.8	5.1	1.9	5.6	0.9	0.7	2.4	1.4	50.0	0.0	1.4	0.5	0.8	6.9	8.9	5.8
252	M	0.3	1.2	0.6	0.0	3.0	3.8	3.4	3.9	1.0	0.3	2.2	0.3	17.	0.1	1.1	0.1	0.2	4.6	4.2	3.3

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253 A	I	0.7	1.7	1.1	0.2	1.8	3.5	2.2	2.0	0.3	1.2	0.8	0.8	0.3	0.0	1.1	0.3	0.5	2.8	2.4	1.9
254 A	S	0.7	1.7	0.4	0.7	2.2	3.6	2.0	0.3	1.2	1.9	2.4	0.0	20.0	0.3	1.2	0.3	0.8	0.7	3.8	1.9
255 A	R	1.4	2.8	2.4	2.5	0.2	5.4	1.1	17.0	1.0	2.2	1.5	1.7	50.0	2.1	0.0	2.3	50.0	17.2	4.0	0.5
256 A	T	0.6	1.8	1.2	1.1	2.7	3.4	2.1	1.4	0.7	1.5	2.4	0.0	0.4	0.1	0.2	0.4	0.9	1.2	5.6	2.7
257 A	P	0.9	7.8	20.0	12.9	50.0	6.2	50.0	20.0	12.3	12.6	14.4	20.0	0.1	13.1	30.0	2.9	16.0	30.0	50.0	50.0
258 A	E	0.0	1.6	4.8	3.6	1.0	4.3	2.2	14.8	4.4	6.2	3.2	2.9	10.4	7.4	6.0	1.0	6.2	17.6	20.0	1.9
259 A	V	3.9	4.3	5.1	8.7	20.0	10.3	6.8	2.3	9.6	2.8	6.2	4.1	50.0	9.2	20.0	5.2	2.1	0.0	20.0	20.0
260 A	T	1.7	2.3	3.3	1.1	20.0	6.6	8.6	0.0	0.2	1.8	2.8	1.8	1.1	0.8	0.9	1.7	0.4	1.9	7.1	20.0
261 A	C	0.0	20.0	20.0	20.0	20.0	3.9	20.0	20.0	20.0	20.0	20.0	20.0	50.0	20.0	20.0	3.6	20.0	20.0	20.0	20.0
262 A	V	1.9	3.2	0.0	3.3	20.0	7.2	20.0	8.3	2.9	2.9	2.2	0.6	50.0	3.8	5.2	3.4	3.0	1.7	20.0	20.0
263 A	V	2.2	2.7	6.0	17.4	20.0	8.8	20.0	10.0	7.1	7.8	16.9	5.2	50.0	19.8	17.7	2.8	1.4	0.0	20.0	20.0
264 A	V	1.9	3.3	2.8	2.2	0.0	6.4	2.1	0.7	2.6	0.9	2.7	2.1	2.3	2.6	2.7	2.2	1.1	0.6	3.9	0.1
265 A	D	9.0	8.1	5.9	8.6	5.3	0.0	7.3	50.0	7.9	9.7	7.5	5.5	50.0	10.2	8.5	7.9	20.0	50.0	20.0	5.7
266 A	V	4.9	5.3	7.1	12.1	20.0	11.2	20.0	0.4	12.2	20.0	8.8	7.1	50.0	12.2	20.0	6.1	3.8	0.0	20.0	20.0
267 A	S	2.3	3.5	7.2	1.3	50.0	7.4	20.0	20.0	0.7	1.4	3.9	4.7	0.0	2.3	3.1	3.0	20.0	20.0	50.0	50.0
268 A	H	1.2	1.9	2.2	1.5	3.7	5.0	4.9	0.4	0.5	3.7	2.7	1.7	0.0	1.4	1.7	1.1	0.2	0.9	5.1	3.7
269 A	E	0.3	1.9	1.3	0.5	1.3	3.7	1.9	1.1	0.8	1.2	2.5	0.0	50.0	0.6	0.8	0.2	0.6	0.7	4.0	1.0
270 A	D	0.2	2.6	2.1	1.9	5.2	3.9	3.1	2.1	1.2	0.0	2.2	1.9	20.0	1.9	1.8	1.2	1.7	4.1	5.1	7.0

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Table 55 (continued)

Pos	WT	A	C	D	E	F	G	H	I	K	L	M	N	P	Q	R	S	T	V	W	Y
271 A	P	0.0	5.3	8.1	9.3	20.0	3.1	9.1	20.0	6.0	9.5	5.3	7.3	5.9	5.9	5.9	1.6	4.1	15.2	20.0	20.0
272 A	Q	0.8	1.9	0.9	1.2	3.0	3.2	3.7	3.7	1.6	1.8	3.2	0.3	50.0	1.1	1.6	0.0	1.0	3.5	4.0	3.4
273 A	V	1.2	2.9	1.8	20.0	20.0	7.1	20.0	6.8	20.0	20.0	20.0	0.0	2.5	20.0	20.0	2.1	1.4	1.7	20.0	20.0
274 A	K	0.4	1.8	1.4	0.8	1.9	3.9	2.4	1.4	0.7	1.1	2.9	0.9	20.0	0.0	0.1	0.0	0.4	0.7	3.3	2.3
275 A	F	8.0	9.5	10.3	9.5	0.0	13.5	5.1	10.1	6.2	6.3	6.0	9.1	6.1	9.1	15.1	9.6	7.2	6.1	13.5	4.3
276 A	N	1.3	2.4	2.4	2.2	0.8	5.1	0.8	1.3	0.6	2.3	2.5	1.8	50.0	1.6	2.5	1.2	0.0	0.3	4.2	3.6
277 A	W	5.5	7.4	8.4	6.4	15.4	11.2	3.2	8.2	1.9	3.9	3.6	6.6	3.5	5.5	15.4	6.9	6.1	14.1	0.0	20.0
278 A	Y	1.6	2.7	3.9	1.6	1.0	7.3	3.4	17.7	1.4	7.5	2.1	0.0	50.0	1.9	2.2	2.6	9.9	20.0	15.8	1.4
279 A	V	3.1	4.1	4.0	2.2	20.0	8.1	9.7	8.5	0.0	1.4	3.1	3.3	20.0	1.9	4.6	4.3	3.4	4.2	20.0	20.0
280 A	D	1.8	2.6	2.7	0.2	11.6	2.9	8.8	20.0	3.4	3.2	2.8	3.8	50.0	0.0	3.7	0.6	6.8	12.7	11.9	11.4
281 A	G	50.0	50.0	50.0	50.0	50.0	0.0	50.0	50.0	50.0	50.0	50.0	50.0	50.0	50.0	50.0	50.0	50.0	50.0	50.0	50.0
282 A	V	0.9	2.1	1.6	1.1	2.9	4.2	3.5	1.4	1.5	1.8	3.6	0.4	18.9	0.5	1.0	0.0	0.6	0.9	4.7	3.1
283 A	E	0.7	1.6	0.7	0.5	1.0	4.4	1.4	0.4	1.2	1.8	1.9	0.0	0.4	0.6	1.5	0.4	0.3	1.2	4.1	0.9
284 A	V	0.0	2.2	3.1	1.2	20.0	5.0	20.0	4.0	0.7	2.6	0.8	2.6	50.0	0.8	0.7	0.8	0.1	1.5	20.0	20.0
285 A	H	0.2	1.4	3.1	1.3	3.0	2.0	2.4	3.6	1.1	2.6	3.0	0.7	2.2	0.2	0.8	0.0	1.1	4.7	4.9	4.0
286 A	N	0.8	2.5	1.2	1.1	2.4	4.7	2.7	2.1	0.0	0.7	1.8	0.6	20.0	1.2	0.7	0.9	1.7	2.1	5.2	2.7
287 A	A	0.6	2.6	5.8	3.3	10.4	5.4	9.1	11.3	0.0	4.4	1.3	3.6	50.0	2.6	2.3	1.0	1.9	12.5	9.1	10.4
288	K	0.8	2.6	2.0	1.3	3.0	3.4	3.8	2.3	1.4	1.7	2.5	0.3	50.	0.5	1.3	0.0	0.4	2.0	4.5	3.6

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289 A	T	0.3	1.9	4.7	1.1	3.1	3.6	2.9	10.5	0.4	2.7	1.6	2.1	8.2	1.2	2.0	0.0	0.4	12.0	3.9	3.2
290 A	K	1.7	2.2	0.5	0.6	3.0	1.3	3.0	3.7	1.7	2.1	3.2	0.0	50.0	0.7	2.0	0.3	1.3	3.3	5.6	3.3
291 A	P	1.6	3.1	1.8	0.5	1.9	5.5	1.8	0.1	0.5	1.5	1.2	1.2	0.7	0.0	2.9	2.2	0.9	1.3	2.6	0.9
292 A	R	1.1	2.2	3.1	0.8	5.9	4.4	8.0	5.0	0.0	1.6	2.1	1.1	8.4	0.2	0.4	1.0	1.3	4.7	8.3	5.7
293 A	E	2.2	6.5	9.0	17.9	16.3	0.0	13.2	50.0	12.8	10.3	10.3	7.2	5.5	15.1	14.5	3.5	20.0	50.0	14.5	17.1
294 A	E	1.5	2.1	2.1	0.7	8.1	2.8	3.3	2.0	2.6	1.8	2.8	1.0	50.0	1.3	1.3	0.5	0.0	3.4	11.2	10.2
295 A	Q	50.0	50.0	50.0	50.0	50.0	0.0	50.0	50.0	50.0	50.0	50.0	50.0	50.0	50.0	50.0	50.0	50.0	50.0	50.0	50.0
296 A	Y	2.8	2.3	1.1	0.4	50.0	0.0	50.0	4.6	2.2	2.3	3.1	0.9	50.0	0.2	1.8	1.3	4.7	4.8	18.2	20.0
297 A	N	0.0	6.5	8.4	5.3	20.0	3.4	20.0	13.8	2.7	20.0	4.8	9.3	50.0	4.4	4.4	1.5	1.6	15.5	20.0	20.0
298 A	S	0.8	2.4	5.7	2.2	20.0	3.7	20.0	6.2	0.9	9.2	1.8	3.3	50.0	1.7	2.1	0.0	2.2	7.3	15.6	20.0
299 A	T	1.9	3.4	6.0	3.1	1.0	7.1	2.9	3.1	0.0	2.7	2.6	3.6	50.0	2.2	2.5	1.1	2.2	5.4	3.6	1.4
300 A	Y	2.8	2.9	2.7	4.5	20.0	4.0	7.5	13.1	1.2	0.0	2.2	2.3	50.0	3.3	4.0	2.6	1.1	1.1	11.0	2.4
301 A	R	3.0	3.5	3.8	2.8	0.8	3.4	1.8	0.0	1.3	0.7	2.6	2.5	50.0	2.8	2.3	2.9	1.8	0.9	9.8	1.8
302 A	V	2.7	4.6	6.7	3.9	2.8	8.9	1.2	6.9	2.7	2.0	2.2	4.8	50.0	4.7	3.2	4.3	7.7	3.8	0.0	8.4
303 A	V	0.0	2.2	3.3	1.0	6.7	4.5	5.3	1.4	2.5	3.1	2.0	3.1	1.0	2.1	2.9	0.4	0.4	2.9	10.9	6.2
304 A	S	0.0	12.1	10.8	20.0	20.0	6.2	20.0	20.0	17.2	20.0	11.9	16.6	50.0	20.0	16.6	2.2	14.2	17.9	20.0	20.0
305 A	V	1.1	2.3	3.3	1.2	0.3	5.4	1.2	0.0	0.9	1.1	2.8	1.1	3.9	1.1	1.4	1.2	0.9	0.0	0.8	0.8

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Table 55 (continued)

Pos	WT	A	C	D	E	F	G	H	I	K	L	M	N	P	Q	R	S	T	V	W	Y
306 A	L	4.3	6.2	7.1	5.9	2.8	10.4	3.4	13.7	3.0	0.0	3.5	6.0	50.0	5.9	9.9	6.2	5.3	11.4	9.6	10.3
307 A	T	1.4	3.2	3.8	2.2	6.5	5.5	4.2	0.5	0.3	4.2	3.0	2.2	0.0	1.9	1.3	1.4	0.9	1.2	6.2	6.5
308 A	V	1.8	5.5	6.5	8.0	50.0	7.9	20.0	4.5	20.0	5.5	19.4	7.8	50.0	7.7	15.5	0.0	0.7	5.9	50.0	50.0
309 A	L	1.1	2.7	0.7	0.7	1.3	4.5	2.7	0.7	1.7	1.0	2.8	0.0	1.6	0.7	1.3	1.0	0.6	0.5	5.0	2.1
310 A	H	2.0	2.6	0.9	4.1	50.0	5.6	0.2	6.8	4.0	7.1	4.0	0.0	0.2	4.9	10.0	2.0	2.5	6.4	50.0	50.0
311 A	Q	0.6	2.5	1.6	1.6	2.5	4.3	1.6	1.4	0.6	0.9	2.9	0.9	1.7	0.8	0.9	0.0	0.3	2.2	4.6	2.0
312 A	N	5.4	5.1	5.9	1.3	20.0	0.0	20.0	10.0	3.4	4.8	3.3	7.1	50.0	2.7	3.9	4.1	3.2	11.9	20.0	20.0
313 A	W	4.6	6.4	5.5	5.6	1.1	10.8	5.0	11.0	5.8	5.2	7.5	5.4	50.0	4.8	12.9	6.0	3.8	6.6	0.0	2.6
314 A	L	2.1	2.9	4.3	2.2	5.7	6.1	7.9	5.4	0.7	0.0	1.7	2.3	50.0	1.6	1.6	3.0	4.7	6.3	8.0	6.0
315 A	D	0.3	1.4	1.5	0.1	3.3	4.2	1.9	1.8	0.8	0.5	1.8	0.6	50.0	0.0	0.7	0.0	0.9	2.4	6.2	3.7
316 A	G	50.0	50.0	50.0	50.0	50.0	0.0	50.0	50.0	50.0	50.0	50.0	50.0	50.0	50.0	50.0	50.0	50.0	50.0	50.0	50.0
317 A	K	0.0	14.0	18.4	17.9	50.0	5.0	50.0	20.0	8.5	12.5	12.7	20.0	15.9	17.2	13.5	2.8	9.2	20.0	50.0	50.0
318 A	E	2.0	3.0	2.7	1.7	2.7	6.7	2.6	0.0	1.1	1.6	1.3	1.7	20.0	1.4	2.6	2.2	1.3	0.0	6.1	9.5
319 A	Y	2.9	4.4	3.9	3.4	0.0	8.8	1.8	20.0	0.5	5.2	0.7	3.2	50.0	3.1	5.6	3.4	3.6	20.0	20.0	0.2
320 A	K	2.3	3.1	3.0	2.7	20.0	7.8	20.0	9.4	0.0	0.6	2.7	1.3	50.0	2.4	1.9	3.3	3.3	7.2	20.0	20.0
321 A	C	0.0	3.2	20.0	18.8	20.0	6.9	20.0	20.0	20.0	20.0	10.4	20.0	50.0	19.6	20.0	1.5	8.7	18.3	20.0	20.0
322 A	K	2.0	2.5	3.5	2.8	2.7	6.4	2.1	0.2	0.1	1.2	2.7	2.7	50.0	2.1	0.0	2.3	1.6	0.9	14.5	2.8
323	V	1.5	2.8	7.3	11.	20.	8.1	20.	6.0	9.6	20.	4.9	8.5	50.	13.	20.	2.8	1.6	0.0	20.	20.

A					9	0		0			0			0	6	0				0	0
324 A	S	2.0	2.1	0.6	0.0	1.9	4.9	3.9	1.5	2.8	0.7	1.9	0.9	50.0	0.8	2.9	2.7	1.9	2.1	3.8	2.5
325 A	N	2.8	3.9	8.4	3.0	20.0	8.3	20.0	0.0	7.7	20.0	6.2	1.6	13.4	0.5	20.0	3.1	0.1	1.3	20.0	20.0
326 A	K	1.0	2.7	3.0	1.6	3.7	4.1	3.1	3.2	1.7	2.4	3.7	1.2	0.0	0.6	1.4	1.0	1.9	2.6	5.6	3.6
327 A	A	0.9	2.8	5.8	3.1	20.0	6.3	16.7	14.7	2.8	20.0	2.5	5.3	20.0	1.3	4.1	0.0	5.2	13.7	20.0	20.0
328 A	L	6.0	6.3	7.0	4.1	50.0	8.6	20.0	50.0	5.7	0.0	7.1	6.0	50.0	3.7	8.2	6.6	50.0	50.0	20.0	50.0
329 A	P	1.0	2.5	0.9	0.6	4.0	3.4	3.3	1.7	1.9	2.5	3.6	0.0	0.3	0.7	1.5	0.1	1.1	1.1	6.2	3.6
330 A	A	0.9	2.0	1.3	0.7	3.4	3.8	3.0	2.0	1.4	2.0	3.4	0.0	20.0	0.6	1.2	0.2	0.6	1.9	7.0	3.4
331 A	P	50.0	50.0	50.0	50.0	50.0	0.0	50.0	50.0	50.0	50.0	50.0	50.0	50.0	50.0	50.0	50.0	50.0	50.0	50.0	50.0
332 A	I	1.9	3.7	4.6	1.7	5.0	7.0	1.9	3.8	1.8	0.0	2.5	3.9	20.0	0.8	2.4	2.3	2.6	4.4	20.0	5.9
333 A	E	0.0	3.1	3.2	0.8	4.1	4.4	4.2	16.9	3.6	2.8	2.8	2.5	1.6	1.3	3.2	1.3	1.4	7.7	4.0	4.8
334 A	K	1.7	2.9	2.5	0.0	1.0	6.1	3.3	1.0	1.5	0.5	3.5	1.5	4.4	0.1	2.7	2.2	0.9	1.3	4.9	1.6
335 A	T	0.5	3.2	4.5	2.7	4.2	4.9	4.1	20.0	2.1	3.1	3.0	1.2	0.0	2.3	2.8	1.4	1.4	7.3	5.1	4.5
336 A	I	1.2	1.6	5.0	1.5	20.0	6.1	16.8	0.7	3.4	7.8	2.5	3.2	20.0	2.8	1.4	0.7	0.6	0.0	20.0	20.0
337 A	S	4.8	4.8	7.5	11.5	10.1	0.0	5.5	50.0	0.9	7.0	7.9	5.0	50.0	11.4	12.7	4.5	2.3	50.0	19.3	10.6
338 A	K	1.0	2.7	2.3	2.2	4.6	5.9	2.4	50.0	0.0	2.1	1.9	1.0	50.0	1.5	0.9	0.7	10.3	50.0	5.4	4.9
339 A	A	1.0	2.5	0.8	1.1	4.4	3.7	3.7	2.1	1.8	2.6	3.6	0.0	0.8	0.6	1.6	0.6	0.9	2.4	6.8	3.8
340 A	K	1.3	2.4	2.3	2.0	1.7	4.1	2.3	1.9	0.0	2.3	1.8	1.0	1.9	0.9	1.3	0.5	0.8	1.7	4.9	2.4

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Table 55 (continued)

Pos	WT	A	C	D	E	F	G	H	I	K	L	M	N	P	Q	R	S	T	V	W	Y
232 B	P	1.3	3.2	2.2	2.2	4.1	2.9	3.6	1.8	2.1	2.8	3.9	1.1	0.0	1.1	1.6	0.7	1.4	3.0	6.2	4.1
233 B	E	0.5	2.2	1.7	0.5	2.6	3.7	2.9	4.4	1.4	1.1	3.2	0.6	2.7	0.4	1.8	0.0	1.2	6.9	5.5	2.6
234 B	L	2.9	4.0	4.8	4.9	2.0	6.1	0.8	1.5	0.0	1.9	2.7	2.6	20.0	3.6	1.2	3.1	2.5	3.4	13.4	0.5
235 B	L	0.5	2.3	2.4	0.9	5.7	4.9	1.4	3.7	0.0	0.0	1.9	1.9	17.3	0.6	1.4	0.8	0.7	5.2	7.8	5.3
236 B	G	3.6	2.5	5.1	11.8	6.8	0.0	2.8	20.0	5.0	20.0	4.5	3.5	50.0	5.5	19.9	2.6	20.0	20.0	20.0	14.1
237 B	G	20.0	50.0	50.0	50.0	50.0	0.0	50.0	50.0	50.0	50.0	50.0	50.0	50.0	50.0	50.0	50.0	50.0	50.0	50.0	50.0
238 B	P	3.5	4.7	6.5	4.2	20.0	9.8	20.0	0.0	5.6	9.6	4.6	8.1	1.3	5.8	20.0	4.9	4.4	1.3	20.0	20.0
239 B	S	1.0	2.5	3.4	2.0	7.2	5.7	3.1	3.1	0.6	0.0	2.0	1.9	50.0	1.7	1.1	1.5	1.5	5.2	20.0	5.2
240 B	V	0.1	2.3	7.0	11.9	20.0	6.5	20.0	8.1	12.7	20.0	12.0	7.6	0.0	11.6	20.0	1.2	1.9	0.8	20.0	20.0
241 B	F	0.0	2.0	1.4	0.8	1.0	4.0	2.0	6.5	1.1	0.6	2.3	0.2	50.0	0.3	1.5	0.1	0.9	5.7	4.1	1.1
242 B	L	2.2	3.3	6.5	6.5	6.9	7.9	4.3	0.0	8.7	3.9	4.8	5.3	0.0	9.1	6.8	2.9	1.1	0.5	20.0	8.7
243 B	F	0.8	2.6	1.9	1.7	0.8	4.9	2.0	3.6	1.2	0.8	2.5	0.0	50.0	1.6	2.7	0.1	1.8	3.9	4.3	1.0
244 B	P	1.1	2.1	4.0	1.1	11.9	3.5	5.4	20.0	1.4	3.2	3.0	2.0	1.8	1.2	1.3	0.0	19.6	20.0	9.1	11.0
245 B	P	3.2	20.0	20.0	20.0	20.0	8.6	20.0	20.0	20.0	20.0	20.0	20.0	0.0	20.0	20.0	6.0	20.0	50.0	20.0	20.0
246 B	K	0.5	2.6	1.4	1.2	2.1	4.4	1.6	0.6	0.9	1.4	2.5	0.2	0.3	0.2	0.3	0.1	0.0	2.0	4.9	2.4
247 B	P	0.8	2.5	0.7	1.0	3.6	3.9	2.6	6.2	1.8	2.1	2.9	0.3	0.0	0.8	1.5	0.3	0.7	9.5	6.6	3.4
248 B	K	0.2	2.2	0.2	0.6	2.2	4.1	2.5	2.4	1.7	1.0	2.2	0.0	1.3	0.8	1.7	0.5	0.7	2.8	4.7	2.3
249	D	2.8	3.3	0.0	4.6	10.	8.2	6.5	50.	4.6	6.2	4.4	0.5	50.	4.7	6.3	3.5	6.1	50.	20.	7.2

B						1			0					0					0	0	
250 B	T	0.0	2.2	4.9	2.8	20.0	6.3	20.0	2.2	4.3	3.2	3.0	9.2	50.0	3.4	4.9	1.3	2.3	3.1	20.0	20.0
251 B	L	0.0	2.4	1.6	1.2	5.6	3.6	2.2	7.4	1.2	0.6	2.3	0.5	50.0	0.6	1.8	0.4	2.5	8.7	8.2	5.9
252 B	M	1.3	2.4	0.8	0.0	1.8	5.7	2.3	0.6	1.6	0.6	2.5	1.0	50.0	1.0	1.8	1.5	1.3	0.8	5.1	1.6
253 B	I	1.6	3.0	2.0	1.2	3.7	4.5	3.5	2.9	0.8	2.4	2.4	1.1	1.0	0.0	1.5	1.2	1.4	3.4	4.4	3.6
254 B	S	1.0	1.5	0.8	0.6	3.8	3.8	3.2	0.5	1.9	2.5	3.1	0.3	6.2	0.5	1.7	0.0	0.1	1.1	5.5	3.7
255 B	R	0.9	2.0	2.0	1.7	0.0	5.4	1.4	20.0	1.0	1.8	1.3	0.8	50.0	1.4	1.1	1.5	20.0	20.0	3.7	0.9
256 B	T	0.6	2.0	1.8	1.1	2.5	3.7	1.9	1.8	1.0	1.4	2.2	0.0	1.2	0.5	0.1	0.8	1.2	1.2	5.5	2.4
257 B	P	2.5	20.0	20.0	20.0	50.0	9.0	50.0	20.0	20.0	20.0	20.0	20.0	0.0	20.0	20.0	4.8	20.0	20.0	50.0	50.0
258 B	E	1.5	2.4	2.7	1.4	2.7	6.4	4.2	0.0	0.2	5.4	2.4	1.1	50.0	1.3	2.5	2.2	1.1	1.0	19.1	3.0
259 B	V	2.9	4.2	6.3	5.2	20.0	9.3	20.0	0.0	8.1	8.9	5.5	5.6	50.0	6.2	20.0	4.5	2.5	0.0	20.0	20.0
260 B	T	0.0	1.6	5.3	1.9	20.0	4.9	20.0	0.6	1.1	2.8	1.4	3.9	0.2	2.3	2.6	0.4	0.1	2.7	20.0	20.0
261 B	C	0.0	10.0	20.0	20.0	20.0	2.6	20.0	20.0	20.0	20.0	20.0	20.0	20.0	20.0	20.0	2.0	16.6	20.0	20.0	20.0
262 B	V	3.1	2.4	2.7	2.4	8.1	7.2	3.8	1.8	3.5	8.8	3.4	2.7	50.0	3.2	4.8	2.9	1.9	0.0	14.7	9.1
263 B	V	2.2	3.7	4.7	11.2	20.0	9.1	20.0	15.0	13.7	2.8	20.0	5.4	50.0	13.0	20.0	3.6	2.1	0.0	20.0	20.0
264 B	V	2.1	3.0	4.6	2.7	8.6	6.8	6.6	0.0	1.8	1.8	3.7	3.6	10.1	3.0	2.2	2.6	2.2	1.0	12.7	20.0
265 B	D	4.5	5.2	4.8	4.7	5.0	0.0	3.8	8.5	1.8	2.6	4.1	1.8	50.0	4.5	5.3	4.5	6.0	9.2	12.2	5.6
266 B	V	5.3	5.5	7.2	12.7	20.0	12.0	20.0	2.1	20.0	20.0	20.0	5.7	50.0	18.3	20.0	5.9	4.7	0.0	50.0	50.0
267 B	S	2.8	4.3	6.2	3.8	0.0	7.4	1.0	50.0	1.0	0.3	3.2	3.2	0.5	1.5	0.8	3.3	11.6	50.0	6.3	50.0

Table 55 (continued)

Pos	WT	A	C	D	E	F	G	H	I	K	L	M	N	P	Q	R	S	T	V	W	Y
268 B	H	2.6	3.7	5.1	4.1	4.9	6.0	1.8	2.6	0.0	2.5	3.8	2.6	3.4	2.1	1.8	2.5	3.8	2.7	7.8	5.5
269 B	E	0.4	2.4	1.7	0.8	2.8	3.7	2.6	1.0	1.0	1.6	3.0	0.0	12.8	0.5	0.7	0.3	0.7	0.6	5.1	2.7
270 B	D	0.0	1.6	1.1	7.3	4.8	4.3	2.6	20.0	3.8	14.5	3.8	1.2	5.9	6.3	2.1	0.3	1.9	5.4	16.3	5.6
271 B	P	1.1	3.3	5.6	3.4	4.1	5.5	4.2	20.0	1.9	3.6	3.9	3.3	7.4	2.7	0.0	1.5	2.2	5.2	4.8	4.4
272 B	Q	0.9	1.9	1.0	0.6	3.0	3.9	2.9	1.5	1.7	2.2	3.5	0.6	4.9	0.0	1.4	0.2	0.6	1.4	3.9	3.2
273 B	V	3.5	4.8	6.2	8.3	20.0	9.2	20.0	4.6	8.4	3.1	3.5	7.4	50.0	10.6	20.0	2.0	0.0	4.8	20.0	20.0
274 B	K	0.1	1.6	0.4	0.9	1.7	3.8	1.8	1.9	0.4	0.6	2.4	0.3	15.8	0.1	0.0	0.0	0.2	1.6	2.2	1.9
275 B	F	5.7	7.0	8.4	9.2	0.0	11.2	3.5	9.2	7.9	5.7	5.1	7.0	4.1	9.7	12.3	6.9	4.5	3.3	10.3	5.0
276 B	N	0.0	6.2	6.9	6.4	20.0	4.7	12.1	20.0	9.3	10.0	7.4	3.8	50.0	6.4	9.2	2.8	20.0	20.0	20.0	20.0
277 B	W	8.3	10.0	10.6	9.2	2.6	14.2	7.4	12.7	6.7	7.4	6.4	10.8	6.8	9.3	11.9	9.7	8.0	14.4	0.0	15.9
278 B	Y	0.0	2.3	17.4	4.0	50.0	5.1	50.0	20.0	2.6	20.0	2.1	12.6	11.0	4.4	2.0	0.8	2.5	19.8	20.0	4.2
279 B	V	3.1	3.5	4.2	2.9	20.0	8.5	13.9	0.4	0.0	2.9	2.0	3.4	20.0	1.4	4.0	4.2	2.4	1.2	20.0	20.0
280 B	D	0.5	3.0	2.1	1.5	6.7	3.1	4.7	12.6	2.9	1.6	2.9	1.6	20.0	1.4	3.1	0.0	2.7	5.5	8.1	7.3
281 B	G	5.6	5.8	5.5	4.8	7.9	0.0	7.2	6.5	5.3	5.7	7.1	3.4	50.0	4.0	5.3	3.6	3.2	6.4	10.3	7.6
282 B	V	0.4	1.9	1.1	0.6	2.9	4.1	2.1	1.3	1.0	1.4	2.9	0.2	50.0	0.0	0.7	0.0	0.4	0.7	6.1	2.8
283 B	E	0.6	1.9	4.3	1.7	6.7	4.2	5.2	2.9	0.5	4.4	0.3	2.5	0.0	1.5	1.6	1.0	1.5	3.9	7.9	6.7
284 B	V	0.4	2.4	2.5	1.1	20.0	5.9	20.0	1.1	1.2	6.2	0.8	2.4	50.0	1.5	3.3	0.0	1.5	1.8	20.0	20.0
285	H	1.3	2.4	2.1	1.7	2.4	3.4	1.2	1.8	0.7	2.3	2.7	0.0	1.6	0.9	0.8	0.5	0.4	2.0	5.8	2.4

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B																					
286 B	N	1.2	2.7	1.0	1.1	3.0	3.1	2.6	0.8	2.0	1.9	2.9	0.0	50.0	0.4	1.6	1.1	0.5	2.9	4.9	3.0
287 B	A	2.5	4.4	6.1	7.5	0.0	8.2	3.0	10.2	5.1	16.5	4.5	0.3	12.3	8.1	9.1	4.1	3.3	7.1	3.4	0.8
288 B	K	0.4	1.9	1.9	0.0	2.9	3.5	2.9	2.5	1.8	2.1	2.5	0.9	15.4	0.6	1.1	0.2	0.9	3.8	5.9	2.7
289 B	T	0.1	1.5	3.7	1.4	2.7	3.9	2.6	1.8	0.0	2.2	1.6	1.5	1.8	1.1	1.7	0.0	0.4	2.3	3.4	2.5
290 B	K	0.9	1.8	0.8	0.5	2.4	0.8	2.7	3.0	1.3	1.3	2.6	0.2	50.0	0.7	1.5	0.0	0.6	2.9	5.0	2.7
291 B	P	1.2	2.1	2.5	0.5	3.9	4.6	3.4	0.7	0.0	3.4	1.5	1.1	0.6	0.1	1.1	1.1	0.9	1.5	3.2	2.6
292 B	R	0.8	2.6	3.3	1.2	4.9	3.6	6.8	3.1	2.0	2.4	2.2	2.2	16.6	1.5	1.8	0.1	0.0	3.2	7.6	5.2
293 B	E	0.0	3.0	4.1	2.8	7.3	3.6	5.8	5.8	2.6	4.5	3.2	2.2	1.3	2.2	2.5	0.0	1.2	7.8	7.0	6.9
294 B	E	2.5	3.3	3.9	2.3	8.3	6.8	4.4	5.6	3.6	2.3	3.7	4.1	0.0	3.3	5.0	2.1	2.9	5.0	6.7	11.9
295 B	Q	1.1	2.2	1.9	0.6	3.8	2.8	3.1	8.0	1.4	2.2	3.4	1.0	0.4	0.4	1.1	0.0	3.9	6.6	6.1	3.5
296 B	Y	1.5	2.7	1.2	1.2	4.1	4.1	3.5	1.1	1.8	2.7	3.5	0.0	20.0	0.6	1.9	1.2	1.4	1.3	6.4	4.0
297 B	N	3.9	4.5	10.1	6.0	15.5	7.3	16.7	6.6	0.0	5.1	4.6	7.3	20.0	4.4	4.2	3.6	4.1	7.9	18.0	15.0
298 B	S	1.7	2.5	3.5	2.5	2.5	3.7	2.4	3.0	0.0	1.8	2.3	0.4	50.0	1.2	1.0	0.9	2.2	3.3	5.5	2.0
299 B	T	0.0	2.7	7.2	11.1	20.0	4.8	20.0	7.5	6.9	20.0	7.1	4.8	50.0	9.8	17.9	0.3	1.3	5.8	20.0	20.0
300 B	Y	3.8	5.2	8.0	4.3	20.0	8.6	20.0	12.2	0.0	4.3	3.2	6.5	50.0	4.0	3.8	4.3	3.6	9.1	20.0	6.4
301 B	R	1.2	1.6	2.3	1.1	20.0	5.8	11.3	5.2	0.3	5.0	2.0	1.6	14.1	0.6	0.4	1.8	1.1	0.0	17.9	20.0
302 B	V	3.5	4.8	5.5	3.7	0.2	9.6	1.1	0.5	2.6	3.5	2.5	4.7	9.6	4.1	0.6	4.3	2.0	0.0	20.0	0.2
303 B	V	0.2	0.0	0.1	1.0	20.0	5.0	13.3	5.1	1.7	10.4	1.9	2.0	8.6	2.0	4.7	0.6	0.5	1.3	20.0	20.0
304	S	1.5	2.3	8.2	20.	20.	7.6	20.	7.6	20.	20.	20.	8.3	50.	20.	20.	0.0	2.7	3.8	20.	20.

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Table 55 (continued)

Pos	WT	A	C	D	E	F	G	H	I	K	L	M	N	P	Q	R	S	T	V	W	Y
304 B	S	1.5	2.3	8.2	20.0	20.0	7.6	20.0	7.6	20.0	20.0	20.0	6.3	50.0	20.0	20.0	0.0	2.7	3.8	20.0	20.0
305 B	V	0.1	1.2	3.3	1.1	20.0	4.6	20.0	3.2	1.1	11.0	1.5	1.8	50.0	0.6	2.0	0.6	0.0	0.7	20.0	20.0
306 B	L	4.7	6.8	6.3	4.3	10.4	11.1	7.8	4.2	3.0	0.0	3.8	5.7	13.4	4.4	14.1	5.5	4.3	6.0	20.0	12.1
307 B	T	1.5	3.0	2.7	1.7	4.1	5.2	3.0	1.6	1.9	3.1	3.4	1.7	0.0	1.7	1.9	1.5	1.4	2.0	4.4	4.3
308 B	V	0.0	0.6	7.6	20.0	20.0	6.6	20.0	20.0	16.1	15.1	20.0	12.4	50.0	20.0	20.0	1.2	3.6	4.3	20.0	20.0
309 B	L	1.4	3.0	2.2	1.1	3.0	6.0	3.5	20.0	2.4	1.7	3.6	0.2	0.0	1.6	2.3	1.8	14.3	20.0	5.1	3.3
310 B	H	2.4	2.9	2.7	4.9	20.0	6.8	4.4	4.8	3.1	15.0	3.4	0.0	2.3	4.6	7.0	1.8	1.6	3.8	20.0	20.0
311 B	Q	0.0	2.2	1.3	0.7	2.1	3.3	2.4	12.6	0.6	0.9	2.3	0.6	3.2	0.4	0.8	0.2	1.6	18.8	4.6	2.0
312 B	N	0.0	1.0	0.2	0.3	6.0	5.4	2.3	12.0	2.1	2.9	1.6	0.9	50.0	1.3	5.7	0.1	5.6	3.8	8.0	7.8
313 B	W	5.3	6.6	7.3	5.4	0.0	11.4	6.2	20.0	4.0	5.2	4.3	8.0	50.0	6.5	8.9	6.6	17.2	20.0	2.1	0.9
314 B	L	1.7	2.2	3.1	0.0	6.4	5.6	1.5	2.1	0.6	0.2	1.1	1.9	50.0	0.8	1.0	1.7	0.9	3.1	3.7	11.3
315 B	D	1.4	2.3	2.4	0.7	6.0	5.5	2.3	4.8	2.2	1.0	2.9	1.8	50.0	1.0	2.2	0.2	0.0	4.5	8.5	6.8
316 B	G	50.0	50.0	50.0	50.0	50.0	0.0	50.0	50.0	50.0	50.0	50.0	50.0	50.0	50.0	50.0	50.0	50.0	50.0	50.0	50.0
317 B	K	0.9	2.3	4.3	2.8	1.2	4.0	0.6	13.9	0.0	4.8	1.6	1.3	50.0	4.2	0.9	0.4	13.8	10.1	20.0	1.7
318 B	E	0.7	1.2	3.1	1.0	7.0	5.1	8.2	0.4	1.0	5.7	1.7	2.3	3.8	1.0	1.6	0.4	0.0	1.0	3.8	7.7
319 B	Y	6.5	7.1	8.5	8.8	0.0	12.5	3.9	3.1	5.2	5.4	8.4	7.2	50.0	9.0	13.7	7.2	5.8	3.9	20.0	1.7
320 B	K	3.1	4.3	7.3	4.3	20.0	8.6	15.0	1.4	0.0	11.6	3.6	6.6	50.0	2.9	2.4	4.0	3.3	2.0	20.0	20.0
321	C	0.0	6.5	20.	20.	20.	6.6	20.	20.	20.	20.	20.	20.	19.	20.	20.	3.1	11.	20.	20.	20.

B				0	0	0		0	0	0	0	0	0	7	0	0		2	0	0	0
322 B	K	2.3	3.2	3.5	1.8	20.0	7.9	20.0	1.1	0.6	4.9	3.7	2.2	50.0	0.9	0.3	3.3	1.6	0.8	20.0	20.0
323 B	V	4.0	4.6	6.9	8.1	20.0	10.6	20.0	9.0	17.1	7.9	8.1	10.5	50.0	8.7	20.0	5.6	4.8	0.0	20.0	20.0
324 B	S	1.3	3.0	1.4	0.0	2.1	6.0	4.4	1.3	2.4	0.6	2.7	2.2	50.0	1.3	3.6	1.5	1.6	1.8	3.6	2.4
325 B	N	3.4	5.1	9.0	4.7	20.0	8.2	20.0	16.6	16.6	20.0	20.0	0.0	50.0	6.3	20.0	4.6	8.8	17.8	20.0	20.0
326 B	K	0.3	2.1	2.0	0.9	1.0	3.5	2.0	2.9	0.9	2.9	2.8	0.1	4.4	0.0	1.1	0.1	3.2	2.1	5.2	0.7
327 B	A	1.9	3.3	4.7	3.5	20.0	7.0	20.0	20.0	0.3	0.0	1.9	1.9	20.0	3.0	2.3	3.3	20.0	20.0	20.0	20.0
328 B	L	3.7	3.6	3.8	4.4	50.0	6.4	7.0	50.0	3.8	0.0	2.6	4.0	50.0	4.2	8.7	4.8	2.9	12.3	50.0	50.0
329 B	P	3.3	8.5	20.0	20.0	50.0	8.0	16.5	50.0	18.5	20.0	14.7	20.0	0.0	20.0	20.0	1.4	17.1	16.4	50.0	50.0
330 B	A	0.5	2.0	2.8	0.5	2.4	3.9	1.2	4.0	0.0	2.0	2.1	0.8	20.0	0.0	0.5	0.8	0.2	4.6	8.2	2.6
331 B	P	1.7	3.8	6.4	10.1	20.0	4.7	11.0	10.1	7.5	20.0	5.5	5.0	0.0	7.6	7.4	2.6	20.0	10.1	17.6	20.0
332 B	I	1.7	2.9	1.3	1.7	14.8	7.0	13.9	1.7	3.1	0.0	1.7	1.7	50.0	1.8	5.3	2.0	1.9	3.4	20.0	20.0
333 B	E	1.9	2.5	1.9	0.0	8.9	5.9	8.2	1.2	3.0	6.4	3.4	2.0	3.1	1.1	2.3	1.8	1.6	1.6	8.9	9.3
334 B	K	2.9	3.9	3.7	2.6	20.0	8.3	12.1	1.5	2.6	5.3	3.7	4.3	50.0	1.9	0.0	3.4	1.8	1.4	9.9	20.0
335 B	T	0.0	2.1	7.2	7.0	4.2	0.4	3.3	17.3	6.5	7.7	5.2	5.5	3.5	7.0	5.7	0.2	5.5	11.5	5.2	3.1
336 B	I	0.5	1.6	2.1	0.7	20.0	5.0	6.1	0.0	1.3	5.3	2.1	1.8	20.0	0.6	3.1	1.1	0.8	0.7	19.4	20.0
337 B	S	1.1	2.1	4.0	2.0	3.1	3.2	2.0	50.0	0.0	1.6	0.9	1.9	15.8	1.1	2.2	1.4	50.0	50.0	5.5	3.9
338 B	K	0.6	2.3	3.0	3.0	9.4	5.3	10.6	2.2	1.1	0.0	3.2	1.5	16.2	2.7	2.7	1.1	2.8	3.5	8.1	11.0
339 B	A	1.1	2.4	1.2	0.8	4.3	3.6	3.7	2.6	1.8	2.6	3.5	0.0	2.3	0.5	1.3	0.2	0.8	2.0	6.7	3.8
340	K	0.9	2.0	1.4	0.8	3.0	3.4	2.9	2.1	0.8	2.5	2.3	0.2	1.0	0.1	1.2	0.0	0.5	2.0	5.5	3.2

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SPA™ technology; 1IIS template structure; - carbohydrate, no fixated positions

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Table 56

Pos	WT	A	C	D	E	F	G	H	I	K	L	M	N	P	Q	R	S	T	V	W	Y
239 A	S	0.2	4.6	2.7	0.0	20.0	4.6	14.6	11.0	1.9	0.3	2.0	1.9	8.1	1.4	2.6	0.4	5.7	11.6	20.0	20.0
240 A	V	1.5	2.4	2.4	6.9	20.0	7.4	20.0	5.1	9.9	5.9	5.5	2.4	1.1	12.3	13.1	2.6	0.5	0.0	20.0	20.0
263 A	V	2.3	2.8	6.3	16.5	20.0	8.8	20.0	9.6	7.3	7.3	15.3	4.8	50.0	16.4	17.4	2.8	1.4	0.0	20.0	20.0
264 A	V	1.8	3.1	2.6	1.8	0.0	6.3	1.9	0.6	2.4	0.8	2.7	2.1	1.6	2.3	2.7	2.3	1.1	0.5	3.5	0.0
266 A	V	4.9	5.2	6.9	12.3	20.0	11.1	20.0	0.6	11.9	20.0	8.5	6.6	50.0	12.5	20.0	6.1	3.7	0.0	20.0	20.0
296 A	Y	3.4	2.7	1.1	0.0	50.0	0.7	50.0	5.0	3.6	3.5	4.2	0.9	50.0	0.9	2.9	2.2	5.3	5.5	16.1	18.4
299 A	T	0.7	3.2	9.9	10.4	20.0	6.2	20.0	10.7	6.7	20.0	4.1	12.9	50.0	5.9	11.8	0.0	2.5	8.2	13.3	20.0
325 A	N	2.5	3.5	7.7	2.5	20.0	8.0	20.0	0.0	6.1	20.0	7.8	1.2	12.8	0.8	20.0	2.7	0.0	1.0	20.0	20.0
328 A	L	6.1	6.3	7.1	4.2	50.0	8.8	20.0	50.0	4.6	0.0	7.2	6.1	50.0	4.0	6.3	6.7	50.0	50.0	20.0	50.0
330 A	A	0.9	1.8	1.2	0.0	2.5	4.0	2.9	1.7	1.2	1.6	2.8	0.9	20.0	0.4	1.0	0.2	0.5	1.7	6.2	2.9
332 A	I	1.9	3.8	4.6	1.3	5.1	7.1	1.8	3.4	0.2	0.0	2.6	3.8	20.0	0.6	2.4	2.3	2.5	4.2	20.0	5.6
239 B	S	1.0	2.4	3.5	2.0	6.7	5.6	2.9	3.1	0.3	0.0	1.9	2.1	50.0	1.5	1.8	1.4	1.4	5.2	20.0	4.2
240 B	V	0.3	2.4	6.9	11.7	20.0	6.6	20.0	8.3	12.3	20.0	14.2	7.4	0.0	13.4	20.0	1.3	1.9	0.9	20.0	20.0
263 B	V	2.4	3.9	4.5	12.5	20.0	9.3	20.0	15.8	17.1	2.1	20.0	5.3	50.0	13.8	20.0	3.9	2.2	0.0	30.0	20.0
264 B	V	2.2	3.2	4.8	2.7	7.4	6.9	6.0	0.0	1.9	1.9	3.8	3.7	9.9	3.1	2.2	2.7	2.4	0.9	14.7	18.2
266 B	V	5.4	5.5	7.5	13.2	20.0	12.1	20.0	2.6	20.0	20.0	20.0	5.4	50.0	16.1	20.0	6.0	4.7	0.0	50.0	50.0
296 B	Y	1.5	2.7	1.3	1.2	4.0	4.1	3.6	1.1	1.9	2.6	3.5	0.0	20.0	0.7	1.8	1.1	1.4	1.3	6.5	4.2
299	T	0.0	2.2	7.5	10.	20.	4.8	20.	7.7	5.8	20.	10.	5.1	50.	10.	18.	0.3	1.1	5.4	20.	20.

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B					2	0		0			0	3		0	2	4				0	0
325 B	N	3.4	5.1	8.6	5.0	20.0	8.2	20.0	16.7	20.0	20.0	20.0	0.0	19.7	6.3	20.0	4.6	8.6	18.2	20.0	20.0
328 B	L	3.6	3.5	3.8	3.9	50.0	8.3	7.0	50.0	2.9	0.0	1.9	3.8	50.0	3.4	8.4	4.7	2.9	12.5	50.0	50.0
330 B	A	0.7	2.1	2.9	0.7	2.7	4.0	1.4	4.8	0.0	2.2	2.3	0.8	20.0	0.2	0.8	1.1	0.2	4.7	7.8	3.2
332 B	I	1.8	2.9	1.2	1.8	13.5	7.0	9.9	1.7	3.2	0.0	1.7	1.9	50.0	1.2	5.4	2.0	2.0	3.3	20.0	20.0

SPA™ technology; D129G 1IIS template structure; + carbohydrate

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Table 57

Pos	WT	A	C	D	E	F	G	H	I	K	L	M	N	P	Q	R	S	T	V	W	Y
239 A	S	1.2	3.5	1.7	0.0	20.0	5.8	11.0	6.6	2.9	3.9	3.9	2.7	8.5	1.3	2.7	0.6	3.5	5.4	20.0	20.0
240 A	V	1.2	2.4	6.0	14.0	20.0	7.1	20.0	6.7	9.4	10.1	7.5	4.4	1.8	14.8	20.0	2.0	0.4	0.0	20.0	20.0
263 A	V	0.0	0.4	1.0	8.7	20.0	6.9	4.4	11.7	4.9	16.0	19.2	0.8	50.0	11.7	20.0	1.4	0.1	1.0	20.0	20.0
264 A	V	2.9	3.7	6.3	2.8	11.6	7.6	13.2	0.0	3.2	3.4	4.1	4.2	7.1	2.9	3.4	3.1	1.9	0.8	12.8	16.3
266 A	V	4.8	6.9	6.8	9.5	50.0	10.3	20.0	3.5	12.7	12.2	12.7	4.1	50.0	11.9	11.9	5.2	2.9	0.0	50.0	50.0
296 A	Y	0.8	2.0	1.5	0.1	0.2	3.4	1.5	6.6	1.7	0.6	1.8	1.2	2.6	0.0	1.6	0.2	2.5	5.6	3.8	0.0
299 A	T	1.9	3.7	7.5	0.0	20.0	7.9	14.2	2.9	0.8	3.4	4.4	2.3	50.0	1.9	3.0	3.5	4.1	3.3	20.0	20.0
325 A	N	1.0	1.4	3.1	2.8	20.0	7.4	20.0	8.5	7.7	10.4	6.1	2.8	15.4	5.4	20.0	0.0	0.1	3.8	20.0	20.0
328 A	L	2.5	5.3	4.0	1.9	50.0	7.5	20.0	20.0	1.6	0.2	0.0	2.9	50.0	0.4	4.8	3.2	2.9	7.0	50.0	50.0
330 A	A	0.9	2.1	1.8	1.2	2.4	2.7	3.1	3.1	1.4	2.1	3.5	0.5	20.0	0.8	1.9	0.0	0.5	2.9	5.2	2.9
332 A	I	2.9	3.7	3.9	0.9	6.1	7.8	2.5	0.0	2.7	0.8	2.8	3.5	50.0	0.7	3.7	2.9	2.5	1.0	8.1	6.9
239 B	S	1.9	3.1	3.0	1.9	1.5	6.2	2.3	14.1	1.8	1.4	2.9	1.8	0.0	1.9	3.2	1.9	2.3	7.7	6.6	15.8
240 B	V	0.5	1.7	5.0	13.3	20.0	6.6	20.0	1.2	12.4	12.1	8.8	4.6	6.3	20.0	20.0	1.0	0.2	0.0	20.0	20.0
263 B	V	2.9	3.2	6.4	18.2	10.1	9.2	6.9	12.8	6.0	20.0	10.3	5.7	50.0	17.5	20.0	3.2	2.2	0.0	20.0	20.0
264 B	V	2.9	3.6	4.4	3.0	8.8	7.1	6.2	0.0	2.3	1.9	4.5	3.4	1.7	3.2	3.5	3.5	2.0	0.9	12.0	18.4
266 B	V	4.4	4.6	2.6	6.6	20.0	10.7	20.0	0.0	4.9	1.7	8.5	5.6	50.0	6.0	12.4	5.3	4.6	1.5	20.0	50.0
296 B	Y	0.0	7.1	6.7	7.2	20.0	0.1	18.6	50.0	7.0	2.7	6.6	6.8	50.0	7.2	9.3	2.3	50.0	50.0	20.0	14.1
299	T	0.0	3.2	10.	6.0	20.	5.5	20.	15.	3.2	5.9	4.4	6.4	50.	5.7	9.4	1.2	1.4	13.	20.	20.

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B				4		0		0	9					0					7	0	0
325 B	N	1.4	2.6	5.0	0.0	20.0	7.9	20.0	20.0	1.0	2.2	1.0	0.3	1.9	1.1	20.0	2.8	5.1	20.0	20.0	20.0
328 B	L	0.4	1.3	5.6	0.0	50.0	4.5	50.0	50.0	1.9	2.4	2.4	8.3	50.0	0.8	16.4	1.0	1.2	50.0	50.0	50.0
330 B	A	0.6	1.4	2.5	0.9	3.1	2.5	1.2	20.0	0.0	2.4	2.1	0.3	20.0	0.4	0.6	0.0	4.0	20.0	13.5	3.4
332 B	I	4.3	5.3	5.7	0.0	11.4	9.3	4.3	2.5	5.8	2.0	4.0	6.5	17.9	3.7	5.9	4.6	4.2	3.7	20.0	11.6

SPA™ technology; D129G 11IX template structure; + carbohydrate

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Table 58

Pos	WT	A	C	D	E	F	G	H	I	K	L	M	N	P	Q	R	S	T	V	W	Y
238 A	S	1.2	2.3	2.2	1.8	7.9	5.5	7.6	0.5	0.2	1.8	2.6	1.4	0.9	1.3	1.9	1.5	0.8	0.0	8.6	9.6
240 A	V	0.7	2.9	6.8	4.3	20.0	6.5	20.0	0.0	10.7	20.0	3.1	9.1	2.1	7.7	20.0	1.4	1.1	2.4	20.0	20.0
263 A	V	1.7	2.9	4.6	18.8	20.0	8.4	5.8	15.1	2.3	14.5	2.1	3.2	50.0	20.0	15.0	3.6	1.2	0.0	20.0	20.0
264 A	V	2.7	3.3	3.6	1.5	13.9	6.7	5.9	0.0	2.3	4.9	3.7	3.2	1.9	2.5	3.0	3.0	2.5	0.7	19.9	19.0
266 A	V	3.5	3.5	5.7	12.4	20.0	10.0	20.0	5.7	6.3	7.8	7.4	5.2	50.0	16.6	20.0	4.2	1.7	0.0	20.0	50.0
296 A	Y	2.8	50.0	50.0	50.0	50.0	0.0	50.0	50.0	18.5	18.0	50.0	50.0	50.0	50.0	50.0	50.0	50.0	50.0	50.0	13.6
299 A	T	0.2	0.7	6.6	1.2	20.0	5.6	9.6	1.6	0.8	1.5	1.8	4.8	50.0	1.0	9.2	0.0	0.0	1.6	20.0	20.0
325 A	N	3.1	3.6	7.3	2.4	20.0	7.7	20.0	20.0	20.0	10.0	13.1	3.6	50.0	0.0	20.0	4.0	9.7	20.0	20.0	20.0
328 A	L	0.6	0.0	1.5	5.4	50.0	1.6	50.0	50.0	3.1	4.2	9.6	1.4	50.0	6.9	9.6	0.6	0.1	50.0	50.0	50.0
330 A	A	1.9	2.5	4.1	2.8	4.5	4.1	3.0	3.2	1.0	2.7	3.5	2.1	20.0	2.4	2.6	1.3	0.0	3.9	7.6	5.3
332 A	I	2.3	3.5	2.2	0.8	20.0	6.8	9.6	0.0	3.4	0.2	2.6	2.8	14.5	3.3	4.6	2.6	1.3	0.9	10.5	20.0
239 B	S	1.4	3.6	2.5	1.4	16.8	5.8	6.2	5.0	2.5	1.4	2.0	3.8	0.3	0.5	2.4	0.0	1.6	5.3	20.0	19.5
240 B	V	0.0	2.6	12.8	16.6	20.0	5.7	20.0	12.7	10.4	20.0	8.5	15.1	3.1	20.0	20.0	1.0	0.2	2.4	20.0	20.0
263 B	V	1.1	2.4	3.6	20.0	20.0	7.8	17.7	11.8	4.5	20.0	6.3	3.3	50.0	20.0	20.0	3.2	1.2	0.0	20.0	20.0
264 B	V	3.3	4.0	6.0	2.9	14.2	7.5	4.8	0.0	2.6	3.6	4.6	3.5	1.7	3.1	4.1	3.9	2.9	1.3	6.9	20.0
266 B	V	2.9	3.3	4.9	11.3	50.0	9.5	20.0	20.0	20.0	7.9	15.0	4.5	50.0	4.9	20.0	1.9	0.0	3.6	50.0	50.0
296 B	Y	2.8	50.0	50.0	50.0	50.0	0.0	50.0	50.0	17.7	18.7	50.0	50.0	50.0	50.0	50.0	50.0	50.0	50.0	50.0	11.3
299	T	0.0	3.8	12.	9.2	20.	5.9	20.	7.3	4.8	3.2	4.3	8.0	50.	12.	8.8	0.2	2.1	4.4	20.	20.

B				6		0		0						0	3				0	0
325 B	N	0.3	2.0	5.5	2.2	50.0	6.1	20.0	0.0	10.5	15.5	14.6	1.3	10.0	2.4	20.0	2.3	2.0	1.0	20.0	50.0
328 B	L	5.4	5.7	7.3	4.4	50.0	9.8	20.0	50.0	2.5	0.0	5.1	5.9	50.0	2.8	7.4	6.1	6.4	50.0	50.0	50.0
330 B	A	0.6	1.4	3.2	1.3	3.9	3.2	2.7	4.0	1.3	3.7	3.1	0.7	20.0	0.6	1.3	0.0	0.4	4.2	8.2	3.6
332 B	I	1.9	3.1	2.7	1.7	5.2	6.9	3.1	0.4	1.3	0.0	1.9	2.6	7.7	1.3	2.2	2.3	1.6	2.0	10.4	5.6

SPA™ technology; D129G 1E4K template structure; + carbohydrate

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Table 59

Pos	WT	A	C	D	E	F	G	H	I	K	L	M	N	P	Q	R	S	T	V	W	Y
239 A	S	1.4	2.6	3.1	1.0	20.0	5.7	4.8	3.4	2.0	1.2	2.6	1.6	4.8	0.0	2.1	1.3	2.1	3.3	13.8	19.6
240 A	V	2.9	3.5	3.7	4.6	20.0	8.2	10.8	0.0	9.1	3.2	5.4	3.1	4.8	5.5	17.5	4.0	1.8	1.2	20.0	20.0
263 A	V	3.6	4.9	6.2	8.7	20.0	9.9	20.0	3.7	4.2	0.5	6.7	6.1	50.0	9.5	20.0	5.1	3.6	0.0	20.0	20.0
264 A	V	1.8	2.8	3.3	2.0	2.9	6.2	3.1	0.0	2.4	0.8	3.0	2.4	6.1	1.4	2.8	2.4	1.9	0.8	10.2	2.2
266 A	V	4.4	5.2	4.9	7.1	20.0	10.6	20.0	1.0	12.1	4.8	9.1	4.6	50.0	7.9	12.6	5.8	3.5	0.0	20.0	20.0
296 A	Y	1.2	2.9	0.7	1.4	3.1	3.9	2.7	2.4	2.3	1.9	2.2	0.0	1.6	1.4	3.0	0.9	1.0	3.5	6.0	2.6
299 A	T	0.0	2.6	6.0	11.5	20.0	5.3	20.0	20.0	6.0	20.0	4.4	3.0	50.0	14.1	13.2	0.9	3.8	15.1	15.0	20.0
325 A	N	5.2	7.0	6.6	6.9	50.0	11.3	20.0	1.3	14.3	13.5	13.9	0.0	5.0	6.0	20.0	6.0	4.6	3.2	20.0	50.0
328 A	L	4.8	5.5	7.0	3.2	20.0	10.5	20.0	50.0	5.1	0.0	8.5	5.5	50.0	3.5	8.2	5.5	13.4	50.0	20.0	50.0
330 A	A	0.9	1.8	1.1	0.9	3.5	4.0	3.0	2.3	1.2	1.6	2.8	0.0	14.5	0.9	1.1	0.1	0.4	2.0	6.4	3.2
332 A	I	5.3	6.4	6.7	4.8	8.2	9.9	5.2	3.1	0.0	3.6	5.2	6.8	20.0	3.5	4.6	5.5	4.8	4.0	11.2	7.1
239 B	S	0.7	2.3	2.6	2.0	5.3	5.1	3.3	1.7	0.0	0.0	2.0	0.8	15.5	0.9	0.8	0.7	0.7	3.3	8.2	6.0
240 B	V	2.3	3.0	4.1	7.3	20.0	8.1	20.0	5.1	20.0	11.8	10.9	3.8	2.0	17.0	20.0	3.6	1.3	0.0	20.0	20.0
263 B	V	3.2	4.3	7.3	8.3	20.0	9.6	20.0	13.3	8.5	0.6	20.0	6.0	50.0	8.5	20.0	4.6	4.0	0.0	20.0	20.0
264 B	V	2.1	3.2	3.7	2.7	17.8	6.6	11.5	0.0	2.0	0.8	3.5	3.0	7.8	2.0	1.5	2.5	1.3	1.0	13.9	20.0
266 B	V	5.0	5.0	5.2	16.3	20.0	11.2	20.0	2.3	20.0	14.3	17.3	2.5	50.0	11.6	20.0	5.4	3.9	0.0	20.0	20.0
296 B	Y	0.9	2.3	1.0	0.5	2.7	3.7	2.5	1.2	1.3	2.1	3.0	0.0	7.0	0.4	1.1	0.3	0.8	1.8	6.0	2.4
299	T	1.1	2.2	7.6	5.4	20.	6.4	12.	1.8	3.9	17.	6.9	3.9	20.	4.6	10.	0.8	0.0	1.9	20.	20.

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B						0		8			5			0		3				0	0
325 B	N	10.1	11.5	13.1	11.2	20.0	15.7	20.0	8.6	14.3	17.1	20.0	0.0	16.1	10.6	20.0	11.1	10.9	10.5	20.0	20.0
328 B	L	2.9	4.1	4.8	3.5	50.0	8.5	1.7	9.6	1.5	0.0	1.5	3.5	50.0	3.3	2.0	3.3	1.9	5.2	50.0	50.0
330 B	A	0.1	2.0	1.4	1.8	1.6	4.0	3.0	2.0	0.5	0.5	2.6	0.0	20.0	0.7	2.0	0.3	0.6	2.1	4.4	2.4
332 B	I	3.4	4.4	3.5	3.1	6.1	8.2	4.1	0.0	3.3	1.3	3.3	4.0	15.7	0.8	2.1	3.9	2.7	1.1	20.0	6.1

SPA™ technology; FcγRIIb model template structure; - carbohydrate

[202] The results of the design calculations presented above in Tables 1 – 59 were used to construct a series of Fc variant libraries for experimental production and screening. Experimental libraries were designed in successive rounds of computational and experimental screening. Design of subsequent Fc libraries benefitted from feedback from prior libraries, and thus typically comprised combinations of Fc variants that showed favorable properties in the previous screen. The entire set of Fc variants that were constructed and experimentally tested is shown in Table 60. In this table, row 1 lists the variable positions, and the rows that follow indicate the amino acids at those variable positions for WT and the Fc variants. For example, variant 18 has the following four mutations: F241E, F243Y, V262T, and V264R. The variable position residues that compose this set of Fc variants are illustrated structurally in Figure 3, and are presented in the context of the human IgG1 Fc sequence in Figure 4.

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Table 60

Position	234	235	239	240	241	243	244	245	247	262	263	264	265	266	267	269	296	297	298	299	313	325	326	327	328	329	330	332	333	334
WT	L	L	S	V	F	F	P	P	P	V	V	V	D	V	S	E	Y	N	S	T	W	N	K	A	L	P	A	I	E	K
1												A																		
2												L																		
3												I																		
4					W																									
5					L																									
6						W																								
7						L																								
8					L	L				I		I																		
9					W	W																								
10					W	W				A		A																		
11					L					I																				
12						L						I																		
13						L				I		W																		
14					Y	Y				T		T																		
15					E	R				E		R																		
16					E	Q				T		E																		
17					R	Q				T		R																		
18					E	Y				T		R																		
19																									M					
20																									E					
21																									F					
22																												E		
23																									M			E		
24							H																							
25								A																						
26									V																					
27																					F									
28							H	A	V																					
29									G																					
30												I																E		

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Table 60 (continued)

Position	234	235	239	240	241	243	244	245	247	262	263	264	265	266	267	269	296	297	298	299	313	325	326	327	328	329	330	332	333	334
WT	L	L	S	V	F	F	P	P	P	V	V	V	D	V	S	E	Y	N	S	T	W	N	K	A	L	P	A	I	E	K
31					E	R				E		R																E		
32					E	Q				T		E																E		
33					R	Q				T		R																E		
34					E	Y				T		R																E		
35																			A											
36																			A									E		
37																			A										A	A
41			E																									E		
42			Q																									E		
43			E																											
44													G																	
45													N																	
46			E										G																	
47			E										N																	
48			E										Q																	
49																	E													
50																	Q													
51																			T											
52																			N											
53																				I										
54																								S						
55																								N						
56															Q									S						
57															L									S						
58																								L						
59																										F				
60																											L			
61																											Y			
62																												D		

Table 60 (continued)

Position	234	235	239	240	241	243	244	245	247	262	263	264	265	266	267	269	296	297	298	299	313	325	326	327	328	329	330	332	333	334
WT	L	L	S	V	F	F	P	P	P	V	V	V	D	V	S	E	Y	N	S	T	W	N	K	A	L	P	A	I	E	K
62																												D		
63																		S												
64																		D												
65																		S										E		
66																		D										E		
67																		E										E		
68													Y					D										E		
69													Y					D										E		
70													F					E										E		
71																									I			E		
72																									Q			E		
73																												N		
74																												Q		
75												T																		
76												F																		
77				I																										
78											I																			
79														I																
80																				A										
81																				S										
82																				V										
83																						Q								
84																						L								
85																						I								
86			D																											
87			N																											
88			F																											
89			D																									D		
90			D																									E		
91			D																									N		
92			D																									Q		

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Table 60 (continued)

Position	234	235	239	240	241	243	244	245	247	262	263	264	265	266	267	269	296	297	298	299	313	325	326	327	328	329	330	332	333	334
WT	L	L	S	V	F	F	P	P	P	V	V	V	D	V	S	E	Y	N	S	T	W	N	K	A	L	P	A	I	E	K
93			E																									D		
94			E																									N		
95			E																									Q		
96			N																									D		
97			N																									E		
98			N																									N		
99			N																									Q		
100			Q																									D		
101			Q																									N		
102			Q																									Q		
103																							E							
104																	D													
105																	N													
106					Y	Y				T		T						D										E		
107																											Y	E		
108												I															Y	E		
109																											L	E		
110												I															L	E		
111	D																													
112	E																													
112	N																													
114	Q																													
115	T																													
116	H																													
117	Y																													
118	I																													
119	V																													
120	F																													
121		D																												
122		S																												

Table 60 (continued)

Position	234	235	239	240	241	243	244	245	247	262	263	264	265	266	267	269	296	297	298	299	313	325	326	327	328	329	330	332	333	334
WT	L	L	S	V	F	F	P	P	P	V	V	V	D	V	S	E	Y	N	S	T	W	N	K	A	L	P	A	I	E	K
123		N																												
124		Q																												
125		T																												
126		H																												
127		Y																												
128		I																												
129		V																												
130		F																												
131			T																											
132			H																											
133			Y																											
134				A																										
135				T																										
136				M																										
137											A																			
138											T																			
139											M																			
140												M																		
141												Y																		
142														A																
143														T																
144														M																
145																H														
146																Y														
147																F														
148																R														
149																	S													
150																	T													
151																	L													
152																	I													

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Table 60 (continued)

Position	234	235	239	240	241	243	244	245	247	262	263	264	265	266	267	269	296	297	298	299	313	325	326	327	328	329	330	332	333	334
WT	L	L	S	V	F	F	P	P	P	V	V	V	D	V	S	E	Y	N	S	T	W	N	K	A	L	P	A	I	E	K
153																			H											
154																				H										
155																											V			
156																											I			
157																											F			
158																											R			
159																											H			
160																						D								
161																						E								
162																						A								
163																						T								
164																						V								
165																						H								
166																									D			E		
167																									E			E		
168																									N			E		
169																									Q			E		
170																									V			E		
171																									T			E		
172																									H			E		
173																									I			E		
174																									A					
175																												T		
176																												H		
177																												Y		
178																												A		
179			E									I																E		
180			Q									I																E		
181			E									I															Y	E		
182			E									I							A								Y	E		

Table 60 (continued)

Position	234	235	239	240	241	243	244	245	247	262	263	264	265	266	267	269	296	297	298	299	313	325	326	327	328	329	330	332	333	334
WT	L	L	S	V	F	F	P	P	P	V	V	V	D	V	S	E	Y	N	S	T	W	N	K	A	L	P	A	I	E	K
183			D															D										E		
184			E															D										E		
185			D										V					D										E		
186			D										I					D										E		
187			D										L					D										E		
188			D										F					D										E		
189			D										Y					D										E		
190			D										H					D										E		
191			D										T					D										E		
192												E						D										E		
193																	D	D										E		
194																	E	D										E		
195																	N	D										E		
196																	Q	D										E		
197																	H	D										E		
198																	T	D										E		
199																		D		V								E		
200																		D		I								E		
201																		D		L								E		
202																		D		F								E		
203																		D		H								E		
204																		D		E								E		
205																		D									Y	E		
206																		D	A								Y	E		
207			D																								Y	E		
208			N																								Y	E		
209			D																								L	E		
210			N																								L	E		
211												I							A									E		
212			D																A									E		

Table 60 (continued)

Position	234	235	239	240	241	243	244	245	247	262	263	264	265	266	267	269	296	297	298	299	313	325	326	327	328	329	330	332	333	334
WT	L	L	S	V	F	F	P	P	P	V	V	V	D	V	S	E	Y	N	S	T	W	N	K	A	L	P	A	I	E	K
213			N																A									E		
214			D									I																E		
215			D									I							A									E		
216			D									I															L	E		

[203] Example 2: Experimental production and screening of Fc libraries

The majority of experimentation on the Fc variants was carried out in the context of the anti-cancer antibody alemtuzumab (Campath®, a registered trademark of Ilex Pharmaceuticals LP). Alemtuzumab binds a short linear epitope within its target antigen CD52 (Hale *et al.*, 1990, *Tissue Antigens* 35:118-127; Hale, 1995, *Immunotechnology* 1:175-187). Alemtuzumab has been chosen as the primary engineering template because its efficacy is due in part to its ability to recruit effector cells (Dyer *et al.*, 1989, *Blood* 73:1431-1439; Friend *et al.*, 1991, *Transplant Proc* 23:2253-2254; Hale *et al.*, 1998, *Blood* 92:4581-4590; Glennie *et al.*, 2000, *Immunol Today* 21:403-410), and because production and use of its antigen in binding assays are relatively straightforward. In order to evaluate the optimized Fc variants of the present invention in the context of other antibodies, select Fc variants were evaluated in the anti-CD20 antibody rituximab (Rituxan®, a registered trademark of IDEC Pharmaceuticals Corporation), and the anti-Her2 antibody trastuzumab (Herceptin®, a registered trademark of Genentech). The use of alemtuzumab, rituximab, and trastuzumab for screening purposes is not meant to constrain the present invention to any particular antibody.

[204] The IgG1 full length light (V_L-C_L) and heavy (V_H-Cγ1-Cγ2-Cγ3) chain antibody genes for alemtuzumab, rituximab, and trastuzumab were constructed with convenient and restriction sites to facilitate subcloning. The genes were ligated into the mammalian expression vector pcDNA3.1Zeo (Invitrogen). The V_H-Cγ1-Cγ2-Cγ3 clone in pcDNA3.1zeo was used as a template for mutagenesis of the Fc region. Mutations were introduced into this clone using PCR-based mutagenesis techniques. Fc variants were sequenced to confirm the fidelity of the sequence. Plasmids containing heavy chain gene (V_H-Cγ1-Cγ2-Cγ3) (wild-type or variants) were co-transfected with plasmid containing light chain gene (V_L-C_L) into 293T cells. Media were harvested 5 days after transfection. Expression of immunoglobulin was monitored by screening the culture supernatant of transfectomas by western using peroxidase-conjugated goat-anti human IgG (Jackson ImmunoResearch, catalog # 109-035-088). Figure 6 shows expression of wild-type alemtuzumab and variants 1 through 10 in 293T cells. Antibodies were purified from the supernatant using protein A affinity chromatography (Pierce, Catalog # 20334. Figure 7 shows results of the protein purification for WT alemtuzumab. Antibody Fc variants showed similar expression and purification results to WT. Some Fc variants were deglycoeylated in order to determine their solution and functional properties in the absence of carbohydrate. To obtain deglycosylated antibodies, purified alemtuzumab antibodies were incubated with peptide-N-glycosidase (PNGase F) at 37°C for 24h. Figure 8 presents an SDS PAGE gel confirming deglycosylation for several Fc variants and WT alemtuzumab.

[205] In order to confirm the functional fidelity of alemtuzumab produced under these conditions, the antigenic CD52 peptide, fused to GST, was expressed in E.coli BL21 (DE3) under IPTG induction. Both un-induced and induced samples were run on a SDS PAGE gel, and transferred to PVDF membrane. For western analysis, either alemtuzumab from Sotec (final concentration 2.5ng/ul) or

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media of transfected 293T cells (final alemtuzumab concentration about 0.1-0.2ng/ul) were used as primary antibody, and peroxidase-conjugated goat-anti human IgG was used as secondary antibody. Figure 9 presents these results. The ability to bind target antigen confirms the structural and functional fidelity of the expressed alemtuzumab. Fc variants that have the same variable region as WT alemtuzumab are anticipated to maintain a comparable binding affinity for antigen.

[206] In order to screen for Fc/FcγR binding, the extracellular regions of human V158 FcγRIIIa, human F158 FcγRIIIa, human FcγRIIb, human FcγRIIa, and mouse FcγRIII, were expressed and purified. Figure 10 presents an SDS PAGE gel that shows the results of expression and purification of human V158 FcγRIIIa. The extracellular region of this receptor was obtained by PCR from a clone obtained from the Mammalian Gene Collection (MGC:22630). The receptor was fused with glutathione S-Transferase (GST) to enable screening. Tagged Fc□RIIIa was transfected in 293T cells, and media containing secreted Fc□RIIIa were harvested 3 days later and purified. For western analysis, membrane was probed with anti-GST antibody.

[207] Binding affinity to Fc□RIIIa and FcγRIIb was measured for all designed Fc variants using an AlphaScreen™ assay (Amplified Luminescent Proximity Homogeneous Assay (ALPHA), PerkinElmer, Wellesley, MA), a bead-based non-radioactive luminescent proximity assay. Laser excitation of a donor bead excites oxygen, which if sufficiently close to the acceptor bead generates a cascade of chemiluminescent events, ultimately leading to fluorescence emission at 520-620 nm. The AlphaScreen™ assay was applied as a competition assay for screening Fc variants. WT alemtuzumab antibody was biotinylated by standard methods for attachment to streptavidin donor beads, and GST-tagged FcγR was bound to glutathione chelate acceptor beads. In the absence of competing Fc variants, WT antibody and FcγR interact and produce a signal at 520-620 nm. Addition of untagged Fc variant competes with the WT Fc/FcγR interaction, reducing fluorescence quantitatively to enable determination of relative binding affinities. All Fc variants were screened for V158 FcγRIIIa binding using the AlphaScreen™ assay. Select Fc variants were subsequently screened for binding to FcγRIIb, as well as other FcγRs and Fc ligands.

[208] Figure 11 shows AlphaScreen™ data for binding to human V158 FcγRIIIa by select Fc variants. The binding data were normalized to the maximum and minimum luminescence signal provided by the baselines at low and high concentrations of competitor antibody respectively. The data were fit to a one site competition model using nonlinear regression, and these fits are represented by the curves in the figure. These fits provide the inhibitory concentration 50% (IC50) (i.e. the concentration required for 50% inhibition) for each antibody, illustrated by the dotted lines in Figure 11, thus enabling the relative binding affinities of Fc variants to be quantitatively determined. Here, WT alemtuzumab has an IC50 of $(4.63 \times 10^{-6})x(2) = 9.2$ nM, whereas S239D has an IC50 of $(3.98 \times 10^{-10})x(2) = 0.8$ nM. Thus S239D alemtuzumab binds 9.2 nM / 0.8 nM = 11.64-fold more tightly

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than WT alemtuzumab to human V158 FcγRIIIa. Similar calculations were performed for the binding of all Fc variants to human V158 FcγRIIIa. Select Fc variants were also screened for binding to human FcγRIIb, and examples of these AlphaScreen™ binding data are shown in Figure 12. Table 61 presents the fold-enhancement or fold-reduction relative to the parent antibody for binding of Fc variants to human V158 FcγRIIIa (column 3) and human FcγRIIb (column 4), as determined by the AlphaScreen™ assay. For these data, a fold above 1 indicates an enhancement in binding affinity, and a fold below 1 indicates a reduction in binding affinity relative to WT Fc. All data were obtained in the context of alemtuzumab, except for those indicated with an asterix (*), which were tested in the context of trastuzumab.

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Table 61

Variant	Substitution(s)	FcγRIIIa Fold	FcγRIIb Fold	FcγIIIa-fold : FcγIIb-fold
1	V264A	0.53		
2	V264L	0.56		
3	V264I	1.43		
4	F241W	0.29		
5	F241L	0.26		
6	F243W	0.51		
7	F243L	0.51		
8	F241L/F243L/V262I/V264I	0.09		
9	F241W/F243W	0.07		
10	F241W/F243W/V262A/V264A	0.04		
11	F241L/V262I	0.06		
12	F243L/V264I	1.23		
13	F243L/V262I/V264W	0.02		
14	F241Y/F243Y/V262T/V264T	0.05		
15	F241E/F243R/V262E/V264R	0.06		
16	F241E/F243Q/V262T/V264E	0.07		
17	F241R/F243Q/V262T/V264R	0.02		
18	F241E/F243Y/V262T/V264R	0.05		
19	L328M	0.21		
20	L328E	0.12		
21	L328F	0.24		
22	I332E	6.72	3.93	1.71
23	L328M/I332E	2.60		
24	P244H	0.83		
25	P245A	0.25		
26	P247V	0.53		
27	W313F	0.88		
28	P244H/P245A/P247V	0.93		
29	P247G	0.54		
30	V264I/I332E	12.49	1.57*	7.96
31	F241E/F243R/V262E/V264R/I332E	0.19		
32	F241E/F243Q/V262T/V264E/I332E			
33	F241R/F243Q/V262T/V264R/I332E			
34	F241E/F243Y/V262T/V264R/I332E	0.10		
35	S298A	2.21		
36	S298A/I332E	21.73		
37	S298A/E333A/K334A	2.56		
41	S239E/I332E	5.80	3.49	1.66
42	S239Q/I332E	6.60	4.66	1.41
43	S239E	10.16		
44	D265G	<0.02		
45	D265N	<0.02		
46	S239E/D265G	<0.02		
47	S239E/D265N	0.02		
48	S239E/D265Q	0.05		
49	Y296E	0.73	1.11	0.66
50	Y296Q	0.62	0.43	1.21

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Table 61 (continued)

Variant	Substitution(s)	FcγRIIIa Fold	FcγRIIb Fold	FcγIIIa-fold : FcγIIb-fold
51	S298T	0.94	<0.02	
52	S298N	0.41	<0.02	
53	T299I	<0.02		
54	A327S	0.23	0.39	0.59
55	A327N	0.19	1.15	0.17
56	S267Q/A327S	0.03		
57	S267L/A327S	<0.02		
58	A327L	0.05		
59	P329F	<0.02		
60	A330L	0.73	0.38	1.92
61	A330Y	1.64	0.75	2.19
62	I332D	17.80	3.34	5.33
63	N297S	<0.02		
64	N297D	<0.02		
65	N297S/I332E	<0.02		
66	N297D/I332E	0.08	<0.02	
67	N297E/I332E	<0.02		
68	D265Y/N297D/I332E	<0.02		
69	D265Y/N297D/T299L/I332E	<0.02		
70	D265F/N297E/I332E	<0.02		
71	L328I/I332E	7.03		
72	L328Q/I332E	1.54		
73	I332N	0.39		
74	I332Q	0.37		
75	V264T	2.73		
76	V264F	0.16		
77	V240I	3.25		
78	V263I	0.10		
79	V266I	1.86		
80	T299A	0.03		
81	T299S	0.15		
82	T299V	<0.02		
83	N325Q	<0.02		
84	N325L	<0.02		
85	N325I	<0.02		
86	S239D	11.64	4.47*	2.60
87	S239N	<0.02		
88	S239F	0.22	<0.02	
89	S239D/I332D	14.10		
90	S239D/I332E	56.10	19.71*	2.85
91	S239D/I332N	7.19		
92	S239D/I332Q	9.28		
93	S239E/I332D	9.33		
94	S239E/I332N	11.93		
95	S239E/I332Q	3.80		
96	S239N/I332D	3.08		
97	S239N/I332E	14.21		
98	S239N/I332N	0.43		

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Table 61 (continued)

Variant	Substitution(s)	FcγRIIIa Fold	FcγRIIb Fold	FcγIIIa-fold : FcγIIb-fold
99	S239N/I332Q	0.56		
100	S239Q/I332D	5.05		
101	S239Q/I332N	0.39		
102	S239Q/I332Q	0.59		
103	K326E	3.85		
104	Y296D	0.62		
105	Y296N	0.29		
106	F241Y/F243Y/V262T/V264T/N297D/I332E	0.15		
107	A330Y/I332E	12.02	4.40	2.73
108	V264I/A330Y/I332E	12.00	3.64	3.39
109	A330L/I332E	10.34	2.03	5.09
110	V264I/A330L/I332E	11.15	1.79	6.23
111	L234D	0.21		
112	L234E	1.34	2.21	0.61
113	L234N	0.56	1.39	0.40
114	L234Q	0.37		
115	L234T	0.35		
116	L234H	0.33		
117	L234Y	1.42	1.08	1.31
118	L234I	1.55	1.14	1.36
119	L234V	0.38		
120	L234F	0.30		
121	L235D	1.66	3.63	0.46
122	L235S	1.25		
123	L235N	0.40		
124	L235Q	0.51		
125	L235T	0.52		
126	L235H	0.41		
127	L235Y	1.19	10.15	0.12
128	L235I	1.10	0.94	1.17
129	L235V	0.48		
130	L235F	0.73	3.53	0.21
131	S239T	1.34		
132	S239H	0.20		
133	S239Y	0.21		
134	V240A	0.70	0.14	5.00
135	V240T			
136	V240M	2.06	1.38	1.49
137	V263A			
138	V263T	0.43		
139	V263M	0.05		
140	V264M	0.26		
141	V264Y	1.02	0.27	3.78
142	V266A	<0.02		
143	V266T	0.45		
144	V266M	0.62		
145	E269H	<0.02		
146	E269Y	0.12		

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Table 61 (continued)

Variant	Substitution(s)	FcγRIIIa Fold	FcγRIIb Fold	FcγIIIa-fold : FcγIIb-fold
147	E269F	0.16		
148	E269R	0.05		
149	Y296S	0.12		
150	Y296T	<0.02		
151	Y296L	0.22		
152	Y296I	0.09		
153	A298H	0.27		
154	T299H	<0.02		
155	A330V	0.43		
156	A330I	1.71	0.02	85.5
157	A330F	0.60		
158	A330R	<0.02		
159	A330H	0.52		
160	N325D	0.41		
161	N325E	<0.02		
162	N325A	0.11		
163	N325T	1.10		
164	N325V	0.48		
165	N325H	0.73		
166	L328D/I332E	1.34		
167	L328E/I332E	0.20		
168	L328N/I332E	<0.02		
169	L328Q/I332E	0.70		
170	L328V/I332E	2.06		
171	L328T/I332E	1.10		
172	L328H/I332E	<0.02		
173	L328I/I332E	3.49		
174	L328A	0.20		
175	I332T	0.72		
176	I332H	0.46		
177	I332Y	0.76		
178	I332A	0.89		
179	S239E/V264I/I332E	15.46		
180	S239Q/V264I/I332E	2.14		
181	S239E/V264I/A330Y/I332E	8.53		
182	S239E/V264I/S298A/A330Y/I332E			
183	S239D/N297D/I332E	0.28		
184	S239E/N297D/I332E	0.06		
185	S239D/D265V/N297D/I332E			
186	S239D/D265I/N297D/I332E			
187	S239D/D265L/N297D/I332E	<0.02		
188	S239D/D265F/N297D/I332E	<0.02		
189	S239D/D265Y/N297D/I332E	0.02		
190	S239D/D265H/N297D/I332E	0.04		
191	S239D/D265T/N297D/I332E	<0.02		
192	V264I/N297D/I332E	0.05		
193	Y296D/N297D/I332E			
194	Y296E/N297D/I332E	<0.02		

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Table 81 (continued)

Variant	Substitution(s)	FcγRIIIa Fold	FcγRIIb Fold	FcγIIIa-fold : FcγIIb-fold
195	Y296N/N297D/I332E	0.04		
196	Y296Q/N297D/I332E	<0.02		
197	Y296H/N297D/I332E	<0.02		
198	Y296T/N297D/I332E	<0.02		
199	N297D/T299V/I332E	<0.02		
200	N297D/T299I/I332E	<0.02		
201	N297D/T299L/I332E	<0.02		
202	N297D/T299F/I332E	<0.02		
203	N297D/T299H/I332E	<0.02		
204	N297D/T299E/I332E	<0.02		
205	N297D/A330Y/I332E	6.43		
206	N297D/S298A/A330Y/I332E			
207*	S239D/A330Y/I332E	129.58		
208*	S239N/A330Y/I332E	14.22		
209*	S239D/A330L/I332E	138.63	7.50	18.48
210*	S239N/A330L/I332E	12.95		
211*	V264I/S298A/I332E	16.50		
212*	S239D/S298A/I332E	295.16	6.16	47.92
213*	S239N/S298A/I332E	32.14	5.15	6.24
214*	S239D/V264I/I332E	36.58	14.39	2.54
215*	S239D/V264I/S298A/I332E			
216*	S239D/V264I/A330L/I332E			

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[209] Example 3: Selectively enhanced binding to FcγRs

A number of promising Fc variants with optimized properties were obtained from the FcγRIIIa and FcγRIIb screen. Table 61 provides Fc variants that bind more tightly to FcγRIIIa, and thus are candidates for improving the effector function of antibodies and Fc fusions. These include a number of variants that comprise substitutions at 239, 264, 330, and 332. Figure 13 shows AlphaScreen™ binding data for some of these Fc variants. The majority of these Fc variants provide substantially greater FcγRIIIa binding enhancements over S298A/E333A/K334A.

[210] Although the majority of Fc variants were screened in the context of the antibody alemtuzumab, select Fc variants were also screened in the context of rituximab and trastuzumab. AlphaScreen™ data for binding of select Fc variants to human V158 FcγRIIIa in the context of rituximab and trastuzumab are shown in Figures 14 and 15 respectively. The results indicate that the Fc variants display consistent binding enhancements regardless of the antibody context, and thus the Fc variants of the present invention are broadly applicable to antibodies and Fc fusions.

[211] Fc variants have been obtained that show differentially enhanced binding to FcγRIIIa over FcγRIIb. As discussed, optimal effector function may result from Fc variants wherein affinity for activating FcγRs is greater than affinity for the inhibitory FcγRIIb. AlphaScreen™ data directly comparing binding to FcγRIIIa and FcγRIIb for two Fc variants with this specificity profile are shown in Figures 16a and 16b. This concept can be defined quantitatively as the fold-enhancement or -reduction of the activating FγR (Table 61, column 3) divided by the fold-enhancement or -reduction of the inhibitory FcγR (Table 61, column 4), herein referred to as the FcγRIIIa-fold:FcγRIIb-fold ratio. This value provided in Column 5 in Table 61. Table 61 shows that Fc variants provide this specificity profile, with a FcγRIIIa-fold:FcγRIIb-fold ratio as high as 86:1.

[212] Some of the most promising Fc variants of the present invention for enhancing effector function have both substantial increases in affinity for FcγRIIIa and favorable FcγRIIIa-fold:FcγRIIb-fold ratios. These include, for example, S239D/I332E (FcγRIIIa-fold = 56, FcγRIIIa-fold:FcγRIIb-fold = 3), S239D/A330Y/I332E (FcγRIIIa-fold = 130), S239D/A330L/I332E (FcγRIIIa-fold = 139, FcγRIIIa-fold:FcγRIIb-feld = 18), and S239D/S298A/I332E (FcγRIIIa-fold = 295, FcγRIIIa-fold:FcγRIIb-fold = 48). Figure 17 shows AlphaScreen™ binding data for these and other Fc variants to human V158 FcγRIIIa.

[213] Because there are a number of FcγRs that contribute to effector function, it may be worthwhile to additionally screen Fc variants against other receptors. Figure 18 shows AlphaScreen™ data for binding of select Fc variants to human R131 FcγRIIa. As can be seen, those aforementioned variants

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with favorable binding enhancements and specificity profiles also show enhanced binding to this activating receptor. The use of FcγRIIIa, FcγRIIb, and FcγRIIc for screening is not meant to constrain experimental testing to these particular FcγRs; other FcγRs are contemplated for screening, including but not limited to the myriad isoforms and allotypes of FcγRI, FcγRII, and FcγRIII from humans, mice, rats, monkeys, and the like, as previously described.

[214] Taken together, the FcγR binding data provided in Figures 11 – 18 and Table 61 indicate that a number of substitions at positions 234, 235, 239, 240, 243, 264, 266, 325, 328, 330, and 332 are promising candidates for improving the effector function of antibodies and Fc fusions. Because combinations of some of these substitutions have typically resulted in additive or synergistic binding improvements, it is anticipated that as yet unexplored combinations of the Fc variants provided in Table 61 will also provide favorable results. Thus all combinations of the Fc variants in Table 61 are contemplated. Likewise, combinations of any of the Fc variants in Table 61 with other discovered or undiscovered Fc variants may also provide favorable properties, and these combinations are also contemplated. Furthermore, it is anticipated from these results that other substitutions at positions 234, 235, 239, 240, 243, 264, 266, 325, 328, 330, and 332 may also provide favorable binding enhancements and specificities, and thus substitutions at these positions other than those presented in Table 61 are contemplated.

[215] Example 4: Reduced binding to FcγRs

As discussed, although there is a need for greater effector function, for some antibody therapeutics, reduced or eliminated effector function may be desired. Several Fc variants in Table 61 substantially reduce or ablate FcγR binding, and thus may find use in antibodies and Fc fusions wherein effector function is undesirable. AlphaScreen™ binding data for some examples of such variants are shown in Figures 19a and 19b. These Fc variants, as well as their use in combination, may find use for eliminating effector function when desired, for example in antibodies and Fc fusions whose mechanism of action involves blocking or antagonism but not killing of the cells bearing target antigen.

[216] Example 5: Aglycosylated Fc variants

As discussed, one goal of the current experiments was to obtain optimized aglycosylated Fc variants. Several Fc variants provide significant progress towards this goal. Because it is the site of glycosylation, substitution at N297 results in an aglycosylated Fc. Whereas all other Fc variants that comprise a substitution at N297 completely ablate FcγR binding, N297D/I332E has significant binding affinity for FcγRIIIa, shown in Table 61 and illustrated in Figure 20. The exact reason for this result is uncertain in the absence of a high-resolution structure for this variant, although the computational screening predictions suggest that it is potentially due to a combination of new favorable Fc/FcγR interactions and favorable electrostatic properties. Indeed other electrostatic substitutions are

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envisioned for further optimization of aglycosylated Fc. Table 61 shows that other aglycosylated Fc variants such as S239D/N297D/I332E and N297D/A330Y/I332E provide binding enhancements that bring affinity for FcγRIIIa within 0.28- and 0.43-fold respectively of glycosylated WT alemtuzumab. Combinations of these variants with other Fc variants that enhance FcγR binding are contemplated, with the goal of obtaining aglycosylated Fc variants that bind one or more FcγRs with affinity that is approximately the same as or even better than glycosylated parent Fc. An additional set of promising Fc variants provide stability and solubility enhancements in the absence of carbohydrate. Fc variants that comprise substitutions at positions 241, 243, 262, and 264, positions that do not mediate FγR binding but do determine the interface between the carbohydrate and Fc, ablate FγR binding, presumably because they perturb the conformation of the carbohydrate. In deglycosylated form, however, Fc variants F241E/F243R/V262E/V264R, F241E/F243Q/V262T/V264E, F241R/F243Q/V262T/V264R, and F241E/F243Y/V262T/V264R show stronger binding to FcγRIIIa than in glycosylated form, as shown by the AlphaScreen™ data in Figure 21. This result indicates that these are key positions for optimization of the structure, stability, solubility, and function of aglycosylated Fc. Together these results suggests that protein engineering can be used to restore the favorable functional and solution properties of antibodies and Fc fusions in the absence of carbohydrate, and pave the way for aglycosylated antibodies and Fc fusions with favorable solution properties and full functionality that comprise substitutions at these and other Fc positions.

[217] Example 6. Affinity of Fc variants for polymorphic forms of FcγRIIIa

As discussed above, an important parameter of Fc-mediated effector function is the affinity of Fc for both V158 and F158 polymorphic forms of FcγRIIIa. AlphaScreen™ data comparing binding of select variants to the two receptor allotypes are shown in Figure 22a (V158 FcγRIIIa) and Figure 22b (F158 FcγRIIIa). As can be seen, all variants improve binding to both FcγRIIIa allotypes. These data indicate that those Fc variants of the present invention with enhanced effector function will be broadly applicable to the entire patient population, and that enhancement to clinical efficacy will potentially be greatest for the low responsive patient population who need it most.

[218] The FcγR binding affinities of these Fc variants were further investigated using Surface Plasmon Resonance (SPR) (Biacore, Uppsala, Sweden). SPR is a sensitive and extremely quantitative method that allows for the measurement of binding affinities of protein-protein interactions, and has been used to effectively measure Fc/FcγR binding (Radaev *et al.*, 2001, *J Biol Chem* 276:16478-16483). SPR thus provides an excellent complementary binding assay to the AlphaScreen™ assay. His-tagged V158 FcγRIIIa was immobilized to an SPR chip, and WT and Fc variant alemtuzumab antibodies were flowed over the chip at a range of concentrations. Binding constants were obtained from fitting the data using standard curve-fitting methods. Table 62 presents dissociation constants (Kd) for binding of select Fc variants to V158 FcγRIIIa and F158 FcγRIIIa obtained using SPR, and compares these with IC50s obtained from the AlphaScreen™ assay. By

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dividing the Kd and IC50 for each variant by that of WT alemtuzumab, the fold-improvements over WT (Fold) are obtained.

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Table 62

	SPR V158 FcγRIIIa Kd (nM)	Fold	SPR F158 FcγRIIIa Kd (nM)	Fold	AlphaScreen™ V158 FcγRIIIa IC50 (nM)	Fold	AlphaScreen™ F158 FcγRIIIa IC50 (nM)	Fold
WT	68		730		6.4		17.2	
V264I	64	1.1	550	1.3	4.5	1.4	11.5	1.5
I332E	31	2.2	72	10.1	1.0	6.4	2.5	6.9
V264I/I332E	17	4.0	52	14.0	0.5	12.8	1.1	15.6
S298A	52	1.3	265	2.8	2.9	2.2	12.0	1.4
S298A/E333A/ K334A	39	1.7	156	4.7	2.5	2.6	7.5	2.3

[219] The SPR data corroborate the improvements to FcγRIIIa affinity observed by AlphaScreen™ assay. Table 62 further indicates the superiority of V264I/I332E and I332E over S298A and S298A/E333A/K334A; whereas S298A/E333A/K334A improves Fc binding to V158 and F158 FcγRIIIa by 1.7-fold and 4.7-fold respectively, I332E shows binding enhancements of 2.2-fold and 10.1-fold respectively, and V264I/I332E shows binding enhancements of 4.0-fold and 14-fold respectively. Also worth noting is that the affinity of V264I/I332E for F158 FcγRIIIa (52 nM) is better than that of WT for the V158 allotype (68 nM), suggesting that this Fc variant, as well as those with even greater improvements in binding, may enable the clinical efficacy of antibodies for the low responsive patient population to achieve that currently possible for high responders. The correlation between the SPR and AlphaScreen™ binding measurements are shown in Figures 23a – 23d. Figures 23a and 23b show the Kd - IC50 correlations for binding to V158 FcγRIIIa and F158 FcγRIIIa respectively, and Figures 23c and 23d show the fold-improvement correlations for binding to V158 FcγRIIIa and F158 FcγRIIIa respectively. The good fits of these data to straight lines (r^2 = 0.9, r^2 = 0.84, r^2 = 0.98, and r^2 = 0.90) support the accuracy the AlphaScreen™ measurements, and validate its use for determining the relative FcR binding affinities of Fc variants.

[220] **Example 7. ADCC of Fc variants**

In order to determine the effect on effector function, cell-based ADCC assays were performed on select Fc variants. ADCC was measured using the DELFIA® EuTDA-based cytotoxicity assay (Perkin Elmer, MA) with purified human peripheral blood monocytes (PBMCs) as effector cells. Target cells were loaded with BATDA at $1x10^6$ cells/ml, washed 4 times and seeded into 96-well plate at 10,000 cells/well. The target cells were then opsonized using Fc variant or WT antibodies at the indicated final concentration. Human PBMCs were added at the indicated fold-excess of target cells and the plate was incubated at 37°C for 4 hrs. The co-cultured cells were centrifuged at 500xg, supernatants were transferred to a separate plate and incubated with Eu solution, and relative fluorescence units were measured using a Packard Fusion™ reader (Packard Biosciences, IL). Samples were run in triplicate to provide error estimates (n=3, +/- S.D.). PBMCs were allotyped for the V158 or F158 FcγRIIIa allotype using PCR.

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[221] ADCC assays were run on Fc variant and WT alemtuzumab using DoHH-2 lymphoma target cells. Figure 24a is a bar graph showing the ADCC of these proteins at 10 ng/ml antibody. Results show that alemtuzumab Fc variants I332E, V264I, and I332E/V264I have substantially enhanced ADCC compared to WT alemtuzumab, with the relative ADCC enhancements proportional to their binding improvements to FcγRIIIa as indicated by AlphaScreen™ assay and SPR. The dose dependence of ADCC on antibody concentration is shown in Figure 24b. These data were normalized to the minimum and maximum fluorescence signal provided by the baselines at low and high concentrations of antibody respectively. The data were fit to a sigmoidal dose-response model using nonlinear regression, represented by the curve in the figure. The fits enable determination of the effective concentration 50% (EC50) (i.e. the concentration required for 50% effectiveness), which provides the relative enhancements to ADCC for each Fc variant. The EC50s for these binding data are analogous to the IC50s obtained from the AlphaScreen™ competition data, and derivation of these values is thus analogous to that described in Example 2 and Figure 11. In Figure 24b, the log(EC50)s, obtained from the fits to the data, for WT, V264I/I332E, and S239D/I332E alemtuzumab are 0.99, 0.60, and 0.49 respectively, and therefore their respective EC50s are 9.9, 4.0, and 3.0. Thus V264I/I332E and S239E/I332E provide a 2.5-fold and 3.3-fold enhancement respectively in ADCC over WT alemtuzumab using PBMCs expressing heterozygous V158/F158 FcγRIIIa. These data are summarized in Table 63 below.

Table 63

	log(EC50)	EC50 (ng/ml)	Fold Improvement Over WT
WT	0.99	9.9	
V264I/I332E	0.60	4.0	2.5
S239D/I332E	0.49	3.0	3.3

[222] In order to determine whether these ADCC enhancements are broadly applicable to antibodies, select Fc variants were evaluated in the context of rituximab and trastuzumab. ADCC assays were run on V264I/I332E, WT, and S298A/D333A/K334A rituximab using WIL2-S lymphoma target cells. Figure 25a presents a bar graph showing the ADCC of these proteins at 1 ng/ml antibody. Results indicate that V264I/I332E rituximab provides substantially enhanced ADCC relative to WT rituximab, as well as superior ADCC to S298A/D333A/K334A, consistent with the FcγRIIIa binding improvements observed by AlphaScreen™ assay and SPR. Figure 25b shows the dose dependence of ADCC on antibody concentration. The EC50s obtained from the fits of these data and the relative fold-improvements in ADCC are provided in Table 64 below. As can be seen V264I/I332E rituximab provides an 11.3-fold enhancement in EC50 over WT for PBMCs expressing homozygous F158/F158 FcγRIIIa. The greater improvements observed for rituximab versus alemtuzumab are

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likely due to the use of homozygous F158/F158 FcγRIIIa rather than heterozygous V158/F158 FcγRIIIa PBMCs, as well as potentially the use of different antibodies and target cell lines.

Table 64

	log(EC50)	EC50 (ng/ml)	Fold Improvement Over WT
WT	0.23	1.7	
S298A/E333A/K334A	-0.44	0.37	4.6
V264I/I332E	-0.83	0.15	11.3

[223] ADCC assays were run on Fc variant and WT trastuzumab using two breast carcinoma target cell lines BT474 and Sk-Br-3. Figure 26a shows a bar graph illustrating ADCC at 1 ng/ml antibody. Results indicate that V264I and V264I/I332E trastuzumab provide substantially enhanced ADCC compared to WT trastuzumab, with the relative ADCC enhancements proportional to their binding improvements to FcγRIIIa as indicated by AlphaScreen™ assay and SPR. Figure 26b shows the dose dependence of ADCC on antibody concentration. The EC50s obtained from the fits of these data and the relative fold-improvements in ADCC are provided in Table 65 below. Significant ADCC improvements are observed for I332E trastuzumab when combined with A330L and A330Y.

Table 65

	log(EC50)	EC50 (ng/ml)	Fold Improvement Over WT
WT	1.1	11.5	
I332E	0.34	2.2	5.2
A330Y/I332E	-0.04	0.9	12.8
A330L/I332E	0.04	1.1	10.5

[224] Figure 26c shows another set of dose response ADCC data at variable antibody concentrations for trastuzumab variants. The EC50s obtained from the fits of these data and the relative fold-improvements in ADCC are provided in Table 66 below. Results show that trastuzumab Fc variants S239D/I332E, S239D/S298A/I332E, S239D/A330Y/I332E, and S239D/A330L/I332E/ provide substantial ADCC enhancements relative to WT trastuzumab and S298A/E333A/K334A; consistent with the FcγR binding data observed by the AlphaScreen™ assay and SPR. S239D/A330L/I332E trastuzumab shows the largest increase in effector function observed thus far, providing an approximate 50-fold enhancement in EC50 over WT for PBMCs expressing homozygous F158/F158 FcγRIIIa.

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Table 66

	log(EC50)	EC50 (ng/ml)	Fold Improvement Over WT
WT	0.45	2.83	
S298A/E333A/K334A	-0.17	0.67	4.2
S239D/I332E	-0.18	0.66	4.3
S239D/A330Y/I332E	-0.29	0.51	5.5
S239D/S298A/I332E	-0.52	0.30	9.4
S239D/A330L/I332E	-1.22	0.06	47.2

[225] Example 8. Complement binding and activation by Fc variants

Complement protein C1q binds to a site on Fc that is proximal to the FcγR binding site, and therefore it was prudent to determine whether the Fc variants have maintained their capacity to recruit and activate complement. The AlphaScreen™ assay was used to measure binding of select Fc variants to the complement protein C1q. The assay was carried out with biotinylated WT alemtuzumab antibody attached to streptavidin donor beads as described in Example 2, and using C1q coupled directly to acceptor beads. Binding data of select Fc variants shown in Figure 27a indicate that C1q binding is uncompromised. Cell-based CDC assays were also performed on select Fc variants to investigate whether Fc variants maintain the capacity to activate complement. Amar Blue was used to monitor lysis of Fc variant and WT rituximab-opsonized WIL2-S lymphoma cells by human serum complement (Quidel, San Diego, CA). The results shown in Figure 27b for select Fc variants indicate that CDC is uncompromised.

[226] Example 9. Protein A binding by Fc variants

As discussed, bacterial protein A binds to the Fc region between the CH2 and CH3 domains, and is frequently employed for antibody purification. The AlphaScreen™ assay was used to measure binding of select Fc variants to the protein A using biotinylated WT alemtuzumab antibody attached to streptavidin donor beads as described in Example 2, and using protein A coupled directly to acceptor beads. The binding data shown in Figure 28 for select Fc variants indicate that the capacity of the Fc variants to bind protein A is uncompromised. These results suggest that affinity of the Fc variants for other Fc ligands that bind the same site on Fc as protein A, such as the neonatal Fc receptor FcRn and protein G, are also unaffected.

[227] Example 10. Capacity of Fc variants to bind mouse FcγRs

Optimization of Fc to nonhuman FcγRs may be useful for experimentally testing Fc variants in animal models. For example, when tested in mice (for example nude mice, SCID mice, xenograft mice, and/or transgenic mice), antibodies and Fc fusions that comprise Fc variants that are optimized for

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one or more mouse FcγRs may provide valuable information with regard to efficacy, mechanism of action, and the like. In order to evaluate whether the Fc variants of the present invention may be useful in such experiments, affinity of select Fc variants for mouse FcγRIII was measured using the AlphaScreen™ assay. The AlphaScreen™ assay was carried out using biotinylated WT alemtuzumab attached to streptavidin donor beads as described in Example 2, and GST-tagged mouse FcγRIII bound to glutathione chelate acceptor beads, expressed and purified as described in Example 2. These binding data are shown in Figure 29. Results show that some Fc variants that enhance binding to human FcγRIIIa also enhance binding to mouse FcγRIII. This result indicates that the Fc variants of the present invention, or other Fc variants that are optimized for nonhuman FcγRs, may find use in experiments that use animal models.

[228] Example 11. Validation of Fc variants expressed in CHO cells

Whereas the Fc variants of the present invention were expressed in 293T cells for screening purposes, large scale production of antibodies is typically carried out by expression in Chinese Hamster Ovary (CHO) cell lines. In order to evaluate the properties of CHO-expressed Fc variants, select Fc variants and WT alemtuzumab were expressed in CHO cells and purified as described in Example 2. Figure 30 shows AlphaScreen™ data comparing binding of CHO- and 293T- expressed Fc variant and WT alemtuzumab to human V158 FcγRIIIa. The results indicate that the Fc variants of the present invention show comparable FcγR binding enhancements whether expressed in 293T or CHO.

[229] Example 12. Therapeutic application of Fc variants

A number of Fc variants described in the present invention have significant potential for improving the therapeutic efficacy of anticancer antibodies. For illustration purposes, a number of Fc variants of the present invention have been incorporated into the sequence of the antibody rituximab. The WT rituximab light chain and heavy chain, described in US 5,736,137, are provided in Figures 31a and 32b. The improved anti-CD20 antibody sequences are provided in Figure 31c. The improved anti-CD20 antibody sequences comprise at least non-WT amino acid selected from the group consisting of X_1, X_2, X_3, X_4, X_5, and X_6. These improved anti-CD20 antibody sequences may also comprise a substitution Z_1. The use of rituximab here is solely an example, and is not meant to constrain application of the Fc variants to this antibody or any other particular antibody or Fc fusion.

[230] All references are herein expressly incorporated by reference.

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[231] Whereas particular embodiments of the invention have been described above for purposes of illustration, it will be appreciated by those skilled in the art that numerous variations of the details may be made without departing from the invention as described in the appended claims.

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CLAIMS

We claim:

1. An antibody comprising an Fc variant portion comprising at least one amino acid modification in the Fc region of said parent Fc polypeptide, wherein said Fc variant modulates binding to an FcγR as compared to the parent Fc polypeptide.

2. An antibody according to claim 1 wherein said modulation is an increase in affinity of said antibody to said FcγR.

3. An antibody according to claim 1 wherein said Fc variant portion comprises at least one substitution at a position corresponding to a position of the human sequence selected from the group consisting of: 234, 235, 239, 240, 241, 243, 244, 245, 247, 262, 263, 264, 265, 266, 267, 269, 296, 297, 298, 299, 313, 325, 326, 327, 328, 329, 330, 332, 333, and 334.

4. An antibody according to claim 1, wherein said Fc variant comprises at least one substitution at a position corresponding to a position of the human sequence selected from the group consisting of: 240, 244, 245, 247, 262, 263, 266, 299, 313, 325, 328, and 332.

5. An antibody according to claim 1, wherein said Fc variant comprises a substitution at position 332.

6. An antibody according to claim 1, wherein at least one substitution is at a position selected from the group consisting of: 239, 264, 297, and 330, with the proviso that if said sequence is substantially human, said substitution is not S239A, V264A, N297A, N297Q, A330D, A330Q, A330K, or A330S.

7. An antibody according to claim 1, wherein said Fc variant comprises at least one substitution selected from the group consisting of 234D, 234E, 234N, 234Q, 234T, 234H, 234Y, 234I, 234V, 234F, 235D, 235S, 235N, 235Q, 235T, 235H, 235Y, 235I, 235V, 235F, 239D, 239E, 239N, 239Q, 239F, 239T, 239H, 239Y, 240I, 240A, 240T, 240M, 241W, 241L, 241Y, 241E, 241R, 243W, 243L 243Y, 243R, 243Q, 244H, 245A, 247V, 247G, 262I, 262A, 262T, 262E, 263I, 263A, 263T, 263M, 264L, 264I, 264W, 264T, 264R, 264F, 264M, 264Y, 264E, 265G, 266N, 265Q, 265Y, 265F, 265V, 265I, 265L, 265H, 265T, 266I, 266A, 266T, 266M, 267Q, 267L, 269H, 269Y, 269F, 269R, 296E, 296Q, 296D, 296N, 296S, 296T, 296L, 296I, 296H,

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297S, 297D, 297E, 298H, 299I, 299L, 299A, 299S, 299V, 299H, 299F, 299E, 313F, 325Q, 325L, 325I, 325D, 325E, 325A, 325T, 325V, 325H, 327N, 327L, 328M, 328D, 328E, 328N, 328Q, 328F, 328I, 328V, 328T, 328H, 328A, 329F, 330L, 330Y, 330V, 330I, 330F, 330R, 330H, 332D, 332E, 332N, 332Q, 332T, 332H, 332Y, and 332A.

8. An antibody according to claim 1, wherein said Fc variant is selected from the group consisting of 264L, 264I, 241W, 241L, 243W, 243L, 241L/243L/262I/264I, 241W/243W, 241W/243W/262A/264A, 241L/262I, 243L/264I, 243L/262I/264W, 241Y/243Y/262T/264T, 241E/243R/262E/264R, 241E/243Q/262T/264E, 241R/243Q/262T/264R, 241E/243Y/262T/264R, 328M, 328E, 328F, 332E, 328M/332E, 244H, 245A, 247V, 313F, 244H/245A/247V, 247G, 264I/332E, 241E/243R/262E/264R/332E, 241E/243Q/262T/264E/332E, 241R/243Q/262T/264R/332E, 241E/243Y/262T/264R/332E, 298A/332E, 239E/332E, 239Q/332E, 239E, 265G, 265N, 239E/265G, 239E/265N, 239E/265Q, 296E, 296Q, 299I, 327N, 267Q/327S, 267L/327S , 327L, 329F, 330L, 330Y, 332D, 297S, 297D, 297S/332E, 297D/332E, 297E/332E, 265Y/297D/332E, 265Y/297D/299L/332E, 265F/297E/332E, 328I/332E, 328Q/332E, 332N, 332Q, 264T, 264F, 240I, 263I, 266I, 299A, 299S, 299V, 325Q, 325L, 326I, 239D, 239N, 239F, 239D/332D, 239D/332E, 239D/332N, 239D/332Q, 239E/332D, 239E/332N, 239E/332Q, 239N/332D, 239N/332E, 239N/332N, 239N/332Q, 239Q/332D, 239Q/332N, 239Q/332Q, 296D, 296N, 241Y/243Y/262T/264T/297D/332E, 330Y/332E, 264I/330Y/332E, 330L/332E, 264I/330L/332E, 234D, 234E, 234N, 234Q, 234T, 234H, 234Y, 234I, 234V, 234F, 235D, 235S, 235N, 235Q, 235T, 235H, 235Y, 235I, 235V, 235F, 239T, 239H, 239Y, 240A, 240T, 240M, 263A, 263T, 263M, 264M, 264Y, 266A, 266T, 266M, 269H, 269Y, 269F, 269R, 296S, 296T, 296L, 296I, 299H, 299H, 330V, 330I, 330F, 330R, 330H, 325D, 325E, 325A, 325T, 325V, 325H, 328D/332E, 328E/332E, 328N/332E, 328Q/332E, 328V/332E, 328T/332E, 328H/332E, 328I/332E, 328A, 332T, 332H, 332Y, 332A, 239E/264I/332E, 239Q/264I/332E, 239E/264I/330Y/332E, 239E/264I/298A/330Y/332E, 239D/297D/332E, 239E/297D/332E, 239D/265V/297D/332E, 239D/265I/297D/332E, 239D/265L/297D/332E, 239D/265F/297D/332E, 239D/265Y/297D/332E, 239D/265H/297D/332E, 239D/265T/297D/332E, 264E/297D/332E, 296D/297D/332E, 296E/297D/332E, 296N/297D/332E, 296Q/297D/332E, 296H/297D/332E, 296T/297D/332E, 297D/299V/332E, 297D/299I/332E, 297D/299L/332E, 297D/299F/332E, 297D/299H/332E, 297D/299E/332E, 297D/330Y/332E, 297D/298A/330YI332E, 239D/330Y/332E, 239N/330Y/332E, 239D/330L/332E, 239N/330L/332E, 264I/298A/332E, 239D/298A/332E, 239N/298A/332E, 239D/264I/332E, 239D/264I/298A/332E, and 239D/264I/330L/332E.

9. An antibody according to claim 7, wherein said Fc variant portion further comprises at least one substitution at a position corresponding to a position of the human sequence selected from the group consisting of: 256, 270, 290, 298, 312, 322, 326, 329, 331, 333, 334, and 339.

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10. An antibody according to claim 1, wherein said FcγR is FcγRIIIa.

11. An antibody according to claim 10, wherein said FcγRIIIa is a V158 or F158 allotype of FcγRIIIa.

12. An Fc variant according to claim 2, wherein said parent Fc polypeptide is substantially human, and said affinity is approximately 5-fold greater than that of said parent Fc polypeptide.

13. An antibody according to claim 12, wherein said parent Fc polypeptide is substantially human, and said affinity is between about 5-fold and about 300-fold greater than that of said parent Fc polypeptide.

14. An antibody according to claim 12, wherein said Fc variant portion comprises at least one substitution at a position corresponding to a position of the human sequence selected from the group consisting 234, 235, 239, 240, 243, 264, 266, 328, 330, 332, and 325.

15. An antibody according to claim 14, wherein said Fc variant comprises at least one substitution selected from the group consisting of 234E, 234Y, 234I, 235D, 235S, 235Y, 235I, 239D, 239E, 239N, 239Q, 239T, 240I, 240M, 243L, 264I, 264T, 264Y, 266I, 328M, 328I, 328Q, 328D, 328V, 328T, 330Y, 330L, 330I, 332D, 332E, 332N, 332Q, and 325T.

16. An antibody according to claim 15, wherein said Fc variant is selected from the group consisting of 264I, 243L/264I, 328M, 332E, 328M/332E, 264I/332E, 298A/332E, 239E/332E, 239Q/332E, 239E, 330Y, 332D, 328I/332E, 328Q/332E, 264T, 240I, 266I, 239D, 239D/332D, 239D/332E, 239D/332N, 239D/332Q, 239E/332D, 239E/332N, 239E/332Q, 239N/332D, 239N/332E, 239Q/332D, 330Y/332E, 264I/330Y/332E, 330L/332E, 264I/330L/332E, 234E, 234Y, 234I, 235D, 235S, 235Y, 235I, 239T, 240M, 264Y, 330I, 325T, 328D/332E, 328V/332E, 328T/332E, 328I/332E, 239E/264I/332E, 239Q/264I/332E, 239E/264I/330Y/332E, 239D/330Y/332E, 239N/330Y/332E, 239D/330L/332E, 239N/330L/332E, 264I/298A/332E, 239D/298A/332E, 239N/298A/332E, 239D/264I/332E, 239D/264I/298A/332E, and 239D/264I/330L/332E.

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17. An antibody according to claim 15, wherein said Fc variant further comprises at least one substitution at a position selected from the group consisting of 256, 270, 290, 298, 312, 322, 326, 329, 331, 333, 334, and 339.

18. An antibody according to claim 1 or 2, wherein said parent Fc polypeptide is substantially human, substantially mouse, substantially rat, or substantially monkey.

19. An antibody according to claim 1 or 2, wherein binding to one or more Fc ligands is unaltered.

20. An antibody according to claim 19, wherein said Fc ligand is selected from the group consisting of C1q, FcRn, protein A, and protein G.

21. An antibody according to claim 1 or 2, wherein CDC is unaffected.

22. An antibody according to claim 1 or 2, wherein binding to one or more Fc ligands is altered.

23. An antibody according to claim 1, wherein said Fc variant has a FcγRIIIa-fold:FcγRIIb-fold ratio greater than 1.

24. An antibody according to claim 23, wherein said Fc variant has a FcγRIIIa-fold:FcγRIIb-fold ratio greater than approximately 11:1.

25. An antibody according to claim 24, wherein said Fc variant has a FcγRIIIa-fold:FcγRIIb-fold ratio between approximately 11:1 and approximately 86:1.

26. An antibody according to claim 23, wherein said Fc variant portion comprises at least one substitution at a position corresponding to a position of the human sequence selected from the group consisting of: 234, 235, 239, 240, 264, 296, 330, and I332.

27. An antibody according to claim 26, wherein said Fc variant comprises at least one substitution selected from the group consisting of: 234Y, 234I, 235I, 239D, 239E, 239N, 239Q, 240A, 240M, 264I, 264Y, 296Q, 330L, 330Y, 330I, 332D, and 332E.

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28. An antibody according to claim 27, wherein said Fc variant is selected from the group consisting of 332E, 264I/332E, 239E/332E, 239Q/332E, 296Q, 330L, 330Y, 332D, 239D, 239D/332E, 330Y/332E, 264I/330Y/332E, 330L/332E, 264I/330L/332E, 234Y, 234I, 235I, 240A, 240M, 264Y, 330I, 239D/330L/332E, 239D/298A/332E, 239N/298A/332E, 239D/264I/332E, 239D/264I/298A/332E, and 239D/264I/330L/332E.

29. An antibody according to claim 28, wherein said Fc variant further comprises one or more substitutions at a position selected from the group consisting of 256, 270, 290, 298, 312, 322, 326, 329, 331, 333, 334, and 339.

30. An antibody according to claim 1, wherein said Fc variant binds to at least one FcγR with reduced affinity relative to the parent Fc polypeptide.

31. An antibody according to claim 30, wherein said FcγR is FcγRIIIa.

32. An antibody according to claim 31, wherein said Fc variant comprises at least one substitution selected from the group consisting of 234D, 234N, 234Q, 234T, 234H, 234V, 234F, 235N, 235Q, 235T, 235H, 235V, 235F, 239E, 239N, 239Q, 239F, 239H, 239Y, 240A, 240T, 241W, 241L, 241Y, 241E, 241R, 243W, 243L 243Y, 243R, 243Q, 244H, 245A, 247V, 247G, 262I, 262A, 262T, 262E, 263I, 263A, 263T, 263M, 264L, 264I, 264W, 264T, 264R, 264F, 264M, 264E, 265G, 265N, 265Q, 265Y, 265F, 265V, 265I, 265L, 265H, 265T, 266A, 266T, 266M, 267Q, 267L, 269H, 269Y, 269F, 269R, 296E, 296Q, 296D, 296N, 296S, 296T, 296L, 296I, 296H, 297S, 297D, 297E, 298H, 299I, 299L, 299A, 299S, 299V, 299H, 299F, 299E, 313F, 325Q, 325L, 325I, 325D, 325E, 325A, 325V, 325H, 327N, 327L, 328M, 328E, 328N, 328Q, 328F, 328H, 328A, 329F, 330L, 330V, 330F, 330R, 330H, 332N, 332Q, 332T, 332H, 332Y, and 332A

33. An antibody according to claim 31, wherein said Fc variant is selected from the group consisting of 264L, 241W, 241L, 243W, 243L, 241L/243L/262I/264I, 241W/243W, 241W/243W/262A/264A, 241L/262I, 243L/262I/264W, 241Y/243Y/262T/264T, 241E/243R/262E/264R, 241E/243Q/262T/264E, 241R/243Q/262T/264R, 241E/243Y/262T/264R, 328M, 328E, 328F, 244H, 245A, 247V, 313F, 244H/245A/247V, 247G, 241E/243R/262E/264R/332E, 241E/243Y/262T/264R/332E, 265G, 265N, 239E/265G, 239E/265N, 239E/265Q, 296E, 296Q, 299I, 327N, 267Q/327S, 267L/327S , 327L, 329F, 330L, 297S, 297D, 297S/332E, 332N, 332Q, 264F, 263I, 299A, 299S, 299V, 325Q, 325L, 325I, 239N, 239F, 239N/332N, 239N/332Q, 239Q/332N, 239Q/332Q, 296D, 296N, 234D, 234N, 234Q, 234T, 234H, 234V, 234F, 235N, 235Q, 235T, 235H, 235V, 235F, 239H, 239Y,

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240A, 263T, 263M, 264M, 266A, 266T, 266M, 269H, 269Y, 269F, 269R, 296S, 296T, 296L, 296I, 299H, 299H, 330V, 330F, 330R, 330H, 325D, 326E, 325A, 325V, 325H, 328E/332E, 328N/332E, 328Q/332E, 328H/332E, 328A, 332T, 332H, 332Y, and 332A.

34. An antibody comprising a variant of a parent Fc polypeptide comprising at least one amino acid modification in the Fc region of said parent Fc polypeptide, wherein said Fc variant modulates effector function as compared to the parent Fc polypeptide.

35. An antibody according to claim 34, wherein said effector function is ADCC.

36. An antibody according to claim 35, wherein said Fc variant improves ADCC as compared to said parent Fc polypeptide.

37. An antibody according to claim 36, wherein said ADCC improvement is approximately 5-fold greater than that of said parent Fc polypeptide.

38. An antibody according to claim 37, wherein said ADCC improvement is between approximately 5-fold and 50-fold greater than that of said parent Fc polypeptide.

39. An antibody according to claim 37, wherein said Fc variant portion comprises at least one substitution at a position corresponding to a position of the human sequence selected from the group consisting of: 234, 235, 239, 240, 243, 264, 266, 328, 330, 332, and 325.

40. An antibody according to claim 39, wherein said Fc variant comprises at least one substitution selected from the group consisting of 234E, 234Y, 234I, 235D, 235S, 235Y, 235I, 239D, 239E, 239N, 239Q, 239T, 240I, 240M, 243L, 264I, 264T, 264Y, 266I, 328M, 328I, 328Q, 328D, 328V, 328T, 330Y, 330L, 330I, 332D, 332E, 332N, 332Q, and 325T.

41. An antibody according to claim 39, wherein said Fc variant is selected from the group consisting of 264I, 243L/264I, 328M, 332E, 328M/332E, 264I/332E, 298A/332E, 239E/332E, 239Q/332E, 239E, 330Y, 332D, 328I/332E, 328Q/332E, 264T, 240I, 266I, 239D, 239D/332D, 239D/332E, 239D/332N, 239D/332Q, 239E/332D, 239E/332N, 239E/332Q, 239N/332D, 239N/332E, 239Q/332D, 330Y/332E, 264I/330Y/332E, 330L/332E, 264I/330L/332E, 234E, 234Y, 234I, 235D, 235S, 235Y, 235I, 239T, 240M, 264Y, 330I, 325T, 328D/332E, 328V/332E, 328T/332E, 328I/332E, 239E/264I/332E, 239Q/264I/332E, 239E/264I/330Y/332E,

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239D/330Y/332E, 239N/330Y/332E, 239D/330L/332E, 239N/330L/332E, 264I/298A/332E, 239D/298A/332E, 239N/298A/332E, 239D/264I/332E, 239D/264I/298A/332E, and 239D/264I/330L/332E.

42. An antibody according to claim 39, wherein said Fc variant further comprises at least one substitution at a position selected from the group consisting of 256, 270, 290, 298, 312, 322, 326, 329, 331, 333, 334, and 339.

43. An antibody according to claim 39, wherein said parent Fc polypeptide is substantially human, substantially mouse, substantially rat, or substantially monkey.

44. An antibody according to claim 35, wherein said Fc variant reduces ADCC as compared to said parent Fc polypeptide.

45. An antibody according to claim 44, wherein said Fc variant comprises at least one substitution selected from the group consisting of 234D, 234N, 234Q, 234T, 234H, 234V, 234F, 235N, 235Q, 235T, 235H, 235V, 235F, 239E, 239N, 239Q, 239F, 239H, 239Y, 240A, 240T, 241W, 241L, 241Y, 241E, 241R, 243W, 243L 243Y, 243R, 243Q, 244H, 245A, 247V, 247G, 262I, 262A, 262T, 262E, 263I, 263A, 263T, 263M, 264L, 264I, 264W, 264T, 264R, 264F, 264M, 264E, 265G, 265N, 265Q, 265Y, 265F, 265V, 265I, 265L, 265H, 265T, 266A, 266T, 266M, 267Q, 267L, 269H, 269Y, 269F, 269R, 296E, 296Q, 296D, 296N, 296S, 296T, 296L, 296I, 296H, 297S, 297D, 297E, 298H, 299I, 299L, 299A, 299S, 299V, 299H, 299F, 299E, 313F, 325Q, 325L, 325I, 325D, 325E, 325A, 325V, 325H, 327N, 327L, 328M, 328E, 328N, 328Q, 328F, 328H, 328A, 329F, 330L, 330V, 330F, 330R, 330H, 332N, 332Q, 332T, 332H, 332Y, and 332A.

46. An antibody according to claim 44, wherein said Fc variant is selected from the group consisting of 264L, 241W, 241L, 243W, 243L, 241L/243L/262I/264I, 241W/243W, 241W/243W/262A/264A, 241L/262I, 243L/262I/264W, 241Y/243Y/262T/264T, 241E/243R/262E/264R, 241E/243Q/262T/264E, 241R/243Q/262T/264R, 241E/243Y/262T/264R, 328M, 328E, 328F, 244H, 245A, 247V, 313F, 244H/245A/247V, 247G, 241E/243R/262E/264R/332E, 241E/243Y/262T/264R/332E, 265G, 265N, 239E/265G, 239E/265N, 239E/265Q, 296E, 296Q, 296I, 327N, 267Q/327S, 267L/327S , 327L, 329F, 330L, 297S, 297D, 297S/332E, 332N, 332Q, 264F, 263I, 299A, 299S, 299V, 325Q, 325L, 325I, 239N, 239F, 239N/332N, 239N/332Q, 239Q/332N, 239Q/332Q, 296D, 296N, 234D, 234N, 234Q, 234T, 234H, 234V, 234F, 235N, 235Q, 235T, 235H, 235V, 235F, 239H, 239Y, 240A, 263T, 263M, 264M, 266A, 266T, 266M, 269H, 269Y, 269F, 269R, 296S, 296T, 296L,

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298I, 298H, 299H, 330V, 330F, 330R, 330H, 325D, 325E, 325A, 325V, 325H, 328E/332E, 328N/332E, 328Q/332E, 328H/332E, 328A, 332T, 332H, 332Y, and 332A.

47. An antibody comprising an aglycosylated Fc variant of a parent Fc polypeptide comprising at least one amino acid modification in the Fc region of said parent Fc polypeptide, wherein said aglycosylated Fc variant has improved stability, solubility, or binding affinity to an Fc ligand relative to the aglycosylated form of said parent Fc polypeptide.

48. An antibody according to claim 47, wherein said aglycosylated Fc variant has improved binding affinity to an Fc ligand as compared to the aglycosylated form of the parent Fc polypeptide.

49. An antibody according to claim 48, wherein said Fc ligand is an FcγR.

50. An antibody according to claim 49, wherein said FcγR is FcγRIIIa.

51. An antibody according to claim 48, wherein said improved binding affinity is within 0.4-fold of the glycosylated form of the parent Fc polypeptide.

52. An antibody according to claim 47, wherein said Fc variant portion comprises at least one substitution at a position corresponding to a position of the human sequence selected from the group consisting of: 239, 241, 243, 262, 264, 265, 296, 297, 330, and 332.

53. An antibody according to claim 52, wherein said Fc variant comprises one or more substitutions selected from the group consisting of 239D, 239E, 241Y, 243Y, 262T, 264T, 264E, 265Y, 265H, 296N, 297D, 330Y, and 332E.

54. An antibody according to claim 52, wherein said Fc variant is selected from the group consisting of 297D/332E, 241Y/243Y/262T/264T/297D/332E, 239D/297D/332E, 239E/297D/332E, 239D/265Y/297D/332E, 239D/265H/297D/332E, 264E/297D/332E, 296N/297D/332E, and 297D/330Y/332E.

55. An antibody according to claim 53, wherein said aglycosylated Fc variant portion comprises at least one substitution at a position corresponding to a position of the human sequence

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selected from the group consisting of: 256, 270, 290, 298, 312, 322, 326, 329, 331, 333, 334, and 339.

56. An antibody according to claim 1 comprising a Fc fusion comprising said Fc variant.

57. An antibody according to claim 1 or 56, wherein said antibody further comprises an engineered glycoform.

58. An antibody according to claim 57, wherein said engineered glycoform improves effector function.

59. A pharmaceutical composition comprising an antibody according to claim 1 and a pharmaceutically acceptable carrier.

60. A method of treating a mammal in need of said treatment, comprising administering an antibody of claim 1.

61. An antibody comprising an Fc variant, said Fc variant comprises at least one substitution selected from the group consisting of: 332D, 332E, 332N, or 332Q, wherein said positions corresponding to the human sequence position, wherein said antibody has specificity for a target antigen selected from the group consisting of CD20, CD22, CD33, CD52, Her2/neu, EGFR, EpCAM, MUC1, GD3, CEA, CA 125, HLA-DR, TNFalpha, and VEGF.

62. An antibody comprising an Fc variant, said Fc variant comprises at least one substitution selected from the group consisting of 264I, 264T, or 264Y, wherein said positions corresponding to the human sequence position, wherein said antibody or Fc fusion has specificity for a target antigen selected from the group consisting of CD20, CD22, CD33, CD52, Her2/neu, EGFR, EpCAM, MUC1, GD3, CEA, CA 125, HLA-DR, TNFalpha, and VEGF.

63. An antibody comprising an Fc variant, said Fc variant comprises at least one substitution selected from the group consisting of 239D, 239E, 239N, 239Q, or 239T, wherein said positions corresponding to the human sequence position, wherein said antibody or Fc fusion has specificity for a target antigen selected from the group consisting of CD20, CD22, CD33,

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CD52, Her2/neu, EGFR, EpCAM, MUC1, GD3, CEA, CA 125, HLA-DR, TNFalpha, and VEGF.

64. An antibody comprising an Fc variant, said Fc variant comprises at least one substitution selected from the group consisting of 330Y, 330L, or 330I, wherein said positions corresponding to the human sequence position, wherein said antibody or Fc fusion has specificity for a target antigen selected from the group consisting of CD20, CD22, CD33, CD52, Her2/neu, EGFR, EpCAM, MUC1, GD3, CEA, CA 125, HLA-DR, TNFalpha, and VEGF.

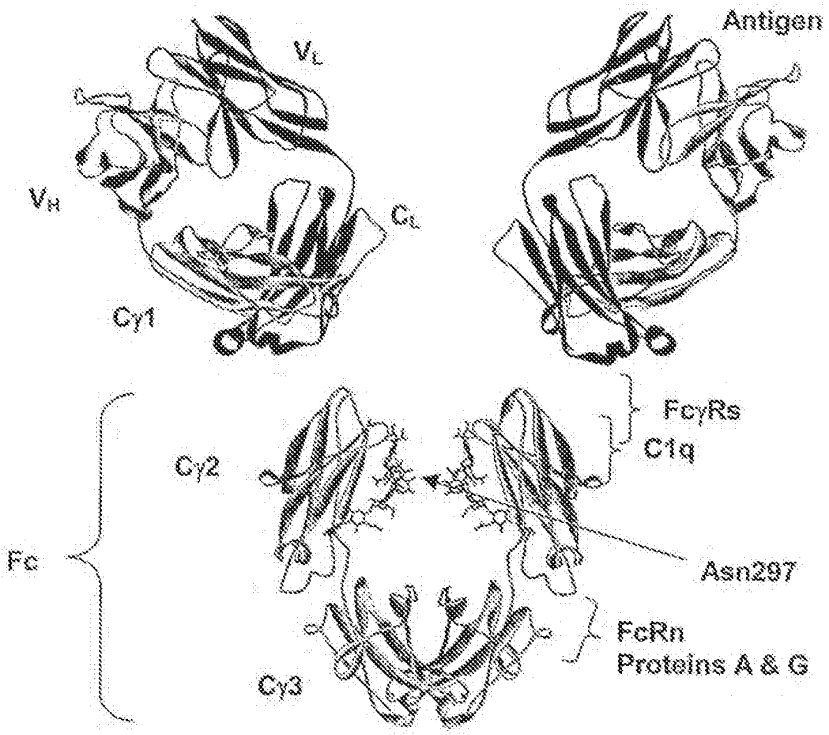
65. An antibody comprising an Fc variant, said Fc variant comprises at least one substitution selected from the group consisting of 240I or 240M, wherein said positions corresponding to the human sequence position, wherein said antibody or Fc fusion has specificity for a target antigen selected from the group consisting of CD20, CD22, CD33, CD52, Her2/neu, EGFR, EpCAM, MUC1, GD3, CEA, CA 125, HLA-DR, TNFalpha, and VEGF.

66. An antibody comprising an Fc variant, said Fc variant comprises a substitution consisting of 297D, wherein said position corresponds to the human sequence position, wherein said antibody or Fc fusion has specificity for a target antigen selected from the group consisting of CD20, CD22, CD33, CD52, Her2/neu, EGFR, EpCAM, MUC1, GD3, CEA, CA 125, HLA-DR, TNFalpha, and VEGF.

67. An antibody according to claims 61, 62, 63, 64, 65 or 66 wherein said Fc variant additionally comprises the substitutions 298A.

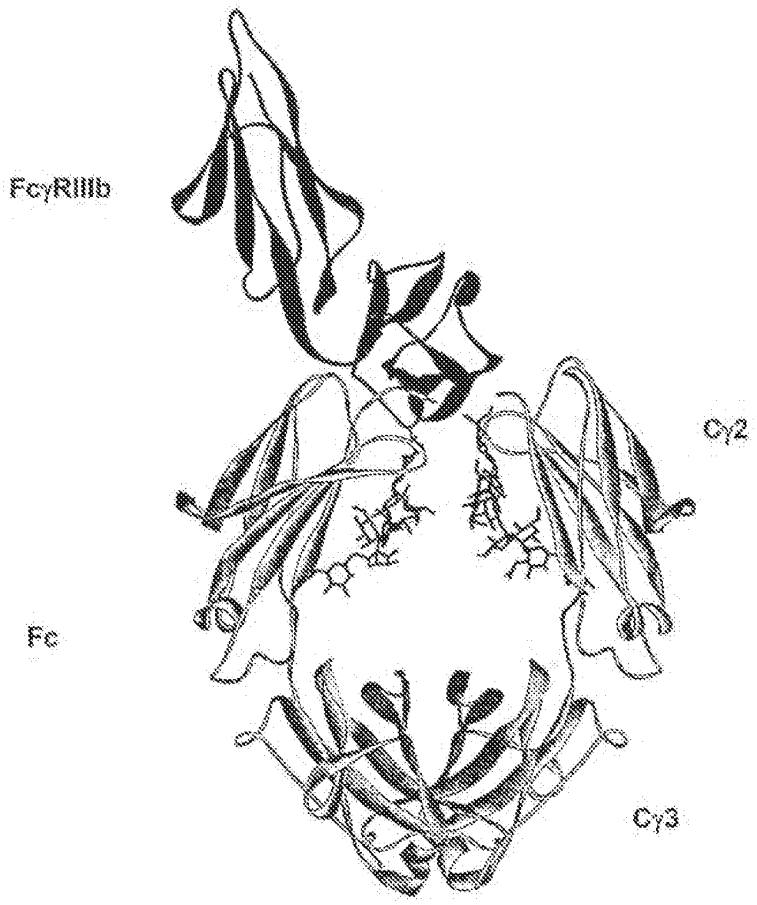
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Figure 1



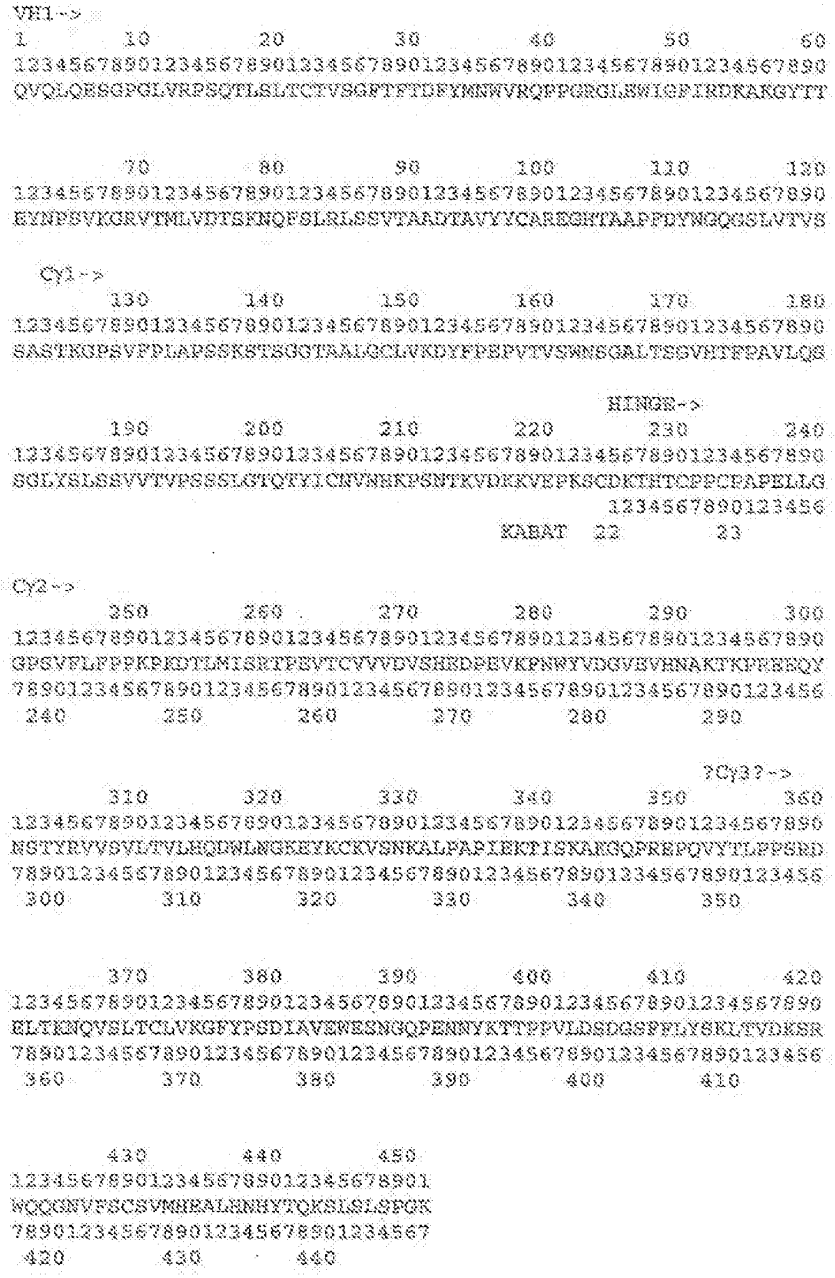
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Figure 2



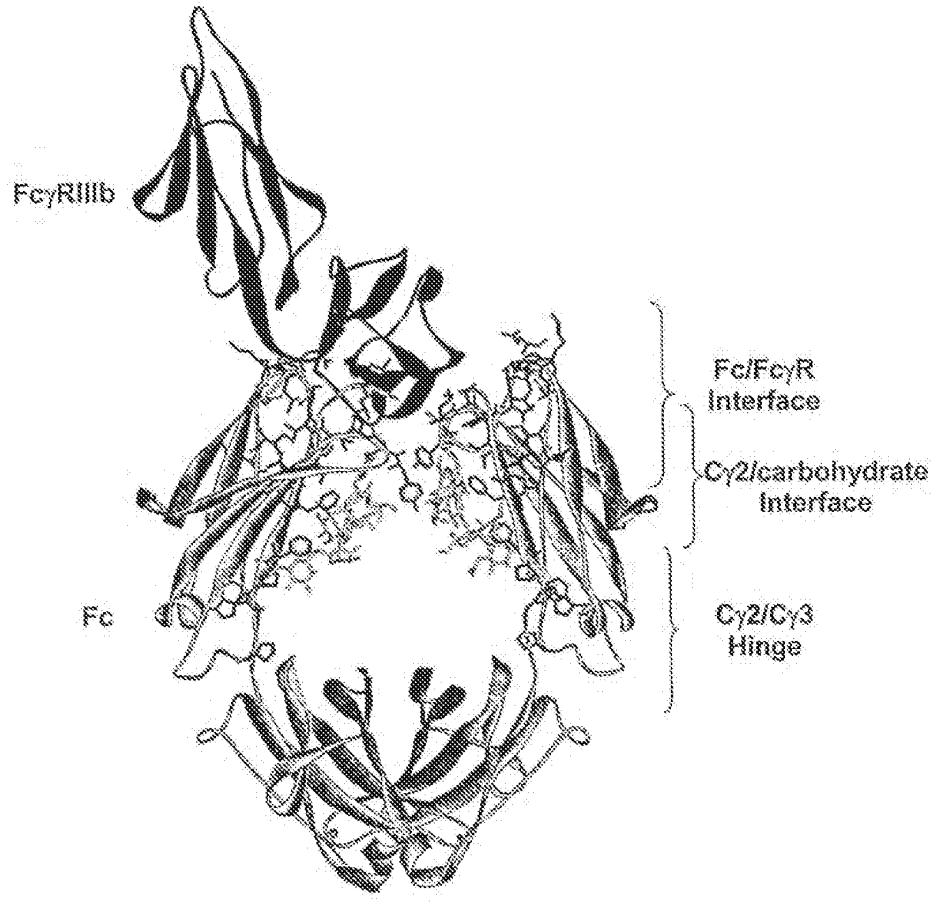
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Figure 3



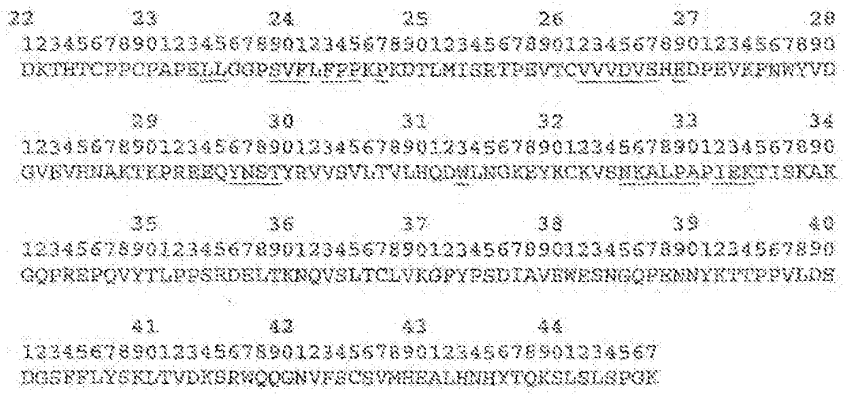
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Figure 4



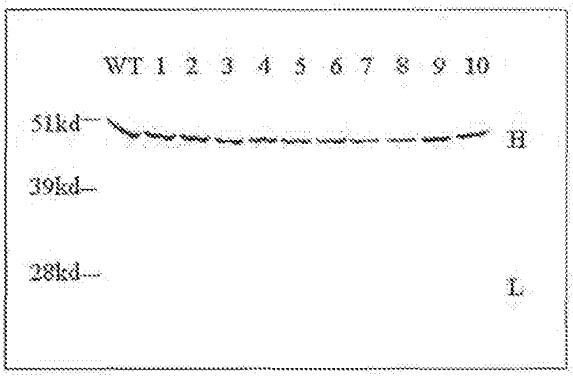
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Figure 5



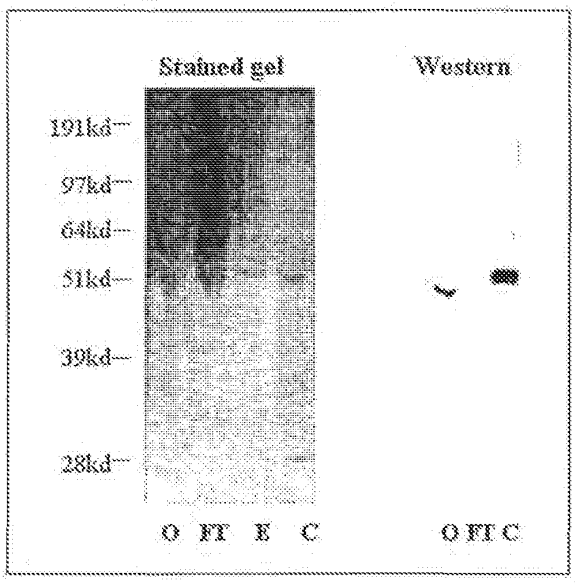
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Figure 6



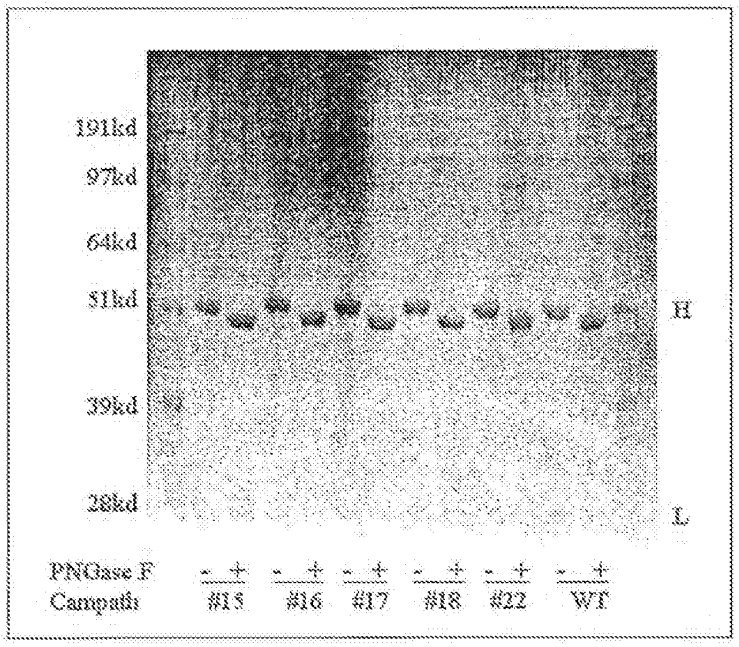
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Figure 7



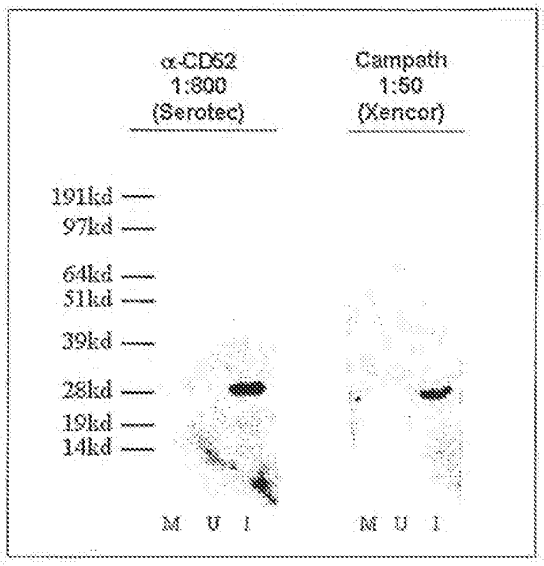
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Figure 8



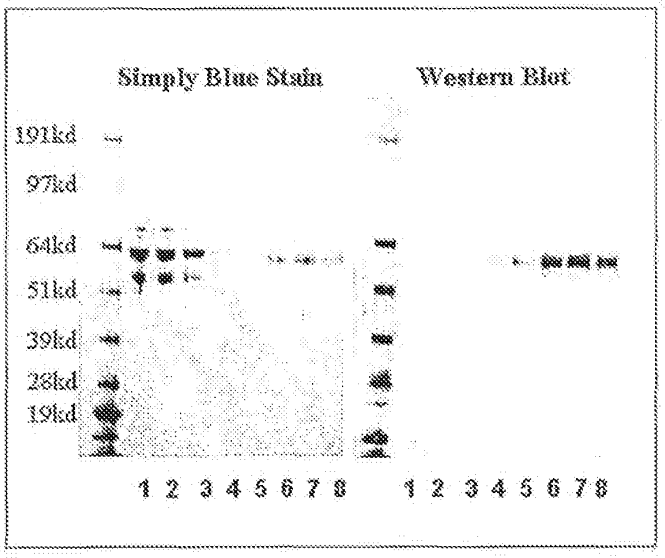
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Figure 9



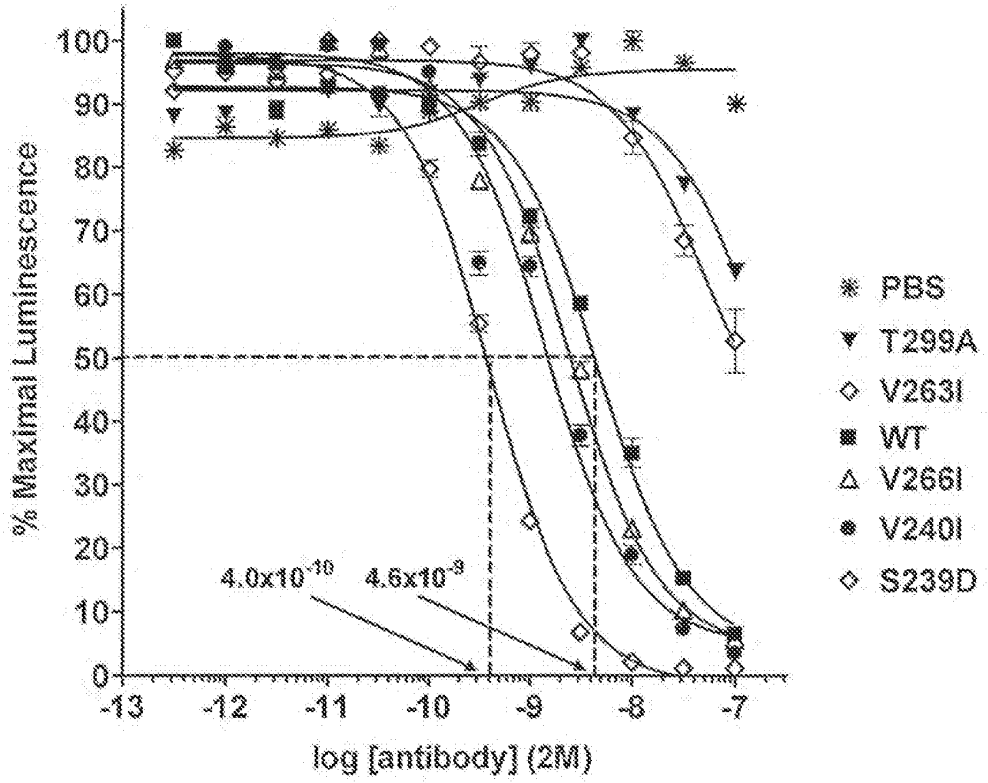
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Figure 10



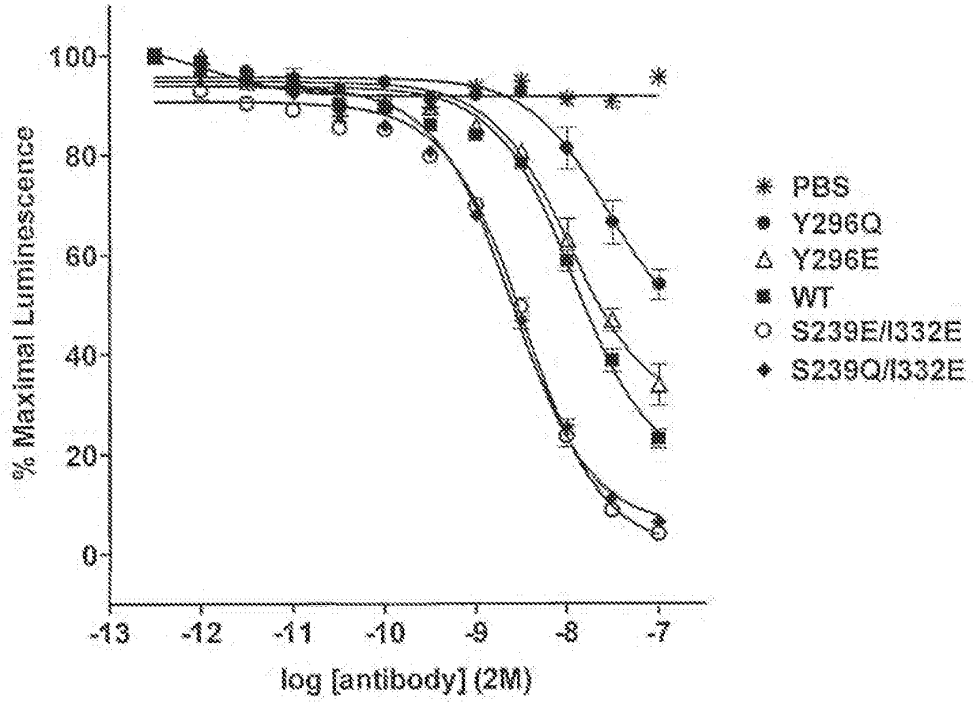
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Figure 11



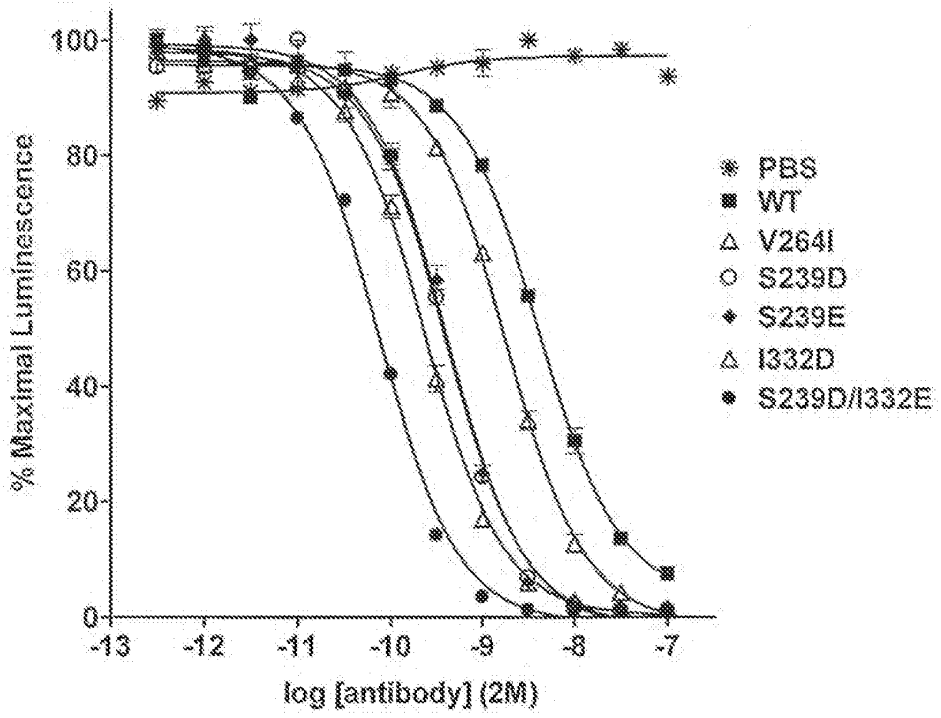
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Figure 12



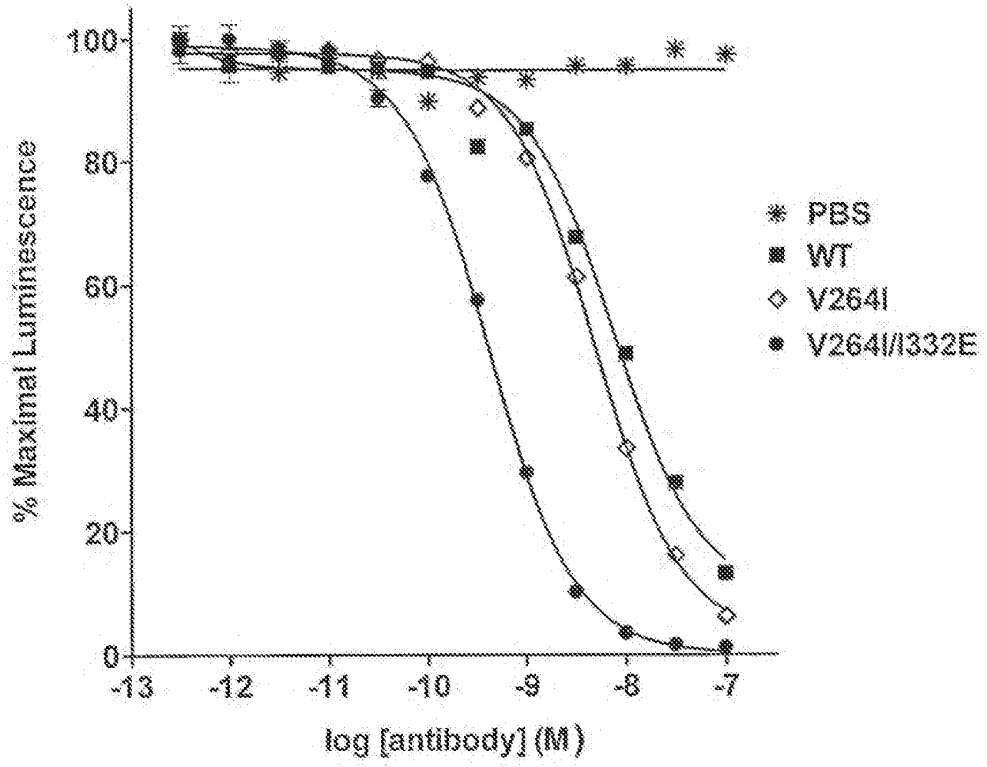
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Figure 13



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Figure 14



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Figure 15

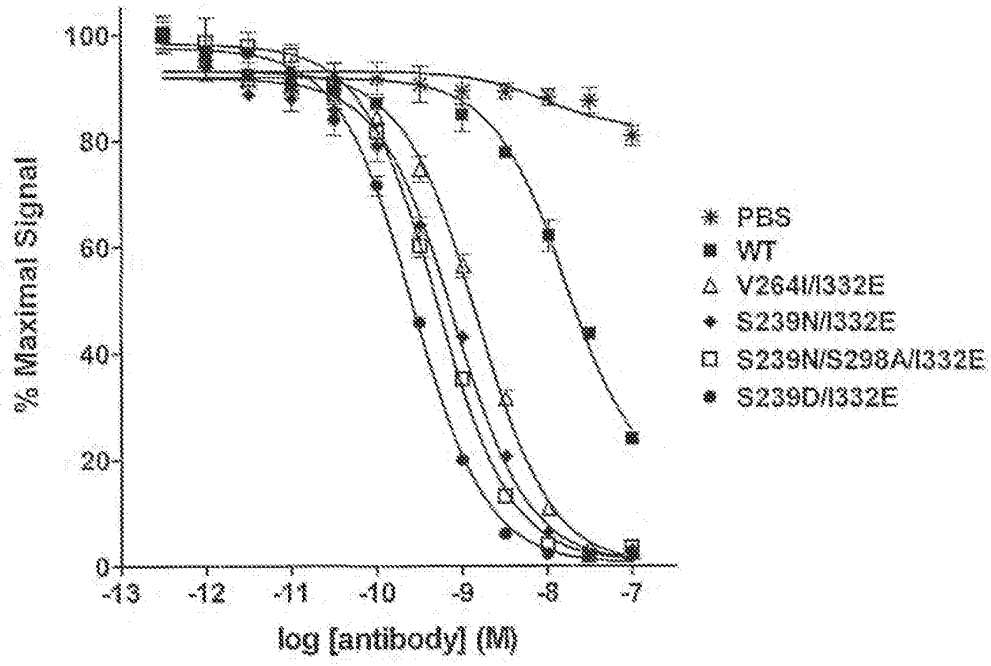

% Maximal Signal
100
80
60
40
20
0
-13
-12
-11
-10
-9
-8
-7
log [antibody] (M)
PBS
WT
V264I/I332E
S239N/I332E
S239N/S298A/I332E
S239D/I332E

Figure 16a

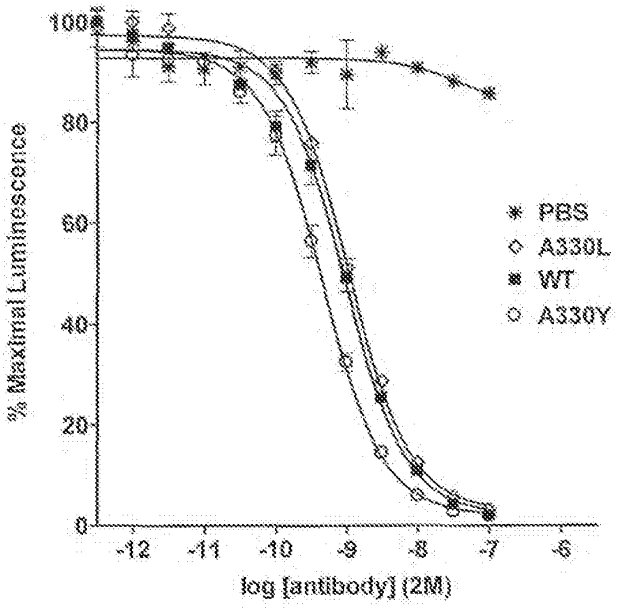


Figure 16b

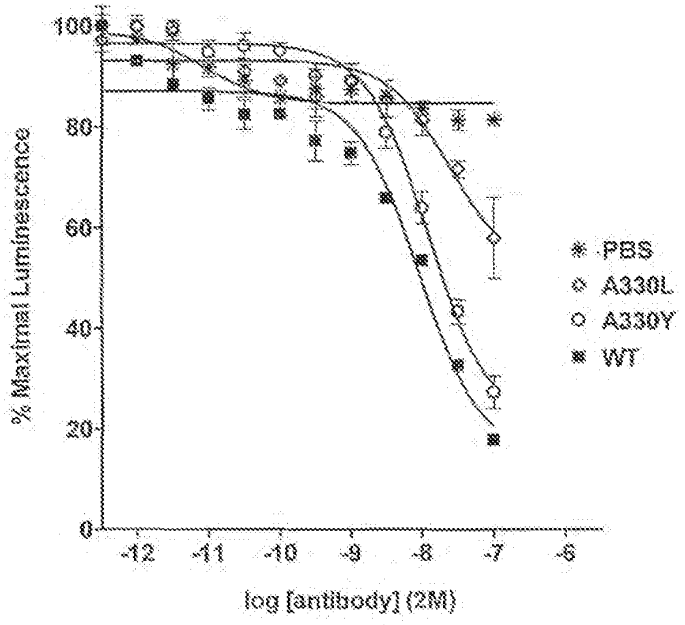


Figure 17

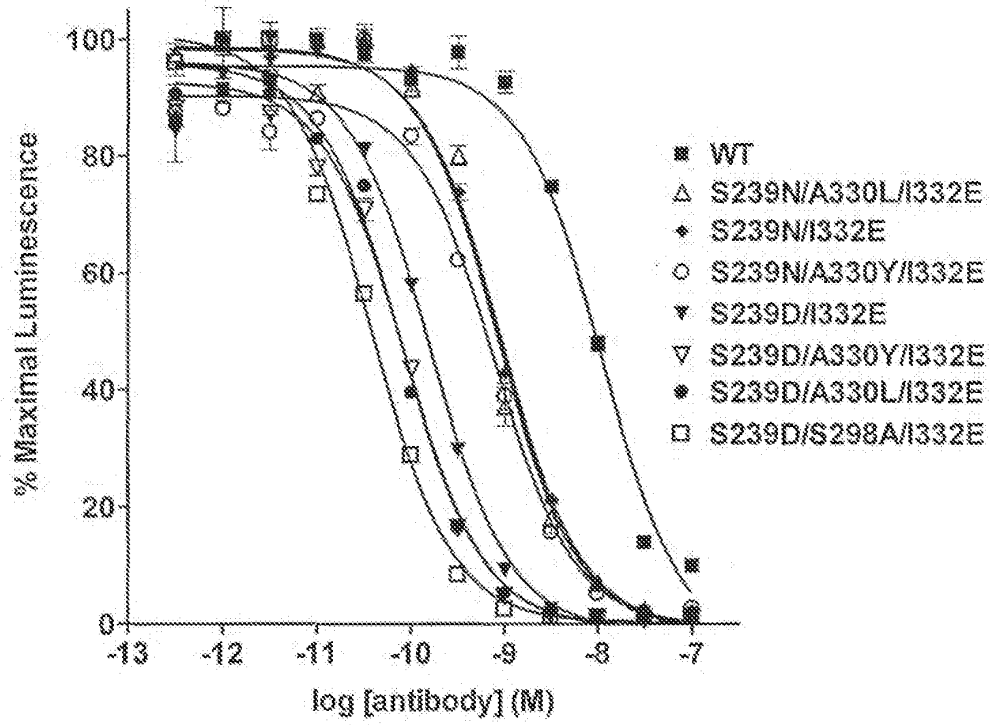

% Maximal Luminescence
100
80
60
40
20
0
-13
-12
-11
-10
-9
-8
-7
log [antibody] (M)
WT
S239N/A330L/I332E
S239N/I332E
S239N/A330Y/I332E
S239D/I332E
S239D/A330Y/I332E
S239D/A330L/I332E
S239D/S298A/I332E

Figure 18

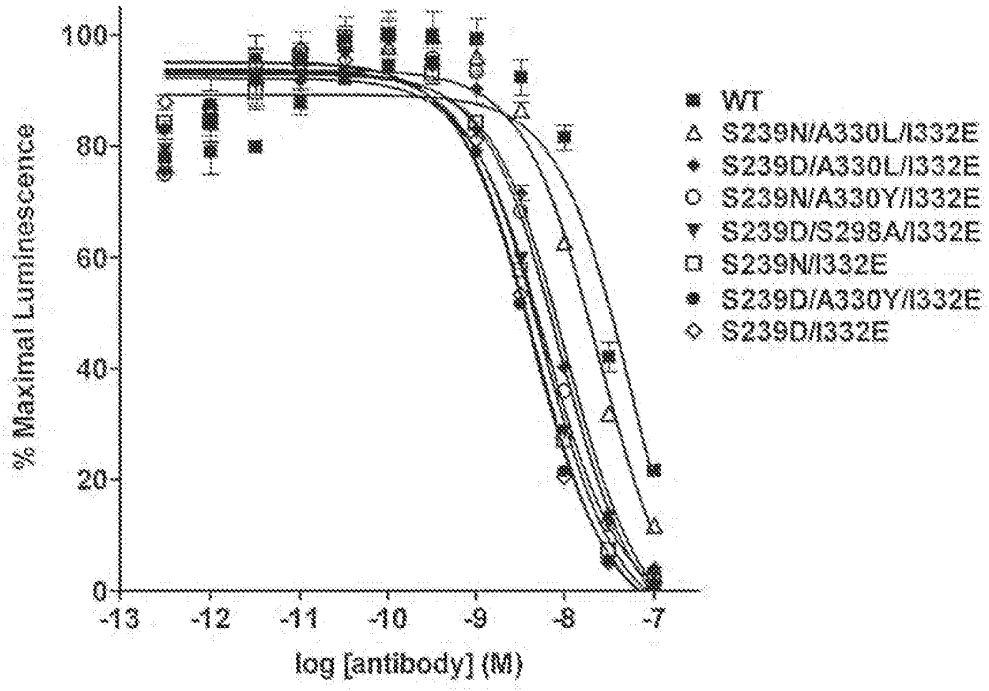

% Maximal Luminescence
100
80
60
40
20
0
-13
-12
-11
-10
-9
-8
-7
log [antibody] (M)
WT
S239N/A330L/I332E
S239D/A330L/I332E
S239N/A330Y/I332E
S239D/S298A/I332E
S239N/I332E
S239D/A330Y/I332E
S239D/I332E

Figure 19a

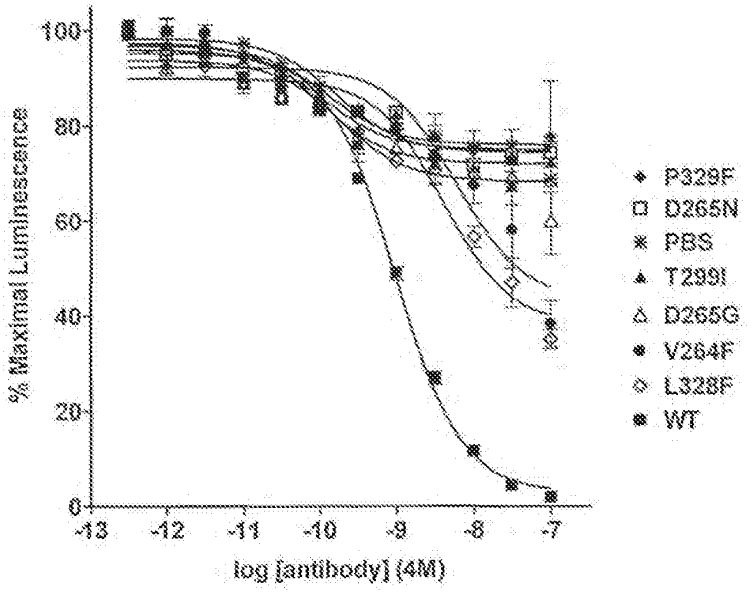
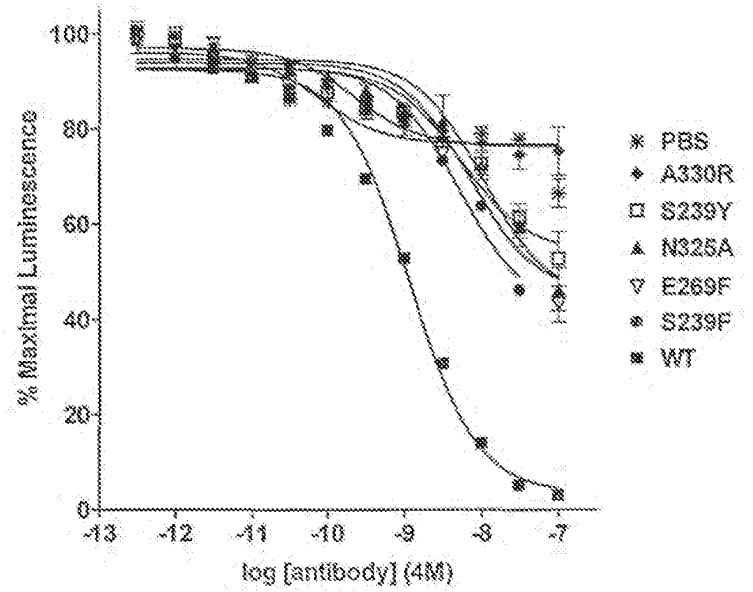


Figure 19b



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Figure 20

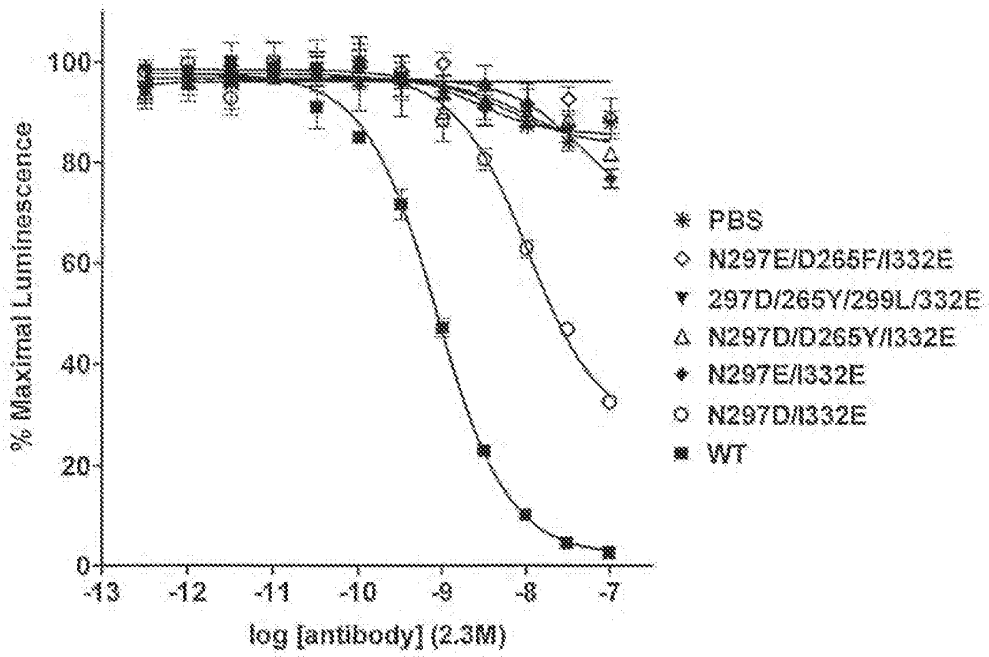

% Maximal Luminescence
100
80
60
40
20
0
-13
-12
-11
-10
-9
-8
-7
log [antibody] (2.3M)
PBS
N297E/D265F/I332E
297D/265Y/299L/332E
N297D/D265Y/I332E
N297E/I332E
N297D/I332E
WT

Figure 21

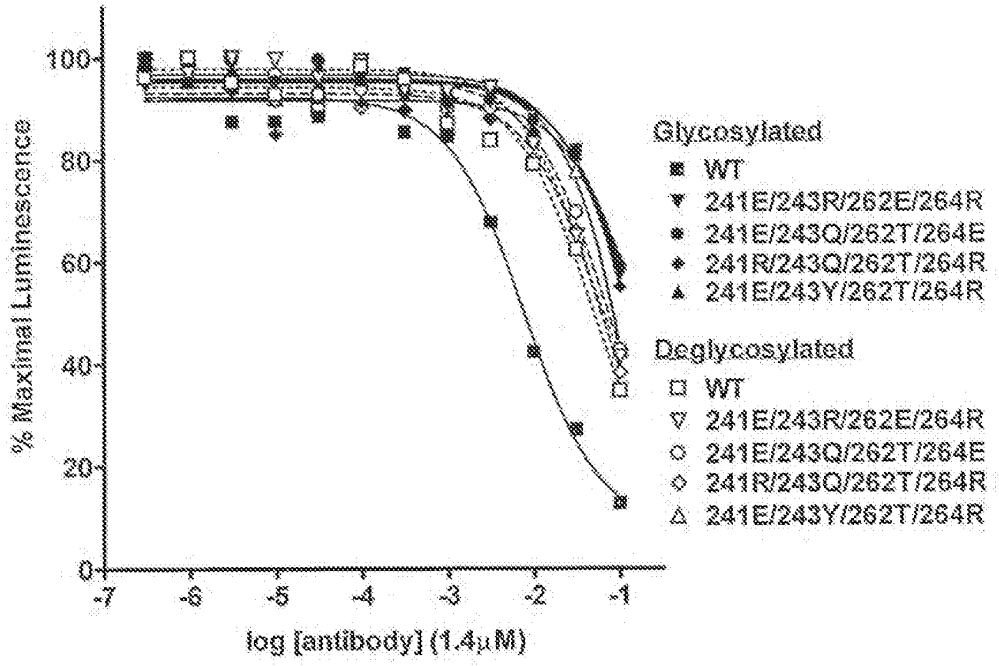

% Maximal Luminescence
100
80
60
40
20
0
-7
-6
-5
-4
-3
-2
-1
log [antibody] (1.4μM)
Glycosylated
WT
241E/243R/262E/264R
241E/243Q/262T/264E
241R/243Q/262T/264R
241E/243Y/262T/264R
Deglycosylated
WT
241E/243R/262E/264R
241E/243Q/262T/264E
241R/243Q/262T/264R
241E/243Y/262T/264R

Figure 22a

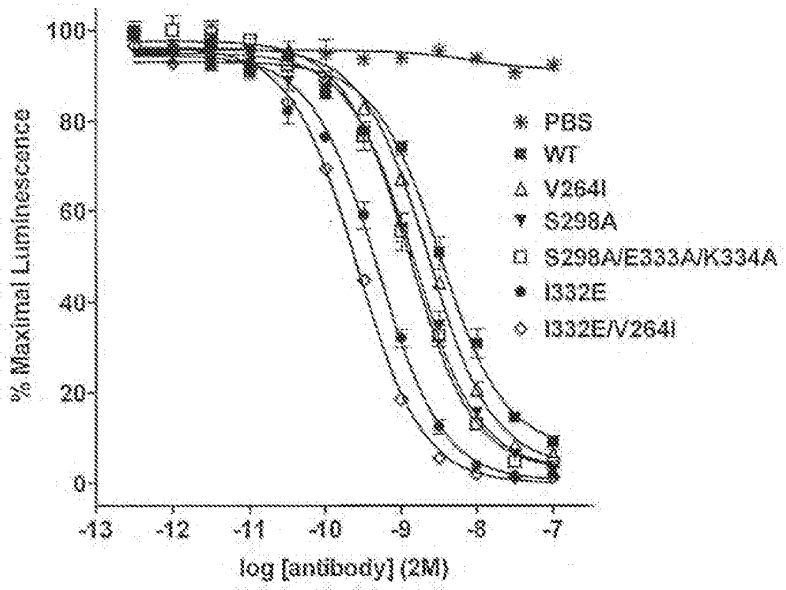


Figure 22b

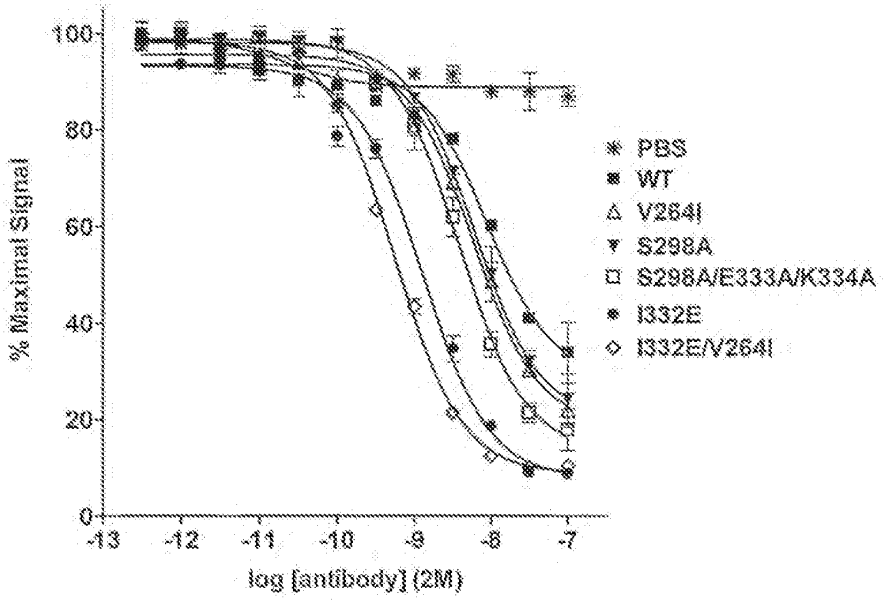


Figure 23a

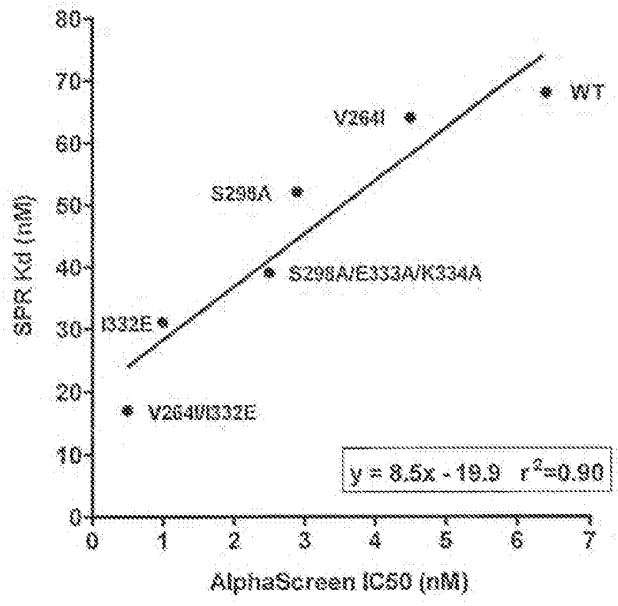
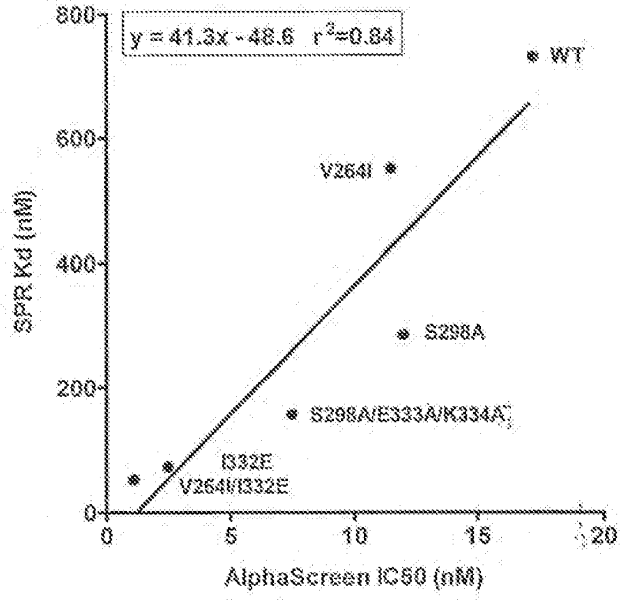


Figure 23b



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Figure 23c

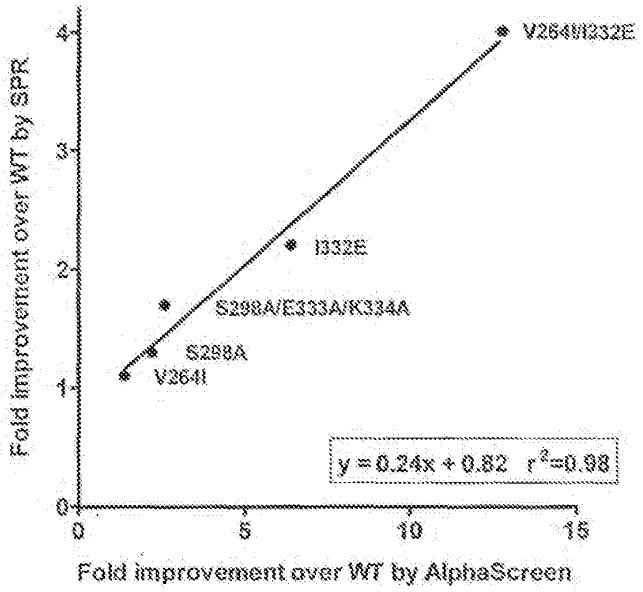
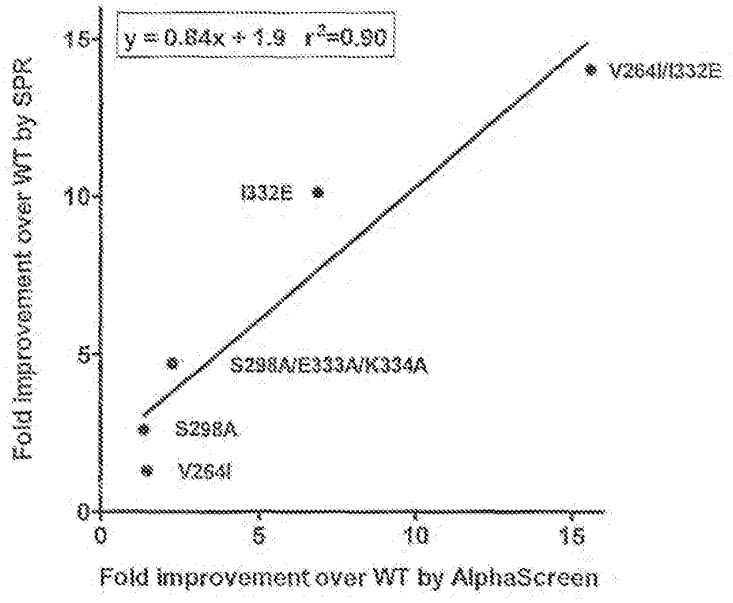
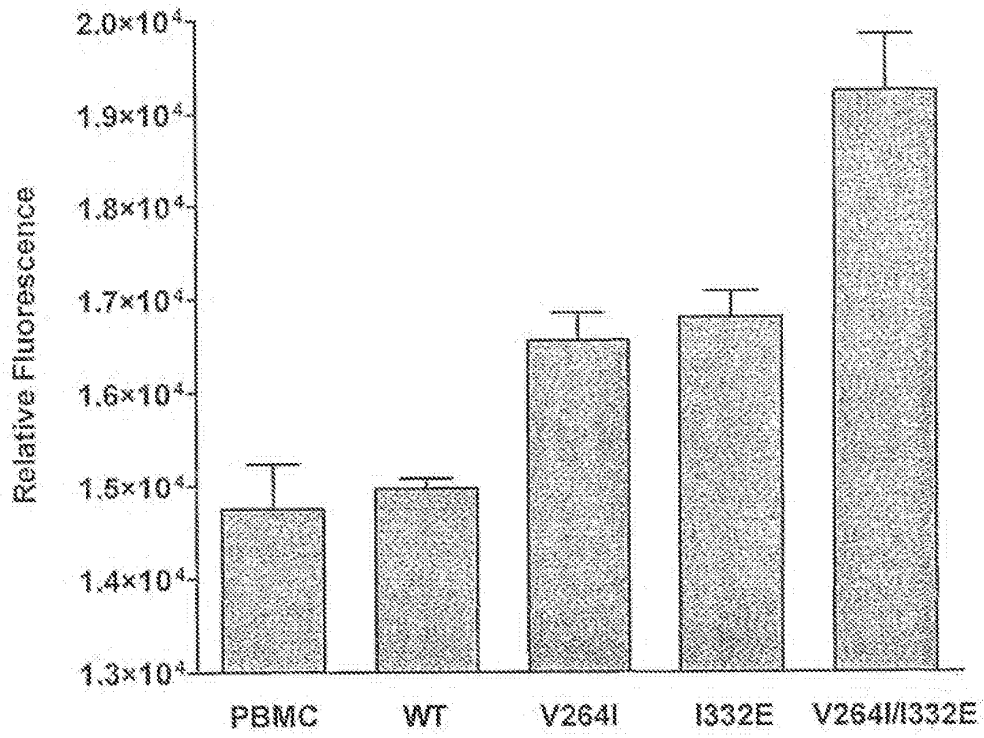


Figure 23d



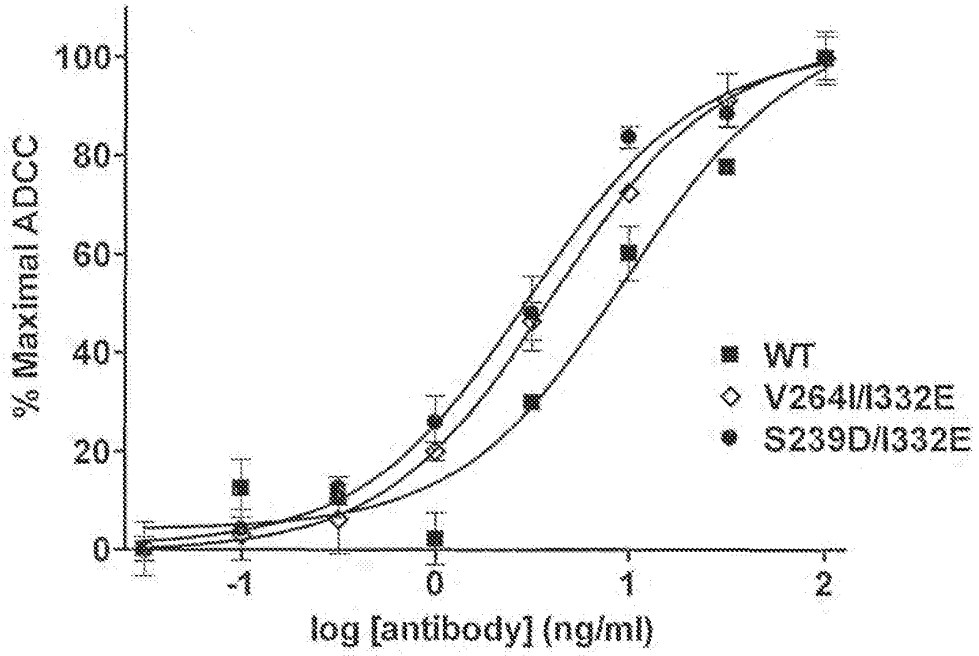
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Figure 24a



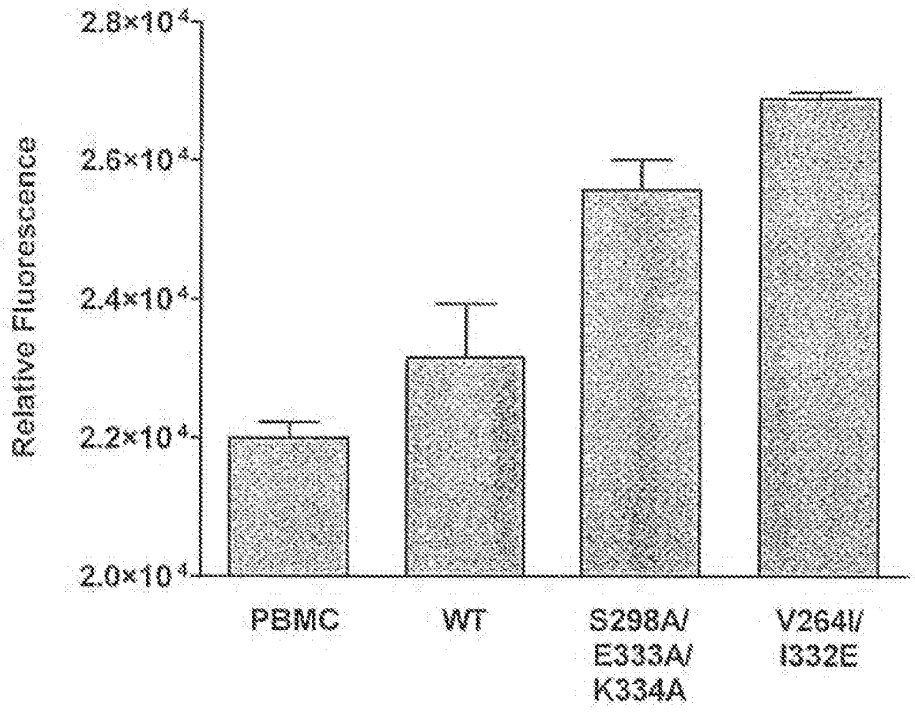
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Figure 24b



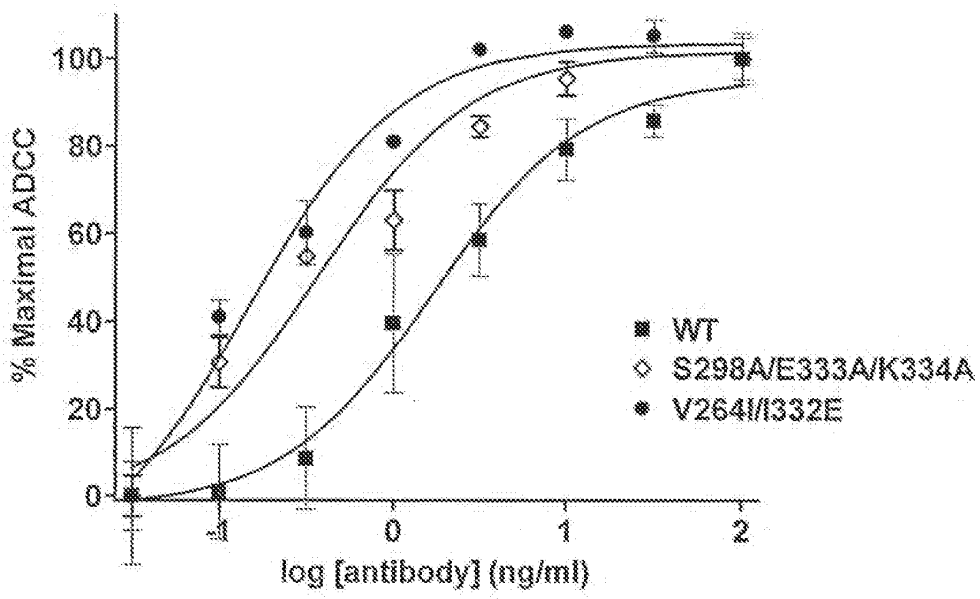
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Figure 25a



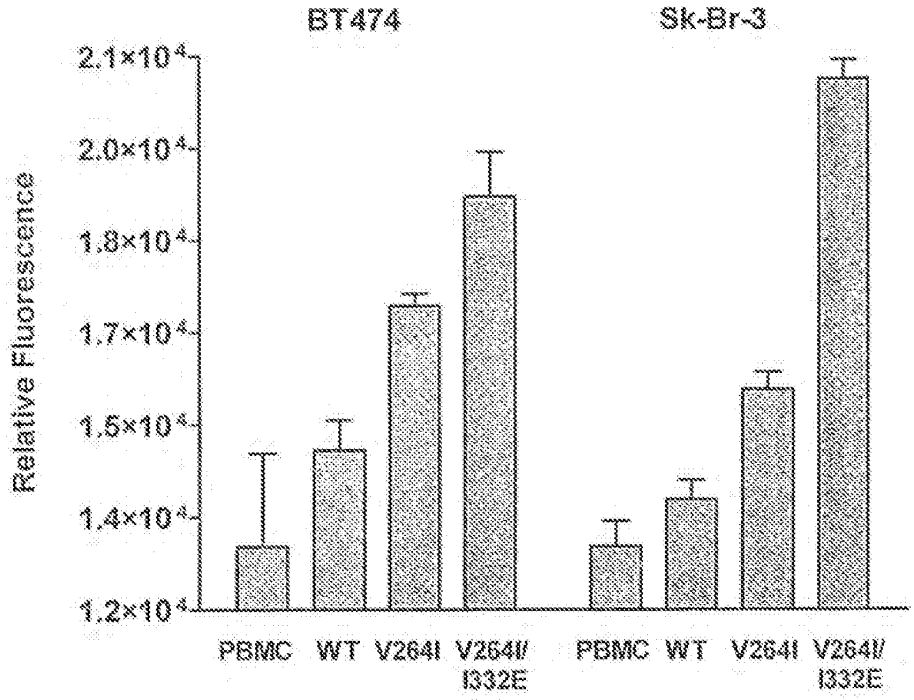
Samsung Bioepis Exhibit No. 1002
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Figure 25b



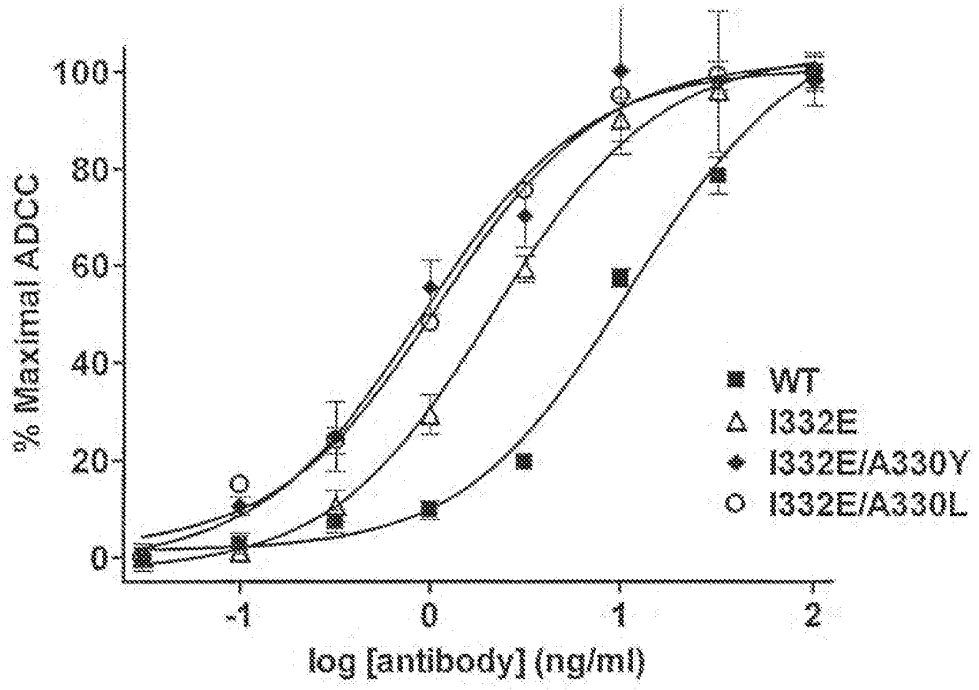
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Figure 26a



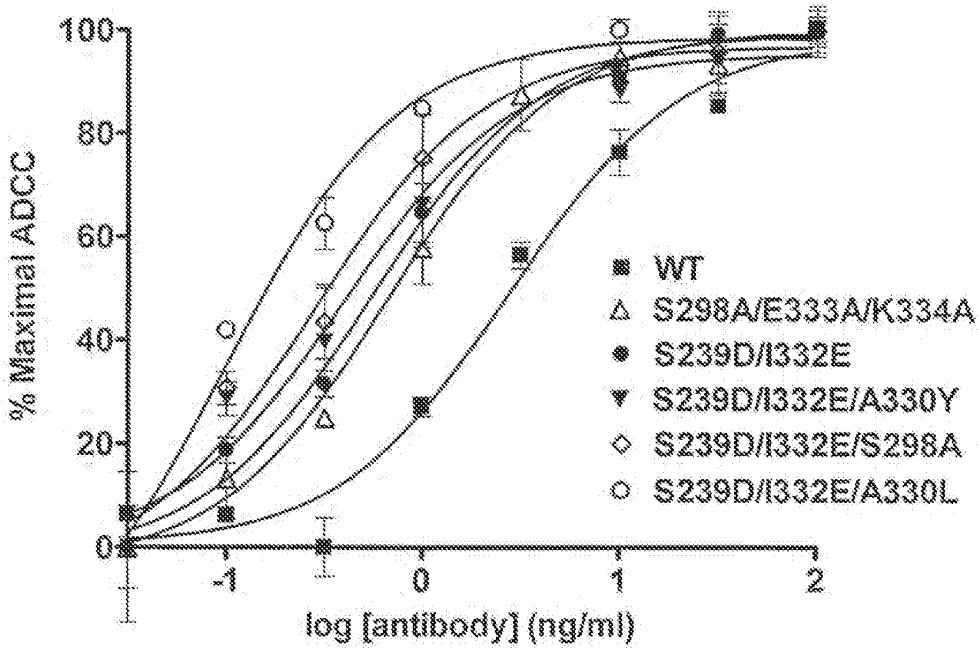
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Figure 26b



Samsung Bioepis Exhibit No. 1002
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Figure 26c



Samsung Bioepis Exhibit No. 1002
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Figure 27a

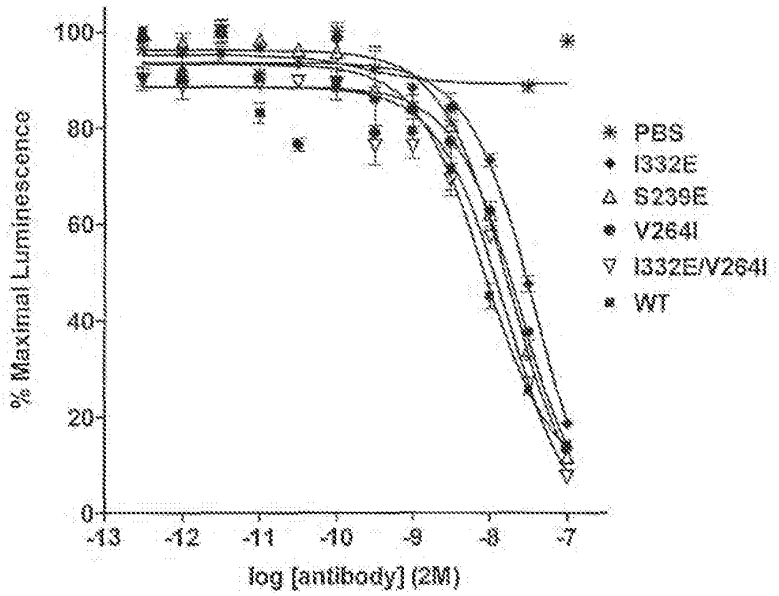
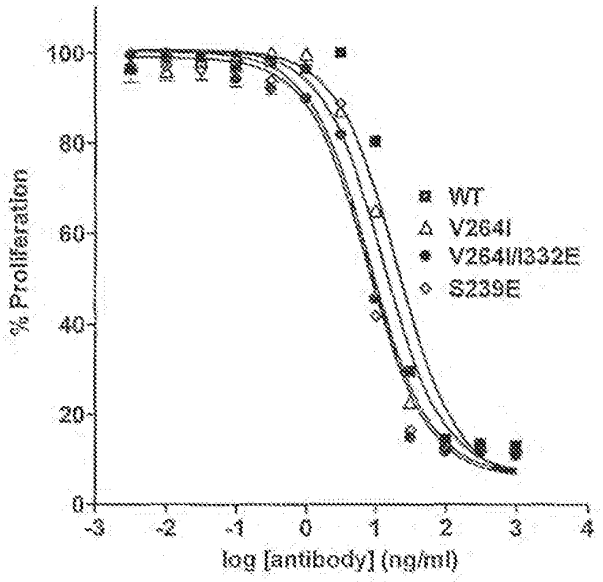
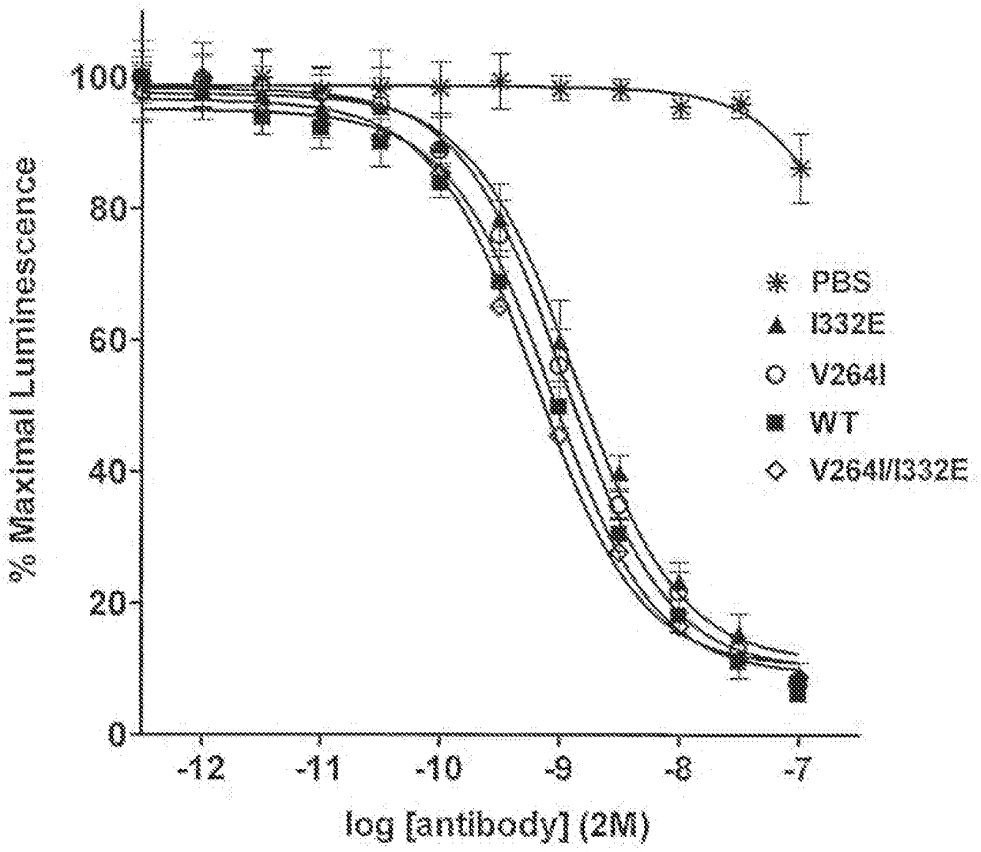


Figure 27b



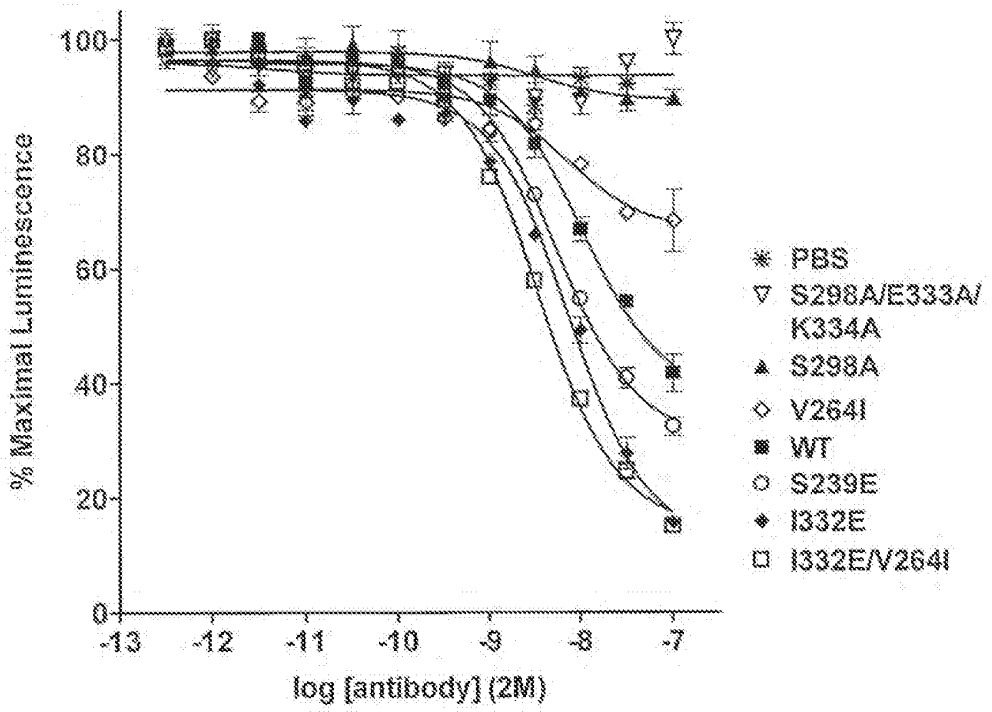
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Figure 28



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Figure 29



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Figure 30

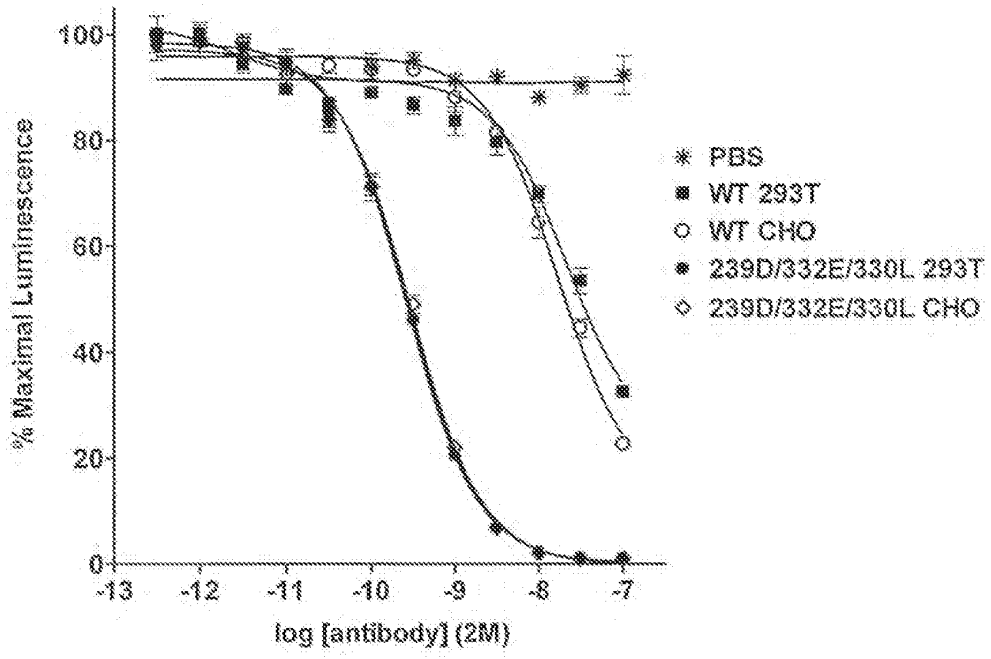

% Maximal Luminescence
100
80
60
40
20
0
-13
-12
-11
-10
-9
-8
-7
log [antibody] (2M)
PBS
WT 293T
WT CHO
239D/332E/330L 293T
239D/332E/330L CHO

Figure 31a

Anti-CD20 light chain
QIVLSQSPAILSASPGEKVTMTCRASSSVSYIHWFQQKPGSSPKPWIYATSNLASGVPVRFSGSGSG
TSYSLTISRVEAEDAATYYCQQWTSNPPTFGGGTKLEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLL
NNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLS
SPVTKSFNRGEC

Figure 31b

Anti-CD20 heavy chain

QVQLQQPGAELVKPGASVKMSCKASGYTFTSYNMHWVKQTPGRGLEWIGAIYPGNGDTSYNQKFK
GKATLTADKSSSTAYMQLSSLTSEDSAVYYCARSTYYGGDWYFNVWGAGTTVTVSAASTKGPSVFP
LAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLG
TQTYICNVNHKPSNTKVDKKAEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCV
VVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKA
LPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTP
PVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK

Figure 31c

Anti-CD20 heavy chain comprising possible Fc variants
QVQLQQPGAELVKPGASVKMSCKASGYTFTSYNMHWVKQTPGRGLEWIGAIYPGNGDTSYNQKFK
GKATLTADKSSSTAYMQLSSLTSEDSAVYYCARSTYYGGDWYFNVWGAGTTVTVSAASTKGPSVFP
LAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLG
TQTYICNVNHKPSNTKVDKKAEPKSCDKTHTCPPCPAPELLGGPX_1X_2FLFPPKPKDTLMISRTPEVTC
VVX_3DVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYX_4Z_1TYRVVSVLTVLHQDWLNGKEYKCKVSN
KALPX_5PX_6EKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNY
KTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK

Position	WT	Possible Substitutions
X_1	S	D, E, N, Q, T
X_2	V	I, M
X_3	V	I, T, Y
X_4	N	D
X_5	A	Y, L, I
X_6	I	D, E, N, Q
Z_1	S	A

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(19) World Intellectual Property Organization
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8 April 2004 (08.04.2004)

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26 September 2003 (26.09.2003)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:

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60/467,606	2 May 2003 (02.05.2003)	US
60/477,839	12 June 2003 (12.06.2003)	US

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(72) Inventors; and

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(74) Agents: **SILVA, Robin, M.** et al.; DORSEY & WHITNEY LLP, 4 Embarcadero Center, Suite 3400, San Francisco, CA 94111 (US).

(81) Designated States (*national*): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW

(84) Designated States (*regional*): ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Declaration under Rule 4.17:

— *as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii)) for the following designations AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, UZ, VC, VN, YU, ZA, ZM, ZW, ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG)*

Published:

— *with international search report*

(88) Date of publication of the international search report:
28 October 2004

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: OPTIMIZED FC VARIANTS AND METHODS FOR THEIR GENERATION

(57) Abstract: The present invention relates to optimized Fc variants, methods for their generation, and antibodies and Fc fusions comprising optimized Fc variants.

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INTERNATIONAL SEARCH REPORT

International application No.
PCT/US03/30249

A. CLASSIFICATION OF SUBJECT MATTER
IPC(7) : A61K 39/00; C07K 16/00
US CL. : 424/133.1; 530/387.3
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
U.S. : 424/133.1; 530/387.3

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
Please See Continuation Sheet

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 2002/0128448 A1 (REFF) 12 September 2002, see entire document	1,2,10,12,13,18-25,,30,31,34-38,44,47-51,56-60,
Y	US 6,194,551 B1 (IDUSOGIE et al.) 27 February 2001, see entire document	1,2,10-13,18-25,30,31,34-38,44,47-51,56-60
Y	US 2002/0004587 A1 (MILLER et al.) 10 January 2002, see entire document.	1,2,10-13,18-25,30,31,34-38,44,47-51, 56-60

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
25 May 2004 (25.05.2004)	13 AUG 2004
Name and mailing address of the ISA/US Mail Stop PCT, Attn: ISA/US Commissioner for Patents P.O. Box 1450 Alexandria, Virginia 22313-1450 Facsimile No. (703) 305-3230	Authorized officer Ron Schwadron, Ph.D. Telephone No. 571 272 1600

Form PCT/ISA/210 (second sheet) (July 1998)

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INTERNATIONAL SEARCH REPORT

International application No.
PCT/US03/30249

Box I Observations where certain claims were found unsearchable (Continuation of Item 1 of first sheet)

This international report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claim Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☒ Claim Nos.: 3-9,11,14-17,26-28,32,33,39-43,45,46,52-55 and 61-67
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
The aforementioned claims require an amino acid sequence search and no CRF has been submitted.

3. ☐ Claim Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of Item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest
☐ The additional search fees were accompanied by the applicant's protest.
☐ No protest accompanied the payment of additional search fees.

Form PCT/ISA/210 (continuation of first sheet(1)) (July 1998)

Samsung Bioepis Exhibit No. 1002
Page 9520

INTERNATIONAL SEARCH REPORT

PCT/US03/30349

Continuation of B. FIELDS SEARCHED Item 3:
WEST 2.1, MEDICINE/BIOTECH (compendium databases on DIALOG) search terms: inventor names, fc, mutant?, substitut?, fcgammar, variant?, c1q, fcrn, adc, adcc

Form PCT/ISA/210 (second sheet) (July 1998)

Samsung Bioepis Exhibit No. 1002
Page 9521

PTO/SB/08a (07-09)
Approved for use through 07/31/2012. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
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Substitute for form 1449/PTO

INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Use as many sheets as necessary)

Sheet 1 of 2

Complete if Known	
Application Number	13/426,973
Filing Date	March 22, 2012
First Named Inventor	Leonard Bell
Art Unit	1644
Examiner Name	J. L. Rogers
Attorney Docket Number	ALXN-P08-114

U.S. PATENT DOCUMENTS

Examiner Initials*	Cite No.[1]	Document Number Number-Kind Code[2] (*if known*)	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear

FOREIGN PATENT DOCUMENTS

Examiner Initials*	Cite No.[1]	Foreign Patent Document Country Code[3]-Number[4]-Kind Code[5] (*if known*)	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages Or Relevant Figures Appear	T[6]

Examiner Signature		Date Considered	

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant. [1] Applicant's unique citation designation number (optional). [2] See Kinds Codes of USPTO Patent Documents at www.uspto.gov or MPEP 901.04. [3] Enter Office that issued the document, by the two-letter code (WIPO Standard ST.3). [4] For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. [5] Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16 if possible. [6] Applicant is to place a check mark here if English language Translation is attached.

PTO/SB/08b (07-09)
Approved for use through 07/31/2012. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
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INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Use as many sheets as necessary)

Sheet 2 of 2

Complete if Known	
Application Number	13/426,973
Filing Date	March 22, 2012
First Named Inventor	Leonard Bell
Art Unit	1644
Examiner Name	J. L. Rogers
Attorney Docket Number	ALXN-P08-114

NON PATENT LITERATURE DOCUMENTS

Examiner Initials*	Cite No.[1]	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, page(s), volume-issue number(s), publisher, city and/or country where published.	T[2]
		Figueroa and Densen, "Infectious Diseases Associated with Complement Deficiencies," Clinical Microbiology Reviews, Vol. 4(3), pp. 359-395 (1991).	

Examiner Signature		Date Considered	

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

[1]Applicant's unique citation designation number (optional). [2]Applicant is to place a check mark here if English language Translation is attached.

Electronic Patent Application Fee Transmittal	
Application Number:	13426973
Filing Date:	22-Mar-2012
Title of Invention:	TREATMENT OF PAROXYSMAL NOCTURNAL HEMOGLOBINURIA PATIENTS BY AN INHIBITOR OF COMPLEMENT
First Named Inventor/Applicant Name:	Leonard Bell
Filer:	Jason S. Cathelyn/ginny blundell
Attorney Docket Number:	ALXN-P08-114
Filed as Large Entity	

Utility under 35 USC 111(a) Filing Fees

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

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Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Miscellaneous:				
Submission- Information Disclosure Stmt	1806	1	180	180
		Total in USD ($)		**180**

Samsung Bioepis Exhibit No. 1002
Page 9525

Electronic Acknowledgement Receipt	
EFS ID:	17855429
Application Number:	13426973
International Application Number:	
Confirmation Number:	8851
Title of Invention:	TREATMENT OF PAROXYSMAL NOCTURNAL HEMOGLOBINURIA PATIENTS BY AN INHIBITOR OF COMPLEMENT
First Named Inventor/Applicant Name:	Leonard Bell
Customer Number:	28120
Filer:	Jason S. Cathelyn/ginny blundell
Filer Authorized By:	Jason S. Cathelyn
Attorney Docket Number:	ALXN-P08-114
Receipt Date:	08-JAN-2014
Filing Date:	22-MAR-2012
Time Stamp:	17:01:32
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	yes
Payment Type	Deposit Account
Payment was successfully received in RAM	$180
RAM confirmation Number	4036
Deposit Account	181945
Authorized User	
The Director of the USPTO is hereby authorized to charge indicated fees and credit any overpayment as follows: Charge any Additional Fees required under 37 C.F.R. Section 1.21 (Miscellaneous fees and charges)	

Samsung Bioepis Exhibit No. 1002
Page 9526

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Transmittal Letter	ALXN-P08-114_SIDS.pdf	70212 7176db7007302f292997f7efbb544a6fb795bd02	no	2
Warnings:					
Information:					
2	Information Disclosure Statement (IDS) Form (SB08)	ALXN-P08-114_SB08.pdf	127981 f2436eabd730ff7add3fe29df6341e1e98a6a78f	no	2
Warnings:					
Information:					
This is not an USPTO supplied IDS fillable form					
3	Non Patent Literature	Figueroa.pdf	11945003 90ca4c9afe6dc453c1ab7d624e3f2676daf1c6ea	no	37
Warnings:					
Information:					
4	Fee Worksheet (SB06)	fee-info.pdf	30523 7270093e0ce5f9bb7fd0140e6a58cbe75311eb9a	no	2
Warnings:					
Information:					
		Total Files Size (in bytes):	12173719		

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.

<u>New Applications Under 35 U.S.C. 111</u>
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.

<u>National Stage of an International Application under 35 U.S.C. 371</u>
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.

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

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Page 9527

Docket No.: ALXN-P08-114
(PATENT)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of:
Bell et al.

Application No.: 13/426,973 | Confirmation No.: 8851

Filed: March 22, 2012 | Art Unit: 1644

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

SUPPLEMENTAL INFORMATION DISCLOSURE STATEMENT (IDS)

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

Dear Madam:

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

This Supplemental Information Disclosure Statement is filed more than three months after the U.S. filing date, and after the mailing date of the first Office Action on the merits, whichever occurs first, but before the mailing date of any of a Final Office Action, a Notice of Allowance (37 C.F.R. § 1.97(c)) or an action that otherwise closes prosecution in the application.

40511171_1

Samsung Bioepis Exhibit No. 1002
Page 9528

Applicants submit herewith a copy of non-patent literature in accordance with 37 C.F.R. § 1.98(a)(2).

In accordance with 37 C.F.R. § 1.97(g), the filing of this Supplemental Information Disclosure Statement shall not be construed to mean that a search has been made or that no other material information as defined in 37 C.F.R. § 1.56(a) exists. In accordance with 37 C.F.R. § 1.97(h), the filing of this Supplemental Information Disclosure Statement shall not be construed to be an admission that any patent, publication or other information referred to therein is "prior art" for this invention unless specifically designated as such.

It is submitted that the Supplemental Information Disclosure Statement is in compliance with 37 C.F.R. § 1.98 and the Examiner is respectfully requested to consider the listed reference.

Please charge our Deposit Account No. 18-1945 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 (or with any paper hereafter filed in this application by this firm) to our Deposit Account No. 18-1945, under Order No. ALXN-P08-114.

Dated: January 8, 2014

Respectfully submitted,

By_/Jason S. Cathelyn/___
Jason S. Cathelyn, Ph.D.
Registration No.: 68,195
ROPES & GRAY LLP
Prudential Tower
800 Boylston Street
Boston, Massachusetts 02199
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(617) 235-9492 (Fax)
Attorneys/Agents For Applicants

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
13/426,973	03/22/2012	Leonard Bell	ALXN-P08-114	8851

28120 7590 01/27/2014

ROPES & GRAY LLP
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PRUDENTIAL TOWER
800 BOYLSTON STREET
BOSTON, MA 02199-3600

EXAMINER	
ROGERS, JAMES L	
ART UNIT	**PAPER NUMBER**
1644	

NOTIFICATION DATE	DELIVERY MODE
01/27/2014	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):

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* 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

Samsung Bioepis Exhibit No. 1002
Page 9535

PTO/SB/08a (07-09)
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Attorney Docket Number	ALXN-P08-114

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FOREIGN PATENT DOCUMENTS

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Examiner Signature		Date Considered	

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant. [1] Applicant's unique citation designation number (optional). [2] See Kinds Codes of USPTO Patent Documents at www.uspto.gov or MPEP 901.04. [3] Enter Office that issued the document, by the two-letter code (WIPO Standard ST.3). [4] For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. [5] Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16 if possible. [6] Applicant is to place a check mark here if English language Translation is attached.

35377602_1

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

Samsung Bioepis Exhibit No. 1002
Page 9536

PTO/SB/08b (07-09)
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U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
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Art Unit	1644
Examiner Name	J. L. Rogers
Attorney Docket Number	ALXN-P08-114

NON PATENT LITERATURE DOCUMENTS

Examiner Initials*	Cite No.[1]	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, page(s), volume-issue number(s), publisher, city and/or country where published.	T[2]
		~~Clinics, Biotechnology News, Vol. 24(30): 10 (2004).~~	
		Hillmen et al., "Eculizumab, a C5 Complement-Blocking Antibody, Controls Hemolysis in Paroxysmal Nocturnal Hemoglobinuria (PNH) with Responses Maintained over prolonged Period of Therapy" Journal of The American Society of Hematology, Vol. 102(11), Abstract 1858 (2003).	
		Hillmen et al., "Eculizumab, a C5 complement-blocking antibody, controls haemolysis in paroxysmal nocturnal haemoglobinuria (PNH) with responses maintained over a prolonged period of therapy," British Journal of Haematology, Vol. 125 (Suppl. 1): 1-72, Abstract 5 (2004).	
		Notice of Opposition for EP Patent No. 1720571, dated 3/18/2013	

Examiner Signature	/James Rogers/	Date Considered	01/16/2014

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[1]Applicant's unique citation designation number (optional). [2]Applicant is to place a check mark here if English language Translation is attached.

35377602_1

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Page 9537

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INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Use as many sheets as necessary)

Sheet 1 of 2

Complete if Known	
Application Number	13/426,973
Filing Date	March 22, 2012
First Named Inventor	Leonard Bell
Art Unit	1644
Examiner Name	J. L. Rogers
Attorney Docket Number	ALXN-P08-114

U.S. PATENT DOCUMENTS

Examiner Initials*	Cite No.[1]	Document Number Number-Kind Code[2] (if known)	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear

FOREIGN PATENT DOCUMENTS

Examiner Initials*	Cite No.[1]	Foreign Patent Document Country Code[3]-Number[4]-Kind Code[5] (if known)	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages Or Relevant Figures Appear	T[6]

Examiner Signature		Date Considered	

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Page 9538

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INFORMATION DISCLOSURE STATEMENT BY APPLICANT

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Sheet 2 of 2

Complete if Known	
Application Number	13/426,973
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First Named Inventor	Leonard Bell
Art Unit	1644
Examiner Name	J. L. Rogers
Attorney Docket Number	ALXN-P08-114

NON PATENT LITERATURE DOCUMENTS

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		~~Clinics, Biotechnology News, Vol. 24(08): 10 (2004).~~	
		Hillmen et al., "Eculizumab, a C5 Complement-Blocking Antibody, Controls Hemolysis in Paroxysmal Nocturnal Hemoglobinuria (PNH) with Responses Maintained over prolonged Period of Therapy" Journal of The American Society of Hematology, Vol. 102(11), Abstract 1858 (2003).	
		Hillmen et al., "Eculizumab, a C5 complement-blocking antibody, controls haemolysis in ~~paroxysmal nocturnal haemoglobinuria (PNH) with responses maintained over a prolonged~~ period of therapy," British Journal of Haematology, Vol. 125 (Suppl. 1): 1-72, Abstract 5 (2004).	
		~~Notice of Opposition for EP Patent No. 1720571, dated 2/18/2013.~~	

Examiner Signature	/James Rogers/	Date Considered	01/16/2014

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EAST Search History

EAST Search History (Prior Art)

Ref #	Hits	Search Query	DBs	Default Operator	Plurals	Time Stamp
L1	48	((C5 near10 antibod$) or eculizumab) near10 (dosage or dose)	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	OFF	2014/01/16 12:42
L2	32	L1 and ((hemolytic near3 disease) or hemolysis or hemoglobinuria)	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	OFF	2014/01/16 12:47

EAST Search History (Interference)

Ref #	Hits	Search Query	DBs	Default Operator	Plurals	Time Stamp
L6	30032	((C5 nera10 antibod?) or eculizumab).clm.	USPAT; UPAD	OR	OFF	2014/01/16 12:54
L7	41342	(dosage or dose).clm.	USPAT; UPAD	OR	OFF	2014/01/16 12:54
L9	2139	("300" near2 mg).clm.	USPAT; UPAD	OR	OFF	2014/01/16 12:55
L10	13	L6 and L7 and L9	USPAT; UPAD	OR	OFF	2014/01/16 12:55

1/16/2014 1:02:34 PM
C:\Users\jrogers\Documents\EAST\Workspaces\13439473.wsp

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INFORMATION DISCLOSURE STATEMENT BY APPLICANT

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Sheet 1 of 2

Complete if Known	
Application Number	13/426,973
Filing Date	March 22, 2012
First Named Inventor	Leonard Bell
Art Unit	1644
Examiner Name	J. L. Rogers
Attorney Docket Number	ALXN-P08-114

U.S. PATENT DOCUMENTS

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FOREIGN PATENT DOCUMENTS

Examiner Initials*	Cite No.[1]	Foreign Patent Document Country Code[3]-Number[4]-Kind Code[5] (if known)	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages Or Relevant Figures Appear	T[6]
		WO 2004/029207 A2	04-08-2004	XENCOR		

Examiner Signature		Date Considered	

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Page 9541

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INFORMATION DISCLOSURE STATEMENT BY APPLICANT

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Sheet 2 of 2

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First Named Inventor	Leonard Bell
Art Unit	1644
Examiner Name	J. L. Rogers
Attorney Docket Number	ALXN-P08-114

NON PATENT LITERATURE DOCUMENTS

Examiner Initials*	Cite No.[1]	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, page(s), volume-issue number(s), publisher, city and/or country where published.	T[2]
		Lee et al., "Neisseria meningitidis Bacteremia in Association with Deficiency of the Sixth Component of Complement," Infection and Immunity, Vol. 24(3): 656-660 (1979).	

Examiner Signature	/James Rogers/	Date Considered	01/16/2014

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INFORMATION DISCLOSURE STATEMENT BY APPLICANT

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Sheet 1 of 2

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Filing Date	March 22, 2012
First Named Inventor	Leonard Bell
Art Unit	1644
Examiner Name	J. L. Rogers
Attorney Docket Number	ALXN-P08-114

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Sheet 2 of 2

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First Named Inventor	Leonard Bell
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		Figueroa and Densen, "Infectious Diseases Associated with Complement Deficiencies," Clinical Microbiology Reviews, Vol. 4(3), pp. 359-395 (1991).	

Examiner Signature	/James Rogers/	Date Considered	01/16/2014

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40511201_1

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

Search Notes	Application/Control No.	Applicant(s)/Patent Under Reexamination
	13426973	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	7/30/2012	JR
EAST: PGPUB, USPAT, JPO, EPO, DRWNT, INVENTOR SEARCH	7/30/2012	JR
updated	5/8/2013	JR
updated	1/16/2014	JR

INTERFERENCE SEARCH			
US Class/ CPC Symbol	US Subclass / CPC Group	Date	Examiner

supplemental STN search

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     BIOTECHDS, CABA, CAPLUS, CEABA-VTB, CIN, CROPB, CROPU, DDFB, DGENE,
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     2014
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Samsung Bioepis Exhibit No. 1002
Page 9546

supplemental STN search

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L95           0 FILE USPAT2
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L97           0 FILE VETU
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L99           0 FILE NAPRALERT
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L101          3 DUP REM L100 (1 DUPLICATE REMOVED)
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POWER OF ATTORNEY TO PROSECUTE APPLICATIONS BEFORE THE USPTO

I hereby revoke all previous powers of attorney given in the application identified in the attached statement under 37 CFR 3.73(b).

I hereby appoint:

[X] Practitioners associated with the Customer Number: 00959

OR

[ ] Practitioner(s) named below (if more than ten patent practitioners are to be named, then a customer number must be used):

Name	Registration Number	Name	Registration Number

as attorney(s) or agent(s) to represent the undersigned before the United States Patent and Trademark Office (USPTO) in connection with any and all patent applications assigned only to the undersigned according to the USPTO assignment records or assignment documents attached to this form in accordance with 37 CFR 3.73(b).

Please change the correspondence address for the application identified in the attached statement under 37 CFR 3.73(b) to:

[X] The address associated with Customer Number: 00959

OR

[ ] Firm or Individual Name	Jane E. Remillard, Esq. NELSON MULLINS RILEY & SCARBOROUGH LLP				
Address	One Post Office Square				
City	Boston	State	MA	Zip	02109-2127
Country	US	Telephone	(800) 237-2000	Email	ipboston.docketing@nelsonmullins.com

Assignee Name and Address:

Alexion Pharmaceuticals, Inc.
352 Knotter Drive
Cheshire, CT 06410
United States

A copy of this form, together with a statement under 37 CFR 3.73(b) (Form PTO/SB/96 or equivalent) is required to be filed in each application in which this form is used. The statement under 37 CFR 3.73(b) may be completed by one of the practitioners appointed in this form if the appointed practitioner is authorized to act on behalf of the assignee, and must identify the application in which this Power of Attorney is to be filed.

SIGNATURE of Assignee of Record

The individual whose signature and title is supplied below is authorized to act on behalf of the assignee

Signature	Todd Spalding	Date	11/26/2013
Name	Todd Spalding	Telephone	(203) 439-9803
Title	Vice President, Head of Intellectual Property		

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Page 9548

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STATEMENT UNDER 37 CFR 3.73(b)

Applicant/Patent Owner: Alexion Pharmaceuticals, Inc.

Application No./Patent No.: 13/426,973 Filed/Issue Date: March 22, 2012

Titled: Treatment of Paroxysmal Nocturnal Hemoglobinuria Patients by an Inhibitor of Complement

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

states that it is:

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

2. [ ] an assignee of less than the entire right, title, and interest in
(The extent (by percentage) of its ownership interest is _____ %); or

3. [ ] an assignee of an undivided interest in the entirety of (a complete assignment from one of the joint inventors was made) the patent application/patent identified above by virtue of either:

A. [X] An assignment from the inventor(s) of the patent application/patent identified above. The assignment was recorded in the United States Patent and Trademark Office at Reel 028696 , Frame 0909 , or for which a copy thereof is attached.

OR

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

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

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

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

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

/Jill Gorny Sloper, Esq./	January 31, 2014
Signature	Date
Jill Gorny Sloper, Esq.	Attorney for Assignee
Printed or Typed Name	Title

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

Dated: January 31, 2014 Electronic Signature for Jill Gorny Sloper, Esq.: /Jill Gorny Sloper, Esq./

Electronic Acknowledgement Receipt	
EFS ID:	18081987
Application Number:	13426973
International Application Number:	
Confirmation Number:	8851
Title of Invention:	TREATMENT OF PAROXYSMAL NOCTURNAL HEMOGLOBINURIA PATIENTS BY AN INHIBITOR OF COMPLEMENT
First Named Inventor/Applicant Name:	Leonard Bell
Customer Number:	28120
Filer:	Jill R. Gorny Sloper/Sandra Nackel
Filer Authorized By:	Jill R. Gorny Sloper
Attorney Docket Number:	ALXN-P08-114
Receipt Date:	31-JAN-2014
Filing Date:	22-MAR-2012
Time Stamp:	14:16:49
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	Power of Attorney	POA.pdf	43735 ea4cb8cb1d44d7e3ea1fa2d50ffa5f1d7a6aa8f4	no	1

Warnings:
Information:

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Page 9550

2	Assignee showing of ownership per 37 CFR 3.73.	Statement.pdf	19301 d4fb200843b9ae8a20a96a84782ee946b2e4d382	no	1

Warnings:	
Information:	
Total Files Size (in bytes):	63036

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

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

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

Samsung Bioepis Exhibit No. 1002
Page 9551

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APPLICATION NUMBER	FILING OR 371(C) DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO./TITLE
13/426,973	03/22/2012	Leonard Bell	ALXN-P08-114

CONFIRMATION NO. 8851

959
NELSON MULLINS RILEY & SCARBOROUGH LLP
FLOOR 30, SUITE 3000
ONE POST OFFICE SQUARE
BOSTON, MA 02109

POA ACCEPTANCE LETTER

OC000000066416369

Date Mailed: 02/07/2014

NOTICE OF ACCEPTANCE OF POWER OF ATTORNEY

This is in response to the Power of Attorney filed 01/31/2014.

The Power of Attorney in this application is accepted. Correspondence in this application will be mailed to the above address as provided by 37 CFR 1.33.

/nhassani/

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

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APPLICATION NUMBER	FILING OR 371(C) DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO./TITLE
13/426,973	03/22/2012	Leonard Bell	ALXN-P08-114

CONFIRMATION NO. 8851

POWER OF ATTORNEY NOTICE

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OC000000066416342

Date Mailed: 02/07/2014

NOTICE REGARDING CHANGE OF POWER OF ATTORNEY

This is in response to the Power of Attorney filed 01/31/2014.

- The Power of Attorney to you in this application has been revoked by the assignee who has intervened as provided by 37 CFR 3.71. Future correspondence will be mailed to the new address of record(37 CFR 1.33).

/nhassani/

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

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www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
13/426,973	03/22/2012	Leonard Bell	AXJ-114BUSCN	8851

959 7590 04/03/2014

NELSON MULLINS RILEY & SCARBOROUGH LLP
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BOSTON, MA 02109

EXAMINER	
ROGERS, JAMES L	
ART UNIT	PAPER NUMBER
1644	

MAIL DATE	DELIVERY MODE
04/03/2014	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.

Applicant-Initiated Interview Summary	Application No.	Applicant(s)	
	13/426,973	BELL ET AL.	
	Examiner	Art Unit	
	JAMES ROGERS	1644	

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

(1) *JAMES ROGERS*.

(2) *DANIEL KOLKER, SPE*.

(3) *JILL SLOPER*.

(4) *JANE REMILLARD*.

Date of Interview: *02 April 2014*.

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: *91,98,100-106,110-113 and 115*.

Identification of prior art discussed: _____.

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

The outstanding obviousness rejection from the prior office action was discussed as well as possible amendments to the claim. 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

/DANIEL E. KOLKER/
Supervisory Patent Examiner, Art Unit 1644
April 2, 2014

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.

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PTO/SB/31 (09-12)
Approved for use through 01/31/2013. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number.

NOTICE OF APPEAL FROM THE EXAMINER TO THE PATENT TRIAL AND APPEAL BOARD	Docket Number (Optional) AXJ-114BUSCN

In re Application of	Leonard BELL *et al.*
Application Number	13/426,973-Conf. #8851
Filed	March 22, 2012
For	Treatment of Paroxysmal Nocturnal Hemoglobinuria Patients by an Inhibitor of Complement
Art Unit	1644
Examiner	J. L. Rogers

Applicant hereby **appeals** to the Patent Trial and Appeal Board from the last decision of the examiner.

The fee for this Notice of Appeal is (37 CFR 41.20(b)(1)) $ 800.00

- [ ] Applicant claims small entity status. See 37 CFR 1.27. Therefore, the fee shown above is reduced by half, and the resulting fee is: $ _____
- [ ] A check in the amount of the fee is enclosed.
- [ ] Payment by credit card. Form PTO-2038 is attached.
- [x] The Director has already been authorized to charge fees in this application to a Deposit Account.
- [x] The Director is hereby authorized to charge any fees which may be required, or credit any overpayment to Deposit Account No. 12-0080 .
- [ ] A petition for an extension of time under 37 CFR 1.136(a) (PTO/SB/22) is enclosed.

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.

I am the

- [ ] applicant /inventor.
- [ ] assignee of record of the entire interest. See 37 CFR 3.71. Statement under 37 CFR 3.73(b) is enclosed. (Form PTO/SB/96)
- [x] attorney or agent of record. Registration number 60,760
- [ ] attorney or agent acting under 37 CFR 1.34. Registration number if acting under 37 CFR 1.34. _____

/Jill Gorny Sloper, Esq./
Signature

Jill Gorny Sloper, Esq.
Typed or printed name

(617) 202-4630
Telephone number

April 24, 2014
Date

NOTE: Signatures of all the inventors or assignees of record of the entire interest or their representative(s) are required. Submit multiple forms if more than one signature is required, see below*.

- [x] *Total of 1 forms are submitted.

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

Dated: April 24, 2014 Electronic Signature for Jill Gorny Sloper, Esq.: /Jill Gorny Sloper, Esq./

Samsung Bioepis Exhibit No. 1002
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Electronic Patent Application Fee Transmittal

Application Number:	13426973
Filing Date:	22-Mar-2012
Title of Invention:	TREATMENT OF PAROXYSMAL NOCTURNAL HEMOGLOBINURIA PATIENTS BY AN INHIBITOR OF COMPLEMENT
First Named Inventor/Applicant Name:	Leonard Bell
Filer:	Jill R. Gorny Sloper
Attorney Docket Number:	AXJ-114BUSCN

Filed as Large Entity

Utility under 35 USC 111(a) Filing Fees

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Basic Filing:				
Pages:				
Claims:				
Miscellaneous-Filing:				
Petition:				
Patent-Appeals-and-Interference:				
Notice of Appeal	1401	1	800	800
Post-Allowance-and-Post-Issuance:				
Extension-of-Time:				

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Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Miscellaneous:				
		Total in USD ($)		**800**

Samsung Bioepis Exhibit No. 1002
Page 9559

Electronic Acknowledgement Receipt	
EFS ID:	18849895
Application Number:	13426973
International Application Number:	
Confirmation Number:	8851
Title of Invention:	TREATMENT OF PAROXYSMAL NOCTURNAL HEMOGLOBINURIA PATIENTS BY AN INHIBITOR OF COMPLEMENT
First Named Inventor/Applicant Name:	Leonard Bell
Customer Number:	959
Filer:	Jill R. Gorny Sloper
Filer Authorized By:	
Attorney Docket Number:	AXJ-114BUSCN
Receipt Date:	24-APR-2014
Filing Date:	22-MAR-2012
Time Stamp:	17:01:42
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	yes
Payment Type	Deposit Account
Payment was successfully received in RAM	$800
RAM confirmation Number	3554
Deposit Account	120080
Authorized User	

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)

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1	Notice of Appeal Filed	Notice_of_Appeal.pdf	21383 597429f4f94c540346429e37b6a20a47f6fb7ea4	no	1
Warnings:					
Information:					
2	Fee Worksheet (SB06)	fee-info.pdf	30170 4a1a16145302dd62b2e7630f1949b03d5ee01054	no	2
Warnings:					
Information:					
		Total Files Size (in bytes):	51553		

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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Injection practices among clinicians in United States health care settings

Gina Pugliese, RN, MS,[a] Cathie Gosnell, RN, MS, MBA,[b] Judene M. Bartley, MS, MPH, CIC,[c] and Scott Robinson, MA, MPH[d]
Charlotte, North Carolina

Background: Improper use of syringes, needles, and medication vials has resulted in patient-to-patient transmission of bloodborne pathogens, including hepatitis C virus. This study examined the injection practices of health care providers to identify trends and target opportunities for education on safe practices.

Methods: An on-line survey was conducted in May and June 2010 of clinicians in US health care settings that prepare and/or administer parenteral medications.

Results: The majority of the 5446 eligible respondents reported injection practices consistent with current recommendations. However, the following unsafe practices were identified: 6.0% "sometimes or always" use single-dose/single-use vials for more than 1 patient; 0.9% "sometimes or always" reuse a syringe but change the needle for use on a second patient; 15.1% reuse a syringe to enter a multidose vial and then 6.5% save that vial for use on another patient (1.1% overall).

Conclusion: Unsafe injection practices represent an ongoing threat to patient safety. Ensuring safe injection practices in all health care settings will require a multifaceted approach that focuses on surveillance, oversight, enforcement, and continuing education.

Key Words: Injection safety; bloodborne pathogens; survey needlestick injuries; safety practices; reuse syringes; reuse vials; propofol.

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Increasing reports of outbreaks in health care settings in the United States involving transmission of hepatitis B virus (HBV) and hepatitis C virus (HCV) to patients associated with unsafe injection practices and breakdowns in basic infection control have uncovered an alarming trend. Recent reviews of HBV and HCV outbreaks showed that, from 1998 to 2009, there were 51 outbreaks involving the notification of more than 75,000 potentially exposed patients and identification of 620 who became infected with HBV or HCV.[1,2] These outbreaks occurred in a variety of health care settings including 9 hospitals; 9 hemodialysis facilities; 16 outpatient clinics and ambulatory surgery centers; and 17 long-term care facilities. The majority resulted from unsafe injection practices and lapses in basic infection control practices, including failure to maintain aseptic technique when preparing or administering parenteral medications (eg, overt syringe reuse or contamination of shared parenteral medications by reused syringes); contamination of equipment and supplies (eg, preparing medications in contaminated area); or improper use and handling of blood glucose monitoring equipment (eg, single patient use fingerstick devices used on multiple patients or blood glucose meters not cleaned between patients). These identified outbreaks may represent a wider problem. For example, 67% of recently surveyed ambulatory surgical centers in 3 states were found to have at least 1 lapse in basic infection control, including unsafe injection and medication practices.[3] It is also believed that identified outbreaks represent only a portion of the true burden of infection. Many outbreaks and sporadic transmission of health care-associated viral hepatitis go unrecognized because most patients with acute HBV or HCV infection are asymptomatic or have mild nonspecific symptoms.[4,5]

Studies in the mid-1990s indicated that 20% to 39% of anesthesia personnel were reusing syringes for multiple patients[6]; by 2002, this rate had dropped to 1% to 3% according to a telephone survey of 500 randomly selected providers, including anesthesiologists, other physicians, certified registered nurse anesthetists, other nurses, and oral surgeons.[7] Limited data in 2008 from an Anesthesia Patient Safety Foundation poll indicated that up to 27% of clinicians could be reusing propofol infusion syringes while changing only the tubing between patients.[8] To gain a full understanding about current injection practice patterns to assist with targeting outreach and education, the Premier

From the Premier Safety Institute,[a,b,c] and Premier Research Services,[d] Charlotte, NC.

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Conflicts of interest: None to report.

0196-6553/$36.00

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Safety Institute conducted a Web-based survey of clinicians that prepare and/or administer parenteral medications across a wide variety of US health care settings.

METHODS

During May and June 2010, we conducted an on-line survey of clinicians practicing in a variety of health care settings using a convenience sample. The survey was posted on the Safety Institute Web site, and an e-mail invitation with a link to the survey was sent to the 39,100 subscribers of Premier's *Safety Share* public newsletter that include clinicians and health care providers from hospital and non-hospital settings. The survey link was also shared via an e-mail invitation and in the newsletters of 10 collaborating organizations. These organizations included the American Academy of Anesthesiologist Assistants; Accreditation Association for Ambulatory Health Care; American Association of Critical-Care Nurses; American Society of Health-System Pharmacists; Association for Professionals in Infection Control and Epidemiology Infusion Nurses' Society; Pittsburgh Regional Health Initiative; Society for Healthcare Epidemiology of America; Society of Gastroenterology Nurses and Associates, and Innovatix (nonacute health care providers).

The survey contained questions about awareness of injection safety and respondents' primary source and method of receiving information on this topic and frequency of performing various injection practices. These practices included those generally considered acceptable if performed with aseptic technique according to current guidelines, as well as those not recommended, having been demonstrated to result in transmission of bloodborne pathogens.[2] The items in the survey that assessed specific injection practices were grouped according to the *type* of practice (eg, syringe use, single-dose vial use, or multidose vial use) and *not* according to recommended or unacceptable practices. Respondents were also asked to indicate their professional training, the type of health care organization, and the department in which they practice the majority of the time. Respondents had the ability to provide comments for each item in the survey. Examples of both the most frequently occurring and revealing comments on current practices are summarized in the results.

The exact number of individuals receiving the link to the survey provided by the Safety Institute and 10 collaborating organizations is not known; however, the combined membership of these organizations represents a wide variety of professions and practice settings. There were a total of 8,035 responses to the survey. All respondents were asked 3 general questions about their knowledge of injection safety and the source and format of this information. This information was analyzed separately.

We eliminated 492 respondents who identified themselves as pharmacists after learning from the open-ended responses that the majority of the pharmacists were working under a sterile pharmacy hood and not preparing or administering parenteral medications at the point of administration. An additional 2,097 responses were eliminated that answered "no" (1,678) or did not respond (419) to the question, "in your current practice do you prepare or administer parenteral medications," at which time the survey automatically closed, and participants were thanked for their participation. Thus, a total of 5,446 respondents was included in the final analysis.

RESULTS

The total number of individuals who actually received the link to the survey (eg, both opened and read the invitation) was not known, thus an overall response rate could not be determined. In the preliminary analysis of the 8,035 respondents, 79.6% answered "yes" to the first item in the survey "prior to receiving the survey, have you ever heard of injection safety?" The next 2 items asked about the source and format of this information. The professional organization was selected as the most frequent source (60.1%) and guidelines as the most common format (59.6%) (Table 1).

The fourth item asked them to indicate "yes or no" to the question, "in your current practice do you prepare or administer parenteral medications?" A total of 5,446 respondents answering yes to this question were included in the final analysis and represented a wide range of health care organizations (both hospital and non-hospital) and departments (Table 2). Of the 5,199 who indicated their health care organization, 66.0% (3,432) were from hospitals and 34.0% (1,767) were from non-hospital settings. The majority of respondents identified themselves as registered nurses (89.5%). Responses on specific injection practices are summarized in Table 3 and below.

Acceptable practices if performed with aseptic technique

Administering a medication in a syringe prepared by someone else. The majority of respondents (71.0%) indicated that they never administered a medication in a syringe that was prepared by someone else. Only 29.0% indicated that they "sometimes or always" administered medications prepared by someone else. The most frequent comments provided by this group described when they engaged in this practice, such as, "*only during a code or emergency, only in vaccine and*

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Table 1. Knowledge-awareness of injection safety

Source	n (%)
How did you hear about injection safety?	
Professional organizations	3568 (60.1)
Coworkers	2750 (45.9)
Centers for Disease Control and Prevention (CDC)	1854 (31.0)
Supervisor	1354 (22.6)
Media	898 (15.0)
Health department	780 (13.0)
Other	1108 (18.5)
How was information received?	
Guidelines	3536 (59.6)
Educational session - seminar	3278 (55.2)
Bulletins	2065 (34.8)
Brochures	1137 (19.2)
Textbook	1059 (17.8)
Other	727 (12.3)

NOTE. Total frequencies vary; multiple responses were possible; some respondents did not answer all questions.

flu clinics," and many pointed out that "*the syringe was always labeled*" or that they "*watched the person preparing the syringe.*"

Enter a single-dose vial more than once for the same patient. A total of 30.2% (1,599 respondents) reported that they "always or sometimes" enter a single-dose/single-use vial more than once for the same patient. However, we did not assess whether the respondents were using the same or a new sterile syringe to obtain the additional doses for that same patient. Comments included reasons such as, "*if it is done within 24 hours; only if a short time has passed; when giving heparin in dialysis lines; as a cost-cutting measure; we don't want to waste the drug; and during a code.*" Many of the respondents indicated that this was a practice for specific drugs, providing examples, such as the following: "*IV Dilaudid, insulin, lidocaine, Narcan, phenylephrine, Ativan, terbutaline, and fentanyl.*"

Use a multidose vial for more than 1 patient. A third of respondents (34.4%) never use a multidose vial on more than 1 patient, with the frequent comment: "*we don't use multidose vials at our organization.*" However, the majority (65.6%) is using multidose vials for more than 1 patient. Approximately half of the comments indicated they were using multidose vials for specific medications, and the most frequent examples were vaccines, tuberculin skin testing, vitamin B12, lidocaine, and insulin. The other half of the comments were about the techniques used, such as the following: "*I use a new syringe for each entry, and we date the vials after opening.*"

Practices not considered appropriate or consistent with current guidelines

Use of single-dose vial for more than 1 patient. A total of 318 respondents indicated that they "sometimes or always" use single-dose/single-use vials for more than 1 patient representing 6.0% of all respondents. Examples of frequent comments to explain this practice were the following: "*as a cost-saving measure, done only when obtaining all of the doses at the same time, always using a new syringe, it depends on*

Table 2. Characteristics of respondents on survey of injection practices

Category	n (%)
Professional training	
Anesthesiologist assistant (AA-C)	120 (2.4)
Anesthetist (CRNA)	49 (1.0)
Dentist (DDS)	9 (0.2)
Licensed nurse (LPN, LVN)	145 (2.8)
Laboratory technologist	13 (0.3)
Operating room technician (ORT)	10 (0.2)
Patient care technician (PCT)	35 (0.7)
Pharmacist	23 (0.5)
Physician (MD, DO, DPM)	120 (2.4)
Registered nurse (RN)	4570 (89.5)
Respiratory therapist	10 (0.2)
Health care organization	
Hospital setting (n = 3432)	
Hospital (<100 beds)	675 (13.0)
Hospital (100-250 beds)	1005 (19.3)
Hospital (251-500 beds)	1145 (22.0)
Hospital (>500 beds)	607 (11.7)
Non-hospital setting (n = 1767)	
Ambulatory surgery center	513 (9.9)
Ambulatory care center (1) (Hospital-based/affiliated)	244 (4.7)
Ambulatory care center (1) (stand alone)	456 (8.8)
Dialysis	10 (0.2)
Home care (2)	133 (2.6)
Long-term care (3)	110 (2.1)
Physician's office	243 (4.7)
Urgent care center (4) (stand alone)	22 (0.4)
Other (5)	36 (0.7)
Primary practice area/department	
Ambulatory (6)	185 (3.6)
Cardiac catheterization/electrophysiology (EP)	56 (1.1)
Emergency care	342 (6.6)
Endoscopy	321 (6.2)
General patient clinical care (7)	1276 (24.6)
Geriatrics/home care (8)	84 (1.6)
Infection control/employee health	233 (4.5)
Infusion therapy	214 (4.1)
Intensive (critical) care (9)	835 (16.1)
Maternal-child (10)	279 (5.4)
Oncology	147 (2.8)
Pain management	52 (1.00)
Radiology-radiation	90 (1.7)
Surgery or anesthesia services	927 (17.9)
Other (11)	146 (2.8)

NOTE. Total frequencies vary; some respondents did not answer all questions. (1) Clinics, public health, ambulatory infusion, behavioral health; (2) home health, home infusion, hospice; (3) assisted living, nursing homes; (4) emergency room (ER), trauma centers; (5) dental, laboratories, outpatient pharmacies, institutional settings; (6) clinics, offices, dialysis; (7) medical/surgical, telemetry, general care units; (8) long-term care, subacute, assisted living; (9) intensive care unit (ICU), coronary care unit (CCU), surgical intensive care unit (SICU), (10) Labor and delivery, mother baby, pediatrics, pediatric intensive care unit (PICU), neonatal intensive care unit (NICU); (11) administration, education, mental health.

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the size of the vial, only with sterile technique, when giving specific drugs (eg, vaccines or insulin), and when giving propofol during the shortage."

Reuse a syringe but change the needle for use on a second patient. Forty-five respondents representing 1.0% reported that they "sometimes or always" administer medication to more than 1 patient using the same syringe but a new sterile needle for each patient. Comments were provided by only 4 of the respondents, and 3 indicated they do this with insulin and 1 with propofol. Of the 37 individuals who provided information on the organization where they work, 24 (64.9%) worked in hospital settings, and 13 (35.1%) worked in non-hospital settings. Twelve of the 13 worked in ambulatory surgery centers, and the 1 remaining person worked in a long-term care facility.

Reuse syringe for additional doses from the same multidose vial. A total of 797 respondents (15.1%) indicated that they are "sometimes or always" reusing a syringe for additional doses from the same multidose vial for the same patient. Frequent comments made by those who reported this practice included the following: *"when giving insulin; for moderate sedation; for conscious sedation; for emergency situation; for critical care patients; for multiple IV medication doses, we use the vial as the cap for the needle if using the syringe more than once."* For those respondents who reported "always or sometimes" engaging in this practice, the survey prompted them to answer an additional question about what they did with the vial after re-entry with same syringe. The majority of those answering the follow-up question, 738 of 789 (93.5%), indicated that they discarded the vial. However, an alarming 51 of the 789 (6.5%) indicated that they *"saved that vial for use on another patient."* Four of the 51 clinicians provided comments: 2 indicated they did this with insulin, 1 stated *"only if there was medication left in the vial,"* and 1 explained *"only if the vial remained sterile."* A number of respondents—who indicated they *"always discard the vial"* after re-entry for the same patient—pointed out that they did observe this practice among other clinicians.

Of the 51 professionals who reported reusing a syringe to obtain an additional dose from a multidose vial and then leaving it for use on another patient, approximately half (52.0%) were from the hospital setting, and the other half (48.0%) were from the non-hospital setting.

Of the 47 who reported their department, 13 (27.7%) indicated they worked in surgery or anesthesia; 9 (19.0%) in general patient care; 3 (6.4%) in endoscopy; 3 (6.4%) in oncology; 3 (6.4%) in a physician office; 3 (6.4%) in emergency care; and the remaining 13 (27.7%) worked in a variety of other departments/locations, such as cardiac catheterization laboratory, employee health, dermatology, pain management clinic, and a travel clinic.

Use a bag or bottle of intravenous solution as a source of supply or medication diluent for more than 1 patient. A total of 448 respondents (9.0%) indicated that they "always or sometimes" use a bag or bottle of intravenous (IV) solution as a source of supply or medication diluent for more than 1 patient. The most frequent comments included the following: *"always use alcohol pad first; with one hour expiration; always a new needle and syringe; draw flushes with a spike; only for 24 hours; only in the med room; use a 500-mL bag of saline with stop-cock to dilute IV meds; only when we are out of single bottles of diluents."*

DISCUSSION

Our 2010 study aimed to identify the current injection practices of clinicians in US health care settings to assess the extent of acceptable and improper use of syringes, needles, and medication vials during preparation and administration of parenteral medications across multiple professions in both the hospital and the non-hospital settings. Although the majority of respondents indicated they were following recommended safe injection practices, even the small percentage of health care providers who were identified as not complying with recommended practices is alarming. Anything less than 100% compliance with infection control guidelines and aseptic technique contributes to risk of transmission of bloodborne viruses resulting in infections; both individual cases and outbreaks may go undetected for some time. In addition to increasing the potential for patient infections, unsafe injection practices put providers themselves at risk of needlestick injuries and potential infections, as well as licensing board actions and malpractice suits.[4]

Mistaken beliefs

There are a number of mistaken beliefs about the risks associated with syringe reuse and aseptic technique when handling injectable medications during preparation and administration that likely contribute to many of the outbreaks of health care-associated viral infections such as HBV and HCV infections.[4,6,7-13] For example, there is the belief that contamination is limited to the needle portion when a syringe and needle are used together as a unit. There is also an incorrect belief that the syringe does not become contaminated if the plunger is only "pushed" to inject medications and not "pulled" to aspirate or withdraw. However, decades old experimental studies have shown that contamination does in fact extend to the barrel of the syringe during intramuscular, subcutaneous,

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intradermal, and IV injections.[4,10-12] There is an additional risk of syringe contamination resulting from the negative pressure that occurs if a contaminated needle is removed from the syringe.

Another mistaken belief, in the case of IV administration, is that there is no risk of syringe contamination if the injection is given into the fluid path of IV tubing that is not visibly contaminated with blood.[4] To the contrary, the risk for syringe contamination is not eliminated by the length of IV tubing or the presence of heparin locks or valves.[13] When a contaminated needle or syringe is used to draw medication from a vial, the contamination can then be transferred to the vial. Professionals unfortunately often cite a need to reduce waste and costs as their rationale for reuse.

Aseptic technique is absolutely essential when handling, preparing, and administering parenteral medications (ie, injection or infusion) to prevent microbial contamination, protect the patient from infection, and prevent the spread of pathogens. Figure 1 summarizes the current recommendation for injection practices for patient safety.

Acceptable practices if performed with aseptic technique

There are a number of injection practices that are considered acceptable only if aseptic technique is strictly maintained. If these practices are not performed aseptically, they can lead to contamination of the injection equipment and supplies and disease transmission.

Administer a medication in a syringe prepared by someone else. Whereas this practice of administering a medication in a syringe prepared by someone else is not addressed in any guidelines, the person administering the injection must assume that aseptic technique was used to draw up the medication. We were glad to see that a common theme of the 1,557 respondents that indicated they always or sometimes engage in this practice was that they "*always watched the person preparing the syringe and ensured it was labeled*," suggesting that they understood the importance of aseptic technique.

Re-entry of single-dose vial for same patient. Approximately one third of our respondents indicated that they enter a *single-dose/single-use vial* more than once for an additional dose for the same patient; however, we did not assess whether they used the same syringe or a new sterile syringe for re-entry. The Centers for Disease Control and Prevention (CDC) guidelines emphasize that needles and syringes are single-use items and that any vial should *not* be entered with a used syringe or needle (Fig 1). First, re-entering a single-dose vial with the same needle is a risky practice because, if strict aseptic technique is not followed, there is a potential for contaminating the needle through inadvertent touch contamination from contact with organisms on the patient's skin, the IV tubing/access device if one is used (eg, heparin lock) that may be contaminated with the patient's blood, or during re-entry into the used vial. The risk of bacterial contamination is especially important for patients who may be immunocompromised. The use of a new sterile syringe and needle for re-entry into the vial does not eliminate the risk of compromising the sterility of single-dose vials of medications *if* strict aseptic technique is not used and the vial becomes contaminated. Once contaminated, the opportunities for bacterial growth are increased the longer the time elapsing between uses and the lack of bacteriostatic or preservative agents in many single-dose vials to inhibit bacterial growth (eg, vaccines). It is also important to note that single-dose vials are intended for a single procedure or injection and should always be discarded at the end of the procedure/injection. They should never be stored for later use or subsequent procedures, even if for the same patient.

Reuse of multidose vials. The majority of respondents (65.6%) reported using multidose vials for more than 1 patient. Although multidose vials contain more than 1 dose of medication because they contain a bacteriostatic agent, there is still a risk that a multidose vial may become contaminated. It is also important to note that bacteriostatic agents are not effective against viruses, such as HBV and HCV. It is for these reasons that the CDC recommends single-dose vials be used whenever possible and that medications packaged as multidose vials be assigned to a single patient whenever possible (Fig 1).

Practices not considered appropriate or consistent with current guidelines

There are certain inappropriate injection practices that have been associated with disease transmission and are dangerous and unacceptable.

Reuse of single-dose vials for multiple patients. The CDC explicitly recommends that single-dose vials or ampoules not be used for multiple patients (Fig 1). However, we found that 318 professionals, 6.0% of the respondents, reported this was their practice, and comments indicated this was often done with vaccines, insulin, and propofol. Another frequent comment was that reuse of the single-dose vial depended on the size of the vial. This comment reflects the confusion that many providers have about large volume vials that are labeled as single use (ie, single dose) believing that the large volume in the container makes it suitable for multiple patients and not to use it would be

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Injection safety is a set of measures taken to perform injections in an optimally safe manner for patients, health care personnel, and others.

Aseptic technique refers to the manner of handling medications and injection equipment to prevent microbial contamination; it applies to the handling, preparation, and storage of medications as well as the handling of all supplies used for injections and infusions, including syringes, needles, and IV tubing.

Recommendations	Practices You Must Know	CDC Category*
Use aseptic technique.	• Avoid contamination of sterile injection equipment.	1A
	• Do not administer medications from a syringe to multiple patients, even if the needle or cannula on the syringe is changed.	1A
Use syringes, needles and cannulae only once.	• Needles, cannulae and syringes are sterile, single-use items; they should not be reused for another patient nor to access a medication or solution that might be used for a subsequent patient.	1A
Use single-dose vials for parenteral medications *whenever possible.*	• Do not administer medications from single-dose vials or ampules to multiple patients or combine leftover contents for later use.	1A
If multi-dose vials are used, assign to a single patient *whenever possible.*	• If multi-dose vials must be used, both the needle or cannula and syringe used to access the multi-dose vial must be sterile.	1A
	• Do not keep multi-dose vials in the immediate patient treatment area and store in accordance with the manufacturer's recommendations; discard if sterility is compromised or questionable.	1A
Use fluid infusion and administration sets (i.e., intravenous bags, tubing and connectors) for one patient only and dispose appropriately after use.	• Do not use bags or bottles of intravenous solution as a common source of supply for more than one patient.	1B
	• Consider a syringe or needle/cannula contaminated once it has been used to enter or connect to a patient's intravenous infusion bag or administration set.	1B

*Category IA: Strongly recommended and supported by well-designed experimental, clinical or epidemiologic studies.
Category IB: Strongly recommended and supported by some experimental, clinical or epidemiologic studies and a strong theoretical rationale.
FROM: Centers for Disease Control and Prevention. Guideline for isolation precautions: preventing transmission of infectious agents in healthcare settings 2007. Atlanta (GA): U.S. Department of Health and Human Services, CDC; 2007. Available at: http://www.cdc.gov/ncidod/dhqp/gl_isolation.html.

Fig 1. Recommended injection practices for patient safety.

wasteful. A number of unsafe practices such as reuse of single-dose vials on multiple patients are done with the notion that they reduce costs without an appreciation of the risks involved. For example, in a Nevada endoscopy center outbreak investigated in 2008, it was discovered that syringes were routinely reused, after changing needles, to obtain additional doses of propofol from single-dose vials for patients who required additional sedation.[14,15] Although the syringe was discarded at the end of the procedure, any remaining medication in the single-dose propofol vial was used for subsequent patients. Over 63,000 patients who had undergone procedures were exposed to this long-standing practice and at risk of bloodborne pathogen transmission. Overall, 106 cases of hepatitis C were linked to this outbreak, costing the health department nearly $21 million for outbreak investigation, response, and testing of potentially exposed patients.[16]

Because propofol is formulated in a lipid emulsion that supports rapid bacterial growth even with inclusion of a bacteriostatic agent, there have also been numerous outbreaks from bacterial pathogens linked to reuse of single-dose vials of propofol.[17] The recent propofol shortage has prompted a number of providers to reuse single-dose vials of propofol, even though this is a very risky practice and has been implicated in numerous outbreaks of both viral and bacterial pathogens.[4,17]

Overt syringe reuse. Any form of syringe reuse is a dangerous practice. An alarming finding was that nearly 1.0% (45 out of 5,472 clinicians) responding to the question indicated that they use the *same* syringe for multiple patients but *change the needle* for each patient. Even 1% of clinician performing this unacceptable practice could translate into thousands of patients at risk and contribute to the burden of bloodborne pathogen transmission.

In an outbreak in Oklahoma, direct syringe reuse resulted in over 100 cases of HBV and HCV infections over a 3-year period.[16] Here, a professional in a pain remediation clinic routinely prepared a single needle and syringe at the beginning of each clinic session for 3 different medications. The 3 needles and syringes were used to administer the 3 medications sequentially to all patients treated in the individual clinic session through a peripheral IV catheter.

We were pleased to see that the majority (99.2%) of respondents indicated they never engaged in this practice and provided comments that reflected their awareness of this practice as egregious. These comments characterized the practice as "*appalling, horrifying, or gross.*"

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Table 3. Injection practices

	Never, n (%)	Combined always + sometimes, n (%)	Sometimes, n (%)	Always, n (%)	Total, n*
Acceptable practices if performed with aseptic technique					
How often do you administer a medication in a syringe that was prepared by someone else?	3813 (71.0)	1557 (29.0)	1482 (27.6)	75 (1.4)	5370
How often do you enter a single-dose/single-use vial more than once to obtain additional doses for the same patient?	3703 (69.8)	1599 (30.2)	1497 (28.2)	102 (1.9)	5302
How often do you use multidose vials for more than one patient?	1827 (34.4)	3484 (65.6)	2296 (43.2)	1188 (22.4)	5311
Practices not considered appropriate or consistent with current guidelines					
How often do you use single-dose/single-use vials for more than 1 patient?	4985 (94.0)	318 (6.0)	296 (5.6)	22 (0.4)	5303
How often do you administer medication to more than 1 patient using the *same syringe* but a *new sterile needle for each patient*?	5247 (99.2)	45 (0.9)	25 (0.5)	20 (0.4)	5292
How often do you use a bag or bottle of intravenous solution as a source of supply or medication diluent for more than 1 patient?	4817 (91.5)	448 (9.0)	403 (7.7)	45 (0.9)	5265
How often do you reuse a syringe to obtain additional doses from the *same multi-dose vial* for the *same patient*?	4492 (84.9)	797 (15.1)	714 (13.5)	83 (1.6)	5289
The disposition of the vial for 789 of the 797 who "always or sometimes" reuse a syringe to obtain additional doses from the *same multi-dose vial* for the *same patient*	Discard vial? 738 (93.5)	Leave for use on another patient? 51 (6.5)			789

*Total n = number of responses to each question. Frequencies vary; some respondents did not answer all questions.

Contamination of shared medications from reuse of syringes

Another deficient practice that has resulted in HBV and HCV transmission involves the reuse of a syringe to withdraw medications or solutions from containers of medication or solution that might be shared. This type of error does not typically involve overt reuse of a syringe for multiple patients. Instead, a syringe is reused to draw up additional medication for a single patient, thereby contaminating the medication vial or IV bag of solution that is subsequently used for multiple patients.[4]

For example, this practice led to the outbreak of HCV in the Nevada endoscopy center described above that involved routine reuse of syringes, after changing the needle, to obtain *additional doses of medication from a single-dose vial of propofol that was used for subsequent patients.*[15]

The current CDC guidelines specifically recommend that syringes, cannulas, and needles be used only once, and, if multidose vials are used, both the needle or cannula and syringe used to access the multidose vial must be sterile (Fig 1).[9] The CDC guidelines also recommend that needles and syringes should not be reused to access a medication or solution that might be used for a subsequent patient. Additionally, the CDC recommends limiting the use of multidose vials of medication to single patients, whenever possible, as an extra barrier of protection against unrecognized syringe reuse or other means of vial contamination.

In our study, the 797 respondents (15.1%) that indicated that they "sometimes or always" reuse a syringe for additional doses from the same multidose vial for the same patient were asked to indicate the disposition of the multidose vial. A total of 51 of the 789 (6.5%) who answered the question on disposition of the vial indicated that "*they saved the vial for reuse on another patient.*" Although only 4 of the 51 provided comments, they do provide some insight into the mistaken belief by some health care professionals that this practice is safe as long as good technique is used, for example, explaining this practice is done "*only if the vial remained sterile.*" A number of respondents who indicated they never engage in this practice did provide a comment that they have observed others doing this, suggesting that this practice may be more common than our data indicate.

Use a bag or bottle of IV solution for more than 1 patient. In another large outbreak, 99 patients treated at a hematology-oncology clinic in Nebraska were infected with HCV when a nurse reused syringes,

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after drawing blood from central venous catheters, to withdraw saline solution from 500-mL bags for flush procedures. Each bag of saline was routinely used as a common source of flush for 25 to 50 patients.[18] Our survey found that at least 448 health care professionals are using a bag or bottle of IV solution as a source of supply or medication diluent for more than 1 patient. There is little doubt that re-entering IV bags to obtain diluents for medications has the potential for outbreaks of significant size if large volume bags are used and aseptic technique is not followed as happened in the Nebraska outbreak. Some comments suggest that there is some awareness of potential risk and certain controls were being put into place that are believed to reduce the risk, for example: "*we limit use to 24 hours*" or "*we only do this in the medication room.*" However, even with limiting the use of IV bags as a common supply to 24 hours, this is still not an acceptable practice. Although it may shorten the duration of potential exposure, it will not prevent potential disease transmission if the IV bag becomes contaminated.

Insulin administration. "During insulin administration" was a common theme among the comments for many of the practices that are considered unsafe, for example, using single-dose vials for more than 1 patient, reusing a syringe on another patient after changing the needle, and reusing a syringe for the same multidose vial and then saving the vial for use on another patient. This finding is disturbing given the frequency of outbreaks of HBV infections from improper use and handling of blood glucose monitoring equipment, such as reusing fingerstick devices for multiple patients and sharing blood glucose meters between patients without disinfecting after each use.[19] Although many of the 15 reported outbreaks in the past decade have affected long-term care residents, the same conditions that facilitate transmission can be present in a wide variety of settings. A recent survey of infection control practices at 68 ambulatory surgical centers in 3 states found lapses in blood glucose monitoring in 46.3% of the centers.[3] Our survey data in combination with these reports suggest that lapses in infection control and aseptic technique for both glucose monitoring and insulin administration may be an under-recognized issue across other health care settings and worthy of increased attention.

Hospital versus non-hospital settings

Much of the recent focus has been on unsafe injection practices in the non-hospital setting[1,3] where it is thought that attention to infection prevention and control is lacking relative to hospital settings. However, our data trends indicate that unsafe injection practices are happening in both hospital and non-hospital settings. Of those who report reusing a syringe to obtain an additional dose from a multidose vial and then leaving it for use on another patient, approximately half were from the hospital setting and the other half were from the non-hospital setting. We also found that, for those who indicated they reused syringes and only changed the needle between patients, the majority (64.9%) of those providing information on their organization worked in hospital settings, and 35.1% (13 of 37) worked in non-hospital settings. Although the proportions of respondents varied by setting, our data suggest that unsafe injection practices likely resulting from mistaken beliefs may be occurring in the hospital setting more frequently than previously thought.

Limitations

Our study has several limitations. First, because our sample was only a convenience sample and not randomized, it may not be representative of all types of health care organizations and departments. Although the respondents represented many different health care professions, the majority was registered nurses. Second, respondents may be over-represented by those who were more interested in safe practices. Third, because it was not an observational study, it relied on self-reported practices that may not fully represent actual practice. We also did not assess the respondents' number of years in practice or the geographic location of their health care setting, which would have provided additional information on where to target outreach and education. As a result, our findings provide only conservative estimates of current injection practices.

Summary: Lessons learned

Our findings provide evidence that health care professionals continue to engage in unsafe injection practices, which represent an ongoing threat to patient safety in the United States and are devastating to all those patients who are impacted. A common theme among all the outbreaks was the failure of health care providers to adhere to the most basic concepts of infection control and injection safety.[9] Despite the availability of guidance on best practices from CDC and other groups, there remains a lack of awareness and implementation of these recommendations by many.

Although non-hospital settings have come under intense scrutiny in the past few years because of the frequency of reported outbreaks and breaches in infection control,[1,3] our data indicate that some of the most flagrant infractions (syringe reuse on multiple patients

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with only a needle change and re-entry into multidose vial leaving it for reuse on another patient) are being reported at least half of the time by professionals in hospital settings.

Preventing the spread of bloodborne pathogens such as HBV, HCV, and HIV is a basic expectation anywhere health care is provided.[2-5] This applies to protection of both the patient and the health care provider. Significant progress has been made in reducing risk of occupational infection with bloodborne pathogens such as HBV following widespread adoption of safer devices, safe work practices, and hepatitis B vaccination. We need to apply the same energy for reducing risks to patients from unsafe injection practices. This will require a multifaceted approach that focuses on surveillance, oversight, enforcement, and continuing educational efforts aimed at ensuring safe injection practices in all practice settings. It will also be important to get additional insight and address some of the incorrect beliefs about injection practices during educational programs. The source and format for receipt of information about injection safety (Table 1) should help guide educational efforts. The trends identified in this survey, including the range of locations and departments where unsafe practices are occurring, indicate the need for education in all settings where health care is provided. There is also a need for targeted educational initiatives, including curricula in nursing, medical, and other health care professional training and vocational programs. In addition to the CDC, a number of organizations and groups have educational resources, videos, guidelines, and position papers to assist in education and training.[20-23] Although there is clear need for more education, this may not necessarily eliminate all unsafe practices. Adopting principles from human factors engineering, we must consider redesigning devices, equipment, and processes to reduce or eliminate risk of bloodborne pathogen transmission. Just as we have seen sharps safety devices reduce risk of occupational needlesticks, we also need to look at engineering changes to reduce risks of unsafe injection practices, for example, redesigns of syringes that make it easy to comply with injection safety and consistent and clear labeling of medications vials to encourage intended usage.

Finally, each and every health care provider has a duty to carefully review their infection prevention and control practices and the practices of any staff peers as well as those they supervise, ensuring they are all following the recommended practices (Fig 1). We must create a safety culture whereby every provider is empowered to take responsibility to stop any colleague from engaging in unsafe practices and help ensure that safe practices are understood and followed by all. Patients must also be educated on safe practices and be empowered to question the practices of any health care provider that may impact the safety of a patient.

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AJIC special article

APIC position paper: Safe injection, infusion, and medication vial practices in health care

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Outbreaks involving the transmission of bloodborne pathogens or other microbial pathogens to patients in various types of health care settings due to unsafe injection, infusion, and medication vial practices are unacceptable. Each of the outbreaks could have been prevented by the use of proper aseptic technique in conjunction with basic infection prevention practices for handling parenteral medications, administration of injections, and procurement and sampling of blood. This document provides practice guidance for health care facilities on essential safe injection, infusion, and vial practices that should be consistently implemented in such settings.

Key Words: Bloodborne pathogens; injection; infusion; medication vial practices; aseptic technique; parenteral medications; administration of injections; procurement of blood.

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The transmission of bloodborne viruses and other microbial pathogens to patients during routine health care procedures continues to occur because of the use of unsafe and improper injection, infusion, and medication vial practices by health care professionals in various clinical settings throughout the United States.[1-13] Breaches in safe injection, infusion, and medication vial practices continue to result in unacceptable and devastating events for patients. More than 35 outbreaks of viral hepatitis have occurred in the United States over the past 10 years because of these unsafe practices and other breaches of infection prevention procedures. These outbreaks have resulted in the exposure of >100,000 individuals to viral hepatitis and the transmission of either hepatitis B virus (HBV) or hepatitis C virus (HCV) to more than 500 patients.[13] The unsafe practices used by health care personnel in these outbreaks can be categorized as (1) syringe reuse between patients during parenteral medication administration to multiple patients, (2) contamination of medication vials or intravenous (IV) bags after having been accessed with a used syringe and/or needle, (3) failure to follow basic injection safety practices when preparing and administering parenteral medications to multiple patients, and (4) inappropriate care/maintenance of finger stick devices and glucometer equipment between use on multiple patients.

In 2001, an anesthesiologist at a New York endoscopy clinic infected 19 patients with HCV by improperly reusing syringes and contaminating a multi-dose anesthesia medication vial subsequently used for multiple patients.[5] A similar HCV outbreak because of unsafe injection practices occurred in New York in 2002 and 2007, affecting a total of 102 patients.[13] In 2002, nearly 100 Nebraska hematology oncology clinic patients contracted HCV after a health care worker (HCW) responsible for medication infusions routinely used the same syringe and needle from a HCV-positive patient's blood draw to obtain saline flush solution from an IV bag. As a result, the patient's blood on the needle of the syringe was inoculated into the IV bag, which was then used as flushing solution for several other patients.[9] One of the most recent HCV

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outbreaks occurred at an endoscopy center in Nevada in 2008, again because of unsafe injection practices involving reusing syringes and sharing single-use medication vials between patients. This outbreak received significant media attention because, in part, of the fact that 63,000 persons were identified as being at potential risk for acquiring hepatitis. More than 12,000 patients have been tested to date, and at least 115 patients have been found to be infected with HCV. The investigation is ongoing.[12]

The Association for Professionals in Infection Control and Epidemiology (APIC) recognizes these outbreaks as unacceptable. Each of the outbreaks could have been prevented by the use of proper aseptic technique in conjunction with basic infection prevention practices for handling parenteral medications, administration of injections, and procurement and sampling of blood. Responsibility for the oversight and monitoring of patient safety must be clearly designated in health care settings to ensure that staff education is available for all health care professionals providing such services to patients. Furthermore, periodic monitoring for absolute adherence to safe injection practices in health care settings is vital to ensure effective engineering of and adherence to safe practices in everyday patient care.

In 2008, the United States Pharmacopeia (USP) published a revised USP General Chapter <797> Pharmaceutical Compounding—Sterile Preparations.[14] These standards apply to compounded sterile preparations (CSPs), which include compounded biologics, diagnostics, drugs, nutrients, and radiopharmaceuticals, including but not limited to the following dosage forms that must be sterile when they are administered to patients: aqueous bronchial and nasal inhalations, baths and soaks for live organs and tissues, injections (eg, colloidal dispersions, emulsions, solutions, suspensions, irrigations for wounds and body cavities, ophthalmic drops and ointments, and tissue implants). This includes manufactured bags or bottles of intravenous or irrigation fluid that may or may not contain additives and any solution drawn into a syringe for injection.

USP <797> applies to the pharmacy setting as well as to *all persons who prepare* medications that are administered and *all settings in which they are prepared* (eg, hospitals, other health care institutions, patient treatment clinics, physician's offices, and others). This chapter includes the standards for preparing, labeling, and time frames for discarding prepared medications. Pharmacies compound sterile preparations in an International Organization for Standardization (ISO) class 5 environment with primary engineering control devices, including laminar flow hoods, located in a "cleanroom" with stringent air quality, ventilation, personal protective equipment, and personnel and surface sanitation requirements to maintain the sterility of the preparation and safety of the compounding personnel. HCWs who prepare medications outside of ISO class 5 settings do so in environments with environmental particulates and microorganisms. Such settings and immediate-use preparation practices can potentially cause contamination of vials, IV solutions, and syringes from both airborne and direct contact sources. For example, clinicians who prepare injections and infusions may perform hand hygiene but not wear sterile gloves and a mask or contain their hair during preparation. When they remove the cap from the needle and insert it into the vial while breathing over the sterile needle and vial stopper, they create the potential for microbial contamination. Spiking a bag, vial, or bottle with a 1-way device and leaving it in place also increases the microbial contamination risk. The spike collects microorganism contamination from the environment, and the sterile solution is then poured out or withdrawn from a contaminated spout. For this reason, spiking any solution with a 1-way device and leaving it in place for multiple entries puts patients at risk for infection and is strongly discouraged.

According to USP <797>, immediate-use CSPs (prepared outside the ISO 5 environment) are exempted from the rigorous environmental purity standards and personnel cleansing and garbing practices that are required for all other categories of CSPs in USP <797>.[14] Immediate-use CSPs allow for certain sterile products to be prepared (compounded) without the need for special facilities (eg, clean room or ISO class 5 hood) and practices (eg, full cleansing or gowning). Dissolving, diluting, measuring, and mixing non-nutrient sterile injections using sterile devices (eg, ampuls, bags, needles, syringes, and vials) in clinical practice facilities (eg, patient care areas in hospitals, clinics, and physician offices) typify the conditions of what USP <797> calls "Immediate-use CSPs." USP <797> requires a 1-hour limit from completing preparation (eg, spiking an IV bag) until beginning administration of the immediate-use CSPs to patients. Their rationale is that the 1-hour limit is expected to preclude microbial population increase when accidental contamination of such drugs occurs with small quantities of microorganisms. Once microbial contamination occurs, the organism replication can begin within 1 to 4 hours with exponential growth occurring rapidly afterward.

For settings that prepare and use immediate-use CSPs (eg, operating rooms, ambulatory surgery centers, specialty clinics, and others), the cost of medication disposal, if administration has not begun 1-hour after preparation, can be daunting. USP recommends that these settings explore the possibility of having the pharmacy prepare the needed injectables and infusions in the ISO class 5 environment by properly trained, cleansed, and garbed personnel to prolong

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the usability of the CSPs. Most such CSPs according to USP <797> would then be classified "low risk level," for which the room temperature beyond-use date is 48 hours. This means that most CSPs prepared in a pharmacy ISO class 5 environment would be considered low risk level and could be stored for 48 hours, at which time the CSP would be discarded if not used. Another option is to locate a manufactured injectable product (eg, prepackaged syringe) that is discarded according to the manufacturer's expiration date.

However, it is important to recognize that many perioperative and clinical settings do not have ISO class 5 environments readily available. Clinicians spike IV solutions and prime IV tubing in operating rooms/departments and on patient care units in advance of their intended use so as to improve work flow and productivity. This advance preparation can occur at set time frames on the morning of or the evening prior to their intended use. USP <797> defines the time frame between preparation and initiating administration as 1 hour. This recommendation for immediate-use CSPs is a controversial unresolved issue and in actual practice difficult to comply with in certain settings. The APIC *does not support* the advance preparation (the night before or hours before administration) of immediate-use IV bags or syringes. The APIC *supports* the practice of preparing parenteral medications as close as possible to the time of administration and stresses the importance of educating designated staff, using tactile learning methods, verifying the competency of those performing the procedure, and periodic monitoring to assure compliance with aseptic technique and prevention of contamination. Proper technique is paramount to preventing accidental contamination during the process. Allowing only trained staff to prepare parenteral medications can decrease the risk of error/contamination. Preparation of parenteral medications must be performed in a clean, dry work space that is free of clutter and obvious contamination sources (eg, water, sinks). Prepared parenteral solutions should be stored in a controlled environment to limit the risk of tampering.

Another controversial and unresolved issue is the beyond-use date for opened multi-dose vials. The beyond-use date is the date after which an accessed product must be discarded. USP <797> requires medication multi-dose vials for injections be given a beyond-use date that is 28 days after initial stopper penetration (USP chapter <51>)[14] unless the product labeling (package insert) states otherwise. USP <797> requires that the vial be dated to reflect the date opened and/or beyond-use date. On the other hand, the Centers for Disease Control and Prevention (CDC) indicates that multi-dose vials can be used until the manufacturer's expiration date unless there are any concerns regarding the sterility of the product.[15] The US Food and Drug Administration defines an expiration date as "the date placed on the container/labels of a drug product designating the time during which a batch of the product is expected to remain within the approved shelf life specifications if stored under defined conditions and after which it may not be used."[16] Given the fact that this practice is variable and remains an unresolved issue at this time, the APIC recommends that facilities develop their policies and procedures based on either one of these recommendations. Rather than concentrate solely on beyond-use date or manufacturer expiration date, users of multi-dose vials must focus on the following: adhering to strict aseptic technique when accessing the vial; using a *new* sterile needle and a *new* sterile syringe for every access; removing all access devices from the vial; storing the vial in a clean, protected location according to the manufacturer's directions (eg, at room temperature or refrigerated); and ensuring that any vial whose sterility may be comprised is immediately discarded. Survey and accrediting agencies expect facilities to have written policies, based on the guidelines selected for use, that are consistently followed by staff.

The APIC strongly supports adherence to the following safe injection, infusion, and medication vial practices.[15-28]

ASEPTIC TECHNIQUE: IN LESS THAN AN ISO 5 ENVIRONMENT

- Perform hand hygiene (handwashing with soap and water or by application of a 60% or greater alcohol-based (In the United States, the alcohol component is predominantly ethyl alcohol (ethanol) or isopropyl alcohol.) hand sanitizer rub that is allowed to dry) before accessing supplies, handling vials and IV solutions, and preparing or administering medications.
- Use aseptic technique in all aspects of parenteral medication administration, medication vial use, injections, and glucose monitoring procedures.
- Store and prepare medications and supplies in a clean area on a clean surface.
- Never store needles and syringes unwrapped because sterility cannot be ensured.
- Discard all opened vials, IV solutions, and prepared or opened syringes that were involved in an emergency situation.
- Avoid contacting sterile drugs and sterile areas of devices and containers with non-sterile objects and/or secretions and particles shed from personnel.[27]

IV SOLUTIONS

- Never use IV solution containers (eg, bags, bottles) to obtain flush solutions or for any other purpose for more than 1 patient.

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- Never use infusion supplies, such as needles, syringes, flush solutions, administration sets, or IV fluids, on more than 1 patient.
- Prepare IV solutions and medications as close to administration as feasible. The time frame that can be allowed between the preparation and initiation of the administration of non-nutrient IV solutions that have been spiked or have had admixtures added in less than an ISO class 5 environment remains an *unresolved issue*. With limited data on actual contamination in real practice and linking contamination with patient infection, recommending a definitive time frame is not feasible at this time.
- Disinfect IV ports and vial stoppers by wiping and using friction with a sterile 70% isopropyl alcohol,[14,17] ethyl/ethanol alcohol, iodophor,[16] or other approved antiseptic swab. Allow the port to dry before accessing.
- Use a USP <797> primary engineering control with an ISO class 5 atmosphere to prepare admixtures of IV solutions when immediate use is not required. An admixture is defined as the addition of one or more concentrated drug injections from ampules and vials to larger volume bags and bottles of intravenous infusion fluids such as dextrose and sodium chloride injections.
- Do not use spiking devices, even if they have a 1-way valve, to remove fluid from IV bottles/bags for multiple uses or patients.

FLUSHING

- Use single-dose containers for flush solutions, whenever possible.
- If a multi-dose vial must be used, use it for only 1 patient and then discard it. Each entry into the multi-dose vial (dedicated to that patient) must be made with a new, unused sterile needle and new, unused sterile syringe.

SYRINGES

- Remove the sterile needle/cannulas and/or syringe from the package immediately before use.
- Never use a syringe for more than 1 patient even if the needle has been changed between patients. Changing the needle but not the syringe is unacceptable.
- Use a new syringe and a new needle for each entry into a vial or IV bag.
- Utilize sharps safety devices whenever possible.
- Discard syringes, needles, and cannulas after use directly on an individual patient or in an IV administration system.
- Dispose of used needles/syringes at the point of use in an approved sharps container.
- Do not prepare medication in one syringe to transfer to another syringe, ie, nurse draws up solution into syringe then transfers the solution to a syringe with plunger removed or injected into the bevel of the syringe to then be injected into the patient.
- Never store or transport syringes in clothing or pockets.
- Prepare syringes as close to administration as feasible.

VIALS

- Always follow the manufacturer's instructions for storage and use.
- Use single-use or single-dose vials whenever possible.
- Always use a new sterile syringe and new needle/cannula when entering a vial. Never enter a vial with a syringe or needle/cannula that has been previously used (eg, to inject a patient or access a medication vial).
- Cleanse the access diaphragm of vials using friction and a sterile 70% isopropyl alcohol,[14,17] ethyl alcohol, iodophor,[17] or other approved antiseptic swab. Allow the diaphragm to dry before inserting any device into the vial.
- Discard single-dose vials after use. Never use them again for another patient.
- Discard any vial that has been placed on a contaminated surface or a used procedure tray or that has been used during an emergency procedure.
- Use multi-dose medication vials for a single patient whenever possible and access all vials using a new sterile syringe and new needle/cannula adhering to aseptic technique. The risk of viral hepatitis transmission posed by multi-dose vials has been clearly demonstrated and mandates a practice of using 1 vial per 1 patient whenever possible. Infection transmission risk is reduced when multi-dose vials are dedicated to a single patient.
- Keep multi-dose vials away from the immediate patient environment.
- Never store or transport vials in clothing or pockets.
- Never pool or combine leftover contents of vials for later use.
- Never leave a needle, cannula, or spike device (even if it has a 1-way valve) inserted into a medication vial rubber stopper because it leaves the vial vulnerable to contamination.
- The beyond-use date and disposal of opened multi-dose medication vials for injection and/or IV administration remains an *unresolved issue* with differing opinions on the approach.
  - USP <797> requires a beyond-use date of 28 days after initial stopper penetration (USP chapter <51>)[14] unless the manufacturer's expiration date will be reached before 28 days or the product labeling (package insert) states otherwise. When

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following USP, date the vial to reflect the date opened and/or beyond use date. Discard the vial when the beyond-use date has been reached.
  - CDC indicates that the beyond-use date can be based on the manufacturer's expiration date.[15] When following CDC guidelines, date the vial to reflect the date opened.
  - Regardless of the beyond-use date or manufacturer's expiration date, a vial should be discarded sooner if the sterility of the product is in question.
  - The CDC Immunization Program recommends discarding of vaccines according to the manufacturer's expiration date.[37]
  - Facilities should develop a policy and procedure for their institution after reviewing and weighing these recommendations, implement an education and competency evaluation program for staff, and consider audits for adherence to the facility's policy/procedure.
- Inspect vials and discard if sterility is known or suspected to be compromised. Examine the vial for any particulate matter, discoloration, or turbidity; if present, do not use and discard immediately. All vials used during an emergency should be discarded because sterility cannot be guaranteed.

BLOOD GLUCOSE MONITORING DEVICES

- Assign a glucometer to each individual patient if possible. Clean and disinfect glucometers if they must be shared between multiple patients.
- Restrict the use of finger stick capillary blood sampling devices to individual patients.
- Maintain supplies and equipment, such as finger stick devices and glucometers, within individual inpatient rooms, if possible.
- Use single-use lancets that permanently retract after puncture.
- Never reuse finger stick devices and lancets. Dispose of them at the point of use in an approved sharps container. Lancets in a pen should be removed by mechanical means (hemostat) to avoid finger contact.
- Thoroughly clean all visible soil or organic material (eg, blood) from the glucometer before disinfection.
- Disinfect the exterior surfaces of the glucometer after each use following the manufacturer's directions. Use an Environmental Protection Agency-registered disinfectant effective against HBV, HCV, and HIV or a 1:10 bleach solution (1 part bleach to 9 parts water).

HCW

- Provide the HBV vaccination series to all previously unvaccinated health care personnel whose activities involve contact with blood or body fluids.[19]
- Check and document postvaccination titers 1 to 2 months after completion of the vaccination series.[19]
- Immediately report body fluid exposures and needlestick/sharps injuries.
- Ensure that staff preparing or administering injections or other parenteral medications are competent to perform these tasks aseptically.
- Periodically assess compliance with safe injection practices by observing and evaluating all personnel performing these procedures.

CONCLUSION

The use of safe injection practices is critical to prevent microbial contamination of products administered to patients. The ongoing reports of HBV and HCV transmission to patients and ongoing outbreaks of bacterial infections[29-31] indicate that much more is needed to ensure that these preventive practices are being scrupulously followed in all health care settings. HCWs and their managers must understand and practice these procedures safely. Administrators of medical facilities must be aware of safe injection practices and ensure that employees have the knowledge, training, and equipment to safely implement these procedures. It is critical that injectable medications, IV delivery systems, and blood glucose monitoring are used safely in all health care settings. As infection preventionists, we have an obligation to reiterate and ensure that safe injection, infusion, and medication vial practices are the absolute standard of care throughout various health care settings and across the continuum of care. We must take a lead role in promoting adherence by HCWs to these safe practices to protect the health and safety of our patients.

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REVIEW

Four policies to reduce HIV transmission through unsterile health care

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Summary: Residents of many developing countries face risks for themselves and their families to contract HIV and other bloodborne pathogens during unsterile health care. Helping people to understand and reduce these risks enlists their assistance to control the HIV/AIDS epidemic. To reduce HIV transmission through health care, we recommend four policies that international, foreign, and local public and private organizations can adopt and begin to implement even with little or no additional funds: (1) Educate the public about risks to contract HIV through unsterile health care. (2) Promote transparent practices for injections and other procedures that allow patients to see and know that care is safe (e.g., taking a new auto-disable syringe out of a sealed package and taking injecta from a single-dose vial). (3) Promote safe health care practices equally for clients and staff. (4) Establish a zero-tolerance policy for iatrogenic HIV infections, with publicly reported monitoring and investigations.

Keywords: HIV prevention, iatrogenic, injections, Africa

Informed opinion and active cooperation on the part of the public are of utmost importance in the improvement of the health of the people.

Constitution of the World Health Organization, 1946[1]

Introduction

Bloodborne pathogens known to be transmissible through unsterile health care include, among others, hepatitis B[2], HIV, and hepatitis C. Increasing international concern about transmission of bloodborne viruses during health care in developing countries[3–6] led to the formation of the Safe Injection Global Network (SIGN) in 1999, an independent organization with its secretariat currently at the World Health Organization (WHO). The SIGN secretariat and associates (individuals and organizations) have spearheaded major improvements in health care safety, including shifting United Nations Children's Fund (UNICEF)-supported immunization programmes to auto-disable (AD) syringes (that cannot be reused). However, this is only a beginning. Immunizations account for only 3% of injections outside rich countries[7]; and not all immunizations are in UNICEF-supported programmes.

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Unsterile health care remains common in many developing countries. According to estimates by WHO, health care providers — including informal providers — during the year 2000 reused syringes without sterilization for 6.6 billion injections (out of 16.7 billion injections, excluding rich countries) leading to an estimated 21 million hepatitis B, 2 million hepatitis C, and 260000 HIV infections[8] (a conservative figure which represents nevertheless about 5% of global HIV incidence; other estimates are higher[9]). Aside from syringes, evidence points to iatrogenic HIV infection via other common medical events such as antenatal care in Malawi and Zimbabwe[9] and collecting blood for tests in Malawi[10] and for plasma in Mexico[11], China[12], and other countries[13]. (Since people in developing countries receive health care from a wide range of formal and informal providers, we use the term 'iatrogenic' to refer to infections transmitted by all formal and informal providers, not only doctors.)

Large and explosive HIV outbreaks have occurred through unsterile health care in countries with better health care systems than are found in many developing countries. In 11 months, medical procedures at two hospitals in Elista, Russia, spread HIV from the index child to 90 children, during which time the number of infections doubled on average in less than two months[14,15]. In Romania in 1989–90, doctors found more than 1000 children infected through health care[16]. An investigation in Libya in 1998, found that

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procedures at a Benghazi hospital had spread HIV to more than 390 children[17]. Reports from China suggest that unsterile procedures during plasma collection in the 1990s infected several hundred thousand rural adults; some estimates indicate more than a million[12,18].

In these outbreaks, rapid HIV spread suggests that transmission through contaminated sharps is far more efficient than the one in 300 probability widely reported for needlestick injuries to health care workers[19]. Most needlestick injuries are superficial scratches; in a case–control study, average transmission through deep needlestick injuries — with the tip penetrating the skin as in an injection — was 2.3%, which is an improved but still uncertain approximation of transmission through contaminated injections[15,20].

In 1993, Mougdil and Daar reported that plasma from four of five HIV-infected volunteers remained infective after seven days at room temperature; decay, measured in tissue culture infective doses per mL, varied by patient but was slow for all in the first three days, ranging from $<1/2$ to 1 log[21]. In 1987, the Centers for Disease Control and Prevention reported that drying HIV caused a 1–2 log reduction in concentration 'within several hours'[22]. Hence, in syringes, tubes, vials, and rinsing pans in medical settings, HIV may remain viable for delayed transmission hours to a week or more later.

Much of the public discussion about how to promote better health care in developing countries has focused on funding. While money helps, money alone — without a change in policies — will not ensure safe care. We recommend four policies for donors, governments, and non-governmental organizations (NGOs) to adopt to ensure sterile practices in most health care exposures in developing countries, no matter how poor. These policies can be introduced through ongoing programmes with little or no additional funding, e.g., by changing posters, clinic practices, content of professional courses, etc. Eventually, new programmes for safe care built around these policies may involve new spending. (These policies do not address continuing HIV transmission through untested blood, which calls for additional — and urgent — changes in policies and programmes.)

Four policies

Educate the public about risks for HIV in health care settings

Health care consumers need to know that unsterile care is a risk for HIV acquisition, and that large HIV outbreaks have been documented through unsafe care.

Rationale: Many people in developing countries do not know that injections may pose a risk for HIV. For example, in a 1996 survey, only 57% of Nigerian secondary students knew that HIV could be transmitted through unsterilized instruments[23]; in other recent surveys, 19% of Zimbabwean women[24] and 28% of South African military recruits[25] did not know that HIV could be contracted from sharing injection equipment.

In countries with generalized HIV epidemics (i.e., HIV prevalence of at least 1% in the general population), unsterile health care threatens everyone. Recognizing such risks, a 1999 UNAIDS booklet on HIV for UN employees gives equal space — two to three pages — to advice for preventing HIV acquisition through health care and sex[26]. Others in Africa and Asia need the same balanced attention to all risks.

Agencies and authorities that could be warning people about health care risks have not done so. For example, the US Agency for International Development estimates that only 0.01% of HIV transmission globally is attributable to health care exposures (aside from blood transfusions, estimated to account for 5%)[27]. The *Lancet* and the *British Medical Journal* have recently published articles presenting similar estimates[28,29].

In developing countries, health care systems comprise a range of sub-systems, including government and private clinics, traditional medicine, and informal providers. Since formal systems are limited by money and personnel, people — even poor people — choose and pay for much of their health care out of pocket[30]. Hence, choices about what safe practices to demand are in consumers' hands. While alternative and untrained providers are often maligned, some are thorough and careful. On the other hand, unsterile practices have been reported at many public and mission hospitals and clinics. Educating health care professionals is important, but decades of experience prove it is not enough to assure sterile care in many developing countries. An educated public can promote safe care — and protect themselves — in all health care settings.

Promote transparent practices for injections and other common health care procedures that allow patients to see and know that care is safe

For injections and other simple invasive procedures, practices can be identified and promoted that allow patients (and parents of young patients) to see that equipment is sterile and that injected substances are not contaminated (aside from fraud or product errors before packing). An acronym for all such transparent practices could be POST, for Patient Observed Sterile Treatment.

Rationale: With a shift to POST practices, health care consumers aware of risks in unsterile care can take an active role in monitoring and promoting safe care. While choice of procedures subject to POST — such as injections and vaginal examinations — and specific POST practices are best

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Table 1. Illustrative list of health care procedures and Patient Observed Sterile Treatment (POST) practices

Procedure	Average events per year	Potential risk	Current standard practices	Suggested POST practices	Higher cost with POST
Injection for immunization	0–5 or more, depending on age and country	Unsterile needle and syringe	Open a new AD syringe in front of the patient	Open a new AD syringe in front of the patient	–
		Contaminated injecta	Take injecta from multidose vials	Open a new single-dose vial in front of the patient	+$0.24 for hepatitis vaccine* Other vaccines?
Injection for treatment	1–10 or more, depending on age and country	Unsterile needle and syringe	Common reuse of unsterilized syringes	Open a new syringe in front of the patient	+$0.13–0.23 for a new AD syringe[32]
		Contaminated injecta	Take injecta from multidose vials	Open a new single-dose vial in front of the patient	?
Drawing venous blood for tests	?	Unsterile equipment		Single-use equipment	?
Drawing blood for transfusion	?	Unsterile equipment		Single-use equipment	?

*Calculated from $0.56 for a single-dose vial versus $0.32 per dose for a 10-dose vial[31]. AD = auto-disable

developed locally, one can anticipate common themes (Table 1). For example, to be sure that injections are safe, a patient could ask to see the provider remove a new AD syringe from a sealed package and take the vaccine or medicine from a single-dose vial. For dental care the solutions are not so obvious. Local research may be required to determine acceptability and reliability of some practices.

Some POST practices might have a cost, and the distribution of costs between consumer and provider may differ from one setting to another. However, these are secondary matters; with POST, consumers have the option to choose safe care and to pay for it if necessary. For many procedures, cost differences are minimal, and costs may be lower for some safe practices; for example, taking oral or no medication instead of injections for many common symptoms. From many studies, 70–90% of health care injections in developing countries are judged unnecessary[33].

Defining and implementing POST practices can begin at any level. A church, for example, may organize meetings between members and local health care providers to discuss and endorse POST practices. Promotion through government and donor programmes could accelerate adoption and acceptability among providers, but the key is that patients understand and appreciate that with POST practices they can ensure sterile care.

For some POST practices, donor and government collaboration — with or without added funding — may be essential. Avoiding use of multidose vials is one such practice. Donor-funded immunization programmes currently rely heavily on multidose vials, many with 10–20 vaccine doses per vial. A patient or parent who sees a nurse withdrawing vaccine from an already opened vial may wonder if previous withdrawals were performed with sterile needles. One option is for governments and donors to shift to single-dose vials and/or pre-loaded syringes, though cost and capacity may be limiting, at least in the short run. Alternatively, governments could supply single-dose vials at a premium, or allow private supply for those who want to pay. Other technical solutions may be found, such as redesigning multidose vials to dispense vaccines in a way that does not allow contamination. With current multidose vials, many patients in poor countries face the unpalatable choice between unsafe health care and no health care — when safe care is a viable third option.

With local initiative, people may extend POST practices to whatever exposures they are uneasy about and are able to change. For example, when a Ugandan patient enters a hospital, family and friends may bring 'a saucepan, cooking stove and fuel. . . . At the surgical ward where most patients are receiving over four injections daily, the[se] attendants would boil the equipment once in the morning and later in the evening'[34]. This is one solution in the POST spirit. Birungi suggests another, that 'People should be given a chance to witness the entire sterilization procedure and, where possible, to participate. The idea is that to restore people's trust in institutional things, they should be personally involved'[34].

Other than health care, parenteral exposure includes tattooing, body piercing, and shaving in the marketplace. For these and other non-medical procedures, POST practices can also be developed to allow consumers to be confident of sterile practices.

Promote safe health care practices equally for clients and staff

All aid agencies and multilateral organizations that fund or promote health care in developing countries should promote POST practices equally

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for clients and staff, so that for simple health care procedures, poor people in poor countries may be as certain as anyone in the world that delivery of medical services is sterile.

Rationale: For decades, foreign and international organizations funding and promoting health care in developing countries have advised their staff that local care is unsafe. For example, a 1999 UNAIDS publication encourages UN employees to 'carry sterile disposable needles and syringes for your personal use (as part of the WHO medical kit)' and to 'make sure that all equipment is properly sterilized. Do not be afraid to ask questions.... Parents should make sure that children know the facts about HIV transmission and... avoid any skin-piercing procedures... from unsterilized needles and other sharp instruments'[26]. Other foreign organizations routinely provide similar advice to employees travelling to Africa. This echoes POST, but only for staff.

Foreign organizations should ensure that the health care programmes they support warn (educate) clients about the risks of unsterile care, and that they implement POST for injections and other simple procedures, so that clients can see and know that the health care they receive is sterile. (Realistically, first and second-class care will continue for some complex procedures such as major surgery, even with diligent efforts to improve infection control in hospitals and clinics in poor countries.)

Establish a zero-tolerance policy for iatrogenic HIV infections, with accountability through publicly reported monitoring and investigations

A zero-tolerance policy means that national and/or sub-national governments monitor sterile conditions in health care settings and monitor and investigate iatrogenic infections (e.g., children with HIV who have HIV-negative mothers). For international and foreign organizations—including NGOs—zero-tolerance means that they cooperate with and support monitoring and investigations, and that their head offices report activities and findings to the foreign public that supports health aid.

Rationale: In many developing countries, monitoring health care safety has been weak, even for immunization programmes, where foreign aid is most influential. In 2001, only 53% of WHO member countries—and only 41% of African members—reported a system to monitor adverse events after immunizations[35].

Sterile conditions in health care settings could be monitored by sampling and testing instruments and partially-full multidose vials. Sampling could be done, for example, by inspectors or secret shoppers (persons posing as patients) collecting instruments and vials ready to use, exchanging new for old. Monitoring could cover all categories of formal and informal providers. Test results could be offered confidentially to individual providers, while composite results for all providers in a region should be reported to the public.

In countries with generalized epidemics, HIV transmission via health care procedures can be discovered by testing mothers of HIV-infected children. We expect that suspected iatrogenic HIV infections will continue to emerge in Africa and Asia in coming years as they have in the past. Over the past 18 years, scores of HIV-infected African children with HIV-negative mothers have been reported[9]. For example, a WHO-sponsored study of children 6–59 months old and their mothers in four African cities reported in 1993 that 61 (1.1%) of 5593 inpatient children were HIV-positive with HIV-negative mothers[36]. After this and many other similar reports, what has been strikingly absent, in sub-Saharan Africa especially, are the kinds of follow-up investigations conducted in Russia, Romania, Libya, and many other countries, where authorities sought out all linked cases, identified clinics and procedures involved in suspected HIV transmission, and terminated further iatrogenic transmission.

Lack of interest to investigate unexplained HIV infections is common among donors as well as many aid-receiving governments. For example, beginning in late 2000, one of us (DG) has presented public and private organizations involved in safe motherhood programmes detailed evidence suggestive of HIV transmission to women during antenatal care in Africa[9]. To our knowledge, no one has done what is necessary to figure out why African women seroconverted in high numbers during and after antenatal care; i.e., no one has collected and tested sharps and multidose vials for contamination or systematically tested husbands of seroconverting pregnant and postpartum women for HIV infections.

To promote appropriate investigations consistent with zero-tolerance, donor organizations with large health aid programmes could pre-commit a percent of their annual health aid budget in each country to investigate unexplained HIV infections. This could ensure that investigations take place when, for example, an HIV-negative mother comes forward with an HIV-infected child.

Conclusion

One common argument against public discussion of health care risks for HIV has been that people might not be able to understand accurate information and might avoid health care. This has led to decisions that endanger patients. For example, in 1990 donors in Uganda worried about 'mothers' refusal to have their children immunized because of resistance to the use of non-disposable injection equipment'. To allay such concerns 'radio messages about AIDS in Uganda [were] modified to ensure that parents are

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aware of the safety of immunizations'[37], even though risks continued[38]. Years later, donors including UNICEF shifted all immunizations in Uganda and throughout the world to AD syringes, implicitly acknowledging the wisdom and leadership of Ugandan mothers who feared injections with non-disposable equipment.

Fortunately, experts have been speaking up for public discussion of iatrogenic HIV risks. For example, in the mid-1990s, a WHO-sponsored study in 12 African countries reported that 'immunization injection practices . . . have not made any progress with regard to safety over the last 10 years', and that safety 'can no longer be ignored in the interests of quantity'. To improve safety, 'social mobilization teams should provide populations with adequate information about immunization so that consumer demand for safe injections can be created and the public receives appropriate information regarding AEFIs (adverse events following immunization)'[39].

During 1980–2000, the World Bank led efforts to reform health care systems in developing countries, urging decentralization, privatization, and fees. This was driven in part by economics, but also by an effort to improve accountability to patients as clients. These reforms have had strengths and weaknesses. On the one hand, they may increase accountability to clients, which is difficult to build into systems dominated by money and staff from national and international capitals. On the other hand, reforms have cut public health spending (which impacts health equity) and introduced fees for primary health services (which can block poor people's access to health services). But increases in funding for health systems must be accompanied by policy changes to ensure sterile care, so that more aid does not expose more people to unsafe health care.

The changes that are required to reduce health care risks are prefigured in the Constitution of the WHO, where member states recognize the importance of 'informed [public] opinion and active cooperation'[1]. We urge public education, transparent sterile procedures, equal advice to clients and staff, and zero-tolerance for iatrogenic HIV infections.

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Dated: June 24, 2014
Electronic Signature for Jill Gorny Sloper, Esq.: /Jill Gorny Sloper, Esq./

Docket No.: AXJ-114BUSCN
(PATENT)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:
Leonard Bell et al.

Application No.: 13/426,973

Confirmation No.: 8851

Filed: March 22, 2012

Art Unit: 1644

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

Examiner: J.L. Rogers

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

APPEAL BRIEF

Dear Madam:

Appellants hereby appeal the final decision of the Examiner in the above-identified application rejecting the subject matter of the pending claims. For the reasons set forth in this Brief, Appellants respectfully request the Board of Patent Appeals and Interferences reverse the Examiner's final rejection of the claimed subject matter.

This brief contains items under the following headings as required by 37 C.F.R. §41.37 and M.P.E.P. §1205.2:

I.	Real Party in Interest
II	Related Appeals and Interferences
III.	Status of Claims
IV.	Status of Amendments
V.	Summary of Claimed Subject Matter
VI.	Grounds of Rejection to be Reviewed on Appeal
VII.	Argument
VIII.	Appendix of Claims
IX.	Conclusion
Appendix A	Claims
Appendix B	Evidence
Appendix C	Related Proceedings

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I. REAL PARTY IN INTEREST

The real party in interest in the above-identified application is Alexion Pharmaceuticals, Inc.

II. RELATED APPEALS AND INTERFERENCES

No related appeals or interferences are known to Appellants, which will directly affect, or be directly affected by, or have a bearing on the Board's decision in the pending appeal.

III. STATUS OF CLAIMS

Claims 91, 98, 100-106, 110-113, and 115 are pending in this application, on appeal, and set forth in the Claims Appendix (Appendix A).

IV. STATUS OF THE AMENDMENTS

All prior amendments have been entered.

V. SUMMARY OF CLAIMED SUBJECT MATTER

Claims 91, 98, 100-106, 110-113, and 115

Claim 91 on appeal is drawn to a method for treating a patient that (i) is afflicted with paroxysmal nocturnal hemoglobinuria (PNH) and (ii) has been vaccinated against *Neisseria meningitides,* the method comprising administering to the patient an effective amount of a pharmaceutical composition comprising a single unit dosage form of an anti-C5 antibody that inhibits cleavage of complement component C5 into fragments C5a and C5b, 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.

Support for independent claim 91 can be found, at least, for example, at page 2 (line 10) to page 3 (line 30); page 4 (line 19) to page 5 (line 18); page 6 (lines 17-25); page 22 (lines 13-17); page 27 (lines 7-15); and page 38 (lines 20-30).

Dependent claims 98, 100-106, 110, and 111 on appeal do not stand or fall together with independent claim 91, or with each other, because the scope of each dependent claim differs from the independent claim, and from each other.

Specifically, dependent claim 98 specifies the anti-C5 antibody be administered to the patient for at least 6 months. Support for dependent claim 98 can be found, at least, for example, at page 4 (line 32) through page 5 (line 1) of the specification.

Dependent claim 100 specifies the patient has a hemoglobin level less than (i) 14 g/dL if a man or (ii) 12 g/dL if a woman. Support for dependent claim 100 can be found, at least, for example, at page 6 (lines 2-3) of the specification.

Dependent claim 101 specifies that the patient has a hemoglobin level less than (i) 13 g/dL if a man or (ii) 11 g/dL if a woman. Support for dependent claim 101 can be found, at least, for example, at page 6 (lines 3-5) of the specification.

Dependent claim 102 specifies that the patient has a hemoglobin level less than (i) 12 g/dL if a man or (ii) 10 g/dL if a woman. Support for dependent claim 101 can be found, at least, for example, at page 6 (lines 5-6) of the specification.

Dependent claim 103 specifies that the patient suffers from hemolysis due to a C3b-mediated, extravascular clearance of PNH erythrocytes through the reticuloendothelial system. Support for dependent claim 103 can be found, at least, for example, at page 38 (lines 28-30) of the specification.

Dependent claim 104 specifies that 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. Support for dependent claim 104 can be found, at least, for example, at page 3 (lines 11-12) of the specification.

Dependent claim 105 specifies that the patient is at least 18 years of age and has: (i) a PNH type III erythrocyte population of $\geq$ 10% and (ii) received at least four transfusions during the 12 months immediately preceding the first treatment with the anti-C5 antibody. Support for dependent claim 105 can be found, at least, for example, at page 27 (lines 7-10) of the specification.

Dependent claim 106 specifies that the patient has aplastic anemia or myelodysplastic syndrome. Support for dependent claim 106 can be found, at least, for example, at page 5 (lines 1-2) of the specification.

Dependent claim 110 specifies that the single unit dosage form is a preservative free formulation. Support for dependent claim 110 can be found, at least, for example, at page 5 (lines 7-9) of the specification.

Dependent claim 111 specifies that the pharmaceutical composition is administered to the patient under the following treatment schedule: (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 ± 2 days after (i), and (iii) 900 mg of the antibody every 14 ± 2 days thereafter, and wherein the administration occurs via 25 to 45 minute intravenous infusion. Support for dependent claim 111 can be found, at least, for example, at page 22 (lines 13-17) of the specification.

Each of dependent claims 98, 100-106, 110, and 111 varies in content matter and scope. Accordingly, dependent claims 98, 100-106, 110, and 111 do not stand or fall together with independent claim 91, or with each other, and the inquiries as to whether claims 98, 100-106, 110-111 are properly rejected under 35 U.S.C. § 103(a) differs for each and every claim on appeal.

Claim 112

Claim 112 on appeal is drawn to a method treating a patient afflicted with paroxysmal nocturnal hemoglobinuria (PNH), the method comprising: vaccinating the patient against *Neisseria meningitides;* and administering to the patient an effective amount of a pharmaceutical composition comprising a single unit dosage form of an anti-C5 antibody that inhibits cleavage of complement component C5 into fragments C5a and C5b, 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.

Support for independent claim 112 can be found, at least, for example, at page 2 (line 10) to page 3 (line 30); page 4 (line 19) to page 5 (line 18); page 6 (lines 17-25); page 22 (lines 13-17); page 27 (lines 7-15); and page 38 (lines 20-30).

Claim 113

Claim 113 on appeal is drawn to a method for treating a patient afflicted with paroxysmal nocturnal hemoglobinuria (PNH), the method comprising administering to the patient an effective amount of a pharmaceutical composition comprising a single unit dosage form of an anti-C5 antibody that inhibits cleavage of complement component C5 into fragments C5a and C5b, 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.

Support for independent claim 113 can be found, at least, for example, at page 2 (line 10) to page 3 (line 30); page 4 (line 19) to page 5 (line 18); page 6 (lines 17-25); page 22 (lines 13-17); page 27 (lines 7-15); and page 38 (lines 20-30).

Claim 115

Claim 115 on appeal is drawn to a method for treating a patient afflicted with paroxysmal nocturnal hemoglobinuria (PNH), the method comprising administering to the patient a pharmaceutical composition comprising a single unit dosage form of an anti-C5 antibody under the following treatment schedule: (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 ± 2 days after (i), and (iii) 900 mg of the antibody every 14 ± 2 days thereafter, wherein the administration is to occur via 25 to 45 minute intravenous infusion, 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, wherein the antibody inhibits cleavage of complement component C5 into fragments C5a and C5b, and wherein the anti-C5 antibody is eculizumab.

Support for independent claim 115 can be found, at least, for example, at page 2 (line 10) to page 3 (line 30); page 4 (line 19) to page 5 (line 18); page 6 (lines 17-25); page 22 (lines 13-17); page 27 (lines 7-15); and page 38 (lines 20-30).

VI. GROUNDS OF REJECTION TO BE REVIEWED ON APPEAL

Appellants present the following issue for review:

1. Whether claims 91, 98, 100-106, 110-113, and 115 are properly rejected under 35 U.S.C. § 103(a), as being unpatentable over Hillmen *et al.* (*N. Engl. J. Med.* 2004; 350:552-9) and Hill *et al.* (*Haematologica* 2005) in view of Evans *et al.* (US 6,355,245 B1 issued 3/12/2002) and Wang (US 2005/0271660).

VII. ARGUMENTS

The Examiner has rejected claims 91, 98, 100-106, 110-113, and 115 under pre-AIA 35 U.S.C. § 103(a) as being unpatentable over Hillmen *et al.* and Hill *et al.* in

view of Evans *et al.* and Wang. The Examiner relies on Hillmen *et al.* for teaching "a pharmaceutical composition comprising eculizumab (anti-C5 monoclonal antibody) which was administered to patients with PNH at 600 mg ever 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 Examiner relies on Hill *et al.* for teaching treating a PNH patient with eculizumab. The Examiner relies on Evans *et al.* for teaching that antibody 5G1.1 is effective at doses of 2.2, 3, or 5 mg per kg body weight (which corresponds to 154, 210, or 350 mg of antibody for a 70 kg adult human) and that "the antibodies are particularly advantageous in that they are highly active when administered in low doses." The Examiner relies on Wang for teaching that "eculizumab is highly soluble, including at up to 30 mg per ml." The Examiner concludes that "given the teachings of Hill with respect to treating the exact same patient population and the same disease with the same antibody...arriving at applicant's 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."

Appellants respectfully traverse the rejection. To establish a *prima facie* cases of obviousness, the Examiner must show some *reason* why a person of ordinary skill in the art would have thought to combine *particular* available elements of knowledge, as evidenced by the prior art, to reach the claimed invention (*see KSR Int'l Co. v. Teleflex, Inc.*, 550 U.S. 398, 418 (2007)).

The pending claims are drawn to methods for treating PNH patients who have been, or are to be, vaccinated against *Neisseria meningitides.* The methods comprise administering to a PNH patient an effective amount of a composition comprising a single unit dosage form of the antagonist anti-C5 antibody, eculizumab. The single unit dosage form comprises: (i) 300 mg of the anti-C5 antibody and (ii) a 10 mg/mL solution of the anti-C5 antibody. The single unit dosage form also has a volume of 30 mL.

None of the cited references teach or suggest a method, which includes a pharmaceutical composition having the particularly claimed limitations, *i.e.*, wherein the composition comprises a single unit dosage form of 300 mg of the anti-C5 antibody, comprises a 10 mg/mL solution of the anti-C5 antibody, and that the single unit dosage form has a volume of 30mL, as acknowledged by the Examiner. Moreover, contrary to the Examiner's assertion, one of ordinary skill in the art would <u>not</u> have

been motivated to have selected the particularly claimed single unit dosage form (*i.e.*, in which volume, concentration, and quantity are defined) out of the vast genus of potential dosage forms for eculizumab – *e.g.*, which vary widely in volume, concentration, and quantity. The Court of Appeals for the Federal Circuit has been quite clear that, in such a case, a finding that this species is obvious cannot be predicated merely on the existence of myriad hypothetical possibilities (see, *e.g.*, *In re Baird*, 16 F.3d 380 (Fed. Cir. 1994).

According to the Examiner, "Hillmen teaches administration of 600 mg and 900mg 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..." and the '245 patent teaches that Eculizumab "is effective at doses of 2.2, 3, or 5 mg per kg body weight; this corresponds to 154, 210, or 350 mg of antibody for a 70 kg adult woman." The Examiner concludes that "the '245 patent teaches that 210 or 350 mg dosage would be expected to be therapeutically effective, arriving at the 300 mg dosage would have been routine, convenient and obvious."

Appellants submit that optimizing the dosage form, as outlined above by the Examiner, is neither routine, obvious, nor a mere matter of convenience. At a very minimum, to arrive at the claimed solutions, the inventors had to know the solubility properties of the claimed antibody, eculizumab. Moreover, for a pharmaceutical solution to be commercially viable, the inventors had to know the shelf-life stability of eculizumab in solution. If its stability was too low, a pharmaceutical solution would not have been an option. None of that knowledge is disclosed or suggested by the cited references.

Further, weekly or biweekly injections of 154, 210, or 350 mg would require the use of multiple 300 mg vials of the instantly claimed formulation or multiple uses of the same vial. That is, doctors or nurses wishing to administer to a patient approximately 154 mg of an anti-C5 antibody formulated at 300 mg/vial would likely have had to either use the same vial: (a) more than once for the same patient or (b) for each of two patients or, otherwise, waste half of the vial's contents. To avoid the same product waste issue, the need to administer approximately 210 mg of an antibody to a patient would have necessitated the: (i) storage of a vial for potentially weeks (using only 210 mg of the 300mg vial for the first does and waiting for the second