

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

**IN THE UNITED STATES PATENT AND TRADEMARK OFFICE**

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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

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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,  $\alpha$ -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 entirety 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”<sup>1</sup> 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:

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<sup>1</sup> 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<sup>2</sup> [hereinafter Wang et al.] and PCT application publication no. WO 95/29697<sup>3</sup> [hereinafter the ‘697 PCT] are submitted herewith for consideration<sup>4</sup>. 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*

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<sup>2</sup> 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.

<sup>3</sup> Submitted herewith as Exhibit E.

<sup>4</sup> 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 may 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; Vancertil™, 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-arthritis agents<sup>5</sup>, 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

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<sup>5</sup> 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<sup>6</sup> [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.

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<sup>6</sup> 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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