UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

AMGEN INC.
Petitioner,

v.

ALEXION PHARMACEUTICALS, INC.
Patent Owner.

Case IPR2019-00741
U.S. Patent No. 9,732,149

DECLARATION OF ARTURO CASADEVALL, M.D., PH.D.

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TABLE OF CONTENTS

I. Introduction ..... Error! Bookmark not defined.

II. Experience and Qualifications 3

III. Bases of Opinions and List of Documents Considered 8

IV. Summary of Opinions 9

V. Legal Standards 10

A. Standards for Anticipation 11

B. Standards for Obviousness 13

VI. Background 15

A. Overview of the '149 Patent 15

B. SOLIRIS® and its Use for Treatment of Paroxysmal Nocturnal Hemoglobinuria ("PNH") 16

C. Mechanism of Action for SOLIRIS® in Treating PNH 18

D. State of the Art Regarding Humanized Monoclonal Antibodies as of March 15, 2007 20

1. General Antibody Structure 20

2. Design and Development of Humanized Monoclonal Antibodies for Human Therapeutic Use 23

3. Nomenclature and Naming for Humanized Monoclonal Antibodies 37

4. Changes to Amino Acid Sequence, Including in the Constant Region, Can Significantly Impact the Binding, Safety, and Efficacy of Therapeutic Antibodies 42

5. A POSA as of March 15, 2007 Would Have Understood "Eculizumab" To Be an IgG4-Isotype Humanized Antibody 52

E. The Novel, Uniquely-Engineered Amino Acid Sequence of SOLIRIS® Was Not Known to a POSA as of March 15, 2007 65

VII. Opinions 68

A. Dr. Balthasar's Opinions Misread the Prior Art and Rely on Hindsight Analysis 68

1. A POSA Before March 15, 2007 Would Not Have Understood "Eculizumab" To Contain the Uniquely-Engineered Heavy Chain Constant Region Reflected in SEQ ID NO: 2 of the '149 Patent 68

2. The Antibody Sequence Recited in the '149 Patent Was Not Publicly Known Before March 15, 2007 76

B. Claim 1 of the '149 Patent Was Not Anticipated by Hillmen or Hill (Grounds 1 and 2) 87

C. Claim 1 of the '149 Patent Was Not Anticipated by Bowdish (Ground 3) 91

D. Claim 1 of the '149 Patent Would Not Have Been Obvious Over Bell, Bowdish, and Evans (Ground 4) 101

1. Bell Did Not Disclose the Specific Sequence of Claim 1, and Would Not Have Motivated a POSA to Make An Antibody With the Claimed Sequence 101

2. A POSA Without the Benefit of Hindsight Would Not Have Been Motivated to Combine Bell with Bowdish and Evans 105

3. A POSA Without the Benefit of Hindsight Would Not Have Reasonably Expected Success in Making An Antibody with the Specific Amino Acid Sequence Claimed in the '149 Patent 114

E. Claim 1 of the '149 Patent Would Not Have Been Obvious Over Evans and Mueller (Ground 5) 119

1. A POSA Without the Benefit of Hindsight Would Not Have Combined Evans and Mueller to Make the Specific Claimed Antibody of the '149 Patent 120

2. A POSA Without the Benefit of Hindsight Would Not Have Reasonably Expected Success in Making An Antibody with the Specific Amino Acid Sequence Claimed in the '149 Patent.....128

F. Objective Indicia Support the Nonobviousness of Claim 1 of the '149 Patent.....130

1. SOLIRIS® is the Commercial Embodiment of the '149 Patent.....131

2. SOLIRIS® Fulfilled a Long-Felt, Unmet Need for a Treatment of PNH, Which Others Failed to Satisfy 133

3. SOLIRIS® Is A Commercial Success.....137

4. Industry Praise.....137

5. Copying.....138

VIII. CONCLUSION 139

I, Arturo Casadevall, hereby declare and say as follows:

I. INTRODUCTION

1. I am over the age of eighteen (18) and otherwise competent to make this declaration.

2. I have been retained by Alexion Pharmaceuticals, Inc. ("Alexion") as an independent expert consultant in this proceeding before the United States Patent and Trademark Office. Although I am being compensated at my normal consulting rate of $ 500/hr for the time I spend on this matter, no part of my compensation is dependent on the outcome of this proceeding, and I have no other interest in this proceeding.[1]

3. I understand the Patent Trial and Appeal Board ("PTAB") issued an Institution Decision (Paper No. 15) granting Amgen Inc.'s ("Amgen") Petition to institute this *Inter Partes* Review ("IPR") regarding claim 1 of United States Patent No. 9,732,149 ("the '149 patent") on five "Grounds" alleging that claim 1 of the '149 patent is unpatentable as anticipated or obvious. I understand that the PTAB's Institution Decision regarding the '149 patent (Paper No. 15) is not a final decision, and is based on the PTAB's "preliminary review of the challenged

[1] All opinions expressed and implied in this Declaration are solely my own and do not represent or reflect the views of my employer, the Johns Hopkins University.

claims, the asserted prior art, and the opinions set forth in the as-yet-unrebutted Balthasar Declaration." (Paper No. 15 at 59-60.)

4. I have reviewed and considered Amgen's Petition regarding the '149 patent (Paper No. 2) ("Amgen's Petition"), the Declaration of Dr. Joseph P. Balthasar regarding the '149 patent (AMG1002) ("Balthasar Declaration"), the Institution Decision regarding the '149 patent (Paper No. 15) ("Institution Decision"), and the other documents cited throughout this Declaration. For the reasons I explain in this Declaration, it is my opinion that Amgen has failed to show that claim 1 of the '149 patent is anticipated or obvious in view of any of Amgen's five "Grounds."

5. As stated in the Institution Decision, the PTAB found based on its "preliminary review" that Amgen had demonstrated a "reasonable likelihood" that it would prevail under two Grounds: (1) alleged anticipation by Bowdish (AMG1008) ("Ground 3"), and (2) alleged obviousness in view of Bell (AMG1005), Bowdish (AMG1006), and Evans (AMG1007) ("Ground 4"). (Paper No. 15 at 36, 45.) For the reasons I explain in this Declaration, it is my opinion that Amgen has failed to show that claim 1 of the '149 patent is unpatentable under either of these Grounds.

6. In its Institution Decision, the PTAB also stated that Amgen had not demonstrated a reasonable likelihood that it would prevail in showing the

challenged claims were unpatentable with respect to three other Grounds: (1) alleged anticipation by Hillmen '04 (AMG1004) ("Ground 1"), (2) alleged anticipation by Hill '05 (AMG1047) ("Ground 2"), and (3) alleged obviousness in view of Evans (AMG1007) and Mueller (AMG1008) ("Ground 5"). (Paper No. 15 at 20, 27, 54.) For the reasons I explain in this Declaration, it is my opinion that Amgen has failed to show that claim 1 of the '149 patent is unpatentable under any of these Grounds.

II. EXPERIENCE AND QUALIFICATIONS

7. I am currently a Bloomberg Distinguished Professor of Molecular Microbiology & Immunology and Infectious Diseases at the Johns Hopkins Bloomberg School of Public Health, and the Alfred and Jill Sommer Professor and Chair of the W. Harry Feinstone Department of Molecular Microbiology and Immunology at the Johns Hopkins Bloomberg School of Public Health.

8. My educational background includes a B.A. in Chemistry, which I received from Queens College, City University of New York, in 1979. In 1983 and 1984, I received my M.S. and Ph.D. in Biochemistry, respectively, both from New York University. I also received my M.D. from New York University in 1985.

9. After I earned my M.D., I went on to complete an internship and residency in internal medicine at Bellevue Hospital from 1985-1988. From 1988-

1989, I completed a fellowship in infectious diseases at the Montefiore Medical Center. Under the guidance of Matthew D. Scharff, I completed a postdoctoral fellowship in cell biology at the Albert Einstein College of Medicine from 1989-1991.

10. I became an Assistant Professor of Medicine and Microbiology & Immunology at the Albert Einstein College of Medicine in 1992, and I was promoted to Associate Professor in 1996 and Professor in 2001. I became the Director of the Division of Infectious Diseases at Montefiore Medical Center in 2000.

11. Between 2002 and 2015, I assumed a number of additional roles at the Albert Einstein College of Medicine. I was named the Selma and Jacques Mitrani Professor in Biomedical Research in 2002. In 2006, I became the Chair of the Department of Microbiology & Immunology, and was named the Leo and Julia Forchheimer Professor of Microbiology & Immunology. In 2013, I became the Director of the Center for Immunological Sciences.

12. In 2015, I accepted my current position at the Johns Hopkins Bloomberg School of Public Health. I was also named a Bloomberg Distinguished Professor.

13. I am a member of multiple scientific societies, including the American Academy of Arts and Sciences and the American Association of

Immunologists. I currently serve as the Elected Chair of the Board of Governors of the American Academy of Microbiology.

14. I also serve on the editorial boards of multiple scientific journals, including the Journal of Infectious Diseases and the Journal of Experimental Medicine. I am the Founding Editor and Editor-in-Chief of mBio, the first open access general journal of the American Society for Microbiology. I am also Deputy Editor of the Journal of Clinical Investigation.

15. During my career, I have served and continue to serve on scientific advisory committees. These include the CDC Advisory Panel on Anthrax Immune Globulin, on which I served in 2004; the Scientific Advisory Board for the NIAID Immune Epitope Database, on which I served from 2004-2006; the Abbott Laboratories Award in Clinical and Diagnostic Immunology Selection Committee, on which I served from 2004 to 2007; and the National Science Advisory Board for Biosecurity, on which I served from 2005-2014.

16. My work has been recognized with a number of awards and distinctions, including a Merit Award from the National Institutes of Health, which I was awarded in 2007. I have been elected to the National Academy of Medicine and the American Academy of Arts and Sciences.

17. Over the course of my career, I have authored over 800 publications, books, book chapters, and monographs. I am also an inventor on multiple issued patents and pending patent applications.

18. I have over 25 years' experience in the fields of immunology and microbiology, including therapeutic antibody design. In particular, I have worked extensively for over 15 years to research the effect of antibody constant regions on antibody binding and specificity. I first started working on this issue in 1992. In 2002, my laboratory published our first significant paper on the subject, McLean *et al.*, Isotype can affect the specificity of an antibody for a polysaccharide antigen, J IMMUNOL., 169:1379-86 (2002) (ALXN2013), which I co-authored.

19. Following McLean 2002, my laboratory continued to publish research related to the impact of antibody constant regions on antibody binding and specificity. For example, I co-authored Torres *et al.*, Variable region identical antibodies differing in isotype demonstrate differences in fine specificity and isotype, J. IMMUNOL., 174:2132-2142 (2005) (ALXN2040), and Torres *et al.*, The Immunoglobulin Heavy Chain Constant Region Affects Kinetic and Thermodynamic Parameters of Antibody Variable Region Interactions with Antigen, J. OF BIOL. CHEM., 282(18):13917-27 (2007) (ALXN2009). I also co-authored a major review article, Janda *et al.*, Ig Constant Region Effects on Variable Region Structure and Function, FRONT. MICROBIOL., 7(22):1-10 (2016)

(ALXN 2010) in 2016. In total, I have published 15 publications related to the effect of antibody constant regions on antibody binding and specificity.

20. In addition to my academic research work, I have also been directly involved in the development of two monoclonal antibodies for therapeutic treatment. The first was an antibody for treatment of cryptococcal meningitis, which was developed in my lab and tested in clinical trials in 2001. The second was an antibody to treat melanoma, which was developed in my lab in partnership with Pain Therapeutics, and tested in clinical trials in 2007. I also served on Pfizer's advisory board for therapeutic antibodies from 2011 to 2014.

21. My additional research interests include fungal and bacterial pathogenesis. Research from my lab has led to development of an antibody to fungal melanin that is currently in evaluation for the treatment of melanoma. We are also currently working to develop antibody-based countermeasures to protect against anthrax.

22. I am board certified in Infectious Diseases and in Internal Medicine until 2023.

23. As reflected by my education and experience discussed above, and further reflected in my curriculum vitae, I am an expert in the design, development, evaluation, and testing (including biological and physiochemical analysis) of monoclonal antibodies for use in human clinical therapy, including humanized

monoclonal antibodies. I was also an expert in these fields prior to March 15, 2007. A copy of my curriculum vitae is attached to this Declaration as **Appendix A** (ALXN2022.)

III. BASES OF OPINIONS AND LIST OF DOCUMENTS CONSIDERED

24. The opinions contained in this declaration are based on the documents I reviewed and my knowledge and professional judgment. In forming the opinions expressed in this declaration, I reviewed the documents discussed throughout this declaration, as well as the documents listed in **Appendix B**. My opinions are further based on background, education, and my over 25 years of experience and knowledge of therapeutic antibody design, including both academic research and development work for monoclonal antibody therapeutics.

25. In forming my opinions, I have also considered the perspective of a person of ordinary skill in the art ("POSA") as of March 15, 2007, including the knowledge available to a POSA as of that date, and how a POSA would have read and understood the literature pertinent to the invention claimed in the '149 patent.

26. I understand that, in its Institution Decision, the Board accepted that a POSA in the field of the '149 patent would typically have "an M.D. and/or Ph.D. in immunology, biochemistry, cell biology, molecular biology, pharmaceutics, or a related discipline," who would have "at least two years of experience engineering monoclonal antibodies for human therapeutic use, either in the laboratory or

industry." (Paper No. 15 at 10-11.) I agree with this definition of a POSA, and provide my opinions in this Declaration from the perspective of a POSA as of March 15, 2007.

IV. SUMMARY OF OPINIONS

27. I have considered the opinions of Dr. Joseph P. Balthasar, as set forth in his February 27, 2019 declaration ("Balthasar Declaration") (AMG1002), and the documents cited therein. I submit this Declaration in order to respond to opinions offered by Dr. Balthasar.

28. It is my opinion that claim 1 of the '149 patent is not anticipated by, or obvious in view of, any of the alleged prior art or combinations of prior art at issue in Amgen's five "Grounds" in this proceeding.

29. I disagree with Dr. Balthasar's conclusions that claim 1 of the '149 patent was anticipated by any of Hillmen '04 (AMG1004) (as alleged in "Ground 1"), Hill '05 (AMG1047) (as alleged in "Ground 2"), or Bowdish (AMG1006) (as alleged in "Ground 3"). In my opinion, none of these three documents disclosed each and every element recited in claim 1 as arranged in the claim, whether expressly or inherently.

30. I further disagree with Dr. Balthasar's conclusions that claim 1 of the '149 patent was obvious in view of the combination of Bell (AMG1005), Bowdish (AMG1006), and Evans (AMG1007) (as alleged in "Ground 4"), or in view of the

combination of Evans (AMG1007) and Mueller (AMG1008) (as alleged in "Ground 5"). In my opinion, a POSA without the benefit of hindsight, and with the benefit of the full scope of prior art available as of March 15, 2007, would not have found the claimed invention obvious; and to the contrary, the art would have led a POSA in a direction divergent to the path taken by the claimed invention. It is also my opinion that a POSA, without the benefit of hindsight, would not have been motivated to combine the teachings of any of these references because there was no teaching, motivation, suggestion, or other reason to do so, and that a POSA would not have had a reasonable expectation of success with respect to the claimed invention.

31. It is also my opinion that "objective indicia" further support the non-obviousness of the invention recited in claim 1 of the '149 patent, including at least the fulfillment of a long-felt, unmet need; commercial success; failure of others; copying; and industry praise.

V. LEGAL STANDARDS

32. I have been advised by counsel of the following legal principles, which I have considered and applied in forming my opinions set forth in this Declaration.

33. I understand the burden of proving unpatentability of the '149 patent rests with Amgen in this proceeding.

A. Standards for Anticipation

34. I have been informed by counsel that, to establish anticipation, Amgen must show that a single prior art reference discloses each and every element of the claimed invention, within the four corners of the document, arranged as in the claim.

35. I understand that a document may "incorporate by reference" the disclosure of another document. I understand that a document may be incorporated by a reference in its entirety, or only with respect to certain information, depending on the language setting out the incorporation by reference. To the extent a document is incorporated by reference, I understand that its disclosures should be considered as part of the incorporating document.

36. I have been informed by counsel that a prior art document may anticipate either expressly or inherently. I understand a document does not anticipate just because it refers to a molecule or formulation that is later revealed to be the one claimed. Counsel has explained that, for a prior art document to inherently anticipate a patent claim, elements that are not disclosed expressly in the reference must be necessarily present in the document. I understand that a document is not anticipatory if any elements are only probably or possibly present.

37. I have been informed that, to anticipate, it is not enough that the prior art document discloses part of the claimed invention, which a POSA might

supplement to make the whole. I also understand from counsel that, to anticipate, it is not enough that the prior art includes multiple, distinct teachings that a POSA might somehow combine to achieve the claimed invention.

38. I have been informed by counsel that, to anticipate, a document must provide every element of the claimed invention arranged or combined as in the claim, or permit a POSA reading the document to "at once envisage" the claimed invention. In other words, I understand that a reference does not anticipate a claimed invention if, on reading it, a POSA would not be able to immediately understand that the claim elements disclosed in the document should be arranged or combined in the manner recited in the claim.

39. Counsel has further informed me that, to anticipate, a single document must describe the claimed invention with sufficient precision and detail to establish that the subject matter existed in the prior art, and that ambiguous references do not anticipate a claim.

40. I have also been informed by counsel that, to anticipate a claimed invention, a prior art reference must be "enabled," such that a POSA could make and use the claimed invention without undue experimentation. I understand that the PTAB will consider the following factors in assessing whether a disclosure requires undue experimentation: (1) the quantity of experimentation necessary; (2) the amount or guidance presented; (3) the presence or absence of working

examples; (4) the nature of the invention; (5) the state of the prior art; (6) the relative skill of those in the art; (7) the predictability or unpredictability of the art; and (8) the breadth of the claims.

B. Standards for Obviousness

41. I have been informed by counsel that, to establish obviousness, Amgen must show that the claimed invention as a whole would have been obvious to a POSA prior to the date on which the claimed invention was invented, without the benefit of hindsight knowledge. I have been informed that, for purposes of these proceedings, the relevant date of invention, or "priority date," is March 15, 2007, the earliest filing date for the '149 patent.

42. I have been informed by counsel that the Board will consider the following factors in determining whether Amgen has met its burden to establish invalidity based on obviousness: (1) the scope and content of the prior art; (2) differences between the prior art and the claims at issue; (3) the level of ordinary skill in the art; and (4) objective evidence of non-obviousness.

43. Counsel has explained that objective indicia supporting nonobviousness can include: that the invention satisfied a long-felt but unmet need that existed at the time of the invention; commercial success of products embodying the claimed invention; failure of others to solve the problem addressed by the claimed invention; copying of the invention; and industry praise.

44. I understand from counsel that, in assessing obviousness, it is improper to use hindsight knowledge of the invention claimed and described in the ’149 patent, or other documents or information that would not have been available to a POSA prior to March 15, 2007.

45. I further understand from counsel that, in the obviousness analysis, that the full scope and content of the prior art available to a POSA must be considered, and it is improper to use hindsight in selecting documents from the prior art for use in an obviousness analysis. I also understand it would be improper to assume obviousness by following the path that led the inventors to the claimed invention, and instead prior art must be viewed from the perspective of a POSA without the benefit of knowing how the inventors successfully achieved the claimed invention.

46. I understand from counsel that, in assessing obviousness, I must consider a prior art reference as a whole, for all that it teaches, including any portions that would have discouraged or pointed away from the claimed invention.

47. I have been informed that, to establish obviousness, Amgen must also show that, for a particular combination of prior art references, a POSA without the benefit of hindsight would have had a motivation or reason to combine those prior art references. I also understand from counsel that Amgen must show that a POSA, without the benefit of hindsight, would have had a reasonable expectation

of success with respect to the claimed invention. I understand that hindsight bias must be avoided in assessing whether a particular combination of references would have been obvious prior to the date of invention.

VI. BACKGROUND

A. Overview of the '149 Patent

48. In forming my opinions, I have reviewed the '149 patent, titled "Treatment of Paroxysmal Nocturnal Hemoglobinuria Patients by an Inhibitor of Complement."

49. I understand from counsel that the '149 patent claims priority back to U.S. Application No. 12/225,040, filed as PCT/US2007/006606 on March 15, 2007. I have been informed that March 15, 2007 is the earliest priority date for the '149 patent.

50. I understand that the '149 patent reflects the work of Alexion scientists in developing SOLIRIS® as a safe and effective treatment for paroxysmal nocturnal hemoglobinuria ("PNH"). The '149 patent has one claim, as follows:

> 1. An antibody that binds C5 comprising a heavy chain consisting of SEQ ID NO: 2 and a light chain consisting of SEQ ID NO: 4.

(AMG1001 at 39:1-4.)

51. Claim 1 of the ’149 patent recites the complete amino acid sequence for the active compound in SOLIRIS® (eculizumab): the heavy chain consisting of SEQ ID NO: 2, and the light chain consisting of SEQ ID NO: 4. (AMG1001 at cols. 31-33, 35.) As I discuss below, a POSA prior to March 15, 2007 would not have known that eculizumab had the specific sequence recited in claim 1, and would not have known of any other monoclonal antibody having that specific sequence.

52. The ’149 patent also provides data from the Phase III “TRIUMPH” clinical study, confirming that the claimed antibody is safe and effective for treating PNH, and identifying the safe and effective dosing regimen for that use. (AMG1001 at abstract, 19:50-28:35.)

53. Claim 1 of the ’149 patent reflects the purpose of the ’149 patent’s invention: the development of a humanized monoclonal antibody that can bind to C5 and thereby block its cleavage, and can be used as a safe and effective therapy for patients with PNH.

B. SOLIRIS® and its Use for Treatment of Paroxysmal Nocturnal Hemoglobinuria (“PNH”)

54. PNH is a rare, life-threatening blood disorder characterized by chronic destruction of red blood cells (“hemolysis”), with periodic acute exacerbations of hemolysis (“paroxysms”) that result in dark urine (“hemoglobinuria”). (AMG1047 at 2559.) Patients afflicted with PNH have

symptoms including chronic and potentially disabling fatigue, dysphagia (difficulty swallowing), and recurrent pain, resulting in an impaired quality of life. (AMG1004 at 6; AMG1047 at 2559; AMG1012 at 1234.) PNH patients also often suffer from severe anemia requiring frequent blood transfusions for survival, and can be susceptible to life-threatening blood clots ("thrombosis"). (AMG1047 at 2559.)

55. Prior to FDA approval of SOLIRIS®, there was a substantial need for a safe and effective therapy for the treatment of PNH. As stated in the pivotal Phase III clinical trial report for SOLIRIS® published in the New England Journal of Medicine, "there [was] no therapy that effectively reduce[d] intravascular hemolysis or improves the symptoms in patients with PNH" prior to SOLIRIS®. (AMG1012 at 1234; *see also* AMG1047 at 2559 ("There is ***no effective treatment*** for the ongoing hemolysis in PNH.").)[2] Before the availability of SOLIRIS®, PNH patients were often "transfusion-dependent," meaning that their survival depended on receiving frequent blood transfusions. (AMG1004 at 557; AMG1047 at 2559.)

56. In clinical trials of SOLIRIS®, PNH patients showed reduced hemolysis and substantial improvements in outcomes, including reduced or eliminated need for blood transfusions, lessened anemia and fatigue, and improved

[2] Unless otherwise indicated, all emphasis is added.

quality of life. (AMG1033 at 1261.) Those trials also confirmed the safety of SOLIRIS® for long-term administration. (AMG1047 at 2564.)

57. SOLIRIS® received accelerated approval (under the "Priority Review" program for groundbreaking therapies) by the U.S. Food & Drug Administration ("FDA") on March 16, 2007. (ALXN2006 at 993; ALXN2030 at 1.) SOLIRIS® was the first therapy approved by the FDA for treatment of PNH. (ALXN2030 at 1.) By improving efficacy outcomes while reducing the need for more invasive therapies, SOLIRIS® represented a significant advance in PNH treatment.

C. Mechanism of Action for SOLIRIS® in Treating PNH

58. The active ingredient in SOLIRIS® is eculizumab, a humanized monoclonal antibody. SOLIRIS® works by binding with high "affinity" (*i.e.*, tightness) and "specificity" (*i.e.*, directed to a single target or "antigen") to the human protein "C5," a key component of the body's "complement" pathway.

59. PNH is caused by a genetic mutation resulting in abnormal blood cells that are unprotected from the body's "complement" system. (AMG1004 at 553; AMG1047 at 2559; AMG1012 at 1234.) The complement system is a component of the human immune system that normally protects the body against invading infectious cells (*e.g.*, pathogenic bacteria), by forming a "membrane-attack complex" that causes invading cells to burst ("lysis"). (ALXN2019 at 1265-66.) If

unimpeded, the complement system also has the potential to attack the body's own cells, causing dangerous disease conditions. (ALXN2019 at 1266-68.)

60. In PNH patients, the red blood cells of PNH patients are constantly under attack by the complement system ("chronic intravascular hemolysis"). (AMG1012 at 1239-1240.) Normally, red blood cells are protected against such attack from the complement system by membrane-bound proteins such as "CD59," which blocks the formation of the cell-lysing "membrane attack complex" on the cell surface. (AMG1012 at 1234.) In PNH patients, however, a genetic mutation in the "PIG-A" gene results in the absence of CD59 on red blood cells, leaving them chronically susceptible to destruction by the complement system. (AMG1012 at 1234.)

61. Without SOLIRIS® treatment, the body naturally cleaves C5 into two components, "C5a" and "C5b," which lead to the various downstream effects of the complement pathway, including hemolysis in PNH patients. When SOLIRIS® is administered, however, it binds to a critical location ("epitope") on C5 with sufficient affinity, specificity, and "fine specificity" (*i.e.*, binding to the right spot) to prevent cleavage of C5 into C5a and C5b. (AMG1004 at 2; AMG1047 at 2559; AMG1012 at 1233.) By binding to C5 and blocking its cleavage, SOLIRIS® blocks the downstream effects of the complement pathway, and spares PNH

patients' red blood cells from destruction. (AMG1004 at 2; AMG1047 at 2559; AMG1012 at 1233.)

D. State of the Art Regarding Humanized Monoclonal Antibodies as of March 15, 2007

1. General Antibody Structure

62. As of March 15, 2007, antibodies were known to be complex three-dimensional proteins characterized by one or more flexible, Y-shaped structures each formed from four polypeptide chains – two identical "heavy chains" and two identical "light chains." (ALXN2007 at 104-05; AMG1018 at 4.)

63. Each heavy and light chain polypeptide can be divided into a "variable" region, where the antigen binds, and a "constant" region, which may interact with other components of the immune system. (ALXN2007 at 105-106.) As discussed below in Section VI.D.4, however, a POSA as of March 15, 2007 would have been aware that antibodies are complex three-dimensional molecules, and that the structure of the constant region could potentially impact the antibody-antigen interactions of the variable region, even if the constant region is not directly in contact with the antigen.

64. The variable region of each of the two heavy chains and two light chains includes three "complementarity-determining regions" ("CDRs"), which together directly interact with a single epitope on a specific antigen. (AMG1018 at

9.) Portions of the variable region flanking the CDRs are termed "framework" regions. (AMG1029 at 6.)

65. Antibodies are divided into classes, or "isotypes," based on their constant regions. (ALXN2007 at 105; AMG1018 at 4; AMG1029 at 5.) There are five different naturally-occurring isotypes – IgA, IgD, IgE, IgG, and IgM – which determine the functional activity of the antibody. (ALXN2007 at 105; AMG1018 at 4-7; AMG1029 at 5.) These isotypes differ structurally in the amino acid sequences of their heavy chain constant regions, the number and location of their disulfide bonds, and the lengths of their "hinge" regions. (*See, e.g.*, ALXN2008 at 172; *see also* ALXN2009 at 13924; AMG1029 at 5.) The IgG isotype is the most abundant in humans and, as of March 15, 2007, was the most common class used for human therapy. (ALXN2007 at 105; AMG1018 at 4; AMG1029 at 2-5.)

66. IgG antibodies contain a single Y-shaped structure. IgG constant regions can be subdivided into different parts, with the light chain including a variable region ("VL") and a constant region ("CL"), and the heavy chain including a variable region ("VH") followed by constant region domains known as "CH1," the "hinge" region, "CH2," and "CH3." (ALXN2007 at 106.)

67. Antibody domains were also sometimes referred to in the art by the fragments that would be produced from proteolytic degradation. For example, the "CH2" and "CH3" domains together form what was known as the "Fc" region

("fragment crystallizable"), and the light chain associated with a truncated heavy chain containing only VH and CH1 form what was known as the "Fab" region ("fragment antigen binding"). (ALXN2007 at 106; AMG1018 at 8.)

68. Figure 1 (adopted from Amgen's Petition) depicts the basic structure of a full-length, intact IgG antibody in a simplified, two-dimensional diagram. This type of diagram is useful for simple illustrations of antibody structure – but as I discuss further below in Section VI.D.4, a POSA as of March 15, 2007 would have understood that these diagrams do not reflect the complexity of the three-dimensional structures of antibodies that are integral to the nature of their antibody-antigen interactions, including binding affinity and specificity (including fine specificity).

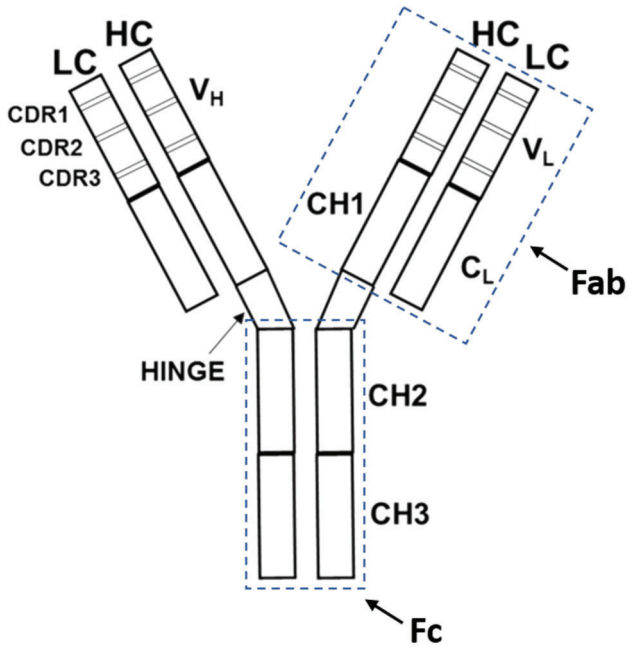

Figure 1: Basic structure of an IgG antibody
(simplified two-dimensional depiction)

2. Design and Development of Humanized Monoclonal Antibodies for Human Therapeutic Use

69. As of March 15, 2007, it was known that antibodies produced in an animal's natural immune response to an antigen are "polyclonal," meaning that they include a set of different antibodies having a mixture of different affinities and specificities. (ALXN2031 at 696; ALXN2032 at 210:18-211:12.) A set of polyclonal antibodies produced in a natural immune response will thus include multiple distinct antibodies, each with their own unique "primary amino acid sequence" for their heavy and light chain polypeptides. (*See* ALXN2031 at 696; AMG1018 at 11-17.)

70. By contrast, a POSA as of March 15, 2007 would have understood a "monoclonal antibody" was a single, unique antibody with one specific, defined structure. (ALXN2031 at 697; ALXN2032 at 10:9-22, 11:10-17.) In contrast to a set of polyclonal antibodies, a POSA would have understood that a monoclonal antibody has a single unique primary amino acid sequence for the entire antibody, including for both the variable region and constant region. (ALXN2031 at 697; ALXN2032 at 10:9-22, 11:10-17.) And associated with that unique sequence and structure, a POSA would have understood that each monoclonal antibody has its own specific binding properties (affinity and specificity) for the antigen against which it is directed. (ALXN2031 at 697; *see* ALXN2032 at 10:9-22, 11:10-17.)

71. As of March 15, 2007, technology existed to produce, isolate and characterize new monoclonal antibodies by laboratory means. Such new monoclonal antibodies were typically developed and discovered using hybrid antibody-forming cells called "hybridomas." (ALXN2031 at 697.) To generate monoclonal antibodies this way, first a mouse would be immunized with a target antigen. (ALXN2031 at 697.) Antibody-producing B cells from the immunized mouse would then be fused with immortalized cells from a mouse myeloma, a type of tumor. (ALXN2031 at 697.) The resulting unique hybrid cell lines cloned from individual antibody-producing cells ("hybridomas") could each make a unique, monoclonal mouse (murine) antibody directed to the target antigen. (ALXN2031

at 697.) Because the cells used to create hybridomas were of mouse origin, hybridomas made using this particular technology would only produce mouse antibodies. (ALXN2031 at 697.)

72. As of March 15, 2007, it was conventional to name a mouse monoclonal antibody after the hybridoma from which it was derived. For example, as I discuss further below, the anti-C5 mouse monoclonal antibody that Alexion obtained from the "5G1.1" hybridoma was referred to in the literature as "the 5G1.1 antibody" or "the 5G1.1 mAb." (AMG1007 at 38:43-67; AMG1023 at 1390, 1393, 1395; ALXN2032 at 10:9-22; 97:23-99:8; 165:11-21.)

73. Hybridomas generated in this process would then need to be screened for those producing mouse monoclonal antibodies with appropriate specificity. (ALXN2031 at 697.) Additional tests would need to be performed to further characterize promising candidates, including assays to assess binding affinity and appropriate biological activity. For example, with respect to the "5G1.1" mouse antibody, Evans states that the researchers (1) identified the "5G1.1" antibody by screening for C5 binding and activity in inhibiting complement-mediated hemolysis; (2) determined the specific binding affinity of "5G1.1" antibody for its antigen target C5; and (3) further studied the "5G1.1" antibody in various in vitro assays showing that it blocked the cleavage of C5 and protected blood cells from lysis. (AMG1007 at 38:43-39:16; 39:36-40:29; ALXN2032 at 165:11-169:23; *see*

also ALXN2029 at 12 (requiring characterization of antibody specificity, cross-reactivity, affinity, avidity, and immunoreactivity prior to human clinical trials).)

74. Finally, after a mouse monoclonal antibody with suitable properties was identified, its amino acid sequence could be determined using sequencing techniques, and the obtained sequence could be used as a basis to make more of the mouse monoclonal antibody, or fragments or derivatives of it. For example, in Evans, after identification and initial characterization, researchers sequenced and cloned the variable light chain and variable heavy chain regions of the "5G1.1" antibody. (AMG1007 at 40:36-42:54; ALXN2032 at 165:11-169:23.)

75. As of March 15, 2007, it was generally understood that, while mouse antibodies may be useful as laboratory research agents, they were generally not desirable for therapeutic use in humans. Specifically, a POSA understood that mouse antibodies can elicit immune reactions in human patients ("HAMA"), which could cause the mouse antibody to be ineffective or even harmful to human patients, particularly upon repeated administration. (ALXN2033 at 18; ALXN2034 at 3-4.) Such immune reactions were particularly undesirable in the context of treating chronic inflammatory or immune conditions requiring prolonged treatment. (*See* AMG1023 at 1390.)

76. For that reason, a POSA would have known of technologies for developing therapeutic antibodies that were intended to reduce immune reactions

to non-human sequences, by designing new antibody structures that combines the mouse-derived sequences associated with antigen binding with human-derived antibody sequences. One such approach involved creating "chimeric" antibodies, where the sequences for variable regions of a mouse-derived antibody were combined with the constant region sequences (CL, CH1, hinge, CH2 and CH3) from a human IgG antibody. (ALXN2033 at 18; ALXN2034 at 3; AMG1029 at 8.) To further reduce the non-human character of therapeutic antibodies for human use, "humanization" technology was developed, whereby mouse sequences thought to be directly involved in antigen binding (including the "CDRs") would be integrated into the sequence of an otherwise fully human antibody or fragment. (ALXN2033 at 18; ALXN2034 at 3; AMG1029 at 8.)

77. While the general concepts of making chimeric and humanized antibodies were known well before March 15, 2007, it was still true at that date that designing antibodies for human therapeutic use was an unpredictable art that required extensive experimentation and testing. (*See, e.g.*, ALXN2035 at 58-59; ALXN2036 at 141.) With humanization technology specifically, a POSA would have understood that there were many choices to make in the process of attempting design an antibody that could potentially be suitable for therapeutic use. Further, a POSA would not have been able to reasonably predict the impact that these various design choices would have upon the safety or efficacy of a newly-designed,

unstudied antibody without conducting at least some human clinical testing. (ALXN2036 at 141 ("Only favorable results from clinical studies can confirm the success of a humanization experiment."); ALXN2037 at 1343-44 (discontinuing clinical trial of humanized monoclonal antibody due to development of human antihuman antibodies ("HAHA") in 73% of study patients); (ALXN2038 at 624 (as of 2008, success rate of humanized monoclonal antibodies entering clinical trials was 17%).)

78. First, a POSA would have had to make choices about, and then empirically test, different designs for the variable regions of the humanized antibody. As of March 15, 2007, humanized antibodies were often constructed using a technique known as "CDR-grafting," also known as "re-shaping," which involved the transfer of mouse CDRs into human framework regions. (ALXN2035 at 58; ALXN2036 at 135-137.) It was known at the time, however, that insertion of the mouse CDRs into a human framework could have unpredictable effects. For example, a POSA would have understood that the simple transfer of mouse CDRs into corresponding positions of the human framework regions could significantly reduce antibody binding and specificity compared to the parent mouse antibody. (ALXN2035 at 58; ALXN2036 at 140; ALXN2033 at 19.)

79. To attempt to maintain the same specificity and binding of the parent mouse antibody, additional amino acids from the mouse framework regions may

have had to be inserted into the framework regions of the humanized antibody, but this could increase the risk of an immunogenic effect. (ALXN2036 at 140.) Furthermore, each modification step carried a risk of losing existing activity since antibody engineering then was a largely empirical exercise. (ALXN2035 at 58-60; ALXN2036 at 140-41; ALXN2033 at 19; *see* AMG1023 at 1394.) Accordingly, a POSA designing a humanized variable region would have had to make various choices, including: (1) the extent of the mouse CDRs to be transferred; (2) the human framework regions to be used; and (3) whether additional amino acids from the parent mouse antibody would need to be inserted into the framework regions (called "back mutation") to maintain the same antibody binding and specificity as the parent antibody. (ALXN2035 at 58; ALXN2036 at 137-141; ALXN2033 at 19.) Finally the POSA would have to make decisions on what cell line to express the recombinant antibody molecule, a choice that could affect immunoglobulin glycosylation, and thus affect antibody functions.

80. Even if a humanized variable region fragment (scFv or Fab, as discussed below) was developed and shown to have the desired antigen-binding and biological properties, a POSA would have understood that further development would be required – and additional choices would have to be made – to design a full-length, intact chimeric or humanized IgG-class monoclonal antibody. For example, a POSA would have had to choose which human constant regions to use.

In designing appropriate constant regions, as of March 15, 2007, a POSA would have understood that there were four naturally occurring subclasses or "isotypes" – IgG1, IgG2, IgG3, and IgG4, and that humanized monoclonal antibodies approved by the FDA were predominantly of the IgG1 or IgG4 isotypes. (ALXN2007 at 105; AMG1029 at 2-4 (Table 1), 5.) As of March 15, 2007, all of the full-length chimeric or humanized commercial antibodies used one of the naturally-occurring IgG constant regions. (AMG1029 at 2-4 (Table 1).)

81. As discussed in Section VI.D.4 below, a POSA would have understood that, while the antibody constant regions do not directly contact the antigen, the choice of isotype for an intact humanized monoclonal antibody could potentially impact many different properties, including antigen binding affinity and specificity; immunogenicity and immune system responses; antibody pharmacokinetics; antibody stability and ultimately, safety and efficacy when administered to people. A POSA would not have reasonably expected that every possible full-length antibody made by combining sequences from a variable region fragment with desirable binding and biological activity and sequences from an intact human constant region or a full human antibody would retain the same properties, and would have understood that empirical testing would be required to assess the efficacy of any full-length humanized antibodies that were generated. (*See* AMG1023 at 1394; Section VI.D.4 below.)

82. Ultimately, a POSA as of March 15, 2007 would not have been able to predict from the primary amino acid sequence alone whether a particular newly-designed humanized antibody would bind to its target with appropriate affinity and specificity, at the appropriate epitope to provide the desired biological activity. These attributes would need to be tested empirically with in vitro studies, including assays of binding affinity and in vitro biological activity assays. (*See* ALXN2036 at 150-153; ALXN2035 at 59; AMG1023 at 1391-1393.) Even such in vitro testing would not reliably predict whether an antibody would ultimately succeed as a therapeutic agent that was suitably safe to give to patients – it would only be the beginning of the analysis.

83. As my group wrote in one of our 2007 studies, "[t]here is extensive anecdotal and unpublished evidence that many attempts to generate humanized mAbs based on mouse V regions have failed to produce useful Abs because of loss of specificity or affinity." (ALXN2039 at 1.) I have personally observed loss of binding affinity and specificity as a result of replacing the mouse constant region with a human constant region while working to develop melanin-binding monoclonal antibodies for the therapy of melanoma. I have also personally observed that exchanging murine and human constant regions alters the binding characteristics of antibodies to Cryptococcus neoformans polysaccharide. (ALXN2039 at 1-2, 3-4.) Finally, we have reported that the simple act of changing

the constant region of antibody could potentially result in new properties such as "polyreactivity," or reactivity with multiple antigens, a phenomenon of particular concern with regards to therapeutic antibodies where it is desirable to avoid all off-target reactivity with host tissues. (ALXN2009 at 13917, 13924-25; ALXN2039 at 4; *see also* ALXN2038 at 626.)

84. As discussed in Section II above, I oversaw development of a murine monoclonal antibody for treatment of cryptococcal meningitis, which began clinical trials in 2001, and in the mid-2000s, I was closely involved with the development of a murine antibody to treat melanoma. In the case of the antibody for the treatment of cryptococcosis we observed that in creating mouse-human chimeric antibodies that these differed in fine specificity from the parent murine mAb. (ALXN2013 at 1379.) In fact, concerns about changing the fine specificity of the anti-cryptococcal antibody were a major consideration in our decision to eventually use the parental murine mAb in human trials.

85. Likewise, in the case of the IgM antibody to melanin that we developed for the therapy of melanoma, efforts to create a mouse-human chimeric antibody led to loss of binding, and the difficulty involved in antibody engineering led this effort to abandon the original murine mAb used in clinical trials in favor of isolating a new murine IgG that could be more amenable to humanization. These

experiences illustrate the unpredictable outcome associated with modifying murine mAbs to create more desirable mouse-human chimeric antibodies.

86. Further, whether or not a POSA had data from in vitro or animal studies, a POSA as of March 15, 2007 would have not reasonably expected success with a newly-designed humanized monoclonal antibody without further conducting clinical testing to study the safety and efficacy of the antibody in a relevant patient population. (*See* ALXN2029 at 29-39 (outlining preclinical and clinical studies for approval of monoclonal antibodies).) A POSA would have understood that at least some human clinical testing was required to demonstrate that the antibody produces the desired clinical effect in people, and that the antibody is otherwise sufficiently safe and suitable for human administration – including whether it results in any undesirable immunogenic effects that limits efficacy or creates potential safety issues. (ALXN2042 at 91; *see* ALXN2029 at 37-39.) For example, although it was generally humanization efforts were generally intended to reduce potential immunogenicity as compared to a fully mouse antibody, a POSA would have understood that humanized antibodies – and even fully human antibodies – could still produce unwanted immune reactions in patients, and that safety would need to be assessed in clinical trials. (*See* ALXN2033 at 22; ALXN2034 at 4.) Those concerns would be exacerbated if a POSA were to consider using a unique, non-naturally occurring constant region for which there

were no published reports of clinical testing in people, such as a hybrid IgG2/IgG4 constant region.

87. Accordingly, if a humanized antibody appeared sufficiently promising based on in vitro testing, a POSA would have understood that the antibody would need to be further studied in clinical trials with human patients. In general, such clinical studies would include "Phase I" studies that primarily assess safety; Phase II studies that further assess safety and also study the desired biological effects in the relevant clinical population; and larger Phase III trials (typically placebo-controlled) to fully establish the drug is safe and effective for human clinical use. (ALXN2042 at 82; *see also* ALXN2029 at 34-37.)

88. As of March 15, 2007, the clinical trials needed to show the safety and efficacy of a therapeutic monoclonal antibody were rigorous, and required substantial resources. Particularly for a rare disease such as PNH, even small clinical trials to test for early signs of therapeutic effect and study safety were challenging, including, among other things, finding a sufficient number of appropriate patients for the study, developing and manufacturing antibody (and pharmaceutical compositions of the antibody) in suitable quantities and of suitable quality to be used in a human clinical trial, and coordinating with investigators across multiple sites.

89. Even prior to the start of human clinical trials, the antibody would have to be tested in preclinical studies, including animal studies assessing cross-reactivity of the antibody with non-target tissues, toxicology, and pharmacokinetics. (ALXN2029 at 29-33.)

90. And, even for use in an experimental, clinical trials, an appropriate pharmaceutical formulation would have to be developed. This would include development of a stability testing program and multiple studies, including accelerated stability testing, to ensure the drug would retain its biological activity and not degrade in the formulation to be administered. (ALXN2029 at 23.) If a new antibody was not sufficiently stable to be developed into a suitable formulation that could be stored and used for testing, it would have been unlikely for the FDA to permit experimental human testing to go forward.

91. A POSA as of March 15, 2007 would have known that, in addition to full-length, intact humanized antibodies, as of March 15, 2007, humanized monoclonal antibody "fragments" could be created for use in laboratory exploration and potential therapeutic applications. While commonly referred to as "fragments," these compounds were typically created using recombinant DNA technology that expressed the protein segment of interest, rather than enzymatic digestion of an intact humanized monoclonal antibody. (*See* ALXN2043 at 456; ALXN2044 at 188.)

92. For example, genetic engineering could be used to produce an antibody portion known as a "single-chain variable fragment," or "scFv." (ALXN2007 at 107; ALXN2044 at 188-189.) An scFv consists of only the variable domain of a light chain (VL) and the variable domain of a heavy chain (VH), connected by a synthetic peptide "linker" sequence. (ALXN2007 at 107; ALXN2044 at 190.) A "Fab" fragment, containing the complete light chain, but only the VH and CH1 domains from the heavy chain (also known as "Fd"), could also be made by recombinant means. (ALXN2007 at 106; ALXN2044 at 190; ALXN2043 at 456.) Figure 2 below presents the basic structure of an scFv and an Fab, in a simplified two-dimensional diagram.

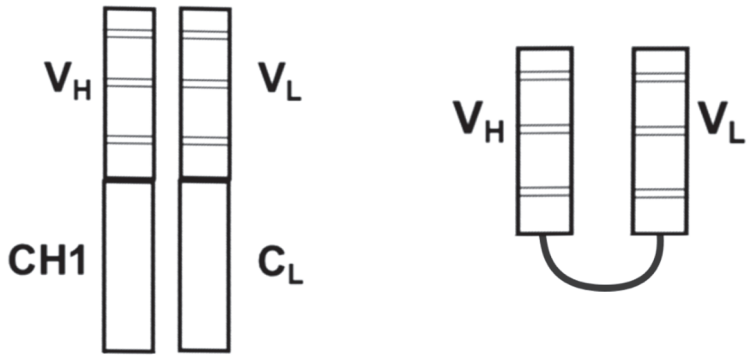

Figure 2: Left: Basic structure of an "Fab" (fragment antigen binding)

Right: Basic structure of an "scFv" (single-chain fragment, variable region)

93. A POSA as of March 15, 2007 would have understood that fragments such as scFv and Fab were structurally and functionally very different from a full-length, intact humanized antibody. Structurally, both the scFv and Fab fragments lack the complete, intact heavy chain constant region. For example, a POSA as of March 15, 2007 would have known that full-length, intact IgG antibodies have a prolonged plasma half-life relative to scFv and Fab fragments, due to their larger size and receptor interactions with the "Fc" region that is absent in the fragments. (AMG1023 at 1399; ALXN2044 at 188; ALXN2043 at 456.) A POSA would also have known that the smaller scFv and Fab fragments have more rapid rates of tissue penetration relative to the larger, full-length IgG antibodies. (AMG1023 at 1390; ALXN2007 at 107; ALXN2044 at 189; ALXN2043 at 456.) Further, as discussed in Section VI.D.4 above, a POSA would have understood that the constant regions of full-length antibodies could impact their binding affinity and specificity as well as immunogenicity and could also have other impacts on the immune system.

3. Nomenclature and Naming for Humanized Monoclonal Antibodies

94. A POSA as of March 15, 2007 would have known of various naming conventions for humanized antibodies used at different stages of development. Certain naming conventions used in early stages of development could be used to refer to groups or classes of related antibodies with different primary amino acid

sequences, and consequently, different binding affinities, specificities, and potentially different profiles in terms of biologic activity, efficacy and safety. In contrast, a POSA would have understood that, in later stages of development, the use of specific, non-proprietary names and proprietary brand names would indicate the identification and development of a single, unique humanized monoclonal antibody with a single primary amino acid sequence and activity profile.

95. In early stages of humanized antibody design and development, it was a common (but informal) convention to refer to such antibodies by reference to the original mouse hybridoma and mouse antibody from which they were developed. For example, Alexion identified the "5G1.1." hybridoma as producing the "5G1.1" mouse antibody, and often referred to the humanized antibodies and fragments derived from the "5G1.1" antibody as "humanized 5G1.1" or "h5G1.1." (*E.g.*, AMG1007 at 38:43-51; 47:28-32; AMG1023 at 1389, 1391; ALXN2032 at 97:22-99:20.)

96. I agree with Dr. Balthasar's deposition testimony that, without further context, the use of the terms such as "h5G1.1" would leave ambiguity as to exactly what particular antibody or set of antibodies are being referred to. (ALXN2032 at 98:2-99:8, 159:1-10, 202:24-203:14.) In fact, as Dr. Balthasar correctly testified, even the use of additional terminology indicating the isotype of a humanized antibody (*e.g.*, "h5G1.1 HuG4" or "h5G1.1 HuG2/G4") would leave ambiguity as

to the exact structure and complete primary amino acid sequence of the antibody. (ALXN2032 at 241:23-242:12.)

97. Likewise, while a POSA would have had a good understanding of the naturally occurring human isotype constant regions (IgG1, IgG4, etc.), the use of terminology such as "IgG2/IgG4" to refer to a non-natural, engineered hybrid of constant region sequences would be unclear, and that terminology would not necessarily specify any one specific constant region structure or sequence.

98. In contrast to the informal naming conventions used by researchers in early development, the international and U.S. naming systems for therapeutic monoclonal antibodies as of March 15, 2007 account for the importance of an antibody's specific amino acid sequence to its activity. A POSA would have understood that, after a specific humanized monoclonal antibody with a single, unique sequence had progressed into clinical development, it may be assigned a "non-proprietary" name by authorities including INN and USAN (*e.g.*, "eculizumab"). (ALXN2045 at 1207; ALXN2046 at 10.) These unique, non-proprietary names were typically assigned around the time of clinical trials or entry into the clinical trial research stage, so that unique names would not be wasted on compounds with no clear potential to becoming a marketed product. (ALXN2045 at 11, 1207 (request should be filed after submission of Investigational New Drug (IND) application); *see also* ALXN2046 at 10.)

99. As explained by the 1997 INN Guidelines, "[a]n International Nonproprietary Name (INN) identifies a pharmaceutical substance or active pharmaceutical ingredient by a unique name that is globally recognized and is public property." (ALXN2046 at 1.) The purpose of assigning non-proprietary names to monoclonal antibodies, as for other drugs, is "to provide health professionals with a unique and universally identifiable name to identify each pharmaceutical substance." (ALXN2046 at 1.)

100. Under the non-proprietary naming system that existed in 2007, monoclonal antibodies all received the suffix "-mab," and humanized monoclonal antibodies in particular were given the suffix "-zumab." (ALXN2045 at 1210; ALXN2046 at 27.) Monoclonal antibodies modifying the body's immune response were given the additional naming element "li" before the suffix. (ALXN2045 at 1210; ALXN2046 at 28.) Accordingly, an immunomodulatory humanized monoclonal antibody would end with the suffix "-lizumab," with a unique, arbitrary prefix (*e.g.*, "ecu-"). (ALXN2045 at 1210; ALXN2046 at 27-28.) A POSA would have understood that these INN/USAN names with respect to humanized monoclonal antibodies would refer to one – and only one – specific antibody as defined by its unique primary amino acid sequence. (*See* ALXN2045 at 1210; ALXN2046 at 1.)

101. Accordingly, I agree with Dr. Balthasar's deposition testimony that a POSA as of March 15, 2007 would have understood that the term "eculizumab" referred to a single, unique antibody with a single defined structure and primary amino acid sequence – not a class or genus of antibodies. (ALXN2032 at 10:9-11:17, 98:19-99:8, 100:3-10; *see also* ALXN2045 at 304 (listing "eculizumab").) I disagree, however, with Dr. Balthasar's unsupported position that a POSA prior to March 15, 2007 would have understood that unique "eculizumab" monoclonal antibody to have a hybrid IgG2/IgG4 constant region, or the specific sequence recited in SEQ ID NOS: 2 and 4 of the '149 patent. As I explain in Section VI.D.5 below, the prior art consistently instructed a POSA that the antibody named "eculizumab" was an IgG4 isotype antibody with a different structure and amino acid sequence than the antibody recited in claim 1 of the '149 patent.

102. A POSA as of March 15, 2007 would have further understood that, when a humanized monoclonal antibody is in the very advanced stages of clinical testing and nearing submission for approval by FDA and other regulatory authorities, the research sponsor can select and propose a unique branded trade name (*e.g.*, "SOLIRIS®"). This is an arbitrary name associated with the specific unique antibody, subject to review by regulatory authorities to ensure no confusion with other brand-name products.

103. In my opinion, a POSA as of March 15, 2007 would have no doubt that a humanized monoclonal antibody assigned a non-proprietary "-zumab" suffix name (*e.g.*, "eculizumab), tested in Phase III clinical trials, and submitted to the U.S. FDA for approval under a proposed trade name (*e.g.*, "SOLIRIS®"), was a single, unique monoclonal antibody with a single, unique amino acid sequence.

4. Changes to Amino Acid Sequence, Including in the Constant Region, Can Significantly Impact the Binding, Safety, and Efficacy of Therapeutic Antibodies

104. As discussed in Section VI.D.2 above, a POSA as of March 15, 2007 would have understood that designing monoclonal antibodies for human clinical therapy was a complex and unpredictable process. One particular complicating factor was the inability to reasonably predict the in vitro and in vivo properties and effects of an untested monoclonal antibody based only on its primary amino acid sequence. A POSA as of March 15, 2007 would have understood that antibodies are not simply flat, two-dimensional "Y" structures, but are complex, three-dimensional molecules that can be sensitive to changes in primary amino acid sequence – such that even small changes to the amino acid sequence could significantly impact antigen-binding affinity and specificity, and clinical safety and efficacy. (*See, e.g.*, ALXN2015 at 506, 508; ALXN2017 at 961-62.)

105. The classical view was that an antibody's variable regions, and its CDRs in particular, were the determinants of antigen binding, since they contained

the amino acid residues that most directly interact with the antigen through non-covalent bonding. (ALXN2013 at 1379; ALXN2009 at 13917.) But well before March 15, 2007, a POSA in the field of the '149 patent would have been attuned to an increasing body of scientific literature showing that antibody binding (including affinity and specificity) could be impacted by amino acid changes outside the CDR regions.

106. For example, a POSA would have known that changes to "framework" amino acids within the variable regions, but outside the CDRs, could have a significant impact on antibody binding. (*See, e.g.*, Foote 1992 at 487; ALXN2052 1995 at 253.) As discussed in Section VI.D.2 above, it was known that the transfer of murine CDRs into human framework regions would often reduce the specificity and affinity of a humanized variable antibody or fragment relative to a parent mouse antibody. (ALXN2035 at 58-60; ALXN2036 at 140-41; ALXN2033 at 19.) For that reason, in the context of designing humanized antibody variable regions, a POSA would have known that amino acid changes might be required to human sequences flanking the mouse-derived CDRs in order to achieve the desired binding properties. (*See* ALXN2035 at 58-60; ALXN2036 at 140-41.)

107. A POSA as of March 15, 2007 also would have known that changes related to the constant regions – whether combining constant region sequences, or

portions thereof, with variable region sequences from other antibodies or truncated antibody derivatives (*e.g.*, "fragments" such as Fab or scFv), or switching the type of constant regions used in a full-length antibody – could impact antigen binding and other properties of the original antibody/fragment. For example, a POSA would have understood that "isotype switching" – changing an antibody's constant region sequences while retaining sequences from the variable region – could impact critical properties such as an antibody's specificity and affinity, as well as other properties such as immunogenicity. (*See, e.g.*, ALXN2013 at 1379.) Prior to March 15, 2007, I personally was involved in research on this phenomenon, and published three articles prior to that date discussing my research. (ALXN2013; ALXN2040; ALXN2009.) In addition, there were several observations in the literature dating to the 1990s that the constant regions could affect the properties of the variable regions. Since that date, I have also published reviews discussing my work and the work of other groups establishing the impact of "isotype switching" on antigen binding, including research that was performed and published prior to March 15, 2007. (*See* ALXN2010.)

108. My laboratory's first major publication on this subject was McLean (ALXN2013), published in 2002. In that article, we compared the binding specificity of chimeric antibodies containing the same mouse antibody variable regions but different human constant regions – specifically, IgA, IgG 1/2/3/4, and

IgM constant regions. (ALXN2013 at 1379.) We performed a number of *in vitro* experiments to assess the specificity and affinity of the chimeric antibodies compared to the parent mouse antibody, including ELISAs and immunofluorescence and competition experiments. (ALXN2013 at 1380-82.) We observed that each of the chimeric antibodies had different binding characteristics from each other, and the parent murine antibody. (*See* ALXN2013 at 1380-81 (Fig. 1).) In particular, we observed that the chimeric antibodies had differences in "fine specificity" from each other and the parent mouse antibody despite having identical variable region sequences – meaning that the antibodies could still bind the target antigen, but they appeared to bind different epitopes, which can significantly impact their biological activity. (ALXN2013 at 1379, 1383-84.) As we described in our paper, "[g]iven that each [chimeric antibody] type had identical [variable] region sequence, we were surprised to find large differences in binding to [target antigens]." (ALXN2013 at 1379.) We concluded that "[o]ur observations add to the growing body of evidence that in certain circumstances, the [immunoglobulin constant] region can affect the fine specificity of an [antibody] molecule," and, further, that "it is critical that each [chimeric antibody] be carefully tested for specificity to insure the fidelity of the [antibody] engineering process." (ALXN2013 at 1385-86.)

109. Our findings in McClean were significant because they contributed to a growing body of work describing the impact of changes to antibody constant regions, including isotype-switching, on antibody binding. Prior to McClean, there were already a number of studies reporting that the constant regions could influence antibody binding. For example, in 1995, Greenspan and Cooper published an article describing how IgG3 monoclonal antibodies had been observed to more effectively bind target antigens than IgG1 and IgG2b monoclonal antibodies or IgG3-derived Fab fragments with the same variable sequences. (ALXN2014 at 227.) As stated in Greenspan, "[t]hus, it was established that differences in the heavy chain constant (CH) domains, and in the Fc region in particular, substantially influence the apparent functional affinities (avidities) of these IgG mAbs." (ALXN2014 at 227.)

110. In 1996, Pritsch et al. published a study comparing the binding activity of two antibodies with identical variable regions sequences and either the IgG or IgA isotype. The authors found that, "in spite of sharing identical variable domain sequences, having identical light chain constant domains and recognizing overlapping epitopes on the [antigen], both [antibodies] significantly differed" in their affinity for the target antigen. (ALXN2011 at 2239.) The authors concluded that "changes in the [constant heavy] domains can affect the functional affinity and specificity of [antibodies], through a complex mechanism involving [antibody]

flexibility and cooperative interactions in the case of [antibodies] bound to multivalent [antigens]." (ALXN2011 at 2242.)

111. A POSA would also have been aware of McCloskey (ALXN2008), also published in 1996. McCloskey taught that, despite having the same variable region sequences, "human antibodies of different IgG subclasses which bind the same antigen have been shown to differ in functional affinity." (ALXN2008 at 169.) The McCloskey publication used surface plasmon resonance (BIAcore) to assess the affinity and binding kinetics of chimeric antibodies made using the same mouse variable region sequences, but combined with different human IgG constant regions. (ALXN2008 at 169.) As illustrated by, *e.g.*, Figure 1, the authors found that each IgG subclass had different antibody binding characteristics. (ALXN2008 at 170-71.) The authors also found that, for IgG2 and IgG4, there was "a significant difference in the [binding] pattern obtained" with the full-length antibodies as compared to antibody fragments. (ALXN2008 at 171.) The authors concluded that, "[e]ngineered antibodies may differ in their functional affinity and hence in their function, depending upon their subclass. Such consideration may be of importance when considering the choice of antibodies for therapeutic use." (ALXN2008 at 172.)

112. Following McClean, in 2005 and 2007, my laboratory published additional studies on the impact of the constant regions on antibody binding and

specificity (ALXN2040; ALXN2009; ALXN2039), which I also co-authored. In all of these papers, we observed that changes to the constant region could affect antibody binding and specificity. (ALXN 2040 at 2132-33, 2135-38, 2140-41 (differences in fine specificity observed in two families of mouse isotype switch variants); ALXN2009 at 13917-18, 13924 (differences in antibody-antigen interactions observed in variable region identical mouse antibody isotype switch variants); ALXN2039 at 1310-11 (mouse antibody and mouse-human chimeric with identical variable regions had different binding affinity).) In our 2005 study, we concluded that "[f]rom a practical perspective, the findings that isotype can influence the fine specificity should be an important consideration in the development of genetically engineered [antibodies] for therapeutic use because it is conceivable that humanization techniques or the synthesis of mouse-human chimeric Abs can alter the fine specificity of the original [antibody]." We also observed that antibodies with the same variable regions – but different constant regions – could exhibit polyreactive characteristics (*i.e.*, could bind multiple antigens), and that this could have implications for self-reactivity. (ALXN2009 at 13924-25; ALXN2039 at 1310 ("[Observed polyreactivity] implies that mouse-human [chimeric antibody] construction may yield [immunoglobulins] with binding characteristics that are different from the parental murine mAb, including the possibility for unexpected self-reactivity.").)

113. Based on publications such as these, by March 15, 2007, a POSA would have understood that the constant regions of an antibody can have an impact on antibody binding. Mechanistically, a POSA would have been aware of publications describing how changes to the "CH1" and "hinge" portions of the heavy chain constant region could impact antibody binding, suggesting that these regions in particular modulated the antibody-antigen interaction. (ALXN2012 at 3388; ALXN2009 at 13924.) For example, in 2000, in a follow-on study to their 1996 publication, Pritsch et al. assessed the impact of heavy chain regions on the antibody-antigen interaction, and concluded that their results provided "definitive evidence" both that "isotype can influence binding affinity to antigen" and that the CH1 domain can play an important role in the antigen-antibody interaction." (ALXN2012 at 3387-88.) In one of our 2007 studies, in which we used surface plasmon resonance (BIAcore) to further assess the impact of the constant heavy chain region on antibody binding, my group similarly concluded it was likely that "structural differences in the CH1 domain are responsible for the differences in affinity constants and, consequently, for variations in [antigen] binding." (ALXN2012 at 13924.)

114. More recently, in 2016, I co-authored a review article, Janda, summarizing the work of various groups related to the impact of the constant regions on antibody binding, including work that was published prior to March 15,

2007. As described in Janda, by the first decade of the twenty-first century, at least eight different groups had independently described changes to antibody specificity resulting from isotype-switching despite the conservation of variable region sequences. (ALXN2010 at 3-4.) These publications, including some of the studies I discussed above, were based on experiments involving a variety of techniques, including ELISA, ITC, and surface plasmon resonance (BIAcore). (ALXN2010 at 3-4.) Based on the growing number of publications showing differences in antibody binding following isotype-switching, by March 15, 2007, a POSA would have been aware that changes to the constant region sequences of an antibody could impact antibody binding, even when leaving variable regions untouched.

115. In addition to potentially affecting binding, by March 15, 2007, a POSA would have understood that switching to a uniquely-engineered, non-naturally occurring (*i.e.*, "foreign") heavy chain constant region, such as a hybrid sequence constructed from portions of the IgG2 and IgG4 heavy chains, could also raise heightened immunogenicity concerns since it could have perceived by the immune system as antigenically "foreign." In particular, a POSA would have known that administering an antibody with a "foreign" heavy chain isotype to human patients could potentially result in harmful immunogenic reactions. (*See, e.g.*, ALXN2015 at 508 (describing how single amino acid substitution in an antibody drastically impacted how other antibodies ("anti-idiotype" antibodies)

would bind to it); ALXN2036 at 141 ("[I]mmunogenicity is a complex issue; intrinsic factors such as protein sequence and structure are likely to be as important as extrinsic ones"); ALXN2037 at 1343-44; ALXN2038 at 624-26.)

116. Because of the unpredictability and complexity inherent in antibody design, a POSA as March 15, 2007 would not have been able to reasonably extrapolate the in vitro or clinical properties of one monoclonal antibody with a unique amino acid sequence to a different antibody with a different sequence. A POSA would have understood that a monoclonal antibody's specific amino acid sequence was critical to its function, and that even small changes in an antibody's sequence could potentially affect its binding affinity and specificity, and thus, its safety and efficacy in humans.[3] (*See, e.g.*, ALXN2010 at 3; ALXN2011 at 2240-42; ALXN2008 at 171-72; ALXN2012 at 3391-92; ALXN2013 at 1384-86; ALXN2009 at 13924-26.)

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[3] Furthermore, a POSA could not reliably predict that a hybrid IgG2/IgG4 would be expressed efficiently in cells in sufficient quantities for therapeutic antibody production since it was known that even point mutations in the constant region affected antibody secretion and here was an antibody with a very different and unnatural constant region. (ALXN2047 McClean 2005 at 1111-12, 1117-18.)

117. In sum, as of March 15, 2007, a POSA would have known that antibody affinity and specificity could be substantially influenced even by sequence changes outside of the antigen-binding site, including changes in the heavy chain constant region. (*See, e.g.*, ALXN2013 at 1379; ALXN2014 at 226-27; ALXN2011 at 2239; ALXN2008 at 169; ALXN2012 at 3388; ALXN2009 at 13924; ALXN2010 at 3-4.) A POSA would have understood that such sequence changes could potentially result in harmful immune reactions following human administration, and that the immune consequences could not be reasonably predicted without human clinical testing. (*See, e.g.*, ALXN2015 at 508; ALXN2036 at 141 ("[I]mmunogenicity is a complex issue; intrinsic factors such as protein sequence and structure are likely to be as important as extrinsic ones"); ALXN2038 at 624-26.)

5. A POSA as of March 15, 2007 Would Have Understood "Eculizumab" To Be an IgG4-Isotype Humanized Antibody

118. In my opinion, a POSA as of March 15, 2007 would have understood that "eculizumab" was a single, unique humanized monoclonal antibody developed by Alexion, having a single, unique structure and primary amino acid sequence. I have reviewed the deposition transcript of Dr. Balthasar, and understand that he agrees with me fully on this point. (ALXN2032 at 10:9-11:17, 98:19-99:8, 100:3-10.)

119. I also have reviewed the Board's Institution Decision, which contained the statement that "'eculizumab' referred to and refers to a class or category of anti-C5 antibodies, also called 5G1.1 or h5G1.1 mAbs." (Paper No. 15 at 21-22.) I respectfully disagree with the Board on this point, and I understand Dr. Balthasar does as well.

120. While it is correct that, as I explain in Section VI.D.3 above, a POSA would have understood that the terms "5G1.1" or "h5G1.1" could potentially refer to multiple different antibody structures (when not further limited or clarified by additional context), a POSA as of March 15, 2007 would have understood that the term "eculizumab" was a non-proprietary name referring to one unique antibody with a unique structure and primary amino acid sequence. And, for the reasons explained below, a POSA would have understood that structure and sequence to be consistent with the intact humanized IgG4 isotype monoclonal antibody described in Thomas (AMG1023).

121. By March 15, 2007, a POSA would have understood that "eculizumab" was at a very late stage of development, with Alexion having published results of Phase II and Phase III human clinical trials showing that "eculizumab" was safe and effective for the treatment of PNH. (*See, e.g.*, AMG1012 at 1239, 1241-1242; AMG1004 at 552, 558; AMG1047 at 2559, 2564; AMG1005 at ¶¶ [0081-0096].) A POSA would have further known that, as of

September 2006, Alexion had applied for marketing approval of "eculizumab" from the U.S. FDA and European authorities based on the results of those human clinical trials, and had proposed the trade name "SOLIRIS®" for marketing the product following a future approval. (ALXN2054; ALXN2055; *see also* AMG1012 at 1239.) A POSA would have had no doubt that "eculizumab" and "SOLIRIS®," at that very late stage of development, was limited to a single humanized monoclonal antibody with a single structure and primary amino acid sequence.

122. If a POSA as of March 15, 2007 were to inquire further as to the specific structure of "eculizumab," they could have reached only one conclusion after considering the full scope of the literature: that "eculizumab" was an intact, humanized monoclonal antibody with the humanized variable region and IgG4 isotype constant region as described in Thomas (AMG1023). That is because, as illustrated in Table 1 below, the literature concerning "eculizumab" and its clinical properties consistently and uniformly cited to Thomas (AMG1023) for the identify of "eculizumab." The only reasonable conclusion in view of the pre-March 15,

2007 literature's repeated reference to Thomas for the description of "eculizumab" was that Thomas in fact described "eculizumab."[4]

Table 1: References to "Eculizumab" as Thomas's Humanized IgG4 Antibody

Exhibit	Statement Identifying "Eculizumab" as the IgG4 Humanized Antibody of Thomas
Hillmen 2004 (AMG1004) at 553, reporting on a Phase II clinical trial for PNH, and citing Thomas, Ref. No. 15	"Eculizumab is a recombinant humanized monoclonal antibody that was designed to block the activation of terminal complement components.[14, 15] It binds specifically to the terminal complement protein C5, inhibiting its cleavage into C5a and C5b. . . ."

[4] A POSA would not have understood these references as citing Thomas only for a general discussion of the "humanization" of "5G1.1," as Dr. Balthasar appeared to suggest at his deposition. (*See* ALXN2032 at 82:10-83:1, 86:6-23.) The references I discuss above cite Thomas for what "eculizumab" *is*, which a POSA would have understood as referring to a specific structure. And Dr. Balthasar does not dispute that Thomas disclosed a full-length, intact, IgG4 isotype humanized antibody derived from the "5G1.1" mouse antibody. (*See* AMG1002 at ¶ 47; ALXN2032 at 242:21-243:4.)

Exhibit	Statement Identifying "Eculizumab" as the IgG4 Humanized Antibody of Thomas
Hill 2005 (AMG1047) at 2559, reporting on a Phase II clinical trial for PNH, and citing Thomas, Ref. No. 9	Eculizumab is a humanized monoclonal antibody that specifically targets the complement protein C5 and prevents its cleavage.[9]"
Hillmen 2006 (AMG1012) at 1234, reporting on a pivotal Phase III clinical trial for PNH, and citing Thomas, Ref. No. 13	Eculizumab (Soliris, Alexion Pharmaceuticals) is a humanized monoclonal antibody directed against the terminal complement protein C5."[13]
Hill 2007 (ALXN2028) at 31, reporting on successful treatment of PNH in a patient with aplastic anemia and citing Thomas, Ref No. 6	"Eculizumab is a novel humanized monoclonal antibody directed against the complement protein C5.[6]"
Bell (AMG1005) at [0052], in a patent application describing results of Phase II clinical trials for PNH, citing Thomas	"Methods for the preparation of h5G1.1-mAb, h5G1.1-scFv and other functional fragments of h5G1.1 are described in U.S. Pat. No. 6,355,245 and [Thomas], the disclosures of which are incorporated herein in their entirety by this reference. The antibody h5G1.1-mAb is currently undergoing clinical trials under the tradename eculizumab."

Exhibit	Statement Identifying "Eculizumab" as the IgG4 Humanized Antibody of Thomas
Kaplan (AMG1021) at 1018, in a review article discussing development of "eculizumab," citing Thomas, Ref. No. [258884]	"Humanized 5G1.1, Fab and scFv molecules were produced by grafting the complementary determining regions of 5G1.1 on to human framework regions [258884]."
Brekke (AMG1019) at 56, in a review article discussing development of therapeutic antibodies, citing Kaplan (AMG1021), Ref. No. 31, which in turn cites to Thomas	"Eculizumab (5G1.1; Alexion Pharmaceuticals) is a humanized monoclonal antibody that prevents the cleavage of human complement component C5 into its pro-inflammatory components[31], ..."

Exhibit	Statement Identifying "Eculizumab" as the IgG4 Humanized Antibody of Thomas
Pierangeli (AMG1020) at 2123, in a journal article studying mechanisms for a complement-mediated disease, citing Hillmen 2004 (AMG1004), Ref. No. 18, which in turn cites to Thomas	Eculizumab (5G1.1), the humanized anti-C5 mAb, is considered a potential treatment for several chronic inflammatory diseases . . . [E]culizumab has been shown to prevent C5 activation in humans and to have beneficial effects in patients with [PNH]; specifically, it reduces intravascular hemolysis, hemoglobinuria, and the need for transfusion in these patients, providing a proof-of-concept that blockade of complement activation is feasible and tolerable in patients with chronic disease (18)."

123. Thomas, in turn, describes Alexion's design and testing of a full-length, IgG4-isotype humanized antibody ("humanized 5G1.1") with anti-C5 affinity, specificity, and complement-blocking activity comparable to the original mouse "5G1.1" antibody. (AMG1023 at 1389.) First, Thomas describes the humanization of variable region sequences from a mouse anti-C5 monoclonal antibody "5G1.1." (AMG1023 at 1393-94.) Next, the humanized variable region sequences were used to produce antibody fragments (*i.e.*, recombinant Fab and scFv), which were assessed for binding to human C5 and the ability to inhibit complement. (AMG1023 at 1394-95.) Finally, Thomas described the production

of “an intact humanized antibody (IgG4 isotype),” which was shown to bind C5 with similar affinity to the original “5G1.1” mouse antibody, and to inhibit complement activity in an in vitro hemolysis assay with equal potency to the mouse “5G1.1” antibody. (AMG1023 at 1396, 1399.) The researchers explained how they specifically selected the human IgG4 isotype because it “does not activate human complement,” and expressed their view that it was “likely to be minimally immunogenic in patients.” (AMG1023 at 1399.)

124. Unlike Thomas and the following literature regarding “eculizumab,” a POSA would not have understood that Evans (AMG1007) disclosed “eculizumab.” A POSA instead would have understood Evans to describe some of the early stage research leading to the later development of the antibody identified as “eculizumab” as described in Thomas. As Dr. Balthasar testified, and I agree, a POSA would have seen that Evans does not ever use the term “eculizumab,” and does not teach any full-length humanized antibodies. (ALXN2032 at 199:15-17, 163:5-15.)

125. Initially, in Example 7, Evans describes the generation of a “hybridoma designated as 5G1.1,” producing a mouse antibody referred to throughout Evans as “the 5G1.1 antibody” or “the 5G1.1 mAb.” (AMG1007 at 37:34-39:30; ALXN2032 at 165:11-21.) Evans also describes experiments to characterize the properties of the “5G1.1” antibody, including assays to assess its

C5 binding and ability to inhibit complement by blocking C5 cleavage. (AMG1007 at 38:43-51, 39:62-40:19; ALXN2032 at 38:43-39:16; 39:62-40:29.) In Example 10, Evans describes experiments to determine the amino acid sequence of "the 5G1.1 mAb" and copy (or "clone") the DNA sequences for its heavy and light chain variable regions. (AMG1007 at 40:32-42:54; ALXN2032 at 169:19-23.)

126. As Dr. Balthasar agreed during deposition, Evans does not teach any full-length antibodies other than the mouse "5G1.1" monoclonal antibody described in Examples 7 through 10. (ALXN2032 at 169:13-18.) In Example 11, Evans only describes the development of mouse and humanized "fragments" by recombinant DNA means, including (1) "Fab" molecules comprised of light chains and "Fd" sequences (the heavy chain portion of an Fab, consisting of VH and CH1 only, *see* AMG1007 at 43:21-61, SEQ ID NOs: 10-12, 16); and (2) "scFv" molecules (variable domain of a heavy chain connected by a synthetic linker to the variable domain of a light chain). (AMG1007, Example 11; ALXN2032 at 169:13-18.) As Dr. Balthasar admitted, these "fragments" were never part of, or extracted from, any full-length antibody, but rather were cloned and produced directly by recombinant means. (ALXN2032 at 163:5-15, 228:4-16.)

127. Figure 3 below illustrates (1) the structures that a POSA as of March 15, 2007 would see when reading Evans – the mouse antibody "5G1.1" and humanized recombinant "fragments" with no intact heavy chain constant region, and (2) what a POSA reading Evans would ***not*** have seen – a full-length, humanized monoclonal antibody.

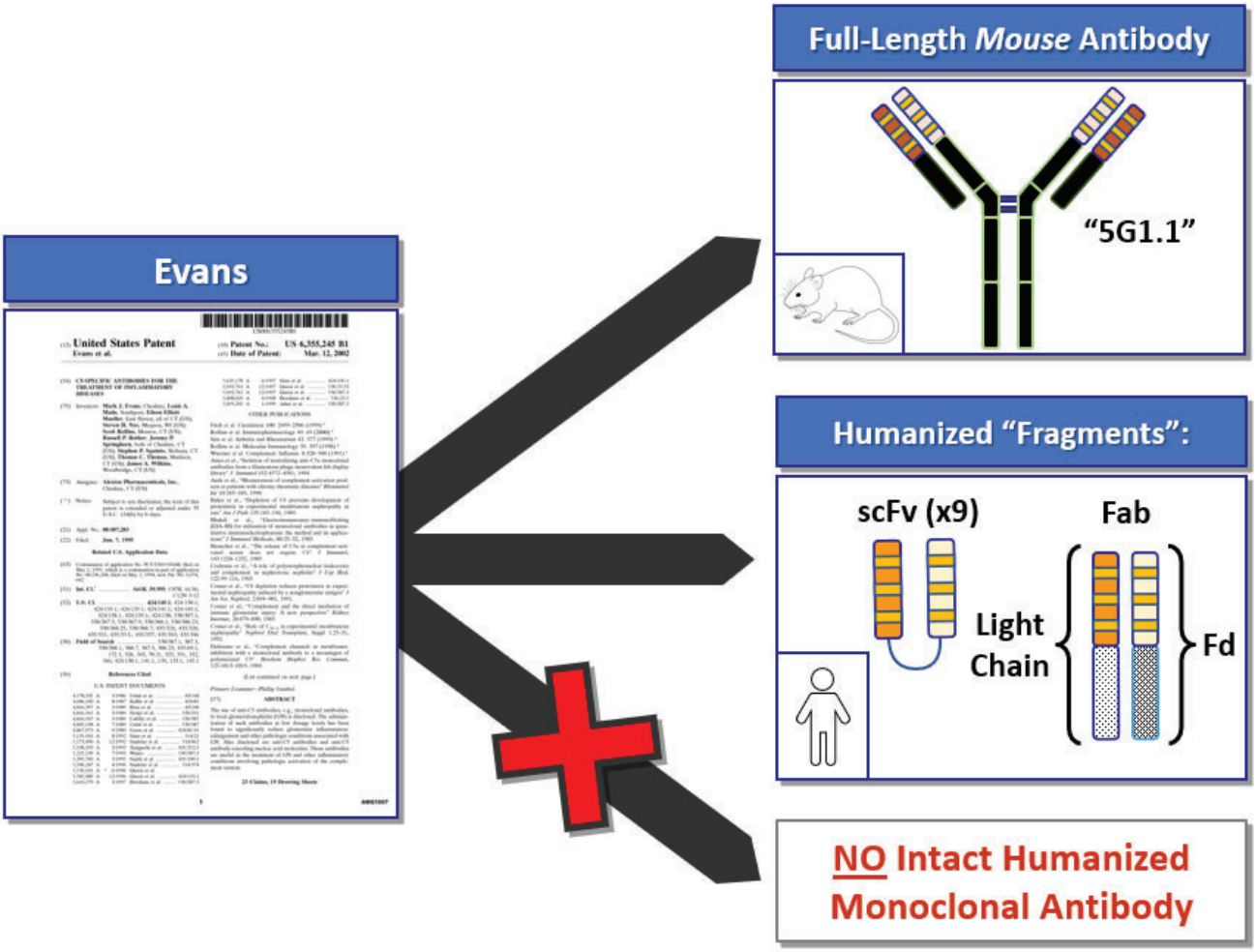

Figure 3: A POSA's understanding of structures disclosed in Evans (AMG1007)

128. Accordingly, I disagree with Dr. Balthasar's Figures 10, 11, 12, 14, 15, and 16 of his Declaration that depict the humanized scFvs of Evans as variable

regions on a full-length, intact, bivalent "Y" antibody structure. (AMG1002 at 42, 60, 62, 72, 81, and 84.) Among other things, by including an image of the full heavy chain regions in his depiction of the disclosure of Evans, Dr. Balthasar's figures suggest that Evans disclosed a full-length humanized monoclonal antibody derived from the original "5G1.1" mouse antibody, when in fact the mouse antibody was the ***only*** full-length antibody that Evans described.

129. I also note that, while Dr. Balthasar has selected one of the scFv sequences from Evans that he says aligns "perfectly" with variable region sequences from SEQ ID NOs: 2 and 4 of the '149 patent (*see* AMG1002 ¶ 55, Figs. 6 and 7), that is only because he used his hindsight knowledge of the sequences disclosed in the '149 patent to identify that alignment. A POSA without hindsight might have instead looked to the humanized Fab sequences of Evans, which are disclosed in Evans as light chain and "Fd" sequences. (SEQ ID NOs: 11 and 12, AMG1007 at 43:22-34 and Certificate of Correction at 21-24.) A POSA would have understood that an Fab was a more "complete" structure as compared to an scFv, since a humanized Fab contains both humanized variable regions and CH1 and CL human constant regions. And as the following Figures 5 and 6 demonstrate, the sequence of the Fab fragments in Evans would not have guided a POSA toward the specific amino acid sequence claimed in the '149 patent, because

in particular, there are significant differences between Evans's "Fd" sequences (the heavy chain portion of an Fab) and the claimed sequence of the '149 patent:

```
  149-2:  -------------------QVQLVQSGAEVKKPGASVKVSCKASGYIFSN
                             |||||||||||||||||||||||||||||||
Evans11:  MKWSWVILFLLSVTAGVHSQVQLVQSGAEVKKPGASVKVSCKASGYIFSN

  149-2:  YWIQWVRQAPGQGLEWMGEILPGSGSTEYTENFKDRVTMTRDTSTSTVYM
          |||||||||||||||||||||||||||||   |  |||||  ||||||  ||
Evans11:  YWIQWVRQAPGQGLEWMGEILPGSGSTEYAQKFQGRVTMTADTSTSTAYM

  149-2:  ELSSLRSEDTAVYYCARYFFGSSPNWYFDVWGQGTLVTVSSASTKGPSVF
          |||||||||||||||||||||||||||||||||||||||||||||||||
Evans11:  ELSSLRSEDTAVYYCARYFFGSSPNWYFDVWGQGTLVTVSSASTKGPSVF

  149-2:  PLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQS
          ||||  |  |||  |||||||||||||||||||||||||||||||||||||
Evans11:  PLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQS

  149-2:  SGLYSLSSVVTVPSSNFGTQTYTCNVDHKPSNTKVDKTVERKCCVECPP
          |||||||||||||||  |||||  |||  |||||||||||  ||  |  |
Evans11:  SGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHT
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Figure 4: '149 patent SEQ ID No. 2 compared with Evans SEQ ID No. 11

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  149-2:  -------------------QVQLVQSGAEVKKPGASVKVSCKASGYIFSN
                             ||||||||||||||||||||||||||||||
Evans12:  MKWSWVILFLLSVTAGVHSQVQLVQSGAEVKKPGASVKVSCKASGYIFSN

  149-2:  YWIQWVRQAPGQGLEWMGEILPGSGSTEYTENFKDRVTMTRDTSTSTVYM
          ||||||||||||||||||||||||||||||||||||||||||||||||||
Evans12:  YWIQWVRQAPGQGLEWMGEILPGSGSTEYTENFKDRVTMTRDTSTSTVYM

  149-2:  ELSSLRSEDTAVYYCARYFFGSSPNWYFDVWGQGTLVTVSSASTKGPSVF
          ||||||||||||||||||||||||||||||||||||||||||||||||||
Evans12:  ELSSLRSEDTAVYYCARYFFGSSPNWYFDVWGQGTLVTVSSASTKGPSVF

  149-2:  PLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQS
          ||||  |  |||  ||||||||||||||||||||||||||||||||||||
Evans12:  PLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQS

  149-2:  SGLYSLSSVVTVPSSNFGTQTYTCNVDHKPSNTKVDKTVERKCCVECPP
          |||||||||||||||  |||||  |||  |||||||||||  ||  |  |
Evans12:  SGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHT
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Figure 5: ’149 patent SEQ ID No. 2 compared with Evans SEQ ID No. 12

130. This would have been consistent with a POSA’s understanding of Evans as describing an early stage of research, prior to the selection of the final, IgG4 isotype, described in clinical study publications.

131. I disagree with Dr. Balthasar’s opinions suggesting that a POSA would have had any reason to look to Bowdish (AMG1006) or Mueller (AMG1008) for the structure or sequence of “eculizumab.” As Dr. Balthasar admitted at deposition, neither Bowdish nor Mueller mention “eculizumab,” and none of the references prior to March 15, 2007 describing “eculizumab” and its clinical properties cite to Bowdish or Mueller for a description of “eculizumab.” (ALXN2032 at 199:9-12, 102:10-19.) Further, neither Bowdish nor Mueller

disclose any in vitro or in vivo data suggesting that an antibody with a structure different from the IgG4-isotype antibody of Thomas would be effective in binding C5, blocking its cleavage, and safety and effectively treating patients with conditions such as PNH.

132. As of March 15, 2007, references relating to anti-C5 binding and clinical trial publications relating to PNH cited either Thomas, teaching an IgG4 isotype antibody, or Evans, which does not provide clear guidance as to isotype for a therapeutically effective antibody. Based on the art as a whole, as of that date, a POSA would have understood "eculizumab" to be an IgG4 antibody.

E. The Novel, Uniquely-Engineered Amino Acid Sequence of SOLIRIS® Was Not Known to a POSA as of March 15, 2007

133. Currently, but not prior to March 15, 2007, it is known that Alexion's SOLIRIS® utilizes a uniquely engineered, non-naturally occurring heavy chain constant region corresponding to SEQ ID NO: 2 of the '149 patent. I understand that SOLIRIS® was the first antibody with a heavy chain of its kind (containing a hybrid of sequences from both IgG2 and IgG4 constant regions) to be clinically tested in humans, and that Alexion was the first to show that such an antibody could be safe and effective when administered to human patients. (AMG1033 at 1257-58.) I also understand that SOLIRIS® was the first FDA-approved product containing Alexion's uniquely-engineered heavy chain constant region.

134. ***Prior*** to March 15, 2007, however, a POSA would not have been aware of any published clinical testing showing the safety or efficacy in humans of an antibody with the uniquely engineered heavy chain constant region known today to be used SOLIRIS®. Rather, POSA as of March 15, 2007 would have understood "eculizumab" to be an antibody with an ***IgG4*** constant region as described in Thomas (*see* Section VI.D.5 above), and would have attributed the safety and efficacy shown in Phase II and Phase III clinical trials (*e.g.* AMG1004, AMG1047, AMG1012, AMG1005) to that IgG4 antibody.

135. Accordingly, from the perspective of a POSA as of March 15, 2007, a humanized derivative of the "5G1.1" antibody with a hybrid IgG2/IgG4 constant region was an unstudied, uncharacterized entity with no known or characterized C5 binding, no known ability to block C5 cleavage, and no evidence that it was therapeutically useful to treat PNH or any other condition, or even suitable for administration to human patients.[5]

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[5] I understand Dr. Balthasar argues that a POSA nonetheless would have been motivated to construct a "humanized 5G1.1" antibody using a hybrid "IgG2/IgG4" constant region, in view of literature at the time that speculated about the potential benefits of such a constant region. (AMG1002 at ¶¶ 22, 46 (citing AMG1031, AMG1032).) As I explain below, a POSA would have

136. The structure of the active molecule in SOLIRIS® that is claimed in the '149 patent and is known today – but was not known before March 15, 2007 – is shown below in comparison to the IgG4 isotype antibody described in Thomas. Unlike the IgG4 antibody of Thomas, the claimed antibody uses the CH1 and "hinge" regions of IgG2, thereby providing a very different antibody than that identified in the literature citing to Thomas.

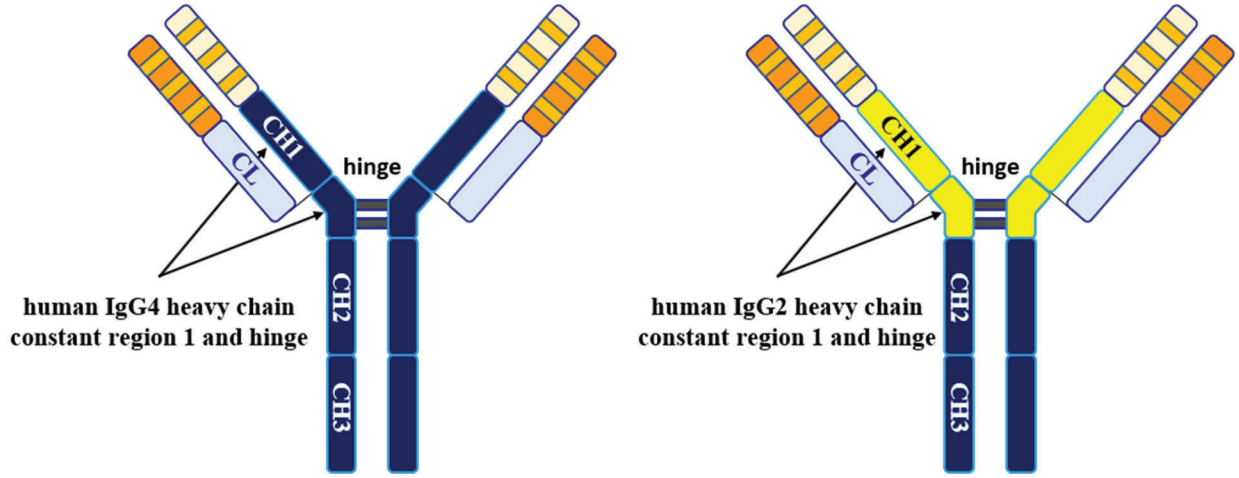

Figure 6: Left – Structure of the IgG4 isotype antibody referenced to as "eculizumab" in the literature as of March 15, 2007

Right – Structure of SOLIRIS®, having a non-naturally occurring, protein-engineered isotype

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viewed such statements as speculation based solely on *in vitro* data, and would not have reasonably expected that such a constant region that had never been clinically tested, let alone commercialized, would result in a product suitable and useful for human administration.

VII. OPINIONS

A. Dr. Balthasar's Opinions Misread the Prior Art and Rely on Hindsight Analysis

137. I have considered Dr. Balthasar's Declaration in this proceeding, dated February 27, 2019. I disagree with a number of Dr. Balthasar's conclusions, which I believe overstate the teachings in the prior art and reflect a narrative created with significant hindsight bias.

1. A POSA Before March 15, 2007 Would Not Have Understood "Eculizumab" To Contain the Uniquely-Engineered Heavy Chain Constant Region Reflected in SEQ ID NO: 2 of the '149 Patent

138. I disagree with Dr. Balthasar's statement that, as of March 15, 2007, "[a] POSA would have been aware that eculizumab was a humanized anti-C5 monoclonal antibody (h5G1.1) containing a hybrid IgG2/IgG4 constant region . . . ." (AMG1002 at ¶ 42.) Taken as a whole, the prior art that described what "eculizumab is" did not disclose an antibody with such a structure; and to the extent the prior art described antibodies with such a structure (*e.g.*, for use as "isotype control" antibodies), a POSA would not have understood such antibodies to be "eculizumab," or to have any of the properties attributed to "eculizumab" in the clinical literature. To the contrary, the prior art repeatedly would have told a POSA as of March 15, 2007 that "eculizumab" contained an IgG4 isotype, as indicated by Thomas and following publications. *See* Section VI.D.5 above.

139. I understand from Dr. Balthasar's deposition testimony that he admits key facts contrary to his position regarding the POSA's understanding of "eculizumab" as of March 15, 2007. For example, Dr. Balthasar agreed that:

- Hillmen '04 (AMG1004), Hill '05 (AMG1047), and Hillmen '06 (AMG1012) all cite to Thomas in statements identifying what "eculizumab" is. (ALXN2032 at 125:13-126:9; 128:20-129:10; 129:13-22.)
- Bell (AMG1005) cites to Thomas and Evans (AMG1007) for "[m]ethods for the preparation of h5G1.1-mAb [identified in Bell as "eculizumab"], h5G1.1-scFv, and other functional fragments" – but only Thomas describes a full-length, intact humanized antibody. (ALXN2032 at 160:18-162:12 (quoting AMG1005 ¶ 52) (quotation marks omitted.).)
- A POSA would have understood that Thomas's IgG4 antibody is different in structure and sequence from a hybrid IgG2/G4 antibody. (ALXN2032 at 97:7-21.)

140. Dr. Balthasar ignores these clear teachings towards Thomas's IgG4 antibody from the clinical literature regarding "eculizumab," and instead relies on a single sentence taken out of context from a single publication, Tacken (AMG1034), to support his conclusion that a POSA as of March 15, 2007 would

have understood "eculizumab" to be a hybrid IgG2/IgG4 antibody. (*See* AMG1002 at ¶¶ 44-45 (citing AMG1034 at 1279.) At his deposition, I understand that Dr. Balthasar admitted that Tacken (AMG1034) was the only document that he relies on dated prior to March 15, 2007 that he contends associates "eculizumab" with an IgG2/IgG4 constant region. (ALXN2032 at 104:6-20.)

141. Specifically, Dr. Balthasar relies on the following statement from Tacken, which ends with a citation to Thomas (footnote 19).

> An isotype control antibody, h5G1.1-mAb (5G1.1, eculizamab [sic]; Alexion Pharmaceuticals) containing the same IgG2/IgG4 constant region, is specific for the human terminal complement protein C5.[(19)]

(AMG1034 at 1279, 1285; ALXN2032 at 78:10-15.)

142. In view of the language of the statement itself, and all the literature available to a POSA as of March 15, 2007, including the many clinical references identifying "eculizumab" as the IgG4 antibody of Thomas, a POSA would not have read this statement in Tacken as teaching that "eculizumab" had a hybrid IgG2/IgG4 isotype. As discussed above in Section VI.D.3, a POSA would have understood that the term "eculizumab" could refer to only one single antibody with a distinct structure and primary amino acid sequence – and this one isolated statement in Tacken regarding an "isotype control antibody" was at most

ambiguous and far outweighed by the repeated, consistent references in the New England Journal of Medicine and other prominent publications identifying eculizumab as Thomas's IgG4 antibody.

143. First, in my opinion, a POSA would have seen that the language in the cited sentence does not unambiguously state that the IgG2/IgG4 "isotype control antibody" used in Tacken is "eculizumab." The cited sentence vaguely refers to both "h5G1.1-mAb," which could refer to a class of humanized antibodies, and "5G1.1," which could refer to multiple antibodies or antibody fragments, including the original mouse 5G1.1 antibody. *(See, e.g.*, ALXN2032 at 98:22-99:8, 100:16-24, 165:5-21; 169:6-18; 202:24-203:16.) Moreover, by citing to Thomas, which describes an IgG4 isotype antibody that the other prior art consistently identified as "eculizumab," this sentence at most would be confusing to a POSA. One possible reading could be that Thomas's antibody was "eculizumab" while Tacken's IgG2/G4 "isotype control" antibody was a different derivative; and another possible interpretation is that Tacken referred to the IgG2/IgG4 "isotype control" antibody as "eculizumab" by mistake (just as it misspelled "eculizamab" [sic]). Either way, a POSA would not have understood Tacken as teaching that "eculizumab" had an IgG2/IgG4 because Tacken does not clearly state what eculizumab is. Moreover, Dr. Balthasar has not explained why a POSA would have credited this isolated, ambiguous statement regarding an "isotype control

antibody" in Tacken, while disregarding the numerous clear statements in the key publications regarding "eculizumab" that identify it as the IgG4 antibody of Thomas.

144. In contrast to the multiple publications referencing Thomas, Tacken contains no assessment of the clinical safety or efficacy of eculizumab, but instead is directed to unrelated subject matter – use of a different antibody, "hD1," to increase vaccine efficacy by targeting antigens to dendritic cells. (*See* AMG1034 at 1278.) Tacken provides neither C5 binding data, nor sequence information, for its isotype control antibody, instead citing to Thomas to support the sentence cited by Dr. Balthasar. (AMG1034 at 1278.) This would have suggested to a POSA that the "eculizumab" referred to was not Tacken's isotype control antibody, but rather the IgG4 antibody described in Thomas.

145. I also disagree with Dr. Balthasar's opinion that Tacken would have indicated to a POSA that Alexion had moved on from the IgG4 isotype antibody of Thomas as its clinical candidate and replaced it with an antibody containing a hybrid IgG2/IgG4 constant region. In particular, references published after Tacken continued to cite Thomas for the structure of "eculizumab." For example, Hillmen 2006 (AMG1012), a September 2006 publication by Alexion in the New England Journal of Medicine, describes a successful Phase III trial of "eculizumab" in

treating PNH and unambiguously references Thomas in defining what "eculizumab" is, stating:

> Eculizumab (Soliris, Alexion Pharmaceuticals) ***is*** a humanized monoclonal antibody directed against the terminal complement protein C5.[(13)]

(AMG1012 at 1234, 1243 (citing Thomas (AMG1023), Ref. No. 13)[6]; *see also* ALXN2032 at 116:16-117:1.) Hill '05 (AMG1047), a one-year extension study of the 11-patient study reported in Hillmen '04 (AMG1004), was notably published two months after Tacken, in the same journal as Tacken (Blood), and like Hillmen '06, identified "eculizumab" as the IgG4 antibody of Thomas. (AMG1047 at 2559, Ref. No. 9; ALXN2032 at 113:14-21, 114:19-115:10.) Bell, published a month after Tacken, and Hill '07, a case report published on March 1, 2007, likewise both identify "eculizumab" as the IgG4 antibody of Thomas. (AMG1005 at ¶ [0052]; ALXN2028 at 31, Ref. No. 6.) These later references would have confirmed to a POSA prior to March 15, 2007 that Tacken did not represent any change in the identify of "eculizumab," which, from the perspective of a POSA, remained the IgG4 antibody structure described in Thomas.

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[6] Unless otherwise noted all emphasis is added.

146. Given Tacken's unrelated subject matter, and only limited and ambiguous reference to "eculizumab," a POSA would not have read Tacken as identifying an IgG2/IgG4 isotype for "eculizumab." Rather, as of March 15, 2007, a POSA would have understood "eculizumab" to have an IgG4 isotype, as taught by the art as a whole. In my opinion, a POSA would have either understood Tacken to be consistent with "eculizumab" being an IgG4 isotype (because of its citation to Thomas as Ref. No. 19), or otherwise, they would have thought that Tacken's referring to its IgG2/IgG4 isotype control antibody by the name of "eculizumab" was a mistake.

147. Dr. Balthasar states that Tacken "cites a publication by Mueller et al. (AMG1031; 'Mueller II') as providing information about the hybrid IgG2/IgG4 constant region portion of eculizumab." (AMG1002 at ¶ 54.) I disagree with this statement. Tacken does not refer to "eculizumab" in connection with Mueller II. Rather, Tacken states:

> The humanized variable heavy and variable light regions [of the hD1 antibody] were then genetically fused with a human hybrid IgG2/IgG4 constant domain[17] and a human kappa chain constant domain, respectively.

(AMG1034 at 1279 (citing Mueller II, Ref. No. 17).) A POSA would not have read this vague reference to Mueller II in the context of an "hD1" antibody as

teaching that the antibody "eculizumab" had an IgG2/IgG4 hybrid constant region. The reference in Tacken to Mueller is for description of the "human hybrid IgG2/IgG4 constant domain" described in Tacken; Mueller is not cited as describing "eculizumab."

148. Dr. Balthasar also cites prosecution history statements in an unrelated Alexion patent application (AMG1049, "the '438 application") that he characterizes as demonstrating a POSA's understanding that "eculizumab" had a hybrid IgG2/IgG4 antibody. (AMG1002 at ¶ 45 (citing AMG1049).) I have been informed that these statements, made after the priority date and in an unrelated patent application, are not prior art to the '149 patent. (*See* ALXN2032 at 61:13-24.) But, even if these statements were to be considered prior art, they would not change my opinion that a POSA would have understood "eculizumab" to have an IgG4 isotype, based on the teachings of the prior art as a whole.

149. I further note that Dr. Balthasar also relies on (1) a non-prior art article by Rother *et al*, published in November 2007, and (2) the non-prior art "Boone Declaration' dated in 2017 from the prosecution history of the '149 patent, for his understanding of "eculizumab's heavy chain." (AMG1002 at ¶ 54 (citing AMG1033); AMG1002 ¶ 13 (citing AMG1015 at 736-738 (Boone Declaration ¶ 6); ALXN2032 at 64:8-19.) I understand that such information was not available to a POSA as of March 15, 2007, and it does not change my opinion that the prior

art as of that date consistently and uniformly indicated to a POSA that "eculizumab" was the IgG4 antibody described in Thomas.

150. Figure 7 below illustrates (1) the consistent teaching in the literature prior to March 15, 2007 that "eculizumab" was identified as the IgG4 antibody of Thomas, and (2) how the information that Dr. Balthasar relies on for identifying "eculizumab" as an "IgG2/IgG4" hybrid isotype antibody was dated after the March 15, 2007 date:

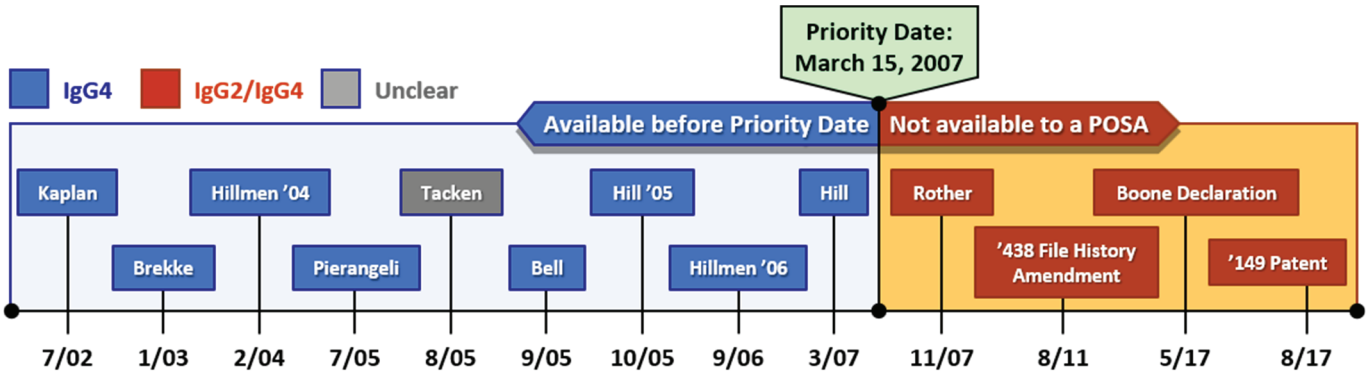

Figure 7: Documents referring to "eculizumab" before and after March 15, 2007

2. The Antibody Sequence Recited in the '149 Patent Was Not Publicly Known Before March 15, 2007

151. I also disagree with Dr. Balthasar's assertion that, prior to March 15, 2007, "[a] POSA would have been aware of the amino acid sequence of eculizumab . . . ." (AMG1002 at ¶ 49.) Before March 15, 2007, a POSA would not have known the complete, full-length amino acid sequence of SOLIRIS® (eculizumab) – now claimed in the '149 patent – which was not publicly available before that date. The references cited by Dr. Balthasar to support his conclusion

do not disclose the complete amino acid sequence claimed in the ’149 patent prior to March 15, 2007, and do not change my opinion that a POSA would not have understood that “eculizumab” or any other antibody had the complete claimed sequence prior to that date.

152. Dr. Balthasar first cites a declaration by an Alexion employee, submitted during prosecution of the ’149 patent, and that Dr. Balthasar characterizes as showing Alexion used eculizumab – which is now known to correspond to claimed SEQ ID Nos: 2 and 4 – in clinical trials prior to March 15, 2007. (AMG1002 at ¶ 49 (citing the Boone Declaration, AMG1015 at 734-741.) Dr. Balthasar does not argue that the full-length sequence of eculizumab was expressly disclosed over the course of any of the eculizumab clinical trials prior to March 15, 2007, and I understand that the declaration Dr. Balthasar cites was submitted on May 11, 2017, and would not have been accessible to a POSA prior to March 15, 2007. (*See* ALXN2032 at 58:23-59:3.) I understand that the use of an antibody in clinical trials by itself is insufficient to disclose the antibody’s sequence, and so this does not change my opinion that the full-length sequence of eculizumab was not publicly available prior to March 15, 2007.

153. In the following paragraphs of his Declaration, Dr. Balthasar also relies on Evans, Bowdish, Mueller, and Mueller II (AMG1031). I disagree with Dr. Balthasar’s depiction of these references in his Declaration, which significantly

overread the references' teachings. When read correctly, it is clear that none of these references, either alone or in combination, teach the specific, full-length antibody sequence claimed in the '149 patent, as described more fully in Sections VII.D and VII.E below.

154. First, Evans does not teach or suggest the specific, full-length antibody sequence described in claim 1 of the '149 patent, or that an antibody having that sequence would bind C5 or be safe and effective in human patients.

155. Evans does not use the term "eculizumab," and does not disclose any full-length humanized antibodies. The only full-length antibody disclosed in Evans is the parental "5G1.1" mouse monoclonal antibody. (*E.g.*, AMG1007 at 38:43-53; ALXN2032 at 169:13-18.) A POSA as of March 15, 2007 would have understood that Evans reflected an earlier stage of research involving discovery of the "5G1.1" mouse antibody and early efforts to design humanized variable region fragments, preceding Alexion's design and selection for clinical testing of a full-length, humanized antibody.

156. Evans provides nine different versions of a humanized "variable" region for anti-C5 antibodies, but does not provide any guidance as to which, if any, were being used in antibodies developed for clinical trials. (*See, e.g.*, AMG1007 at 43:6-14, 43:62-45:4.)

157. Evans includes only a brief, generic statement regarding "constant region domains," and does not identify any specific heavy chain constant region that could be used in a humanized antibody, or describe any specific full-length humanized antibodies that were actually made and confirmed to bind C5. (*See* AMG1007 at 45:24-33; ALXN2032 at 163:5-15, 165:5-21, 169:6-23.) Evans does not suggest or disclose the hybrid IgG2/IgG4 corresponding to SEQ ID NO:2 of the '149 patent, or teach that an antibody incorporating that sequence would be "[a]n antibody that binds C5." In fact, the only constant regions disclosed in Evans are the CH1 regions of Fd fragments, which appear to correspond to IgG1 CH1 sequences rather than IgG2/IgG4.[7] (*See* Section VI.D.5 above.)

158. Bowdish, Mueller, and Mueller II also did not disclose the specific, full-length antibody described in claim 1 of the '149 patent, or that an antibody with that sequence would bind C5 or be safe and effective in human patients.

159. The subject matter of Bowdish was unrelated to "eculizumab," C5 binding or the of PNH. (*See, e.g.*, ALXN2032 at 199:9-12, 175:22-25.) Bowdish concerned the use of an antibody for use as a "scaffold" to house a peptide (*e.g.*, the hormone TPO), thereby providing greater stability and longer half-life for the

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[7] Evans refers to the chimeric version of its "Fd" series of compounds as "5G1.1M1 VH HuG1." (AMG1007 at 43:18-20.)

peptide in vivo. (AMG1006 at [0005]-[0006].) The antibody used for the "scaffold" in Bowdish could be any antibody, as the technique reported in Bowdish is not specific for any individual antibody sequence. (AMG1006 at [0066].)

160. Bowdish did not describe any assays related to C5 binding or blocking complement-mediated lysis. Example 4 of Bowdish, which Dr. Balthasar relies on in his Declaration, assesses the binding of TPO-mimetic peptide (presented on an antibody scaffold) with a TPO receptor (the "cMpl receptor") – a biological interaction that is not part of the complement pathway and is unrelated to cleavage of C5. (AMG1006 at [0192].)

161. I disagree with Dr. Balthasar's characterization of Bowdish as disclosing sequences of "eculizumab" or an "eculizumab-based immunoglobulin." (*See, e.g.*, AMG1002 at ¶¶ 50-51, 55.) Bowdish never uses the term "eculizumab." (*See* ALXN2032 at 199:9-12.) Further, a POSA would not understand Bowdish to be disclosing sequences of the humanized antibody "eculizumab" described in clinical trials based on Bowdish's references to "5G1.1."

162. A POSA would have understood Bowdish's incorporation by reference of Evans to be more limited than is depicted in Dr. Balthasar's Declaration. For example, in his Declaration, Dr. Balthasar states, "Bowdish references U.S. Pat. No. 6,355,245 (AMG1007; 'Evans') as describing the generation of the h5G1.1 antibody." (AMG1002 at ¶ 52.) But Bowdish does not

use the term "h5G1.1." Instead, paragraph [0191] of Bowdish states, "Construction of 5G1.1 is described in U.S. Application. Ser. No. 08/487,283, incorporated herein by reference." (AMG1006 at ¶ [0191].) A POSA would have understood that Evans,[8] in turn, used the term "5G1.1" to refer to its ***mouse*** antibody from the original hybridoma, which is the only full-length antibody disclosed in Evans. In particular, Evans consistently uses the phrase "the 5G1.1 antibody" or "the 5G1.1 mAb" to describe the original mouse antibody obtained from the 5G1.1 hybridoma. (AMG1007 at 19:47-49, Figs. 18-19, Examples 7-10 (37:34-40:29); *see also* AMG1023 at 1389, 1395 (Thomas referring to the original mouse antibody as "5G1.1" and "the 5G1.1 mAb").) Likewise, a POSA would

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[8] I understand from counsel that Bowdish does not cite Evans (AMG1007) itself, but rather cites to the "'283 application" from which Evans issued. For convenience and to address the arguments Dr. Balthasar actually made, I will use "Evans" to refer to the document referenced in Bowdish for "[c]onstruction of 5G1.1," and will discuss the contents of Evans (AMG1007) in connection with that reference. But by doing so, I am not admitting that the "'283 application" and Evans are the same document. I understand from counsel that the "'283 application" has not been introduced by Amgen in this case, and that Dr. Balthasar did not consider it. (ALXN2032 at 191:2-11, 192:7-11, 208:3-8.)

have recognized that Evans was not a proper reference for a full-length "h5G1.1" antibody, because Evans did not disclose any full-length humanized antibodies. (*See* ALXN2032 at 163:12-15, 169:6-18.)

163. Thus, neither Bowdish's reference to using "5G1.1" as a scaffold for a TPO-mimetic peptide (AMG1006 at [0066], [0191]), nor Bowdish's citation to Evans for "[c]onstruction of 5G1.1" (AMG1006 at [0191]), would have indicated to a POSA that Bowdish's TPO-mimetic compound relates to the structure of "eculizumab," or that the "scaffold" used to make Bowdish's compound had any C5 binding activity or utility in humans.

164. I also disagree with Dr. Balthasar that a POSA would have necessarily inferred that Bowdish disclosed a "humanized 5G1.1" based on a "goat anti-human" assay reagent in a FACS experiment with the TPO-mimetic peptide compound. (AMG1002 at ¶ 50.) As Dr. Balthasar admitted Bowdish provided no information about that "goat-anti-human" reagent, including its source, its specific target ("epitope"), whether it distinguishes between "humanized" antibodies and other antibodies such as "chimeric" mouse/human hybrids, or its cross-reactivity with antibodies from other species. (ALXN2032 at 210:13-21, 211:13-23, 212:5-9.) It was understood in the field that anti-immunoglobulin antibodies could cross-react with antibodies from non-target species. (ALXN2018 at 623.) Particularly given Bowdish's earlier reference to the mouse "5G1.1" antibody in Evans at

¶ [0191], a POSA could not have been certain from Bowdish's use of an unidentified, uncharacterized "anti-human" reagent alone whether Bowdish's TPO-mimetic compound was based on a humanized, chimeric, or mouse immunoglobulin structure.

165. Mueller and the associated article, Mueller II, relate generally to developing antibodies for vascular cell adhesion molecules ("VCAM") to block transplant rejection, again a subject unrelated to C5-binding. Mueller and Mueller II describe anti-VCAM antibodies with "IgG4" and hybrid "IgG2/IgG4" isotypes, as well as negative "isotype control" constructs with the same IgG4 and IgG2/IgG4 constant region, but different variable regions that would not bind VCAM. (AMG1008 at 12:19-32; AMG1031 at 442-443.) Neither Mueller nor Mueller II disclose the amino acid sequences of any anti-C5 antibody. (*See e.g.*, ALXN2032 at 232:17-21.)

166. I disagree with Dr. Balthasar's characterization of Mueller as disclosing "eculizumab's hybrid IgG2/IgG4 heavy chain constant region." (AMG1002 at 55.) Neither Mueller nor Mueller II use the term "eculizumab" or disclose the full-length antibody sequence claimed in the '149 patent. To support his assertions, Dr. Balthasar references Mueller's use of "h5G1.1 CO12 HuG2/G4 mAb" as a control antibody. (AMG1002 at 55.) A POSA, however, would not understand this antibody to correspond to "eculizumab" because, as discussed

above, the prior art consistently described "eculizumab" as an IgG4 antibody through references to Thomas. While Mueller also refers to an "h5G1.1 CO12 HuG4" control antibody, it identified ***only*** the "HuG4" control antibody as "anti-C5." (AMG1008 at 12:1-2; *see also* AMG1031 at 446.) A POSA would have understood that to be consistent with Thomas's teachings of a "h5G1.1 HuG4" antibody that binds C5 and blocks complement activity. (*See* AMG1008 at Figs. 11-13, 15, and 11:36-12:17, 12:34-13:2; AMG1023 at 1396, 1399.)

167. Mueller further did not teach: any complete "h5G1.1" or anti-C5 binding antibody sequence; the precise boundaries of the IgG2/IgG4 constant region that would be used with any "h5G1.1" or anti-C5 binding variable region; or any guidance as to what "h5G1.1" or anti-C5 binding variable region should be used with any constant regions used in Mueller,[9] and would have been too ambiguous to have led a POSA to any particular variable region sequence. (*See* Section VII.E.1 below.)

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[9] As discussed below, I disagree with Dr. Balthasar that Mueller's vague use of the alphanumeric "CO12" in naming its "h5G1.1" isotype control antibodies would have been understood by a POSA to correspond to any particular sequence or structure in Mueller or any other document.

168. I further disagree with Dr. Balthasar that, as of March 15, 2007, a POSA would have understood the full-length, specific sequence described in claim 1 of the ’149 patent based on some combination of Evans, Bowdish, Mueller, and Mueller II. A POSA would not have looked to Bowdish, Mueller, or Mueller II for guidance on designing anti-C5 antibodies for human administration because the subject matter of those references was entirely unrelated to anti-C5 binding. A POSA also would not have read Bowdish as disclosing the ’149 patent’s claimed sequence through its incorporation of Evans because, as discussed above, this incorporation is ambiguous in scope and appears to refer to construction of the mouse 5G1.1 monoclonal antibody rather than humanized sequences.

169. References to the term “5G1.1” in Bowdish (AMG1006 at [0191]-[0193] and “h5G1.1” in Mueller / Mueller II (AMG1008 at 12:1-2, 12:35-37; AMG1023 at 1396, 1399) would not have led a POSA to look to those references for the structure of the anti-C5 antibody, “eculizumab,” whose safety and efficacy had been reported in clinical trials. As discussed in Section VI.D.3 above, and as Dr. Balthasar agreed at his deposition, without further context, the terms “5G1.1” and “h5G1.1” could refer to multiple potential antibodies or antibody fragments. (*See* ALXN2032 at 97:23-99:8, 159:1-13, 241:23-242:12.) Accordingly, a POSA would not have understood these terms in Bowdish and Mueller / Mueller II to refer to the antibody known as “eculizumab.” Further, multiple publications

discussing C5-binding and clinical trials involving "eculizumab" also used these terms – a POSA would have looked to these, more relevant publications, citing Thomas as describing the "eculizumab" antibody, rather than Bowdish or Mueller / Mueller II. (*See, e.g.*, AMG1023 at 1389; AMG1005 at ¶ [0052]; AMG1021 at 1017; AMG1019 at 56.)

170. As discussed above, as of March 15, 2007, a POSA would have understood that the design of monoclonal antibodies for human clinical therapy was a complex and unpredictable process. A POSA would have understood that small changes to antibody sequence – including in the constant region – could significantly impact antibody binding, safety, and efficacy. (*See* Sections VI.D.2 and VI.D.4 above.) Dr. Balthasar's assertions that a POSA would have read Bowdish or Mueller / Mueller II in combination with Evans to reach the full sequence claimed by the '149 patent ignore that, given the unpredictability and complexity in the art at the time, a POSA would have had no reasonable expectation that such a combination would comprise an antibody that could bind C5 or provide a therapeutic benefit to human patients.

171. With a POSA understanding that, in contrast, the IgG4 isotype antibody of Thomas was reported prior to March 15, 2007 as binding C5, blocking its cleavage, and having been used in clinical trials to safely and effectively treat PNH, a POSA would not have any reason or motivation to deviate from that

antibody, and instead combine Bowdish or Mueller / Mueller II with Evans to obtain an uncharacterized antibody with unknown properties that could not have reasonably been predicted.

B. Claim 1 of the ’149 Patent Was Not Anticipated by Hillmen or Hill (Grounds 1 and 2)

172. Amgen’s Grounds 1 and 2 contend that claim 1 of the ’149 patent would have been anticipated by the clinical trial publications Hillmen (AMG1004) or Hill (AMG1047), respectively. As Grounds 1 and 2 raise overlapping issues, I disagree with both for the same reasons, and I will address them both together here.

173. In my opinion, Amgen’s Grounds 1 and 2 fail because, among other things, Amgen cannot show that either Hillmen or Hill disclose each element of the claimed invention, either expressly or inherently. Neither Hillmen nor Hill disclose the full-length sequence recited in claim 1 of the ’149 patent.

174. Hillmen and Hill are both journal publications reporting on the successful use of “eculizumab,” a humanized monoclonal antibody targeting C5, to treat PNH in human clinical trials. (AMG1004 at 553; AMG1047 at 2564.) Neither Hillmen nor Hill disclose any amino acid sequences for “eculizumab.”

175. I understand from counsel that, for a document to anticipate a patent claim, every element of the patent claim needs to be disclosed in that one document, either expressly (*i.e.*, as stated in the document), or inherently (meaning

that, based on what is stated in the document itself, a POSA prior to March 15, 2007 would know that the claimed invention was necessarily disclosed by that document).

176. In my opinion, neither Hillmen or Hill disclosed the claimed sequence of the ’149 patent (SEQ ID NOs: 2 and 4) by their mention of “eculizumab,” because a POSA prior to March 15, 2007 would not know from reading Hillmen and Hill that the term “eculizumab” ***necessarily*** disclosed an amino acid sequence corresponding to SEQ ID NOs: 2 and 4. As discussed above, the full-length sequence claimed in the ’149 patent was not publicly known prior to March 15, 2007. (*See* Section VI.E above.) And in fact, a POSA reading Hillmen and Hill would have understood that “eculizumab” had a ***different*** structure and sequence than the antibody with SEQ ID NOs: 2 and 4 claimed in the ’149 patent.

177. In particular, a POSA reading Hillmen, Hill, and the other literature available as of March 15, 2007 would have understood “eculizumab” to have be the IgG4 isotype antibody described in Thomas (AMG1023). *See* Section VI.D.5. As I discuss above, both Hillmen and Hill cite to Thomas for a disclosure of what “eculizumab is.” (AMG1004 at 553, n. 15; AMG1047 at 2559.) This is consistent with the teachings of the prior art as a whole, and would have indicated to a POSA that the “eculizumab” antibody used in Hillmen and Hill contained an IgG4 isotype, as taught by Thomas. (*See* Section VI.D.5 above.)

178. A POSA would have understood that an IgG4 isotype antibody would have a different heavy chain sequence from the sequence contained SEQ ID NO: 2, which, as we know today, corresponds a non-natural, engineered IgG2/IgG4 hybrid constant region sequence. As of March 15, 2007, it was not publicly known that the unique, monoclonal antibody "eculizumab," which had been successfully tested in clinical trials, had an IgG2/IgG4 hybrid constant region, and all of the evidence in the literature as of that date pointed to it having a naturally-occurring IgG4 constant region.

179. A POSA would not have been able to independently determine the amino acid sequence of the antibody clinically tested in Hillmen and Hill because Alexion did not disclose the sequence of the clinical study drug, kept study participants under strict confidentiality, and maintained the physical antibody supplies under lock and key with strictly limited access. (AMG1015 at 734-741.) And even if the eculizumab protein was available to the public, which it was not, determining the entire sequence of a full-length antibody from protein alone would have required considerable specialized skill in protein sequence determination beyond the abilities of a POSA for the '149 patent.

180. I disagree with Dr. Balthasar's assertions that Hillmen and Hill are enabling – *i.e.*, they would have allowed a POSA to practice the claimed invention without undue experimentation – because, according to Dr. Balthasar, a

POSA would have looked to Bowdish and Evans, or Mueller and Evans, for the sequence of eculizumab. (*See* AMG1002 at ¶¶ 75, 85.) First, neither Hillmen nor Hill cite or incorporate by reference Bowdish, Evans, or Mueller, and I understand from counsel that it is improper to combine multiple documents for purposes of anticipation. Second, neither Hillmen nor Hill contain any indication that the "eculizumab" antibody used in those studies would have the sequences that Dr. Balthasar selects from Bowdish, Evans, and Mueller. Hillmen and Hill both cite Thomas as describing "eculizumab," from which a POSA would have understood "eculizumab" to be an IgG4 antibody with a very different sequence than the one Dr. Balthasar improperly combines from Bowdish, Evans, and Mueller. (*See* AMG1004 at 553, n. 15; AMG1047 at 2559, n. 9.) Finally, there is nothing in Bowdish, Evans, and Mueller that disclosed the specific amino acid claimed in the '149 patent in any case, for the reasons stated in Section VI.E.

181. With no sequence information available directly from Hillmen and Hill, and both these references citing Thomas, which teaches a very different antibody structure than the specific amino acid sequence claimed in the '149 patent, a POSA would not have been able to create an anti-C5 antibody, with the specific amino acid claimed in the '149 patent, based on the disclosures of Hillmen or Hill without significant experimentation.

C. Claim 1 of the ’149 Patent Was Not Anticipated by Bowdish (Ground 3)

182. Amgen’s Ground 3 contends that claim 1 of the ’149 patent would have been anticipated by Bowdish.

183. In my opinion, Amgen’s Ground 3 fails, because, among other things, Amgen cannot show that Bowdish disclosed each element of the claimed invention, either expressly or inherently. Bowdish did not disclose a full-length antibody with the specific amino acid sequence recited in claim 1 of the ’149 patent, either alone or when read in combination with Evans. Further, nothing in Bowdish would have disclosed to a POSA that the antibody with the sequence recited in claim 1 of the ’149 patent would be “an antibody that binds C5.”

184. In particular, I disagree that a POSA reading Bowdish – even to the extent that it incorporates the disclosure of the ’283 application or Evans (AMG1007) with respect to “[c]onstruction of 5G1.1” – would have understood that Bowdish necessarily disclosed the invention recited in claim 1 of the ’149 patent, without the need for picking and choosing from Bowdish’s (and Evans’s) disclosures to reconstruct the claimed invention in hindsight. Dr. Balthasar overlooks the extensive ambiguity in Bowdish’s disclosures, including its limited reference to “[c]onstruction of 5G1.1” in Evans, and reconstructs the antibody recited in claim 1 of the ’149 patent only by using his present-day knowledge of what that antibody is.

185. There is no dispute that Bowdish did not disclose the entire amino acid sequence recited in claim 1 of the ’149 patent. (ALXN2032 at 181:18-182:4.) Further, Dr. Balthasar admits that the amino acid sequences that he relies on from Bowdish – the sequences described in Bowdish Figs. 13A and 13B – are not the antibody recited in claim 1 of the ’149 patent. (ALXN2032 at 184:10-16.) Dr. Balthasar also admits that neither Bowdish nor Evans used the term “eculizumab.” (ALXN2032 at 199:9-17.)

186. Instead, I understand Dr. Balthasar goes beyond the information and sequences described in Bowdish, and combines sequences in Bowdish with other sequences that he pulls from Evans (AMG1007). (*See* AMG1002 at ¶¶ 94-96.) I further understand that Dr. Balthasar claims that, because of Bowdish’s statement regarding “incorporation” of the application corresponding to Evans (AMG1007), he is entitled to combine sequences from Bowdish with any sequences taken from anywhere within Evans. (ALXN2032 at 189:23-191:1.)

187. I disagree with Dr. Balthasar’s reading of Bowdish’s single statement regarding Evans regarding “[c]onstruction of 5G1.1.” In my opinion, Dr. Balthasar’s interpretation of that statement is mistaken and contrary to how it would have been understood by a POSA. Further, I understand from counsel that Dr. Balthasar’s interpretation of Bowdish’s statement concerning Evans is legally mistaken as well.

188. The statement at issue appears in Example 4 of Bowdish, which stated:

> The TPO mimetic peptide graft in Fab clone X4b has been transplanted into the heavy chain CDR3 region of another antibody framework, 5G1.1. Construction of 5G1.1 is described in U.S. Application Ser. No. 08/487,283,[10] incorporated herein by reference.

(AMG1006 at [0191].)

189. First, a POSA would have understood Bowdish's reference to Evans, "Construction of 5G1.1 is described in U.S. Application Ser. No. 08/487,283, incorporated herein by reference," to be a limited statement referencing Evans's disclosure of the "5G1.1" parental mouse monoclonal antibody. As discussed above, and as Dr. Balthasar agreed at deposition, a POSA reading Evans would have understood that the "5G1.1" antibody of Evans was the original mouse

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[10] As noted above, I understand from counsel that "U.S. Application Ser. No. 08/487,283" is the patent application from which Evans issued, and that Dr. Balthasar's opinion is deficient because he failed to consider and discuss the application. For purposes of this Declaration, however, I will address Dr. Balthasar's arguments as if they were proper.

"5G1.1" antibody, and that Evans did not describe any other full-length antibody. (ALXN2032 at 165:11-24, 169:6-18.) I understand from counsel that a statement regarding "incorporation by reference" must be read in its context[11] – and nothing in that statement would have indicated to a POSA any intent to have incorporated the disclosures of Evans beyond what was stated: "construction of 5G1.1," a mouse antibody. Accordingly, a POSA would not have read the statement in Bowdish as incorporating, *e.g.*, the humanized scFv fragments described in Evans, which were created after construction of the 5G1.1 mouse antibody. (*See* AMG1007 at 42:56-45:48.)

190. A POSA reading Bowdish, and seeing its incorporation by reference of Evans's mouse "5G1.1" antibody, would not have understood that it necessarily disclosed the claimed antibody of the '149 patent, which is a humanized antibody. If a POSA were to have considered the sequence of Evans's mouse "5G1.1" antibody in view of Bowdish's Figs. 13A and 13B sequences, they would have seen misalignment beyond the region of Bowdish's "TPO-mimetic" peptide, and

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[11] For example, in contrast to Bowdish's incorporation by reference of Evans, ¶ [0001] of Bowdish incorporates three provisional patent applications "in their entirety." (AMG1006 at ¶ [0001].)

would not have further envisioned any combination of sequences that would have resulted in the claimed antibody of the ’149 patent.

191. And even if Bowdish and Evans were combined in full, they did not disclose or render obvious the uniquely engineered amino acid sequence recited in claim 1 of the ’149 patent. For example, if a POSA were to have looked to Evans for construction of the “scaffold” antibody used to generate Bowdish’s TPO-mimetic peptide, they would have been lost. As Dr. Balthasar admitted, Evans did not describe ***any*** full-length antibody (including Bowdish’s “scaffold” antibody), aside from the “5G1.1” mouse antibody, which would not have aligned with the sequences disclosed in Bowdish. (ALXN2032 at 163:12-15, 169:6-23, 221:14-16.)

192. A POSA also would not have looked to the scFv fragments of Evans to understand the sequence of the full-length “scaffold” antibody in Bowdish. As discussed in Section VI.D.2 and IV.D.4 above, scFv and full-length antibodies were understood to be very different structures with very different properties, and a POSA would not have confused an scFv for a full-length immunoglobulin from which Bowdish’s TPO-mimetic compound was made.

193. I also disagree that a POSA would have understood Bowdish to have necessarily disclosed the specific claimed amino acid sequence of the ’149 patent, when Dr. Balthasar’s theory of anticipation requires a POSA to pick and choose through Evans’s sequences, including scFv sequences not referenced anywhere in

Bowdish. (AMG1002 at ¶¶ 94-96.) Again, I note that Dr. Balthasar's figures are misleading in this regard, because a POSA would not have understood Evans's scFv sequences as being part of an intact antibody structure such as was used to generate Bowdish's TPO-mimetic compound, but would have understood Evans's scFvs to be a distinct, recombinant DNA compound different from the full-length structures described in Bowdish.

194. Figure 8 below illustrates (1) how a POSA prior to March 15, 2007 would have understood the information disclosed in Bowdish as it incorporates the '283 application (a mouse antibody); (2) how a POSA would have understood the other disclosures of Evans that Bowdish did not incorporate ("fragments" including scFvs and Fabs,), and (3) how Dr. Balthasar's Figure 10 is mistaken for depicting Evans as describing part of a full-length humanized antibody – which is not actually described anywhere in Evans or in Bowdish.

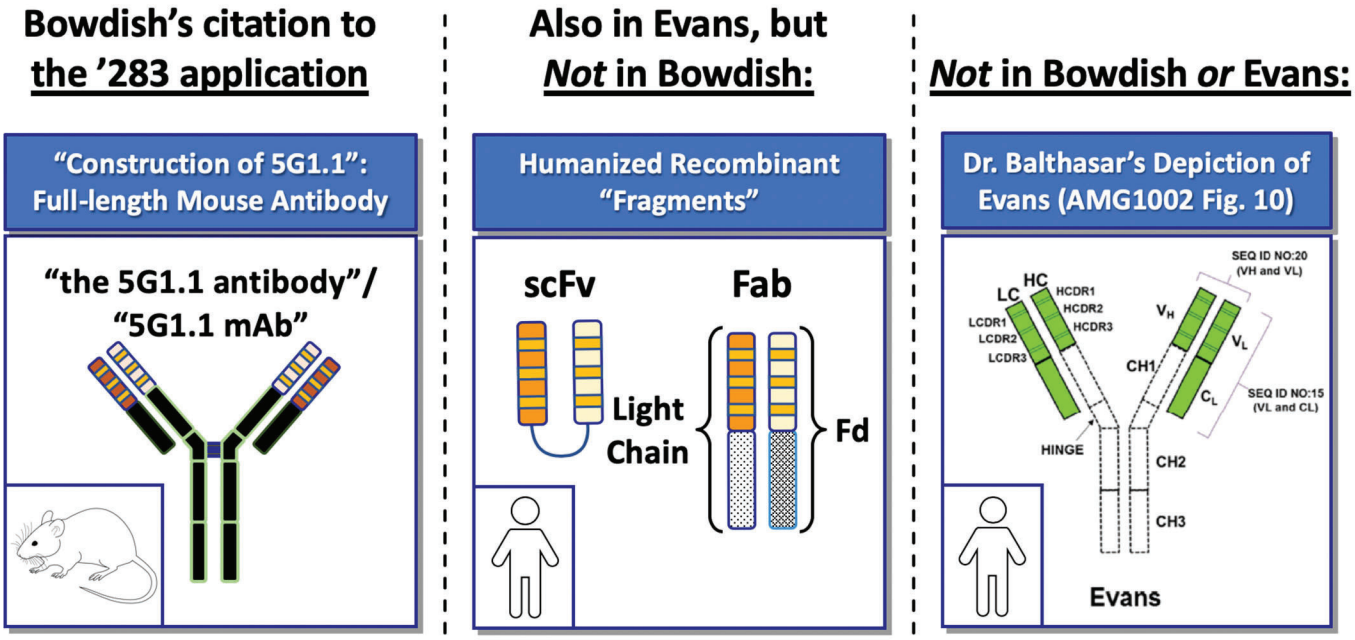

Figure 8: A POSA's understanding of Bowdish's reference to the '283 application, and what material was outside the referenced subject matter

195. A POSA further would not have understood the "5G1.1" antibody referenced in Bowdish to have necessarily disclosed SEQ ID NO: 2 because Evans referred to at least two, and possibly at least four potential definitions of the CDR region: the "sequence variability" definition (Kabat), the "structural variability" definition (Chothia), and the overlap between them. (AMG1007 at 5:15-36.) Dr. Balthasar is incorrect when he states that "all of the 5G1.1 heavy chains in Evans contain the same CDR3 sequence," as Evans actually disclosed at least two CDR3 regions – one containing 11 amino acids, and one containing 13 amino acids, and possibly two sequences of 12 amino acids in their region of overlap – based on use

of the two definitions. (*See, e.g.*, AMG1007 at 5:15-36, 42:64-43:5, Figs. 18 and 19.)

196. It is my opinion that Dr. Balthasar's Declaration demonstrates a significant use of hindsight. For example, I disagree with Dr. Balthasar's sequence alignments in Figures 5 and 13, which compare sequences from Bowdish to the claimed SEQ ID NO: 2 from the '149 patent. "SEQ ID NO: 2" was not publicly available as of the priority date. A POSA would not have had the guidance of the disclosure of SEQ ID NO:2 from the '149 patent to help select sequences to combine from Bowdish and Evans and, as a result, for the reasons stated here, a POSA would not have understood Bowdish to necessarily disclose the claimed sequence, based on the vague disclosures in Bowdish.

197. I also disagree with Dr. Balthasar's statement, "[A] POSA would have known that the only portion of the sequence disclosed in Bowdish's Figures 13A-13B that is different from the original h5G1.1 'scaffold' antibody disclosed in Bowdish is the portion of SEQ ID NO: 67 that corresponds to the TPO peptide." (*See* AMG1002 at ¶ 92.) This is not correct. Bowdish did not use the term h5G1.1, and as discussed above, a POSA would have understood based on Example 4 of Bowdish that the original "5G1.1" scaffold antibody was the mouse antibody in Evans. Comparing the mouse antibody in Evans with the sequence in

Figure 13, there are additional sequence differences outside of the TPO peptide region, which give the humanized and mouse antibodies different properties.

198. I also disagree with Dr. Balthasar's depiction in Figure 12. (AMG1002 at ¶ 96.) As I discussed above (*see* Section VI.D.5 above), I disagree with Dr. Balthasar's depiction of the disclosure from Evans, because Evans did not disclose a full-length, humanized antibody – only humanized antibody fragments, such as scFv. A POSA would have understood that the scFv structures of Evans were not partial sequences from a full-length antibody, but they were their own stand-alone, recombinantly-generated compounds, which were never part of any full-length humanized antibody.

199. I further disagree with Dr. Balthasar's use of the term "h5G1.1" in his depiction of the "scaffold" that was used in Bowdish. The term "h5G1.1" is not used in Bowdish, Bowdish did not describe the antibody in Example 4 of Bowdish as being humanized, and Evans did not disclose any full-length, humanized antibody sequences. I further disagree with Dr. Balthasar's depiction in Figure 14. Again, Dr. Balthasar does not accurately depict the disclosure of Evans, which did not disclose a full-length humanized antibody, but only humanized antibody fragments, such as scFv. I also disagree with the use of the term "h5G1.1," which was not used anywhere in Bowdish. Neither Figure 12 nor Figure 14 reflect the multiple steps of sequence selection and combination that a POSA would have to

have undertaken to arrive at the claimed full-length sequence from the disclosures of Bowdish.

200. A POSA also would not have understood that an antibody made from a combination of constant regions from Bowdish with a CDR from Evans would work to bind C5. Bowdish makes no disclosure regarding C5 binding activity. Bowdish Example 4 assessed binding for the cMp1 receptor, which was the target of Bowdish's TPO-mimetic construct and is unrelated to C5 or the complement pathway. (AMG1006 at ¶¶ [0192]-[0193].) Further, a POSA would have understood that if a CDR region from Evans was combined with constant regions from Bowdish, there would be a significant risk that the resulting antibody would not bind C5, due to the known complexity and unpredictability of antibody design. (*See* Sections VI.D.2 and VI.D. 4 above.)

201. I disagree with Dr. Balthasar that Bowdish would have enabled a POSA to make the claimed antibody. (*See* AMG1002 at ¶¶ 101-02.) For the reasons discussed above in Sections IV.D.2 and IV.D. 4, a POSA would have understood that changes to an antibody's sequence, including in the constant region, can significantly affect binding and specificity, as well as safety and efficacy in patients. A POSA would not have understood that the combination of a CDR from Evans with constant regions disclosed in Bowdish would effectively bind C5, or be safe for human therapy, without substantial additional study.

D. Claim 1 of the ’149 Patent Would Not Have Been Obvious Over Bell, Bowdish, and Evans (Ground 4)

202. Amgen’s Ground 4 contends that claim 1 of the ’149 patent would have been obvious over the combination of Bell, Bowdish, and Evans.

203. In my opinion, Amgen’s Ground 4 fails, because, among other things, Amgen cannot show that each element of the claimed invention was known or obvious in view of Bell, Bowdish, and Evans. None of Bell, Bowdish, nor Evans, when read alone or in combination, disclosed the specific amino acid sequence claimed in the ’149 patent.

1. Bell Did Not Disclose the Specific Sequence of Claim 1, and Would Not Have Motivated a POSA to Make An Antibody With the Claimed Sequence

204. Dr. Balthasar relies on Bell for its disclosures regarding “eculizumab” – but he admits that Bell did ***not*** disclose the claimed amino acid sequence of the ’149 patent. (AMG1002 ¶ 107; ALXN2032 at 146:17-25.) Bell, in fact, would have guided a POSA towards use of an IgG4 isotype that is different from the claimed antibody of the ’149 patent, which has a different, uniquely-engineered amino acid sequence corresponding to a hybrid IgG2/IgG4 constant region. A POSA would have had no reason or motivation to deviate from the IgG4 antibody structure of Thomas that Bell associated with the therapeutically useful “eculizumab” antibody, and turn instead to (1) Bowdish, which Bell did not cite, and contained no information regarding anti-C5 antibodies; or (2) Evans, which

did not disclose any full-length humanized antibodies, and at best may have suggested an IgG1 antibody based on the Fd sequences it disclosed. (See Section VI.D.5 above.) And, a POSA provided with Bell would not have been motivated to make a new, untested antibody using a clinically-untested non-naturally occurring hybrid constant region, when Bell taught that "eculizumab," identified as an IgG4 antibody, was safe and effective for human use.

205. Bell was a U.S. Patent application relating to use of compounds to block complement for the treatment of PNH. A POSA would have read paragraph 52 of Bell as teaching that the "eculizumab" antibody described in Bell had an IgG4 isotype, based on Bell's citation and incorporation by reference of Thomas, which taught the IgG4 isotype. (*See* Section VII.D.5 above.) Specifically, Bell stated:

> Particularly useful anti-C5 antibodies are h5G1.1-mAb, h5G1.1-scFv and other functional fragments of h5G1.1. ***Methods for the preparation of h5G1.1-mAb,*** h5G1.1-scFv and other functional fragments of h5G1.1 are described in U.S. Pat. No. 6,355,245 and "Inhibition of Complement Activity by Humanized Anti-C5 Antibody and Single Chain Fv," ***Thomas et al., 1401, 1996***, the disclosures of which are incorporated herein in their entirety by this reference. ***The***

antibody h5G1.1-mAb is currently undergoing clinical trials under the trade-name eculizumab.

(AMG1005 at ¶ [0052].)

206. Although paragraph 52 of Bell also cited and incorporated by reference Evans, a POSA would not have understood this as teaching an alternative isotype for the "eculizumab" antibody. As discussed above, while Evans did disclose "scFv" compounds and other functional fragments like "Fab," Evans did not disclose any full-length humanized antibodies, and only described human constant regions generically. (*See* Section VI.D.5 above.) Evans in particular did not make any reference to IgG2/IgG4 antibodies. (ALXN2032 at 163:25-164:19.) In fact, the only heavy chain constant regions described in Evans are the CH1 regions of "Fd" fragments[12] (SEQ ID NOs: 11 and 12) that do not align with the constant regions of the claimed sequence. (*See* Section VI.D.5 above.)

207. Accordingly, Bell's citation to Evans was not inconsistent with the understanding that Bell, and the other available literature, identified "eculizumab" as having an IgG4 isotype. A POSA would have understood that

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[12] Evans defines an "Fd" fragment as the heavy chain portion of an "Fab," meaning a truncated heavy chain that contains VH and CH1. (AMG1007 at 43:18-19.)

Bell could have only referenced Evans for the humanized "fragments" it disclosed, and that Bell in turn cited Thomas for the disclosure of the full-length "eculizumab" antibody that was the subject of Bell's clinical trials in PNH. The following figure illustrates how a POSA would have understood Bell's teaching that "eculizumab" was the IgG4 antibody of Thomas, consistent with the other prior art available prior to March 15, 2007:

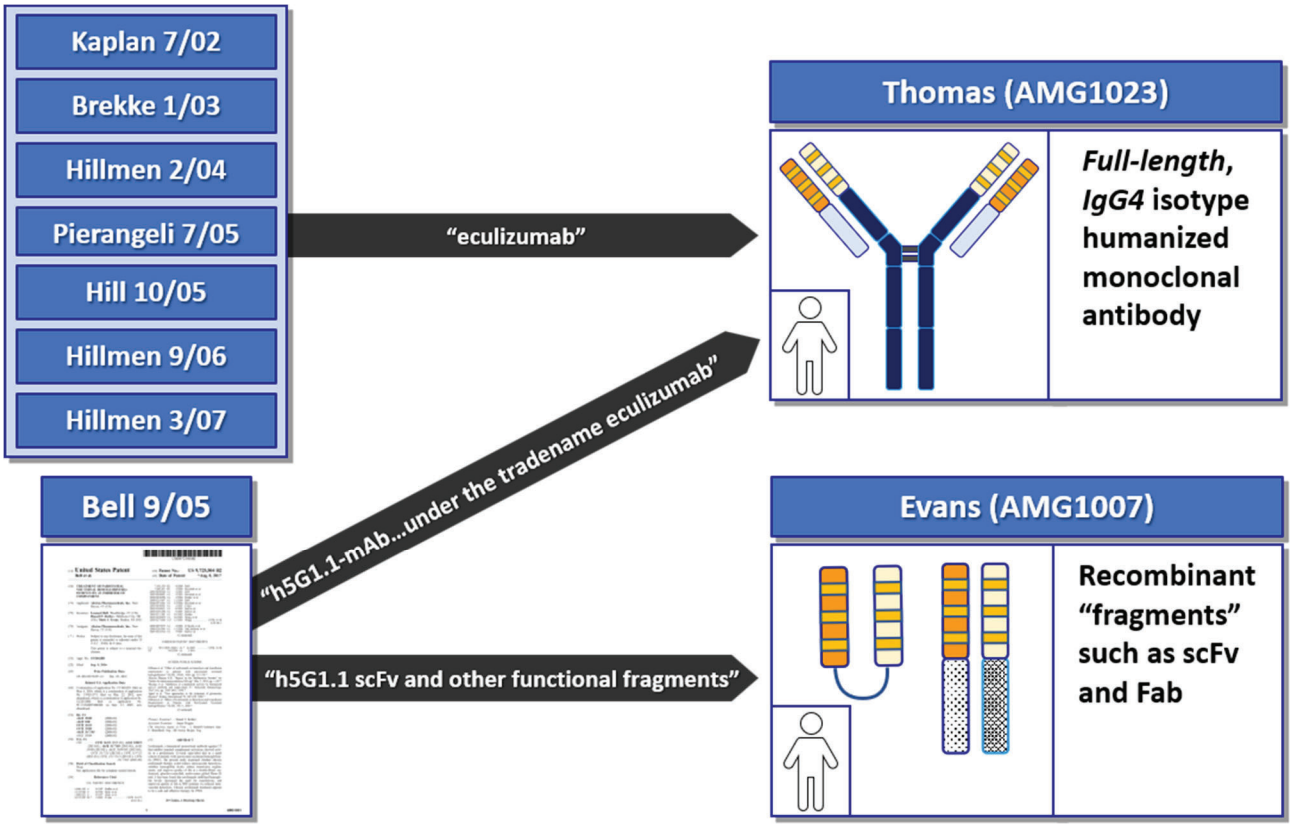

Figure 9: A POSA's understanding of Bell's teaching regarding "eculizumab," "h5G1.1 scFv," and "other function fragments

208. And if there was any doubt regarding the structure of the "eculizumab" antibody Bell referred to with respect to its evidence of clinical

safety and efficacy in treating PNH (AMG1005 at [0081]-[0096]), a POSA's review of the other related literature would have confirmed that Bell was referring to Thomas's IgG4 antibody. In particular, as Dr. Balthasar acknowledged, the clinical studies reported in Bell for "eculizumab" were the same as those reported in Hillmen (AMG1004) and Hill (AMG1047) – two references that unambiguously cited Thomas as the reference for what "eculizumab is." (AMG1004 at 553, Ref. No. 15; AMG1047 at 2559, Ref. No. 9; ALXN2032 115:16-23.)

2. A POSA Without the Benefit of Hindsight Would Not Have Been Motivated to Combine Bell with Bowdish and Evans

209. A POSA starting with Bell for its teaching of "eculizumab" as a safe and effective treatment for PNH, as Dr. Balthasar does, would have had no reason or motivation to deviate from the IgG4 antibody structure of Thomas that Bell associated with the therapeutically useful "eculizumab" antibody, and turn instead to (1) Bowdish, which Bell did not cite, and contained no information regarding anti-C5 antibodies; or (2) Evans, which did not disclose any full-length humanized antibodies, and at best may have suggested an IgG1 antibody based on the "Fd" sequences it disclosed. (*See* Section VI.D.5 above.) And, a POSA provided with Bell would not have been motivated to make a new, untested antibody using a clinically-untested non-naturally occurring hybrid constant

region, when Bell taught that "eculizumab," identified as an IgG4 antibody, was safe and effective for human use.

210. I disagree with Dr. Balthasar's arguments regarding why he claims a POSA would have been motivated to combine Bell, Bowdish, and Evans. Dr. Balthasar's sole explanation for why a POSA would have been motivated to combine these references is that a POSA would have looked to Bowdish and Evans to try to determine the sequence of "eculizumab" following review of Bell. I disagree that a POSA would have read Bell, and then looked to Bowdish and Evans for the "eculizumab" sequence, as Dr. Balthasar asserts. (*See* AMG1002 at ¶ 114.)

211. First, I note that that neither Bell, nor the Thomas or Evans references cited in Bell, cited to Bowdish for teaching "eculizumab," or for any other antibody. Nor would anything else in Bell have directed a POSA to Bowdish. For example, nothing in Bowdish concerns the subject matter of Bell, including, e.g., antibody binding of C5, using anti-C5 antibodies to block complement activity, or treatment of PNH.

212. Bowdish's use of the term "5G1.1" in connection with its TPO-mimetic construct would not have guided a POSA to Bowdish for teaching of "eculizumab" because, as discussed above, the term 5G1.1 was not understood to unambiguously refer to the antibody "eculizumab." (*See* Section VI.D.3 above.)

And as used in Bowdish, when referring to "[c]onstruction of 5G1.1," a POSA would have understood Bowdish to be referring to the mouse antibody of Evans, not "eculizumab" – a full-length intact antibody that was not disclosed anywhere in Evans.

213. Dr. Balthasar's argument to connect Bell to Bowdish requires him to assume that a POSA understood that "eculizumab" had a hybrid IgG2/IgG4 constant region. (AMG1002 ¶¶ 114-115; ALXN2032 at 196:15-23, 198:21-199:3.) His argument fails for that reason alone, because as I explained above, the teaching in Bell and the other predominant clinical literature as of March 15, 2007 was that "eculizumab" was an IgG4 isotype antibody of Thomas, not a hybrid IgG2/IgG4 isotype. (*See* Section VI.D.5 above.)

214. Bowdish's reference to Evans's mouse "5G1.1" antibody would not have taught a POSA anything about the C5 binding properties or other properties of Bowdish's TPO-mimetic compound or the "scaffold" it came from, because a POSA would that Bowdish's TPO-mimetic compound had a very different sequence and structure from Evans's original mouse antibody. The following figure illustrates the sequence alignment of Bowdish's Figs. 13A (SEQ ID NO: 67, heavy chain) and 13B (SEQ ID NO: 69, light chain) with the variable heavy chain and variable light chain of the "5G1.1" mouse antibody from Evans (Evans Fig. 19 (variable heavy chain) and Evans Fig. 18 (variable light chain)). This figure

confirms that a POSA looking from Bowdish to Evans for "[c]onstruction of 5G1.1" would not be guided towards the claimed antibody of the '149 patent:

```
Bowdish13A:  QVQLVQSGAEVKKPGASVKVSCKASGYIFSNYWIQWVRQAPGQGLEWMGE
             |||| |||||  ||||||| |||| |||||||||||  | || |||| ||
   Evans19:  QVQLQQSGAELMKPGASVKMSCKATGYIFSNYWIQWIKQRPGHGLEWIGE

Bowdish13A:  ILPGSGSTEYTENFKDRVTMTRDTSTSTVYMELSSLRSEDTAVYYCARLP
             |||||||||||||||||    | |||  | || |||| ||| |||||||||
   Evans19:  ILPGSGSTEYTENFKDKAAFTADTSSNTAYMQLSSLTSEDSAVYYCAR--

Bowdish13A:  IEGPTLRQWLAARAP-----VWGQGTLVTVSS
             ||||||||      ||||||||| || |||||
   Evans19:  --------YFFGSSPNWYFDVWGAGTTVTVSS
```

```
Bowdish13B:  DIQMTQSPSSLSASVGDRVTITCGASENIYGALNWYQQKPGKAPKLLIYG
             |||||||| |||||||  |||||||||||||||||| | || | |||||
   Evans18:  DIQMTQSPASLSASVGETVTITCGASENIYGALNWYQRKQGKSPQLLIYG

Bowdish13B:  ATNLADGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCQNVLNTPLTFGQ
             |||||||  |||||||||    | |||| | | |||||||||||||||||
   Evans18:  ATNLADGMSSRFSGSGSGRQYYLKISSLHPDDVATYYCQNVLNTPLTFGA

Bowdish13B:  GTKVEIK
             ||| | |
   Evans18:  GTKLELK
```

Figure 10: Bowdish Figure 13A (SEQ ID NO: 67) compared to Evans Fig. 19
Bottom: Bowdish Fig. 13B compared to Evans Fig. 18

215. Further, I understand that Alexion has obtained the full amino acid sequence of the "5G1.1" antibody of Evans from the HB-11625 hybridoma. (ALXN2075 at 2-3.) The following figure illustrates the sequence alignment of Bowdish's Fig. 13A (SEQ ID NO: 67) with the full heavy chain of the "5G1.1" mouse antibody from Evans. As with the figure above, this further confirms that a POSA looking from Bowdish to Evans for "[c]onstruction of 5G1.1" would not be guided towards the claimed antibody of the '149 patent:

```
Bowdish13A:  -------------------QVQLVQSGAEVKKPGASVKVSCKASGYIFSN
                                 |||| |||||  ||||||| |||| ||||||
   5G1.1HC:  MEWTWVFLFLLSVTAGVHSQVQLQQSGAELMKPGASVKMSCKATGYIFSN

Bowdish13A:  YWIQWVRQAPGQGLEWMGEILPGSGSTEYTENFKDRVTMTRDTSTSTVYM
             |||||  | || |||| |||||||||||||||||    | |||  | ||
   5G1.1HC:  YWIQWIKQRPGHGLEWIGEILPGSGSTEYTENFKDKAAFTADTSSNTAYM

Bowdish13A:  ELSSLRSEDTAVYYCARLPIEGPTLRQWLAARAP-----VWGQGTLVTVS
              |||| |||||||||||                 ||||||||| || ||||
   5G1.1HC:  QLSSLTSEDSAVYYCAR----------YFFGSSPNWYFDVWGAGTTVTVS

Bowdish13A:  SASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSG
             || |  ||| ||||    |  |   |||||| |||||||  |||| | ||
   5G1.1HC:  SAKTTAPSVYPLAPVCGDTTGSSVTLGCLVKGYFPEPVTLTWNSGSLSSG

Bowdish13A:  VHTFPAVLQSSGLYSLSSVVTVPSSNFGTQTYTCNVDHKPSNTKVDKTVE
             ||||||||||  || ||| ||| ||    |  |||| |  | |||||  |
   5G1.1HC:  VHTFPAVLQSD-LYTLSSSVTVTSSTWPSQSITCNVAHPASSTKVDKKIE

Bowdish13A:  RK--CCVECPP--CPAPP-VAGPSVFLFPPKPKDTLMISRTPEVTCVVVD
                     |||  |||| |  ||||| |||| || |||  || |||||||
   5G1.1HC:  PRGPTIKPCPPCKCPAPNLLGGPSVFIFPPKIKDVLMISLSPIVTCVVVD

Bowdish13A:  VSQEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLN
             ||  || ||  | |  |||| | |    || ||| |||| |   ||||
   5G1.1HC:  VSEDDPDVQISWFVNNVEVHTAQTQTHREDYNSTLRVVSALPIQHQDWMS

Bowdish13A:  GKEYKCKVSNKGLPSSIEKTISKAKGQPREPQVYTLPPSQEEMTKNQVSL
             ||| |||| || ||  || |||| ||  | |||| |||  ||||| || |
   5G1.1HC:  GKEFKCKVNNKDLPAPIERTISKPKGSVRAPQVYVLPPPEEEMTKKQVTL

Bowdish13A:  TCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSRLTVDKS
             || |  | | || |||  ||  | ||| | |||||||| | || | | |
   5G1.1HC:  TCMVTDFMPEDIYVEWTNNGKTELNYKNTEPVLDSDGSYFMYSKLRVEKK

Bowdish13A:  RWQEGNVFSCSVMHEALHNHYTQKSLSLSLGK
              | | |  |||| || |||| | || |   ||
   5G1.1HC:  NWVERNSYSCSVVHEGLHNHHTTKSFSRTPGK
```

Figure 11: Bowdish Figure 13A (SEQ ID NO: 67) compared to heavy chain of 5G1.1 antibody from HB-11625

216. Even assuming Dr. Balthasar's incorrect position that a POSA would have understood "eculizumab" to already have an IgG2/IgG4 isotype, a POSA would not have combined Bell with Bowdish because a POSA would not have immediately recognized that the sequences in Figure 13 of Bowdish included humanized constant regions or an IgG2/IgG4 isotype. As Dr. Balthasar testified, Bowdish does not state that the sequences in Figure 13 are humanized or that they correspond to an IgG2/IgG4 constant region, and a POSA would have had to perform a sequence alignment using "BLAST" or another tool to determine these characteristics. (ALXN2032 at 199:19-23, 212:10-214:13.) A POSA attempting to design an anti-C5 antibody would have had no motivation to perform such an alignment, however, because Bowdish's TPO-mimetic was not identified as targeting C5, and, as discussed, Bowdish's reference to "5G1.1" would not have unambiguously identified the antibody "eculizumab." Nothing in Bowdish specifically guided a POSA to use BLAST or a similar search tool to analyze the sequences for its TPO-mimetic compound. (ALXN2032 at 214:19-24.) Further, Dr. Balthasar's Declaration does not provide any demonstration of what the results would have been if a POSA had performed such an alignment prior to March 15, 2007. (ALXN2032 at 214:25-215:8.)

217. I also disagree with Dr. Balthasar's conclusion that a POSA would have understood that the sequences in Bowdish Figure 13 were humanized based

on the FACS experiment described in Bowdish Example 4. (*See* AMG1002 at ¶ 90.) As I noted above (*see* Section VII.A.2 above), a POSA would not have been able to conclude that the sequences in Bowdish were humanized solely because Bowdish referred to use of an unspecified, uncharacterized "anti-human IgG" reagent that could have had any of a number of possible epitopes and levels of cross-reactivity.

218. Accordingly, given the unpredictability associated with humanized therapeutic antibody design as discussed in Sections VI.D.2 and VI.D.4 above, and the substantial expense and unpredictability of developing and testing a humanized monoclonal antibody for human therapeutic use as discussed in Section VI.D.2 above, a POSA would have no motivation to deviate from the thoroughly-studied "eculizumab" antibody that a POSA would have believed was an IgG4 isotype. A POSA in particular would not have been motivated to make such an untested, unstudied antibody with a non-naturally occurring hybrid IgG2/IgG4 isotype region, because there were no reports in the literature of ***any*** antibody with that isotype that had been clinically tested, and accordingly, a POSA could not have reasonably expected such an antibody to be therapeutically useful or suitable for human administration.

219. A POSA further would not have combined Bell and Bowdish based on Bell's reference to Evans. (*See* AMG1005 at ¶ [0052].) A POSA would not

have been motivated to combine Bowdish after review of Evans because Evans does not reference Bowdish, and Bowdish is directed to unrelated subject matter – it does not discuss antibody binding of C5 to block complement, or treatment of PNH, which is the subject of Evans. Nor would a POSA have associated Bowdish with Bell and Evans just because they all included some variant of the term "5G1.1" (*e.g.*, "5G1.1" in Evans and Bowdish; "h5G1.1-mAb" in Bell). As I discuss above in Section VI.D.3, a POSA would have understood that the term "5G1.1" and its derivates (*e.g.*, "h5G1.1") were terms that could refer to many different variants depending on their context. A POSA searching for information on "eculizumab" would have known that a search for "5G1.1" instead would have been overbroad, and would have captured information that was not instructive on the specific structure and specific properties of "eculizumab." For example, Evans used the term "5G1.1" to refer to the original mouse antibody from the "5G1.1" hybridoma, which a POSA would have understood was not "eculizumab." (AMG1007 at 19:47-49, Figs. 18-19, Examples 7-10 (37:34-40:29); *see* ¶ 164 above.) And I agree with Dr. Balthasar that, even when the term "h5G1.1" was used – which it was ***not*** in Bowdish – a POSA would have understood that term could refer to a variety of different antibody variants that are not "eculizumab," unless "eculizumab" was expressly specified. (ALXN2032 at 98:2-99:8, 159:1-10, 202:24-203:14.) Bell did specify that its "h5G1.1-mAb" was "eculizumab," but

then further identified it as the IgG4 antibody of Thomas (*see* Section VII.D.1 above) – which would not have motivated a POSA to look to Bowdish for its reference to "5G1.1" of Evans.

220. Even if a POSA were to have turned from Bell to Bowdish and Evans – despite there being no reason for a POSA without hindsight to have done so – nothing in the combination of those three documents would have disclosed the specific amino acid sequence recited in claim 1 of the '149 patent, or motivated a POSA to make an antibody with that sequence. Bowdish and Evans, when read alone or in combination, did not disclose the specific claimed amino acid sequence of the '149 patent, and would not have motivated a POSA to make an antibody with such a sequence, for the reasons I discussed in Section VII.C above.

3. A POSA Without the Benefit of Hindsight Would Not Have Reasonably Expected Success in Making An Antibody with the Specific Amino Acid Sequence Claimed in the '149 Patent

221. I disagree with Dr. Balthasar that a POSA would have reasonably expected success in combining Bell, Bowdish, and Evans to prepare the full-length sequence claimed in the '149 patent. (AMG1002 at ¶ 106.) In my opinion, Dr. Balthasar ignores the known complexity and unpredictability in antibody design as of March 15, 2007, including the design of humanized monoclonal antibodies; the rounds of *in vitro* and preclinical testing for such antibodies; and the challenges,

expenses and unpredictability of clinical research. (*See* Sections VI.D.2 and VI.D.4 above.)

222. Dr. Balthasar conclusively states that "a POSA would have had reason to combine the disclosures of Bell, Bowdish and Evans to arrive at the antibody of claim 1, and would have had a reasonable expectation of doing so because these three references provide complementary information relating to an anti-C5 antibody that would have required only routine techniques to combine." (*See* AMG1002 at ¶ 106.) He also conclusively states that such a combination would require only "basic molecular and cellular biology techniques." (AMG1002 ¶ 118.)

223. Dr. Balthasar is mistaken, because he equates the antibody he constructs from Bowdish and Evans with "eculizumab" as taught by Bell and the other clinical literature. But, as discussed above, that literature consistently identified "eculizumab" as a very different antibody (Thomas's IgG4 isotype antibody) than the claimed antibody sequence. Nothing in Bowdish and Evans, or Bell, would have taught or given a POSA a reasonable expectation of success that a different antibody with the specific amino acid sequence of claim 1 of the '149 patent would "bind[] C5," or whether it would be safe or provide a therapeutic benefit to patients.

224. Even if the IgG4 antibody of Thomas identified in the pre-March 15, 2007 literature as "eculizumab," and the different antibody with the sequence

claimed in the ’149 patent, shared some amino acid sequences in common, a POSA would not have reasonably expected that the two antibodies shared properties in common, because the impact of their differences in amino acid sequence could not have been reasonably predicted. (*See* Section VI.D.4 above.) A POSA would have been aware that those differences impacted by amino acid sequence could include, for example, differences in affinity and specificity for C5; differences in “fine specificity” for C5 (*i.e.*, the epitope, which as discussed below, could be critical); differences in pharmacokinetic properties; differences in safety or immunogenicity in humans; differences in therapeutic effect in humans; and differences in the ability to be formulated into a pharmaceutical composition suitable for human administration. (*See* Sections VI.D.2 and VI.D.4 above.)

225. With respect to binding interactions, a POSA would have understood that, for therapy with an anti-C5 antibody, not only were binding affinity and specificity important, but “fine specificity” (the ability of the antibody to bind the antigen at a specific epitope) was understood to be critical to therapeutic activity. For example, the following figure, contained in a review article published in 1995, illustrates the complement pathway, and highlights the target of anti-C5 monoclonal antibody therapy as understood at that time (such as with Thomas’s IgG4 isotype anti-C5 antibody):

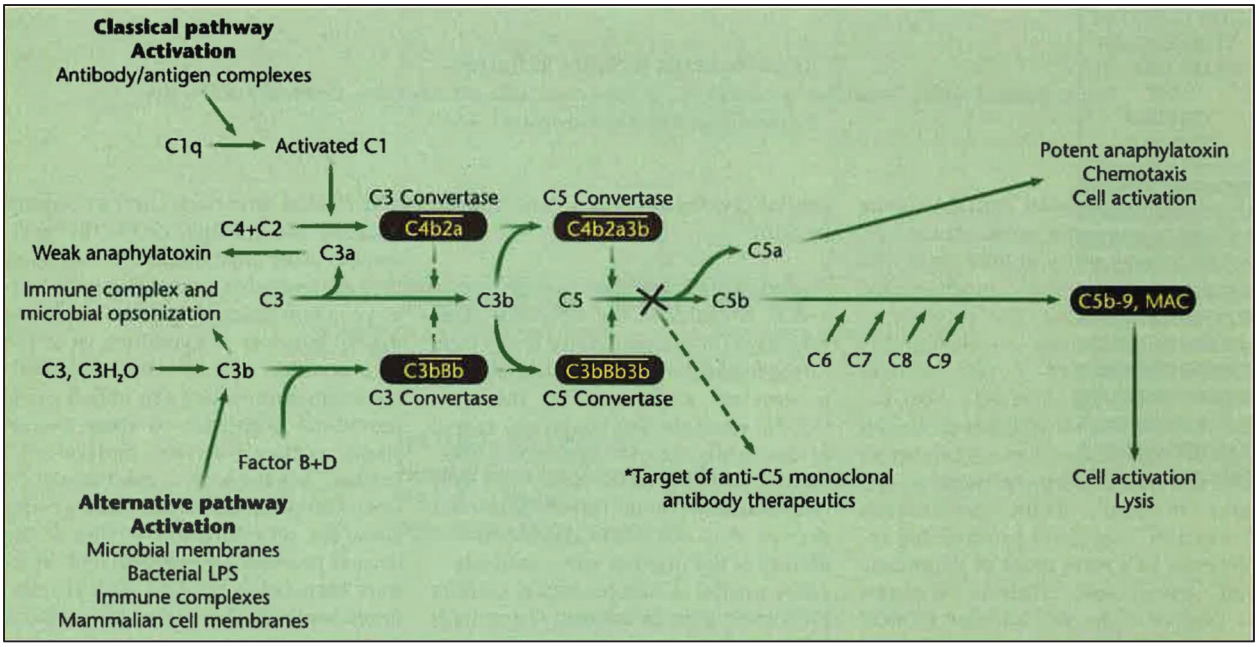

Figure 12: Mattis & Rollins (1995), Fig. 1 (AMG1039 at 840)

226. For the antibody that Dr. Balthasar constructs in hindsight from Bowdish and Evans to match the claimed sequence, a POSA would have had no information regarding any of its critical properties, including any of its binding properties, its in vitro biological assay activity (*e.g.*, in hemolytic assays), its ability to be formulated into a pharmaceutical composition, or usefulness of the antibody in treating PNH or any other condition.

227. As this figure illustrates, a POSA would have understood that it was not enough for an anti-C5 to merely bind to C5 to have its therapeutic effect, but the antibody would have to bind C5 in a way that blocks its enzymatic cleavage into C5a and C5b, and the downstream effects that result from the components C5a and C5b. For example, Thomas noted that "[a] clinically useful C5 inhibitor must

block generation of both C5a and C5b-9, as both of these molecules have potent pro-inflammatory effects," and pointed to a prior compound ("N19-8 scFv") that bound to C5 but did not effectively block C5 generation. (AMG1023 at 1398-99.)

228. The following figure illustrates how (1) a POSA prior to March 15, 2007 would have believed that there was extensive information confirming the C5 binding, *in vitro* activity, safety and efficacy for the IgG4 isotype antibody of Thomas, which the art identified as "eculizumab," and (2) how a POSA would have had no information regarding an antibody with the specific claimed sequence of the '149 patent, which was not disclosed prior to March 15, 2007 and was not reported in the literature prior to that date as having been tested *in vitro*, in animals or in humans:

Understanding of a POSA Prior to March 15, 2007

	Identified as "Eculizumab"?	Binds to C5?	Blocks C5 activity in vitro?	Treats PNH?	Suitable for formulation and human administration?
"h5G1.1 HuG4" of Thomas	YES	YES Similar binding to mouse 5G1.1	YES Same *in vitro* activity as mouse 5G1.1	YES Efficacy reported in Phase II/Phase III studies	YES No major safety/ immunogenicity issues in clinical trials
Claimed Antibody – Sequence *Not Known* Prior to March 15, 2007	NO	?	?	?	?

Figure 13: A POSA's understanding prior to March 15, 2007 of (1) the IgG4 humanized antibody of Thomas, and (2) an antibody with the then-unknown amino acid sequence claimed in the '149 patent

229. Accordingly, even if a POSA provided with Bell, Bowdish and Evans could have somehow envisioned or made an antibody with the specific claimed amino acid sequence prior to March 15, 2007, they still would not have been motivated or had a reasonable expectation of success in doing so.

E. Claim 1 of the '149 Patent Would Not Have Been Obvious Over Evans and Mueller (Ground 5)

230. Amgen's Ground 5 contends that claim 1 of the '149 patent would have been obvious over the combination of Evans and Mueller.

231. In my opinion, Amgen's Ground 5 fails, because, among other things, Amgen cannot show that each element of the claimed invention was known or obvious in view of Evans and Mueller.

1. A POSA Without the Benefit of Hindsight Would Not Have Combined Evans and Mueller to Make the Specific Claimed Antibody of the '149 Patent

232. Neither Evans nor Mueller, alone or in combination, would have disclosed the specific, full-length antibody sequence claimed in the '149 patent. (*See* Section VII.A.2.)

233. I disagree with Dr. Balthasar that a POSA would have been motivated to combine Evans and Mueller. Evans and Mueller did not reference each other, and a POSA would not have looked to Mueller to design constant regions for the humanized variable regions described in Evans because Mueller was not related to C5-binding or treatment of PNH, the subject of Evans. Mueller disclosed no experiments or data on C5 binding or blocking complement. Mueller only referenced "h5G1.1" antibodies, with either IgG4 or IgG2/G4 heavy chain constant regions, as "isotype control[s]" in studies measuring the activity of anti-VCAM antibodies. (AMG1008 at 12:27-30; AMG1031 at 442-43, 448.)

234. Additionally, a POSA would not have looked to Mueller to design constant regions for the Evans' variable regions because the prior art taught that the clinically proven anti-C5 therapy for PNH, "eculizumab," had an IgG4 isotype.

Based on the teachings of Thomas and multiple other references guiding a POSA towards the IgG4 isotype, a POSA would have had no motivation to look to Mueller to alter what a POSA would have understood to be the isotype of an already tested antibody with therapeutic effect.

235. I disagree that a POSA would have been motivated to look to Mueller because of any alleged benefits regarding its hybrid "G2/G4" constant region which, from the perspective of a POSA prior to March 15, 2007, had never been used in any antibody that had been formulated as a pharmaceutical composition or tested in a clinical trial. As disclosed by Thomas and the numerous references citing Thomas, a POSA would have understood that there was already an effective, anti-C5 antibody used for treatment of PNH – eculizumab – and that this antibody had an IgG4 isotype. (AMG1004 at 553; AMG1047 at 2559; AMG1012 at 1234; ALXN2028 at 31; AMG1005 at ¶ [0052]; AMG1021 at 1018; AMG1019 at 56; AMG1020 at 2123.) As discussed in Section VI.D.2 above, as of March 15, 2007, the process of designing a functional, humanized monoclonal antibody was known to be complex and time-consuming, involving multiple rounds of design iteration and testing. Understanding the unpredictability and expense associated with this process, including due to the potential negative impacts of isotype-switching on antibody function (*see* Sections VI.D.2 and VI.D.4 above), a POSA would not have been motivated to investigate a new isotype, and risk losing the already

established therapeutic benefit of "eculizumab," which a POSA would have understood to be an IgG4 tested in clinical trials.

236. Even if a POSA had chosen to adopt an IgG2/IgG4 hybrid isotype – which a POSA would not have considered, given the unpredictability of antibody design, and the absence of any evidence regarding how such an isotype would perform in humans or in pharmaceutical compositions – a POSA would not have necessarily selected the IgG2/IgG4 hybrid constant regions described in Mueller. As of March 15, 2007, a POSA would have understood that a hybrid IgG2/IgG4 isotype could be constructed in multiple ways, and would have had many choices for this design other than the sequence described in Mueller.

237. I disagree with Dr. Balthasar's assertion that Evans and Mueller would have been linked because both allegedly disclosed "humanized 5G1.1" or "h5G1.1." (AMG1002 at ¶ 127.) First, this statement is inaccurate because Evans did not disclose any full-length humanized 5G1.1 antibodies, but instead only humanized antibody "fragments." Again, to be clear, a POSA would have understood that the "fragments" of Evans were not the partial sequences of a full-length antibody, in the way that Evans disclosed the variable region sequences of a full-length mouse antibody. Evan's "fragments" were standalone molecules manufactured by recombinant DNA means from the ground up, and they never

belonged to, and were not pieces or components of, any larger full-length humanized antibody. (*See* Section VI.D.5 above; ALXN2032 at 228:2-16.)

238. Moreover, as explained in Section VI.D.3 above, and as Dr. Balthasar confirmed at his deposition, the term "5G1.1" could encompass multiple antibodies and antibody fragments, and a POSA would not have understood "5G1.1" as necessarily identifying "eculizumab." (ALXN2032 at 97:23-99:20, 100:3-12.) For example, Dr. Balthasar admitted he could not determine that the "h5G1.1 IgG4" antibody described in Mueller was the same as the IgG4 antibody described in Thomas. (ALXN2032 at 241:23-242:12.) Multiple prior art references used the "5G1.1" terminology, including clinical publications describing C5 binding and clinical testing of eculizumab, and a POSA would not have looked to Mueller over these other, more relevant publications.

239. In addition, Dr. Balthasar cites the alphanumeric "CO12" as providing guidance for the combination of a particular variable region disclosed in Evans with constant regions disclosed in Mueller. A POSA would not have understood "CO12" to refer specifically to the clinically-tested antibody "eculizumab." A POSA would have understood "eculizumab" to be the unique name for which Alexion had sought approval for its clinical tested antibody (*see* Section VI.D.3 above), but a POSA could not have been sure what "CO12" was or referred to. For example, "CO12" is used in Evans to describe an scFv, whereas in Mueller it refers

to a full-length antibody. (*See* AMG1007 at 44:4-13; AMG1008 at 12:34-37.) Accordingly, a POSA could not have reasonably assumed that the term always referred to the same molecule. Particularly in view of teachings in the art that eculizumab had an IgG4 isotype, a POSA would not have been guided to Mueller, or towards any combination of sequences from Evans in combination with Mueller, based on use of the undefined designation "CO12."

240. I disagree with Dr. Balthasar that "[o]verlapping sequences" would have caused a POSA to combine sequences from Mueller and Evans. (AMG1002 at ¶ 128.) Dr. Balthasar appears to base this conclusion on overlap between the light chain constant region of Mueller's 3F4 antibody and the light chain constant region from "5G1.1 scFv CO12." Dr. Balthasar fails to explain, however, why a POSA would have been motivated to combine Evans' variable region sequences with an IgG2/IgG4 constant region, given that Mueller also disclosed a second control antibody, "h5G1.1 CO12 HuG4 mAb," that a POSA would have believed to be the clinically effective "eculizumab," and would have been more likely to follow.

241. It is my opinion that a POSA would not have been able to readily combine the correct variable region sequences from Evans with Mueller's hybrid IgG2/IgG4 constant region based on the teachings of those references. Rather, Dr.

Balthasar uses significant hindsight to pick and choose sequences from Evans and Mueller to reach the specific sequence claimed in the ’149 patent.

242. For example, as Dr. Balthasar admitted at his deposition, Mueller did not indicate exactly where the IgG2/IgG4 heavy chain sequences in its anti-VCAM antibodies began or ended. (ALXN2032 at 233:22-234:4.) Dr. Balthasar uses hindsight to extract the correct constant regions from Mueller’s disclosure of a full length “3F4” anti-VCAM antibody by inferring that the correct boundaries of the IgG2/IgG4 constant regions sequences would be what remained after subtracting the 3F4 variable region, and through comparison to the claimed sequence, which would not have been available to a POSA before March 15, 2007. (*See* AMG1002 at ¶¶ 132-135; ALXN2032 at 233:3-234:4.) As Dr. Balthasar further testified, Mueller did not disclose any complete “h5G1.1” or anti-C5 binding antibody sequences. (ALXN2032 at 232:22-233:14.) Accordingly, there is no disclosure in Mueller of how the IgG2/IgG4 constant sequences he extracts would fit with any particular, undefined “h5G1.1” variable region.

243. Even if a POSA would have understood that the term “CO12” in Mueller referred to the “CO12” scFv in Evans – which Dr. Balthasar has not shown – neither Mueller nor Evans provided guidance as to exactly which sequences, or the precise extent of the sequences, a POSA would have used from the Mueller “h5G1.1 CO12 HuG2/G4” and Evans “5G1.1-scFv-CO12” constructs

to create a functional, full-length, anti-C5 antibody. Without such guidance, a POSA could have easily selected sequences that failed to correspond to the claimed antibody sequence rather than those selected by Dr. Balthasar.

244. Dr. Balthasar also does not explain why, even if a POSA were to have considered using IgG2/IgG4 constant regions described in Mueller, a POSA would have selected variable regions from Evans, rather than Thomas, to combine with those constant regions. The light chain variable region sequences described in Thomas differed from the variable regions of Evans's "5G1.1-scFv-CO12" construct at light chain position 38. (*See* AMG1023 at 1396 (Fig. 4); AMG1007 at 42-44 (Certificate of Correction).) Accordingly, a POSA that chose to follow Thomas (which Bell also cited) as opposed to Evans for the variable region sequences would not have arrived at the claimed amino acid sequence of the '149 patent.

245. A POSA as of March 15, 2007 would have had no motivation to select any of the variable regions disclosed in Evans and combine them with the IgG2/IgG4 constant regions described in Mueller, thereby potentially destroying the desirable clinical properties associated with the IgG4 isotype described in Thomas and publications citing Thomas, and understood at the time to be the isotype for "eculizumab." As discussed above, the term "CO12" would have been too ambiguous to provide guidance to a POSA to select a particular set of variable

region sequences from the multiple variable region sequences disclosed in Evans, and combine it with a particular set of constant regions disclosed in Mueller.

246. Even if a POSA had sought to combine variable sequences from Evans with constant regions from Mueller, there was no guidance in either Evans or Mueller as to how to do so – for example, neither reference provided guidance as to exactly what lengths of the disclosed variable and constant regions should be combined. (*See* ALXN2032 at 233:22-234:4.) The Mueller II publication would only have created further ambiguity regarding the boundaries of the "HuG2/G4" construct, because Mueller I contained an extra amino acid after its disclosed variable regions that does not appear in the "HuG2/G4" construct described in Mueller II. (*See* AMG1008 at 59 ("3F4 Human G2/G4 Expression Plasmid Insert Sequence" at position 138); AMG1031 at 449 (Fig. 9).)

247. It is also my opinion that Dr. Balthasar's depiction of the combination of Evans and Mueller in his Declaration reflects significant use of hindsight. For example, I disagree with Dr. Balthasar's alignments in Figures 17-18 of his Declaration (*see* AMG1002 at ¶¶ 85-86), which compare sequences from Mueller and Evans against SEQ ID NO: 2 and SEQ ID NO: 4 recited in the '149 patent. A POSA as of March 15, 2007 would not have had the guidance of the disclosure of SEQ ID NO: 2 and SEQ ID NO: 4 from the '149 patent to help select sequences to

combine from Evans and Mueller, and accordingly would not have reached the claimed full-length sequence of the ’149 patent.

2. A POSA Without the Benefit of Hindsight Would Not Have Reasonably Expected Success in Making An Antibody with the Specific Amino Acid Sequence Claimed in the ’149 Patent

248. As with Ground 4, I disagree with Dr. Balthasar that a POSA would have reasonably expected success in combining Evans and Mueller to prepare the full-length sequence claimed in the ’149 patent. (AMG1002 at ¶ 136.) In my opinion, Dr. Balthasar ignores the known complexity and unpredictability in antibody design as of March 15, 2007, including the design of humanized monoclonal antibodies; the rounds of *in vitro* and preclinical testing for such antibodies; and the challenges, expenses and unpredictability of clinical research. (*See* Sections VI.D.2 and VI.D.4 above.)

249. Dr. Balthasar conclusively states that a POSA would have had a reasonable expectation of success in making the specifically claimed antibody because it “would have required only basic molecular and cellular biology techniques.” (AMG1002 ¶ 122.) Dr. Balthasar is mistaken, because he equates the antibody he constructs from Evans and Mueller with “eculizumab” as taught by Bell and the other clinical literature. But, as discussed above, that literature consistently identified “eculizumab” as a very different antibody (Thomas’s IgG4 isotype antibody) than the claimed antibody sequence. Nothing in Mueller or

Evans would have taught or given a POSA a reasonable expectation of success that a different antibody with the specific amino acid sequence of claim 1 of the ’149 patent would “bind[] C5,” or whether it would be safe or provide a therapeutic benefit to patients.

250. Even if the IgG4 antibody of Thomas identified in the pre-March 15, 2007 literature as “eculizumab,” and the different antibody with the sequence claimed in the ’149 patent, shared some amino acid sequences in common, a POSA would not have reasonably expected that the two antibodies shared properties in common, because the impact of their differences in amino acid sequence could not have been reasonably predicted. (*See* Section VI.D.4 above.) A POSA would have been aware that those differences impacted by amino acid sequence could include, for example, differences in affinity and specificity for C5; differences in “fine specificity” for C5 (*i.e.*, the epitope); differences in pharmacokinetic properties; differences in safety or immunogenicity in humans; differences in therapeutic effect in humans; and differences in the ability to be formulated into a pharmaceutical composition suitable for human administration. (*See* Sections VI.D.2, VI.D.4 and VII.D.4 above.)

251. For the antibody that Dr. Balthasar constructs in hindsight from Mueller and Evans to match the claimed sequence, a POSA would have had no information regarding any of its critical properties, including any of its binding

properties, its *in vitro* biological assay activity (*e.g.*, in hemolytic assays), its ability to be formulated into a pharmaceutical composition, or usefulness of the antibody of the antibody in treating PNH or any other condition.

252. Accordingly, even if a POSA provided with Bell, Bowdish and Evans could have somehow envisioned or made an antibody with the specific claimed amino acid sequence prior to March 15, 2007, they still would not have been motivated or had a reasonable expectation of success in doing so.

F. Objective Indicia Support the Nonobviousness of Claim 1 of the '149 Patent

253. I understand from counsel that the nonobviousness of a patented invention may be supported by objective evidence ("objective indicia of nonobviousness").

254. In my opinion, objective evidence supports the nonobviousness of the invention claimed in the '149 patent, including: (1) a long-felt but unmet need in the industry that was satisfied by the patented invention; (2) the failure of others to develop the patented invention; (3) copying of the patented invention by others; (4) the commercial success of the patented invention; and (5) praise in the industry for the patented invention. I disagree with Dr. Balthasar's opinions to the contrary. (*See* AMG1002 ¶¶ 138-41.)

1. SOLIRIS® is the Commercial Embodiment of the ’149 Patent

255. I understand from counsel that, to be considered, objective evidence of nonobviousness should have a “nexus” to the claimed invention. Counsel has informed me that if (1) the objective evidence is tied to a specific product, and (2) that product embodies the claimed features of the claimed invention, then there is a presumption that the objective evidence has a “nexus” to the claimed invention.

256. In my opinion, the commercial product SOLIRIS® embodies the claimed features of claim 1 of the ’149 patent. Claim 1 of the ’149 patent covers an antibody with the unique amino acid sequence reflected in heavy and light chain sequences SEQ ID NOs: 2 and 4. (AMG1001 at 39:2-4.) As discussed above, it is known today (but was not known prior to March 15, 2007) that the active ingredient in SOLIRIS® (eculizumab) is an antibody comprising SEQ ID NOs: 2 and 4, which works to treat PNH and other indicated complement-mediated conditions by binding to C5 and blocking its cleavage. (*See* Section VI.E above; ALXN2032 at 262:2-19.)

257. I also understand that SOLIRIS® was originally approved for, and presently has an indication for, “[t]he treatment of patients with [PNH] to reduce hemolysis.” (ALXN2005 at 1, 2 (Section 1); ALXN2053 at 1, 3.) I further understand that SOLIRIS® is in supplied as a 300 mg single-dose vial that contains 30 ml of a 10 mg/ml solution of eculizumab, which is known today to have the

specific amino acid sequence of SEQ ID NOs: 2 and 4 recited in the ’149 patent. (ALXN2005 at 1, 5 (Section 11); ALXN2053 at 1, 21.)

258. In my opinion, the objective evidence showing the success of SOLIRIS® -- therapeutically as a long-needed, life-saving therapy, as well as commercially – has a direct nexus with the patented invention of the ’149 patent. The specially engineered anti-C5 antibody claimed by its unique amino acid sequence in claims 1 of the ’149 patent is the agent that is directly responsible for the outstanding clinical benefits that SOLIRIS® provides as the first-approved treatment for patients suffering from PNH. (ALXN2053 at 22 (Section 12.1); ALXN2030 at 1.)

259. I further note that the claimed antibody of the ’149 patent is also responsible for the clinical benefits to patients effectively treated by SOLIRIS® for several other rare conditions, including: (1) the life-threatening hemolytic condition atypical hemolytic uremic syndrome (“aHUS”); (2) the chronic autoimmune neuromuscular disease myasthenia gravis (“MG”); and (3) neuromyelitis optica spectrum disorder (“NMOSD”), a debilitating autoimmune disease of the central nervous system. (ALXN2053 at 1.)

2. SOLIRIS® Fulfilled a Long-Felt, Unmet Need for a Treatment of PNH, Which Others Failed to Satisfy

260. In my opinion, SOLIRIS® fulfilled a long-felt, unmet need for a treatment of PNH.

261. As I discuss in Section VI.A above, PNH was known prior to March 15, 2007, and is known today, as a chronic, debilitating and potentially life-threatening disease, where patients' red blood cells are constantly under attack by the body's own complement system. PNH has been referred to as the "most vicious acquired thrombophilic state known." (ALXN2050 1161-1170.) Symptoms of PNH, such as hemoglobinuria (dark urine caused by periods of acute hemolysis ("paroxysms"), chronic and potentially disabling fatigue, dysphagia, recurrent pain, and severe anemia, severely impacted patients' quality of life. (AMG1004 at 6; AMG1047 at 2559; AMG1012 at 1234.) Patients could also experience life-threatening blood clots, or "thrombosis." (AMG1004 at 6; AMG1047 at 2559; AMG1012 at 1234.)

262. SOLIRIS® was not only first anti-C5 antibody approved for any condition, but was the first treatment approved by the FDA for patients suffering from PNH. I understand that the FDA considered SOLIRIS® to be a significant medical breakthrough, granting it an expedited "Priority Review" that is reserved for drugs that are expected to have a substantial impact on the treatment of a serious disease. (ALXN2006 at 993; ALXN2030 at 1.) SOLIRIS® was also

granted "Orphan Drug" status for treatment of PNH in the FDA and the EU, recognizing that it was a much-needed therapy for a rare and untreated disease. (ALXN2019 at 1270.)

263. Prior to SOLIRIS®, there were no drugs directed to regulation of the body's complement system to treat PNH. Symptoms of PNH, such as hemoglobinuria (dark urine caused by periods of acute hemolysis ("paroxysms"), chronic and potentially disabling fatigue, dysphagia, recurrent pain, and severe anemia, severely impacted patients' quality of life. (AMG1004 at 6; AMG1047 at 2559; AMG1012 at 1234; ALXN2049 at 1-2.) Patients could also experience life-threatening blood clots, or "thrombosis." (AMG1004 at 6; AMG1047 at 2559; AMG1012 at 1234; ALXN2049 at 1-2.) Because there were no drugs directed towards regulation of complement as a treatment for PNH, patients were forced to rely on other, potentially invasive, therapies that could only address individual symptoms of the disease, such as blood transfusions. (*See* AMG1004 at 6; AMG1047 at 2559; AMG1012 at 1234.)

264. Reporting on the lack of effective treatments for PNH, Hillmen 2006, a pivotal Phase III clinical trial report for SOLIRIS® published in the New England Journal of Medicine stated, "there [was] no therapy that effectively reduce[d] intravascular hemolysis or improves the symptoms in patients with PNH" prior to SOLIRIS®. (AMG1012 at 1234; *see also* AMG1047 at 2559 ("There is no

effective treatment for the ongoing hemolysis in PNH.”).) Prior to SOLIRIS®’s approval, PNH patients were often “transfusion-dependent,” meaning that their survival depended on receiving frequent blood transfusions. (AMG1004 at 557; AMG1047 at 2559.)

265. The approval of SOLIRIS® “marked a distinct change in how physicians were able to treat patients with paroxysmal nocturnal hemoglobinuria.” (ALXN2049 at 1.) I note how that physicians specializing in hematology – those responsible for managing and treating PNH patients – have praised SOLIRIS® for its marked therapeutic benefits and improvement in the lives of PNH patients. For example, as said by Dr. Peter Hillmen, a consultant hematologist at Leeds Teaching Hospital, “[e]culizumab has dramatically changed PNH…[u]ntil eculizumab arrived there was no specific treatment for PNH apart from transfusion and occasionally bone marrow transplant.” (ALXN2049 at 1.)

266. Dr. Robert A. Brodsky, director of the division of hematology and Clara Lucas Lynn Chair in Medicine at The John Hopkins University, similarly praised eculizumab as a groundbreaking first-in-class treatment. According to Dr. Brodsky, prior to SOLIRIS®, “We had very little to offer patients. . . . Several years ago the only thing we would have had to offer [a PNH patient in crisis] was narcotics and maybe fluids. Now that eculizumab is approved, all I have to do is call down to the pharmacy and tell them that we need to start the patient on this

drug." (ALXN2049 at 2.) Others in the hematology field have offered similar testimonials and accolades for SOLIRIS®. (ALXN2050 at 1169) ("The advent of eculizumab has resulted in a dramatic improvement of the natural history of PNH patients with improvement in virtually every aspect of these patients' lives.").)

267. In sum, there is no question that the invention claim 1 of the '149 patent, as embodied by SOLIRIS®, satisfied a long-felt need, unmet need for a safe and effective means for treating the rare, debilitating, and potentially fatal blood disease, PNH, where prior existing treatment options had been limited and ineffective.

268. In my opinion, the nonobviousness of the '149 patent is also supported by the failure of others to solve the problem that was addressed by the claimed invention of the '149 patent and its commercial embodiment, SOLIRIS®. As Dr. Balthasar notes, researchers were interested in, and had published on, the concept of anti-C5 monoclonal antibody therapy, including its potential for use in the treatment of PNH, as early as the mid-1990s. (AMG1002 at ¶ 35; ALXN2032 at 262:23-264:13; AMG1039 at 2-3.) But it was not until the launch of SOLIRIS® that any solution to the severe problem of untreated PNH was introduced into the market.

269. The failure of others to develop an anti-C5 therapy, or any therapy, for the treatment of PNH over the course of more than a decade is, in my view, strong

objective evidence of the difficulty of developing monoclonal antibodies for human therapeutic use, and the nonobviousness of the claimed invention of the ’149 patent in particular.

3. SOLIRIS® Is A Commercial Success

270. SOLIRIS® was approved by the FDA on March 16, 2007 for the treatment of patients with PNH to reduce hemolysis. (ALXN2005; ALXN2006 at 993; ALXN2030 at 1.)

271. I understand that since its approval, SOLIRIS® has been commercially successful, with over $1 billion in U.S. sales each year in each of the last three years.

272. In my opinion, the commercial success of SOLIRIS® is directly linked to the claimed invention of the ’149 patent. As I explain in Section VII.F.1 above, the invention of claim 1 of the ’149 patent is coextensive with the clear therapeutic benefits of SOLIRIS® that are highly valued by physicians and their patients suffering from PNH (*see* Section VII.F.2 above).

4. Industry Praise

273. Praise in the industry for SOLIRIS® further supports my opinions on the nonobviousness of the ’149 patent. As shown above in Section VII.F.2, SOLIRIS®, the commercial embodiment of the claimed invention of the ’149 patent, has received extensive praise from the medical industry, and in particular

from the physicians who are responsible for maintaining the survival and quality of life of their PNH patients, and had few options before SOLIRIS®.

274. I also understand that Alexion has received several significant awards honoring the groundbreaking nature of its development and introduction of SOLIRIS®, including the Prix Galien USA 2008 Award for Best Biotechnology Product, and the Prix Galien France 2009 Award for Most Innovative Drug for Rare Disease. (ALXN2020; ALXN2021.)

5. <u>Copying</u>

275. I am also aware that Amgen, who is challenging the ’149 patent in this case, and other companies including Samsung Bioepis and Generium, are seeking to copy, or have already copied, eculizumab – which, as we known today, is the uniquely engineered antibody with SEQ ID NOs: 2 and 4 that is the sole active agent in SOLIRIS and the claimed pharmaceutical compositions of the ’149 patent. (ALXN2088; ALXN2090; ALXN2089.)

276. The copying by others of the claimed antibody comprising SEQ ID NOs: 2 and 4 is, in my view, further objective evidence of the nonobviousness of the ’149 patent’s invention. If it were simple to recreate the clinical benefits of properties of SOLIRIS without using the specific amino acid sequence of eculizumab (as known today) claimed in the ’149 patent, then these companies could have tried to develop their own antibodies with different amino acid

sequences not recited in the ’149 patent claims. But they did not do so. Instead, it appears that these companies took the exact amino acid sequence recited and claimed in the ’149 patent, and have tried to copy it in an effort to provide patients with the same clinical benefits provided by SOLIRIS®.

277. This supports my opinion, as explained in Sections VI.D.2 and VI.D.4 above, the process for designing a humanized, monoclonal antibody is unpredictable and requires an extensive investment of resources with no guarantee of eventual success – and these companies are more willing to copy SOLIRIS® and the claimed invention rather than develop their own unique antibodies, as Alexion did.

VIII. CONCLUSION

278. For the reasons stated above, claim 1 of the ’149 patent was not anticipated or made obvious in view of any of the art or combinations of art alleged in Amgen’s Grounds.

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

Arturo Casadevall, M.D., Ph.D

Dated: November 22, 2019

Appendix A

Sept. 17, 2019

CURRICULUM VITAE

Arturo Casadevall

PERSONAL DATA

W. Harry Feinstone Department of Molecular Microbiology and Immunology
Johns Hopkins Bloomberg School of Public Health
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Baltimore, MD 21205
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FAX: 410-955-0105
E-Mail: acasad1@jhu.edu

EDUCATION AND TRAINING

Degree/Year Institution and Field Postdoctoral Training Medical or Other Licensure

Year	Degrees/Certificate	Discipline	Institution
Undergraduate			
1979	B.A. (Magna Cum Laude)	Chemistry	Queens College, CUNY
Doctoral/graduate			
1983	M.S.	Biochemistry	New York University
1984	Ph.D.	Biochemistry	New York University
1985	M.D.	Medicine	New York University
Postdoctoral			
1985-1988	Bellevue Hospital - NYU Medical Center Internship and Residency in Internal Medicine		
1988-1989	Albert Einstein/Montefiore Medical Center Fellowship in Infectious Diseases		
1989-1991	Postdoctoral Fellowship with Dr. Matthew D. Scharff of Cell Biology, Albert Einstein College of Medicine		
1991	Cold Spring Harbor Course on Yeast Genetics		

Medical Board or Other Certification

2013-2023	American Board in Internal Medicine Certified in the Subspecialty of Infectious Diseases American Board in Internal Medicine Specialist in Internal Medicine
1990	Diplomate in the Subspecialty of Infectious Diseases
1988	Diplomate in the Specialty of Internal Medicine
1986	National Board of Medical Examiners Diploma

PROFESSIONAL EXPERIENCE *(annotate as appropriate)*

Alfred & Jill Sommer Prof. & Chair Dept of Molecular, Microbiol. & Immunol	2015-Present	JH Bloomberg Sch. of Public Health
Visiting Prof of Med. & Microbiol. & Immunol.	2015-present	Albert Einstein College of Medicine
Director, Ctr for Immunological Sciences	2013-15	Albert Einstein College of Medicine
Leo and Julia Forchheimer Professorship	2006-15	Albert Einstein College of Medicine
Chair, Dept of Microbiology & Immunology	2006-15	Albert Einstein College of Medicine
Interim Chair, Dept of Microbiol. & Immunol.	2005-06	Albert Einstein College of Medicine
Selma and Jacques Mitrani Professorship	2002-06	Albert Einstein College of Medicine

Director, Division of Infectious Diseases	2000-06	Montefiore Medical Ctr-Albert Einstein
Professor, Med. & Microbiol. & Immunology	2001-15	Albert Einstein College of Medicine
Assoc. Prof, Med. & Microbiol. & Immunol.	1996-01	Albert Einstein College of Medicine
Asst. Prof. Med. & Microbiol. & Immunol.	1992-96	Albert Einstein College of Medicine

PROFESSIONAL ACTIVITIES

American Association for the Advancement of Science
American Association of Immunologists
American Society for Clinical Investigation
American Society for Microbiology
Medical Mycology Society of the Americas
Fellow, Infectious Disease Society of America
Harvey Society
Interurban Clinical Club
Practitioner's Society
National Academy of Medicine
American Academy of Arts and Sciences

Service to Scientific Societies

1998-2000	Vice-President, New York Mycology Society
2000-02	President of New York Mycology Society
1998, 2002	Nominating committee for American Society for Microbiology (ASM) Division F officers
1998-2000	Councilor, New York Society for Infectious Diseases
2005	ASM Division F Chair Elect
2005	Nominated as Candidate for President of ASM
2006-09	Chair, ASM Career Development Committee
2004-07	ASM Abbot Award Selection Committee
2007-10	ASM Committee on Awards
2008-11	ASM Membership Election committee
2008-11	ASM Communications Committee
2008-11	ASM Minority Recruitment Committee
2008-present	ASM Minority Affairs Committee
2014-16	American Association of Immunology Minority Affairs Committee
2008-09	Medical Mycology Society of America President
2011-14	Elected Member-at-Large, AAAS Section on Medical Sciences
2014-16	American Association for Immunology Minority Affairs Committee
2012-15	Research Committee of the IDSA
2016-19	Elected Chair of the Board of Governors of the American Academy of Microbiology
2017	Elected Member of the American Academy of Arts and Sciences

Conference Organizer, Session Chair

1997 13th Congress of the International Society of Human and Medical Mycology, Parma Italy. Convener of symposium titled: Cell-mediated versus antibody mediated-protection mechanisms in fungal diseases: an ongoing dilemma.

1997 Program committee: The Fourth NIAID Workshop in Medical Mycology, Lake Tahoe

1999 Scientific Committee: Fourth International Meeting on Cryptococcus and Cryptococcosis, London

2000 Organizer, Bacteriology and Mycology Horizons for the 21st century. A symposium in honor of Dr. William Branche, NIH, Shannon Building

2001 Convener, Symposium Host defense against fungi: application toward therapeutics and vaccine development. American Society of Microbiology, Orlando

2002 Scientific Committee: Fifth International Meeting on Cryptococcus and Cryptococcosis, Adelaide, Australia
2005 Scientific Committee: Six International Meeting on Cryptococcus and Cryptococcosis, Boston
2005 United States National Organizing Committee. International Union of Microbiological Societies Meeting. Representative for the American Society of Microbiology. San Francisco
2004 IDSA Program Committee
2006 IDSA Program Chair
2006 Scientific Committee. 13th Congress of the International Society of Human and Medical Mycology, Paris, France
2006 Scientific Committee. ASM Biodefense Meeting, Baltimore
2007 Co-chair, ASM colloquium on 'The fungal kingdom: diverse and essential roles in the earth's ecosystem' Developer of Division F program for ASM General meeting
2009, 2010 ASM Colloquium Advisory Committee
2010, 2012, 2015, 2017 Organizing committee for Model Host Meeting, Crete
2011 Gordon Conference on Chemical & Biological Terrorism Defense 2011 organizing committee
2010-2013 Keystone Symposia Scientific Advisory Board
2013-16 ASM General Meeting Program Chair

Consultantships
2006-11 Consultant, Pain Therapeutics
2012-14 Pfizer Resident Professors Program

Research Program Building / Leadership
2000-06 Director, Div. of Infectious Diseases Montefiore Medical Ctr-Albert Einstein
I was responsible for: 1) supervising clinical activities of the Division of Infectious Diseases in two hospitals (Montefiore and Weiler); 2) recruitment physician scientists; 3) mentoring faculty and fellows.

2006-14 Chair, Dept of Microbiology & Immunology Albert Einstein College of Medicine
I was responsible for: 1) supervising basic science department; 2) recruited siz new faculty scientists; 3) mentored faculty, fellows and graduate students.

2015-present Chair and Alfred and Jill Sommer Professor, Bloomberg Distinguished Professor, W. Harry Feinstone Department of Molecular Microbiology & Immunology Johns Hopkins Bloomberg School of Public Health

EDITORIAL ACTIVITIES
1994 Journal of Medical and Veterinary Mycology, Guest Section Editor
1995-1997 Journal of Medical and Veterinary Mycology, Associate Editor
1995-2001 International Journal of Infectious Diseases, Editor
1997-2005 Infection and Immunity - Editorial Board
2005-2009 Infection and Immunity, Editor
1997-present Revista Iberoamericana de Micologia, Editorial Board
1996-present Emerging Infections Disease Editorial Board
2000 Section Editor-Host-Pathogen Interactions. Current Opinion in Microbiology
2004-present Expert Opinion on Emerging Drugs, Editorial Board
2005-present BMC Infectious Diseases, Editorial Board
Future Microbiology – Editorial Board
Faculty of 1000 Contributor
2003-present Nature Reviews in Microbiology – Highlights Advisor
2007-present Journal of Experimental Medicine – Editorial Board
2004-2012 Journal of Clinical Investigation – Editorial Board

2012-present Journal of Infectious Diseases Editorial Board
2010-present mBio – Founding Editor and EIC
2013 Section Editor-Host-Pathogen Interactions. Current Opinion in Microbiology

Journal Reviewer (partial list)
Antimicrobial Agents and Chemotherapy
American Journal of Epidemiology
American Journal of Pathology
Canadian Journal of Microbiology
Cell
Cellular Immunology Clinical Microbiology Reviews
Clinical Infectious Diseases
Emerging Infectious Diseases
FEMS Immunology and Medical Microbiology
Fungal Genetics and Biology
Genes and Development
Journal Clinical Investigation
Journal of Experimental Medicine
Journal of Infectious Diseases
Infection and Immunity
Immunity
Journal of Clinical Microbiology
Journal of Molecular Evolution
J. Immunological Methods
Journal of Immunology
Journal of Medical and Veterinary Mycology
J. Neuroimmunology
International Journal of Infectious Diseases
Immunity
Infectious Diseases in Clinical Practice
Lancet
Microbes and Infection
Journal of Molecular Biology
Nature Medicine
Revista Iberoamericana de Micologia
Molecular and Cellular Biology
Laboratory Investigation
Life Sciences
Microbes and Infection
New England Journal of Medicine
J. Dental Res.
Pediatric Infectious Diseases
PNAS
Trends in Microbiology

Advisory Committees, Review Groups/Study Sections
1994 National Cooperative Drug Discovery Group Study Section
1995, 1996 (Member 1996-2000); Chair 1998-2000NIH Bacteriology and Mycology 2 Study Section
1995 NSF Outside Reviewer
1998 Italian AIDS Program outside Reviewer
1996, 1997, 1998, 1999, 2003 Burroughs Wellcome Trust (United Kingdom) Outside Reviewer

1998	VA Merit Review outside Reviewer
1999	AIDS Study Section AAR1 Ad hoc Reviewer
2000	USDA SBIR Ad hoc Reviewer
1999	NIAID Strategic Plan Task Force
2000-15	St. Jude Fellowship for Pediatric Infectious Diseases
2002-07	Burroughs Wellcome Fund Advisory Committee
2001-5	NIH MIDRC (Microbiology and Infectious Diseases Research Committee) Study Section
2002	NIAID Blue Panel on Bioterrorism Research
2002-05	City University of New York Jonas Salk Award reviewer
2002	Ad Hoc Consultant to Board of Scientific Counselors for NCI
2002	Ad Hoc Consultant to Board of Scientific Counselors for NIAID
2003	National Research Council Workshop on Biotechnology and Bioterrorism
2004	Chair, Expert Panel for NIAID Invasive Aspergillosis Animal Models contract
2004	External Advisory Comm. for Pathomics Strategic Initiative, Lawrence Livermoreational Lab
2004	CDC Advisory panel on Anthrax Immune Globulin
2004-06	Scientific Advisory Board for the NIAID Immune Epitope Database contract
2004-07	Abbot Laboratories Award in Clinical and Diagnostic Immunology Selection Committee
2007-10	NIAID Board of Scientific Counselors 2005-2010; Co-Chair
2005-14	National Science Advisory Board for Biosecurity (NSABB)
2005	Chair, NAS Workshop 'NEW DIRECTIONS IN THE STUDY OF ANTIMICROBIAL THERAPEUTICS – IMMUNOMODULATORS
2005	Chair, NHLBI Working group Innate Immunity HIV & HIV-related Lung Infections
2007	Army Basic Research Review
2009	External Reviewer University of Colorado Department of Microbiology 2009
2011	Keystone Symposia SAB (ad hoc) 2009; Member 2010-2013; Cbair Immunology section
2010-16	National Academy Sci Committee on Science Technology and Law
2009-11	National Academy Sci Committee to Review the FBI Investigation of the 2001 Bacillus anthracis Mailings
2010	NIAID Genomics Blue Ribbon Panel
2012	Pioneer Award Review Panel
2012-17	Co-Chair, N IAID Board of Scientific Counselors
2013	Review of Boston University Microbiology Program
2013-17	Scientific Council Institut Pasteur, Paris, France
2014	Co-Chair, Committee on the Future Direction of the NIAID Intramural Research Program
2014	NIH Advisory Council to the Director on long-term planning for the NIH intramural research program
2014	Review of Washington University Department of Microbiology
2014	Advisory Comm to the (NIH) Director Long-Term Intramural Research Program (LT-IRP)
2015	Review of Jefferson University Department of Microbiology
2015-2016	National Academy of Sciences Comm of Federal Regulations and Reporting requirement
2015-present	National Commission Forensic Science Board, Commissioner
2016	External Advisory Committee for the Mount Sinai Department of Microbiology
2016-present	National Academy of Sciences Committee on Dual Use Research of Concern: Options for Limited Communication 2016
2018	Advisory Board Center for Integrity in Forensic Science

HONORS AND AWARDS

Awards, Honors

1979	Stanley Konkol Memorial Award
1979	Chemistry Department Service Award

1979-83	Salk Scholarship
1979-85	Medical Scientist Training Program Fellowship
1989	Montefiore Fellow of the Year Award
1990	Pfizer Postdoctoral Fellowship Award
1992	James S. McDonnell Scholar Award
1996	Burroughs Wellcome Trust Fund Developmental Therapeutics Award
1997-98	Foundation for Microbiology Lectures Program
1999	Elected to the American Society for Clinical Investigation
1999	Melini Award
2001	Leo M. Davidoff Society (for outstanding teaching)
2001	Sam Rosen Award for outstanding teaching in Pre-Clinical Curriculum
2002	Alpha Omega Alpha
2002	Elected to Fellowship in American Academy of Microbiology
2002	Burroughs Wellcome Visiting Professorship to University of Wisconsin
2004	Elected to American Association of Physicians
2005	Solomon A Berson Medical Alumni Achievement Award in Basic Science -NYU Sch. of Med
2006	Elected AAAS Fellow
2006	Maxwell L. Littman Award (mycology award)
2007	Rhoda Benham Award from Medical Mycology Society of America
2007	NIH Merit Award
2008	ASM William Hinton Award (for mentoring scientists from underrepresented groups)
2008	Albert Einstein College of Medicine Faculty Mentoring Award
2010	Elected to the Interurban Club
2014	Commencementt Speech, Albert Einstein College of Medicine graduation
2014	ASM Founders Award Distinguished Service Award
2014	Elected to Institute of Medicine of the National Academy of Sciences
2015	Delta Omega Alpha Chapter

Invited Talks, Panels

NAMED LECTURES

2008 IDSA Kass Lecturer
2009 14th Farness Lecturer, U. Arizona 2009
2010 Marshall S. Horwitz Faculty Achievement Award 2010
2010 Nelson Lecture, Bozeman, Montana
2010 Theobald Smith Lecture at Albany
2010 Arthur White Lecture, U Indiana
2011 Louis Weinstein Lecture, Tufts University
2012 Jessie Boden Lloyd Visiting Professor for 2012 and gave the Jessie Boden Lloyd Lecture in Immunology, Calgary.
2012 ICAAC Lecturer
2012 Jenner Lecture, St Georges Hospital, London
2013 Michael Apicella Lecture, Iowa
2013 NIAID Kinyoun Lecture, Bethesda, MD
2013 Faculty of Science 50th Anniversary Speaker, University of British Columbia, Vancouver CA
2014 Bernard Fields Lecture Scripps, CA
2014 American Association of Immunology Minority Affairs Committee Guest Lecture
2015 McGinnis Memorial Lecture at Duke University, NC
2015 McCollum Colloquium Speaker, Dartmouth (student invited speaker)
2015 Douglas D. McGregor Research Lecture, Cornell University, Ithaca
2016 Naff Lecture, Case Western Reserve, Cleveland
2016 Robert McGhee Distinguished Lecture, University of Arkansas

2016 Medoff Lecture, Washington University Division of Infectious Disease
2016 Karling Lecture, Mycology Society of America
2017 Harry Smith Memorial Lecturer, Birmingham, United Kingdom
2017 Westmere Lecturer, Birmingham, United Kingdom
2017 Brown-Williamson Lecturer, Queens College, The City Univeristy of New York

PUBLICATIONS (813)

1. Baker AD, **Casadevall A**, Gafney HD, Gellender M (1980) Photochemical Reactions of Tris (Oxalato) Iron III. J. Chem. Ed. 57:314-315.

2. Baker AD and **Casadevall A** (1980) A Clock Reaction with Paraquat. J. Chem. Ed. 57:515-516.

3. **Casadevall A**, Day LA (1982) DNA Packing in the Filamentous Viruses fd, xf. Pf1, and Pf3. Nucleic Acids Res. 10:2467-2481.

4**. Casadevall A**, Day LA (1983) Silver and Mercury Probing of Deoxyribonucleic Acid Structures in the Filamentous Viruses fd, If1, IKe, Xf, Pf1, and Pf3. Biochem. 22:4831-4842.

5. Putterman DG, **Casadevall A**, Boyle PD, Yang H-L, Frangione B, Day LA. (1984) Major Coat Protein and Single-Stranded DNA-binding Protein of the Filamentous Virus Pf3. PNAS 81:699-703.

6. **Casadevall A**, Day LA (1985) The Precursor Complex of the Pf3 Bacteriophage. Virology 45:260-272.
7. Day LA, **Casadevall A**, Prescott B, Thomas GJ (1988) Raman Spectroscopy of Mercury (II) Binding to Two Filamentous Viruses: Ff (fd, M13, f1) and Pf1. Biochem. 27:706-711.

8. **Casadevall A**, Day LA (1988) Thermal Differences Circular Dichroism of Pf1 Filamentous Virus and Effects of Mercury (II) Siver (I), and Copper (II). Biochem. 27:3599-3602.

9. Day LA, Marzec CJ, Reisberg SA, **Casadevall A.** (1988) DNA Packing in Filamentous Bacteriophages. Ann. Rev. Biophys. Biophysical Chem. 17:509-539.

10. **Casadevall A**, Pirofski L, Catalano MT (1990) Primary Group A Streptococcal Peritonitis in Adults. Am. J. Med. 88:5-63N-64N.

11. Pirofski L, **Casadevall A**. (1990) Mixed Staphylococcal and Cryptococcal Epidural abscess in a patient with AIDS. Rev. Infect. Dis. 12:964-965.

12. Pirofski L, **Casadevall A**, Rodriquez L, Zuckier L, Scharff MD (1991) Current State of the Hybridoma Technology. J. Clin. Immunol., 10, No. 6 (November Supplement), 5S-14S.

13. **Casadevall A**, Scharff MD (1991) The Mouse Antibody Response to Infection with *Cryptococcus neoformans*: V_H and V_L Usage in Polysaccharide Binding Antibodies. J. Exp. Med. 174:151-160.

14. Pettoello-Mantovani M, **Casadevall A**, Kollmann TR, Rubinstein A, Goldstein H. (1992) Enhancement of HIV-1 Infection by the Capsular Polysaccharide of *Cryptococcus neoformans*. Lancet 339:21-23.

15. **Casadevall A**, Mukherjee J, Devi S, Schneerson R, Robbins J, Scharff, M.D. (1992) Antibodies elicited by a *Cryptococcus neoformans* -tetanus toxoid conjugate vaccine have the same specificity as those elicited in infection. J. Infect. Dis. 165:1086-93.
16. **Casadevall A**, Dobroszycki J, Small C, Pirofski, L. (1992) *Haemophilus Influenzae* Type b Bacteremia in Adults with AIDS and at Risk for AIDS. Am. J. Med. 92:587-590.

17. **Casadevall A**, Freundlich LF, Pirofski L. (1992) Septic shock from *Pseudomonas paucimobilis*. Clin. Infect. Dis. 14:784.

18. **Casadevall A**, Freundlich L, Marsh L, Scharff MD. (1992) Extensive Allelic Variation in *Cryptococcus neoformans*. J. Clin. Microbiol. 30:1080-1084.

19**. Casadevall A**, Mukherjee J, Scharff MD. (1992). Monoclonal antibody based ELISAs for Cryptococcal polysaccharide. J. Immunol. Methods. 154:27-35.

20. Mukherjee J, Scharff MD, **Casadevall A** (1992). Protective murine monoclonal antibodies to *Cryptococcus neoformans*. Infection and Immunity 60:4534-4541.

21. Mukherjee J, **Casadevall A**, Scharff, MD (1993) Molecular characterization of the humoral responses to *Cryptococcus neoformans* infection and glucuronoxylomannan-tetanus toxoid conjugate immunization. J. Exp. Med. 177:1105-1116.

22**. Casadevall A**, Fan M. (1992) The *URA5* gene of *Cryptococcus neoformans* var. *gattii*: Evidence for a close phylogenetic relationship between *C. neoformans* var. *gattii* and *C. neoformans* var. *neoformans*. J. Gen. Appl. Microbiol. 38:491-495.

23. Spitzer, ED, Spitzer S, Freundlich L, **Casadevall A.** (1993) Persistence of initial infection in recurrent *Cryptococcus neoformans* meningitis. Lancet 341:595-596.

24. **Casadevall A**, Dobroszycki J Small C, Pirofski, L. (1993) Bacteremic *H. influenzae* type b infection and HIV. Am. J. Med. 95:119.

25. Mukherjee J, Pirofski L, Scharff MD**, Casadevall A**. (1993) Antibody mediated protection in mice with lethal intracerebral *Cryptococcus neoformans* infection. PNAS 90:3636-3640.

26**. Casadevall A**, Spitzer ED, Webb D, Rinaldi MG (1993) Susceptibilities of serial *Cryptococcus neoformans* isolates from patients with recurrent cryptococcal meningitis to Amphotericin B and fluconazole. Antimicrobial.Agents.Chemotherapy 37:1383-1386.

27. Mukherjee J, **Casadevall A**, Scharff MD (1993) Mu switch region deletion is associated with both T cell independent and T cell dependent responses. Molecular Immunology 30:1049-1055.

28. Currie BP, Freundlich LF, Soto MA, **Casadevall A** (1993) False negative cerebrospinal fluid cryptococcal latex agglutination tests for patients with culture positive cryptococcal meningitis. J. Clin. Microbiol. 31:2519-2522.

29**. Casadevall A** (1993) Cryptococcosis: The case for immunotherapy. CliniGuide to Fungal Infections 4:1-5.

30**. Casadevall A** (1993) *Cryptococcus neoformans*: Ecology and Pathogenesis. CliniGuide to Fungal Infections 4:1-5.

31. Mantovani MP**, Casadevall A**, Goldstin H, (1993) The Presence of Cryptococcal Capsular Polysaccharide Increases the Sensitivity of HIV-1 Coculture in Children. Annals New York Academy of Sciences 693:281-283.

32. Mukherjee S, Lee S, Mukherjee J, Scharff, MD, **Casadevall A** (1994). Monoclonal antibodies to *Cryptococcus neoformans* capsular polysaccharide modify the course of intravenous infection in mice. Infect. Immun. 62:1079-1088.

33. Mukherjee J, Zuckier, L, Scharff, MD, and **Casadevall A** (1994). Therapeutic efficacy of monoclonal antibodies to *Cryptococcus neoformans* Glucuaonoxylomannan alone and in combination with amphotericin B. Antimicrob. Agents Chemotherap. 38:580-587.

34. Currie BP, Freundlich LF, **Casadevall A** (1994) Restriction fragment length polymorphism analysis of Cryptococcus *neoformans* isolates from environmental (pigeon excreta) and clinical sources in New Yor*k* City. J. Clin. Microbiol. 32:1188-1192.

35. Fan M, Currie BP, Guttell R, Ragan M**, Casadevall A** (1994). The 16S-like, 5.8S, and 23-S-like rRNAs of the two varieties of *Cryptococcus neoformans*: sequence, secondary structure, and phylogenetic analysis and restriction fragment polymorphisms. J. Med. Vet. Mycology 32:163-180.

36. **Casadevall A**, Scharff, M.D. (1994). Serum Therapy Revisited: Animal models of infection and the development of passive antibody therapy. Antimicrob. Agents Chemotherap. 38:1695-1702.

37. Lee SC, Dickson DW, Brosnan CF, **Casadevall A** (1994) Human astrocytes inhibit *Cryptococcus neoformans* by a nitric oxide-mediated mechanism. J. Exp. Med. 180:365-369.

38. Wang Y**, Casadevall A** (1994) Susceptibility of melanized and non-melanized *Cryptococcus neoformans* to nitrogen and oxygen-derived oxidants. Infect. Immun. 62:3004-3007.

39. **Casadevall A**, DeShaw M, Fan M, Dromer F, Kozel TR, Pirofski L. Molecular and idiotypic analysis of antibodies to *Cryptococcal neoformans* Glucuronoxylocannan. Infect. Immun. 62:3864-3872.

40. Zebedee SL, Koduri RJ, Mukherjee J, Mukherjee S, Lee S, Sauer DF, Scharff MD, **Casadevall A** (1994) Mouse-Human chimeric Immunoglobulain G1 Chimeric antibodies with activities against *Cryptococcus neoformans*. Antimicrob. Agents Chemotherap. 38:1507-1514.

41. Ghannoum MA, Spellberg BJ, Ibrahim AS, Ritchie JA, Currie BP, Spitzer E, Edwards J, **Casadevall A** (1994) Sterol composition of *Cryptococcus neoformans* in the presence and absence of fluconazole. Antimicrob. Agents Chemotherap. 38:2029-2033.

42. Currie BP, **Casadevall A** (1994) Estimation of the prevalence of *Cryptococcus neoformans* infections among patients infected with the Human Immunodeficiency Virus in New York City. Clin. Infect. Dis. 19:1029-1033.

43. Pettoello-Mantovani M, **Casadevall A**, Goldstein H. (1994) Enhancement of HIV-1 Infectivity *in Vitro* by Capsular Polysaccharide of *Cryptococcus neoformans* and *Haemophilus influenzae.* AIDS Research and Human Retroviruses 10:1079-1087.

44. **Casadevall A**, Mukherjee J, Yuan R, Perfect J. (1994) Management of injuries caused by *Cryptococcus neoformans*-contaminated needle. Clin. Infect. Dis. 19:951-3.

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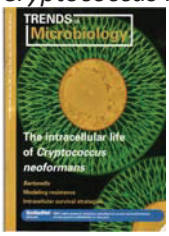

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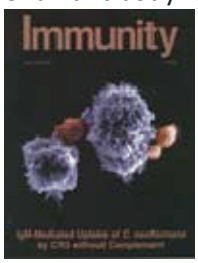

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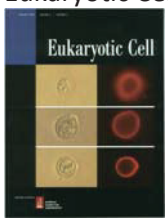

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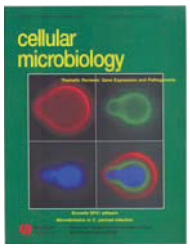

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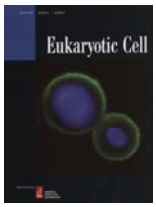

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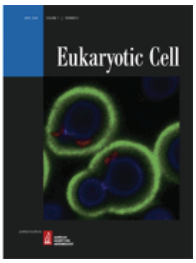

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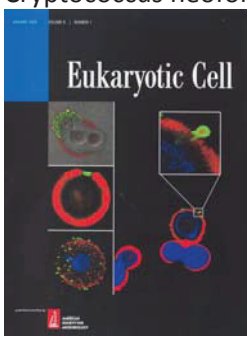

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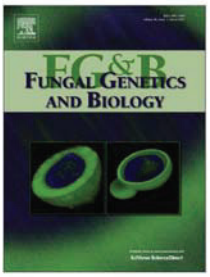

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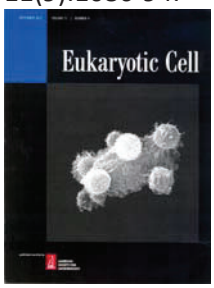

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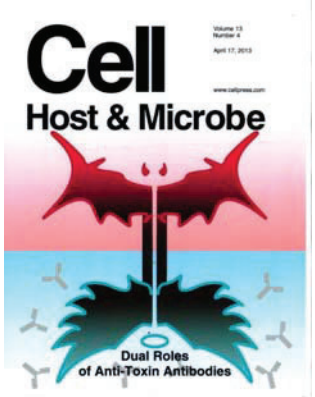

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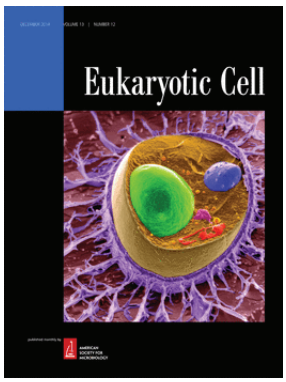

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This article was published simultaneously by the following ASM journals: Antimicrobial Agents and Chemotherapy, Applied and Environmental Microbiology, Clinical Microbiology Reviews, Infection and Immunity, Journal of Clinical Microbiology, mBio, mSphere, and mSystems.
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Voice of America interview on science fraud and misconduct
http://www.voanews.com/audio/2969854.html

Inventions, Patents, Copyrights
US Patent 6,509,325. Nosanchuk Joshua D, Casadevall Arturo, Ovalle; Rafael. Method for inhibiting melanogenesis and uses thereof.
US Patent 6,545,130. Glatman-Freedman; Aharona, Casadevall; Arturo. Monoclonal antibodies to mycobacterium tuberculosis and a modified ELISA assay
US Patent 7,402,385 B2 E. Dadachova, J.D. Nosanchuk and A. Casadevall Radiolabeled antibodies and peptides for treatment of tumors.
US Patent 7,651,689 E. Dadachova, A. Casadevall and A. Nakouzi Methods of applying ionizing radiation for therapy of infections
US Patent 7,402,385 E. Dadachova, J.D. Nosanchuk and A. Casadevall Radiolabeled antibodies for treatment of tumors
Canadian Patent No. 2,606,022; European Patent No. 1868639 (validated in France, Germany, Italy, United Kingdom; Hong Kong Patent No. HK1117035; South African Patent No. 2007/08539) E. Dadachova, A. Casadevall and H. Goldstein. Methods of applying ionizing radiation for therapy of HIV infection.
US Patent 8,187,611 B2 N. Abboud and A. Casadevall. Anti-peptide antibodies that cross react with protective antigen *of Bacillus anthracis* and uses thereof.
US Patent 8,652,827 E. Dadachova, R. A. Bryan and A. Casadevall Radiosynthesis as an alternative energy utilization process in melanized organisms and uses thereof.
US Patent 8,586,090 E. Dadachova and A. Casadevall Melanin nanoshells for protection against radiation and electronic pulses.

Applications pending
J. Achkar, A. Casadevall, R. Rosales and A. Ziegenbalg Serologic test for the rapid diagnosis of tuberculosis.
E. Dadachova, A. Casadevall, H. Strickler and R.D. Burk Radioimmunotherapy and imaging of tumor cells that express viral antigens.
E. Dadachova, A. Casadevall, M.A. Sesay, H. Damania, P.E. Smariga Radiolabeled monoclonal antibodies, methods of preparation using TCEP and uses thereof.
E. Dadachova, A. Casadevall, M.A. Sesay, H. Damania, P.E. Smariga Disposable column system for purification of radiolabeled antibodies.
E. Dadachova and A. Casadevall Methods for increasing efficacy of radioimmuno-therapy of melanoma.
JM Friedman, AJ Friedman, G. Han, MS Navati, KP Davies, MT Tar, AA Alfieri, A Casadevall, E Dadachova, HC Eisenman, Jasmin and D Spray Versatile nanoparticulate biomaterial for controlled delivery and/or containment of therapeutic and diagnostic material.
E. Dadachova, C. Gravekamp, A. Casadevall. Radiobacteria for therapy of cancer.
E. Dadachova and A. Casadevall. Oral administration of melanin for protection against radiation.

TEACHING

Mentoring
Advisees (predoctoral PhD advisor)

1996	Yulin Wang	Ph.D.
1997	Sarah Franzot	Ph.D.
1998	Lin Chen	Ph.D.

1999	Wendy Cleare	Ph.D.
1999	Nikoletta Lendvai	Ph.D.
2000	Neely Mozaffarian	Ph.D.
2000	Angel Rosas	Ph.D.
2002	Johanna Rivera	Ph.D.
2002	Reid Schwebach	Ph.D.
2003	Judith Steenbergen	Ph.D.
2004	Javier Garcia-Rivera	Ph.D.
2006	Marcela Torres	Ph.D.
2006	Luis Martinez	Ph.D.
2007	Yong Luo	Ph.D.
2008	Mauricio Alvarez	Ph.D.
2009	Magdia DeJesus	Ph.D.
2009	Carolyn Saylor	Ph.D.
2010	Cara Chrisman	Ph.D.
2011	Patricia Andrade	Ph.D.
2011	Andres Nicola	Ph.D. (University of Brasilia)
2012	Radames Cordero	Ph.D.
2012	Alena Janda	Ph.D.
2013	Jacky Chow	Ph.D.
2013	Carolina Coelho	Ph.D. (University of Coimbra)
2014	Sabriya Stukes	Ph.D.
2015	Lisa Brown	Ph.D.
2016	Anthony Bowen	Ph.D.
2017	Carlos de Leon Rodriguez	Ph.D.
2017	Eric Jung	Ph.D.
2018	Joudeh Freiji	M.D.

Postdoctoral Fellows (Name, Years, Current Position)

Brian Currie, M.D., M.P.H. 1992-1993 Assist. Dean, Clinical Research, Montefiore Med. Center; Professor, Dept. Med., Dept. Epidemiology & Population Health, Albert Einstein College of Medicine, Bronx, NY

Sushovita Mukherjee, M.D. 1992-1996 Not Available

Jean Mukherjee, D.V.M., Ph.D. 1996-1997 Assist. Prof., Dept. Biomed. Sci. (Infectious Diseases), Cummings Sch. Vet Med., Tufts University, North Grafton, MA

Aharona Freedman, M.D. 1993-1998 Assist. Clinical Prof., Dept. Pediatrics (Infectious Diseases), Albert Einstein College of Medicine, Bronx, NY

Joshua Nosanchuk, M.D. 1996-1998 Prof., Dept. Med. (Infectious Diseases), Dept. Microbio. & Immuno., Albert Einstein College of Medicine, Bronx, NY

Bettina Fries, M.D. 1997-1999 Prof., Dept. Med. (Infectious Diseases), Stony Brook University, NY

Marta Feldmesser, M.D. 1994-2001 Assoc. Prof., Dept. Med. (Infectious Diseases), Dept. Obstetrics & Gynecology and Women's Health, Dept. Microbio. & Immuno., Albert Einstein College of Medicine, Bronx, NY

Carlos Taborda, Ph.D. 1999-2002 Assoc. Prof., Dept Microbio., Institute Biomed. Sci., University of Sao Paulo, Sao Paulo, Brazil

David Goldman, M.D. 1996-2003 Assoc. Prof., Dept. Med. (Infectious Diseases), Dept. Pediatrics, Dept. Microbio. & Immuno., Albert Einstein College of Medicine, Bronx, NY

Stephanie Tucker, Ph.D. 1999-2003 Not Available

Oscar Zaragoza, Ph.D. 2001-2006 Principal Investigator, Dept. Microbio., Instituto de Salud Carlos III, Marid, Spain

Diane McFadden, Ph.D. 1999-2006 Assoc. Director, Northeast Biodefense Center, Columbia University, New York, NY
Marcela Torres, Ph.D. 2006-2007 Scientist, Regeneron Pharmaceuticals Inc., Tarrytown, NY
Helene Eisenman, Ph.D. 2003-2008 Assist. Prof., Dept. Microbio., Baruch College, New York, NY
Erin McClelland, Ph.D. 2003-2008 Assist. Prof., Dept. Basic Sci. (Microbio. & Immuno.), The Commonwealth Medical College, Scranton, PA
Susana Frases-Carvajal, Ph.D. 2004-2009 Scientist, Biotech. Lab., National Institute of Metroloy, Rio de Janeiro, Brazil
Yong Luo, M.D., Ph.D. 2007-2009 Residency, Long Island Jewish Medical Center, New Hyde Park, NY
Aviva Diamond, Ph.D. 2009-2010 Post-doc with Ian Willis, Albert Einstein College of Medicine, Bronx, NY
Emma Robertson, Ph.D. 2008-2011 Post-doc with Kirsten Nielsen, University of Minnesota, Minneapolis, MN
Andre Nicola, M.D., Ph.D. 2006-2011 Prof. and Researcher, Graduate Program in Genomic Sciences and Biotechnology, Catholic University of Brasilia, Brazil
Nareen Abboud, Ph.D. 2009-2011 Research Program Manager, Montefiore Medical Center, Bronx, NY
Monica Garcia-Solache, M.D., Ph.D. Postdoctoral fellow with Louis Rice, Brown University.
Rafael Prados, Ph.D. 2009-2014 Assist. Prof., Albert Einstein College of Medicine, New York, NY
Mary Pohl, Ph.D. 2011-2014 Senior Scientisit, Oncobiologics, Inc.
Julie Wolf, Ph.D. 2010-2015 ASM, Washington, DC
Radames Cordero, Ph.D. 2015-2017, Research Associate, Johns Hopkins University
Coelho, Carolina, Ph.D. 2015-2018, MRC Centre for Medical Mycology, University of Exeter
Maggie Wear, Ph.D. 2016-2019, Assistant Scientist, Johns Hopkins University

Awards for junior scientists in Dr. Casadevall laboratory

1995-2000	David Goldman MD	NIH Physician Scientist Award
1996-99	Rona Freedman MD	Aaron Diamond Scholarship
1999-2004	Rona Freedman MD	NIH Physician Scientist KO8 Award
1993	Wendy Cleare	American Heart Minority Scholarship
1994	Wendy Cleare	NIH Minority Award Supplement
1996-2001	Marta Feldmesser MD	NIH Physician Scientist KO8 Award
1995-97	Sarah Piancastelli Franzot (PhD student)	Fulbright Scholarship
1997-99	Joshua Nosanchuk MD	Mycology IDSA Award
1997-2002	Joshua Nosanchuk MD	NIH Physician Scientist KO8 Award
	Johanna Rivera	NIH Marc Graduate Student Fellowship.
1998-2000	Bettina Fries MD	Mycology IDSA Award (Declined due overlap)
1998-2001	Bettina Fries MD	Howard Hughes Postdoctoral Award
	Bettina Fries MD	NIH Physician Scientist KO8 Award
2001-03	Dianne McFadden PhD	Life Sciences Postdoctoral Fellowship Award
	Dianne McFadden PhD	NIH F32 Postdoctoral Award (Declined due to overlap)
	Javier Garcia	NIH Marc Graduate Student Fellowship
	Helene Eisenman PhD	NIH F32 Postdoctoral Award
	Erin McClelland PhD	Revson Fellowship
2007-12	Jacqueline Achkar MD	NIH K23 Award

Thesis committees

I have participated in dozens of PhD committees and defenses but did not keep track of these

Training grant participation

9/1/97-5/31/13 Molecular Pathogenesis of Infectious Diseases 5T32AI007506-09
NIH/NIADD
PI: Casadevall

Until 06 (training faculty) after 06 (PI)

9/1/94-6/30/21 The Molecular and Cellular Basis of Infectious Diseases (MCBID) Program
2T32AI007417-21A1
NIH/NIADD
PI: Casadevall

Teaching

Course Leader for **GRADUATE MICROBIAL PATHOGENESIS**; 6 credit graduate school course at the Albert Einstein College of Medicine Sue Golding Graduate Division which teaches the fundamentals of microbial pathogenesis. 1996 and 1999.

2000-present	Lecturer in Graduate Pathology Course - Albert Einstein College of Medicine
	Lecturer in Graduate Critical Reading Course- Albert Einstein College of Medicine
2001-present	Lecturer in Immunology Medical School Module - Albert Einstein College of Medicine
2000-2014	Lecturer in Graduate Immunology Course - Albert Einstein College of Medicine
2000-14	Lecturer in Infectious Disease Course - Albert Einstein College of Medicine
1999	Lecturer at Rockefeller Microbial Pathogenesis course
2000-14	Lecturer at NYU Microbial Pathogenesis course
2013-present	Lecturer at Columbia Ethics Course
2015	Lecturer in IBS course, Johns Hopkins Sch of Public Health
2015	Lecturer in Graduate Immunology Course, Johns Hopkins Sch of Public Health
2015	Lecturer in Biology of Parasitism, Johns Hopkins Sch of Public Health
2016	Lecturer in Graduate Immunology Course, Johns Hopkins Sch of Public Health
2016	Lecturer in Public Health Biology Course, Johns Hopkins Sch of Public Health
2016	Lecturer in Biomedical Sciences, Johns Hopkins Sch of Public Health
2017	Lecturer in Biology of Parasitism, Johns Hopkins Sch of Public Health
2017	Lecturer in Bacterial Pathogenesis course, Johns Hopkins Sch of Public Health
2017	Lecturer in Responsible Conduct of Research course, Columbia University
2017	Lecturer in Biophysics course, Johns Hopkins University
2017	Lecturer in Current Issues in Public Health, Johns Hopkins Sch of Public Health
2017	Lecturer in Evolution of Infectious Diseases, Johns Hopkins Sch of Public Health
2017	Lecturer in Graduate Immunology, Johns Hopkins Sch of Public Health
2017	Lecturer in Introduction to the Biomedical Sciences, Johns Hopkins Sch of Public Health
2017	Lecturer in Pathobiology of Disease, Johns Hopkins Sch of Medicine
2017	Lecturer in Pediatric Ground Rounds, Johns Hopkins Sch of Medicine
2017	Lecturer in Public Health Biology, Johns Hopkins Sch of Public Health
2018	Lecturer in Biology of Parasitism, Johns Hopkins Sch of Public Health
2018	Lecturer in Bacterial Pathogenesis course, Johns Hopkins Sch of Public Health
2018	Lecturer in Responsible Conduct of Research course, Columbia University
2018	Lecturer in Biophysics course, Johns Hopkins University
2018	Lecturer in Current Issues in Public Health, Johns Hopkins Sch of Public Health
2018	Lecturer in Evolution of Infectious Diseases, Johns Hopkins Sch of Public Health
2018	Lecturer in Graduate Immunology, Johns Hopkins Sch of Public Health
2018	Lecturer in Introduction to the Biomedical Sciences, Johns Hopkins Sch of Public Health
2018	Lecturer in Pathobiology of Disease, Johns Hopkins Sch of Medicine
2018	Lecturer in Parasitology, Johns Hopkins Sch of Public HEalth
2018	Lecturer in Public Health Biology, Johns Hopkins Sch of Public Health
2019	Lecturer in R3 Course, Johns Hopkins Sch of Public Health
2019	Lecturer in Responsible Conduct of Research course, Columbia University
2019	Lecturer in Biophysics course, Johns Hopkins University
2019	Lecturer in Current Issues in Public Health, Johns Hopkins Sch of Public Health

2019 Lecturer in Evolution of Infectious Diseases, Johns Hopkins Sch of Public Health
2019 Lecturer in Graduate Immunology, Johns Hopkins Sch of Public Health
2019 Lecturer in Introduction to the Biomedical Sciences, Johns Hopkins Sch of Public Health
2019 Lecturer in Pathobiology of Disease, Johns Hopkins Sch of Medicine
2019 Lecturer in Parasitology, Johns Hopkins Sch of Public HEalth
2018 Lecturer in Public Health Biology, Johns Hopkins Sch of Public Health

PART II

RESEARCH GRANT PARTICIPATION

Current Grants:

Period of Performance: 04/01/2015–01/31/2020
Title of Grant: Biology of Fungal Melanin
Grant Number: 5 R01 AI052733-13
Sponsoring Agency: NIH/NIAID
Direct Costs/yr: $131,898
PD/PI: Casadevall
Objective: The specific aims of this grant are to establish the mechanism by which melanin promotes the virulence of *C. neoformans in vivo*, to establish the protective efficacy of antibody to *Cryptococcus neoformans* melanin and laccase and the mechanism of antibody action, to investigate the molecular events of *C. neoformans* melanin biosynthesis.

Period of Performance: 08/01/2015–05/31/2020 (NCE)
Title of Grant: Synergy of Host Defense Mechanisms in the Lung
Grant Number: 5 R01 HL059842-17
Sponsoring Agency: NIH/NHLBI
Direct Costs/yr: $250,000
PD/PI: Casadevall
Objective:The goal of this project is to establish the relationship between macrophage damage and CN non-lytic exocytosis, to establish the mechanism by which host annexins contribute to CN non-lytic exocytosis, and to identify the fungal components that facilitates non-lytic exocytosis.

Period of Performance: 11/01/2016 – 10/31/2021
Title of Grant: Host inositol regulation of AIDS-Associated Cryptococcus brain infection
Grant Number: R01 AI123315
Sponsoring Agency: NIH
Direct Costs/yr: $60,000
PD/PI: Xue
Objective: Performing detailed GXM analysis using physical chemistry approaches, including using monoclonal antibody and light scattering; detection and isolation of different polysaccharide fractions under conditions with different carbon sources (inositol or glucose) for their role in BBB crossing in vitro; and potential development of protective antibody for inositol transporters.

ACADEMIC SERVICE

Institutional Administrative Appointments

1995-7 Member, Graduate Committee, Albert Einstein College of Medicine
1998-9 Member, Assistant Professor Promotion Committee, Albert Einstein College of Medicine
2005-6 Member, Search committee Dean, Albert Einstein College of Medicine
2012-3 Member, Search Committee Chair of Pediatrics, Albert Einstein College of Medicine
2013-4 Member, Search committee Chair of Medicine, Albert Einstein College of Medicine

2015 Member, Search Committee for Bloomberg Distinguished Professor, Johns Hopkins Sch Med
2015 Member, Committee Department of Biochemistry & Molecular Biology review site visit
2015 Member, Committee Sidney Kimmel Medical College of Thomas Jefferson University, Department of Microbiology & Immunology External Review

PRESENTATIONS

INVITED PRESENTATIONS (Partial List)

1992 Grand Rounds. Downstate Department of Medicine
Grand Rounds. New York University Department of Medicine
Dept of Pathology. Stony Brook University

1993 2nd International Conference on Cryptococcus and Cryptococcosis Milan, Italy

1994 Dept of Med. Grand Rounds. Newark School of Medicine
Systemic antifungals: discovery, development and applied therapeutics. New York City
Dept of Medicine. Mount Sinai School of Medicine
Dept of Medicine. Memorial Sloan-Kettering Hospital
Medical Mycology Society of the Americas, Las Vegas Meeting
New York University. Update on Fungal Infections Symposia, NY
Dept of Rheumatology. New York University, NY
Infectious Disease Society of America, Orlando, FL
International Congress of Mycology-Vancouver, Canada
2nd NIAID Workshop on Medical Mycology, Flagstaff, Az.
Dept of Medicine. Boston University.

1995 Dept of Structural Biology. Public Health Res. Institute, NYC
Dept of Medicine. Torrance-UCLA Med. Ctr., Los Angeles, CA
Dept of Medicine. Cincinnati School of Medicine. Cincinnati, OH
Dept of Microbiology. Georgetown School of Med., Georgetown, MD
Div. of Infectious Diseases. Memorial Sloan-Kettering Hospital, NYC
3rd NIAID Workshop on Medical Mycology. Big Ski, Montana
International Workshop on Molecular Pathogenesis of Fungal Infections. Wurzburg, Germany
Infectious Diseases, Duke University, Durham, NC
Dept of Chemistry, Queens College, CUNY

1996 Medical Mycology Society of the Americas, New Orleans
3rd International Conference on Cryptococcus and Cryptococcosis, Paris, France
Spanish Mycology Association, Valencia, Spain
Cuban Medical Convention, Miami Beach, Fla.
Dept of Biology, Hunter College, CUNY
ESATYBC Conference, Catskills, NY
Hunter College, NYC
NIH Workshop on The role of humoral immunity in the treatment and prevention of Infectious Diseases Washington, DC
Dept of Microbiology. Medical College of Ohio, Toledo
Merck Pharmaceuticals, Rahway, NJ
Medical Mycology Society of New York Lecture

1997 13th Congress of the International Society of Human and Medical Mycology, Parma Italy. Convener of symposium titled: Cell-mediated versus antibody mediated-protection mechanisms in fungal diseases: an ongoing dilemma.
American Society of Microbiology General Meeting Symposium, Miami, Fla.
FASEB conference, Colorado
New York Academy of Sciences Lecture
Rockefeller University
IDSA Symposium on new therapeutic strategies for fungal infections
Department of Microbiology, Oklahoma Health Sciences Center
Mount Sinai School of Medicine-Molecular Medicine Seminar Series
Woods Hole Mycology Course Lecturer
NIAID Workshop: Bridging the gap for Underrepresented Minority Research Scientists

1998 Wistar Institute
Grand Rounds Beth Israel Hospital
Department of Microbiology, Medical College of Ohio
Division of Infectious Diseases, Columbia University
Society for Industrial Microbiology Annual Meeting, Denver, Co
Department of Health, State of New York, Albany, NY
Department of Microbiology, Stony Brook University, NY
Anderson Lecture, Charlottesville, Va
Woods Hole Mycology Course Lecturer

1999 ASM Division F Divisional Lecture
Cold Spring Harbor Symposium on Microbial Pathogenesis and Host Response.
1999 Joint Committee Meeting of the US-Japan Cooperative Medical Science Program
Nelson Lecture at the University of Montana in Bozeman
Santa Fe symposia on Defense of the Brain
International Meeting on Tuberculosis, Stockholm, Sweden
ASM Symposium Millennial Challenges to Vaccines
Trudeau Institute
NHLBI Symposium on Pulmonary Immunobiology and Inflamation, NIH
U.S.-Japan Cooperative Science Program Joint Committee, Bethesda, MD
Woods Hole Mycology Course Lecture
NIAID Workshop: Bridging the gap for underrepresented Minority Research Scientists

2000 Boston University
14th Congress of the International Society of Human and Medical Mycology, Buenos Aires, Argentina. Convener of symposium titled: Vaccines and Preventive Antibodies; Also speaker on symposium on Fungal Morphogenesis and Virulence
1st Japanese Mycology Forum, Tokyo, Japan, Keynote Speaker
Foundation Lecture British Mycology Society Meeting, Stratford-upon-Avon, England
Gordon Conference on Fungal Pathogenesis
New York University - Division of Infectious Diseases
40th ICAAC. Toronto. Vaccines for the 21st Century: New disease Targets on Horizon.
Ritterson Memorial Lecture, University of Rochester Medical Center
Genome Therapeutics Corporation, Waltham, MA
Immunology for nonviral infections, Trudeau Institute, Saranac Lake
Yale University

2001 ASM Symposium Host defense against fungi: application toward therapeutics and vaccine development, Orlando, FL
New York Medical College (Division of Infectious Disease)
University of Minnesota (Department of Microbiology)
Elli Lilly, Indianapolis, IN
CSH Symposium on Microbial Pathogenesis and Host Response
22nd International Conference Chemotherapy (Amsterdam)
Fungal Therapy, NJ Medical School Symposium
Dept of Microbiology, University of Pennsylvania
National Institute of Health
Department of Microbiology, Charleston
Newark School of Medicine

2002 Keystone Symposia on Molecular and Cellular Biology
5th Conference on Cryptococcus and Cryptococcosis, Adelaide Australia
Gordon Conference on Fungal Pathogenesis
IUMS Symposium, Paris
ASM Symposium New Concepts in Physiology and Biochemistry of Pathogenic Fungi Salt Lake City, UT
Woods Hole Mycology Course Lecture
Dept of Microbiology, University of Michigan
Dept of Microbiology, University of Wisconsin
Dept of Microbiology, University of Louisiana
Division of Infectious Diseases, Albany
2nd Conference on Vaccines, Instituto Superiore di Sanita, Rome
Division of Infectious Diseases, Columbia University

2003 Dept of Genetic Medicine, Cornell University
Dept of Immunology and Virology, U. Mass Medical School
9th Congress of the European Confederation of Medical Mycology, Amsterdam, Netherlands
15th Congress of the International Society of Human and Animal Mycology
Duke University Medical School
Participant, Banbury Conference. Toward a More Unified Understanding of Infectious Disease
CSH Symposium on Microbial Pathogenesis and Host Response
15th Congress of the International Society of Human and Medical Mycology, San Antonio. Convener of symposium titled: Protective Antibodies; Also speaker on symposium on Fungal Morphogenesis and Virulence
Keynote Speaker, Mount Sinai Medical Resident Forum
NABI Pharmaceuticals, Rockville, MD
South Dakota Health Research Foundation
ACS Glycobiology Symposium, ACS Meeting, New York.
Washington University School of Medicine
Miami University, Oxford Ohio
New York University Division of Infectious Diseases
Grand Rounds Memorial Sloan Kettering

2004 Immune Compromised Host Society - Grenada, Spain
Keystone Symposia on Bioterrorism and Emerging Infectious Diseases, Keystone, CO.

Mathematical Biosciences Inst. 'Disease Models of Host-Pathogen Interactions' Columbus OH
Public Health Research Institute, Newark, NJ
ASM Meeting Symposium: 'Immune Mechanisms in Polymicrobial Infections', New Orleans
Keynote Speaker, Candida Meeting, Austin. TX
11th International Congress of Infectious Diseases, Cancun, Mexico
Mycology Unit, Pasteur Institute
Coexistence and Collisions at the Host/Microbe Interface, Burroughs Wellcome Fund, Miami, Fl.
American Phytopathological Society Mycology Committee, Anaheim, CA
New York University – Department of Microbiology
FASEB Summer Research Conference on Polysaccharides, Tucson, AZ
University of Iowa – Division of Infectious Diseases
University of Gainesville, FL -- Department of Oral Biology
Wyeth Vaccine Division, Pearl River, NY
University of Colorado Health Science Center – Dept of Microbiology
Biodefense Regional Center of Excellence meeting in Bethesda, MD
Environmental Protection Agency workshop on Virulence Factor-Activity Relationships
American Society of Tropical Medicine and Hygiene
5th Louis Pasteur Conference on Infectious Diseases, Pasteur Institute

2005 Plenary Session, Mycology Division of IUMS, San Francisco
La Jolla Institute of Allergy and Immunology
Scripps Institute
Keynote Speaker – 6th International Conference on Cryptococcus and Cryptococcosis
Focus on Fungal Infections 15, Miami, FL
ASM Biodefense Workshop
ASM Meeting Symposium, Atlanta, GA
IUMS Meeting, San Francisco
CDC Distinguished Lecturer
Koch Centennial Postulates Workshop, Berlin
Keynote Speaker, University of Michigan Public Health Retreat
New York Hospital in Queens
Maimonides Hospital
NIH, Biodefense Clinical Research Branch
FDA, Immunology Section
JASON General Meeting, San Diego
Monoclonal Antibody Meeting, Rome, Italy
Eastern Pennsylvania Branch of the American Society for Microbiology
Thaler Lecture, Aeras Global TB Vaccine Foundation
Koch's postulate - Centennial Workshop
University of Kansas, Department of Microbiology
New York Academy of Sciences
NIAID scientists from the Division of AIDS (DAIDS)

2006 Biodefense clinical research workshop (poxvirus meeting) Bethesda, MD
ASM 2006 Biodefense meeting. Panel Discussion
Grand Rounds, University of Virginia
Department of Microbiology, Drexel University
ASM 2006 Candida Meeting

International Conference on Emerging Infectious Disease, Atlanta
International Society for Human and Animal Mycoses, Paris
Maxwell L. Littman Award Lecture – New York Society for Medical Mycology
ASM General Meeting in Orlando, FL
B cell workshop Trudeau Institute
New York Medical College
Maxwell L. Littman Award Lecture – New York Society for Medical Mycology

2007 University of Texas Southwestern Medical School
University of Connecticut
Keynote speaker, XIII Fungal Genetics Conference
Berkeley U
University of California San Francisco
University of Illinois – Urbana Champaign
ASM General Meeting Toronto Canada
Princeton U - Program on Science and Global Security's Carnegie Biodefense Seminar
Keynote Speaker Second FEBS Advanced Lecture Course Human Pathogens
U. Louisville Distinguished Speaker Lecture
Harold C. Neu Conference (Chicago)
University of Wisconsin – Graduate Student Invited Speaker
University of Alabama
Keynote Speaker Merck Retreat
APUA Congress - Boston

2008 IDSA Kass Lecture
U Mass Worcester
ISDA/ICAAC
Schimelbureau Amsterdam
Gordon Conference
EPA conference on emerging threats
Brooklyn College Dept Biology Keynote Retreat Speaker
St. Louis University
VA ASM Branch Lectureship speaker
NIAID Biodefense Network Meeting
University of Minnesota

2009 Aztra Zeneca, MA, Waltham
University of Buffalo
Rio Grande ASM Branch Keynote speaker
UAB Program in Immunology
Puerto Rico ASM Branch Keynote Speaker
Critical Path for ID Therapeutics Targeting Host NIAID/DMID/OBRA Workshop
Forum on Microbial Threats (IOM)
Rinat-Pfizer, SF
IOM Committee on Science, Technology and Law
Semmering Vaccine Symposium, Vienna
University of Wurzburg symposium on Living with Pathogens
University of Pittsburg
Merck
Medical Mycology Society of New York
Novartis

Tufts University
Wadsworth Center
Intermountain ASM Branch Keynote Speaker
Southeastern ASM Branch Keynote Speaker
Florida ASM Branch Keynote Speaker
Hawaii Branch ASM Keynote Speaker
Farness Lecture, Tucson, AZ
Duke University, Dept of Genetics

2010 Keynote Speaker, First International Conference on Model Hosts, Crete Greece
Keynote Speaker European Fungal Genetics Conference, Amsterdam, Netherlands
Distinguished Faculty Seminar in Infectious Diseases, Medical College of Wisconsin
Association of Medical School Microbiology and Immunology Chairs
Forum on Microbial Threats (IOM)
Vienna Biocenter, Vienna, Austria.
Columbia University Dept of Microbiology and Immunology
Mount Sinai Dept of Infectious Diseases
8th World Congress on Trauma, Shock, Inflammation and Sepsis, Munich, Germany
ASM General Meeting, San Diego
ICCAC, Boston
IDSA, Vancouver
Ann Arbor, MI
University of Rio de Janeiro
IOM Forum on Fungal diseases
2010 Nelson Lecture, Bozeman, Montana
2010 Theobald Smith Lecture at Albany
2010 Arthur White Lecture, U Indiana

2011 Scripps Institute, La Jolla
Stanford University
Naval Research Laboratory, Washington DC
GRC Immunology of Fungal Infections (Galveston)
Mark Wilson Conference, San Juan
Keystone Symposia on Lung Immunity
University of Pennsylvania, Philadelphia
Keynote Speaker, Annual Pew Scholars Meeting, Cozumel
Keynote Speaker, GRC on Chemical and Bioterrorism Threats
Department of Microbiology and Immunology, Loyola University
Inter Urban Clinical Club
National Biodefense RCE Meeting, Denver
Cryptococcus and cryptococcosis meeting
Weinstein Lecture, Tufts
Keynote Speaker, Brazilian Microbiology Society
Keynote Speaker, Australian Microbiology Society
Bacterial Toxins Meeting, Oslo Norway
Brown University
Massachusetts General Hospital
Merck Vaccine Symposium (Toronto)
ICAAC Boston
Brown University
University of North Carolina

National Plant Diagnostic Network
Harvard University

2012 Bard College
Keystone meeting on Fungal pathogenesis and drug discovery, Santa Fe
University of Calgary
University of Tennesse
University of Puerto Rico
Pasteur Institute
2012 Pugwash Conference
Symposium on fungal pathogenesis, Oviedo, Spain
ICAAC Lecture 2012
Translational Sciecne 2012 Meeting, Washington DC
University of Arkansas
International Conference of Emerging Infectious Diseases (Emerging Fungal Diseases) Atlanta
Keynote speaker, 8th National Symposium on Recent Advances in Carborhydrate Sci. Banff, Alberta
Vanderbilt University
Duke Mycology Symposium
NYAS Symposium 'Discovering antibacterial and anticancer therapeutics in unexpected places'
Keynote speaker – Tularemia meeting, Breckenridge CO
Keynote Speaker – U Cleveland Immunology retreat
Health Research Alliance, Washington DC
Jenner Lecture, St. Georges Hospital, London

2013 Human Fungal Pathogens 2013 Nice, France
NIH Immunology Program, Bethesda MD
GRC Fungal Infections – Galveston, TX
Ohio State University, Columbus, OH
ASM Biodefense and Emerging Infectious Meeting, Washington, DC
Virginia Commonwealth University, Richmond, VA
Columbia University (Responsible conduct of research course)
Texas A&M, College Station, TX
University of Texas at San Antonio
University of Texas at Austin
University of Jena
American Society for Microbiology General Meeting, Denver, CO
BWF Meeting in Calgary, Canada
Swiss Society for Microbiology, Interlaken
Capetown, South Africa
Human Fungal Pathogens Course, Nice, France
Keynote Speaker, Donaghue Foundation
Rheumatology Division, Beth Israel Medican Center
Snowmass Microbial Pathogenesis Meeting
Kynnoun Lecture, NIAID

2014 Association of American Law Schools (AALS) Annual Meeting, New York
Bridging Lecture, International Union of Microbiological Societies 2014 meeting, Montreal, Canada

Departmet of Microbiology and Immunology, UC Davis
2014 Keystone Symposium on Prophylactic and Therapeutic Antibodies
Keynote Speaker, Israeli Society of Microbiology 2014 meeting
Keynote Speaker 17th Upstate NY Immunology Conference
Keynote Speaker International Life Sciences Institute Annual meeting, Bermuda
Keynote Speaker, The 2nd Annual Infection, Inflammation, and Immunity Summer Symposium, U Utah
Benard Fields Memorial Lecture, The Scripps, La Jolla
2014 American Association of Immunology Minority Affairs Guest Lecturer
Student Invited Speaker, Graduate Biosciences Society at the University of Virginia, Charlottesville
Invited speaker, GRC Cellular and Molucular Fungal Biology
Group on Research Advancement and Development (GRAND), AAMColleges
San Antonio Vaccine Development Center Conference titled "Infections, Immunity and Vaccines
Keynote Speaker Department of Microbiology and Molecular Genetics Retreat, UTHSCenter, Houston
Keynote Speaker Upstate NY Immunology Conference, Lake George
Keynote Speaker ASM Eastern NY Branch, Albany, NY
Symposium on Microbes in Health and Disease at Weill Medical College
Keynote Speaker XII International Meeting on Paracoccidioidomycosis, Brasilia, Brasil.

2015 14th Annual St. Jude/PIDS Pediatric Infectious Diseases Research Conf., Memphis, TN
Invited Speaker, Icahn School of Medicine at Mount Sinai, New York, NY
Invited Speaker, Albert Einstein, New York, NY
Invited Speaker, Princeton University, Princeton, NY
Invited Speaker, Baylor College, Houston, TX
Invited Speaker and Organizer, Model Host Conference, Crete, Greece
Invited Speaker, Universidad de la RepAblica, Montevideo, Uruguay
Invited Speaker, North Dakota State University, Fargo, ND
Invited Workshop Speaker, National Diversity Equity Workshop, Arlington, VA
Invited Speaker, Merck, East Brunswick, NJ
Invited Speaker, University of Kentucky, Lexington, KY
Invited Speaker, University of Maryland, Baltimore, MD
Invited Speaker, Nationwide Children’s Hospital, Columbus, Ohio
Invited Speaker, ASM Maryland Branch, Hunt Valley, MD
McCollum Colloquim, Dartmouth, Hanover, NH
Columbia University ethics course, New York, NY
NIH Director's Wednesday Afternoon Lecture Series, NIH, Bethesda, MD
Invited Speaker, East Tennessee University, Johnson City, TN
Keynote Speaker, New York Hospital Queens, New York, NY
Douglas McGregor Keynote Address, Cornell University, Ithaca, NY
McGinnis Memorial Lecture, Duke University, Durham, NC
Annual Microbial Sciences Symposium, Harvard University, Cambridge, MA
Keynote Speaker, University of California Irvine, Lake Arrowhead, CA
3rd Conference on Model Hosts, Crete, Greece

2016 Plenary Speaker, ASM Biodefense Conference, Arlington VA
Microbiology 2016, Liverpool, UK
Medoff Lecture, Washington University, St. Louis
Department of Biomedical Sciences, East Tenesse University, TN

Naff Lecture, Case Western Reserve
McGhee Lecture, University of Arkansas
National Library of Medicine
Keynote Speaker, Canadian Society of Microbiology, Toronto
Microbe 2016, American Society of Microbiology, Boston, NY
Karling Lecture, The Mycological Society of Americas, Berkeley, CA.
Emerging Infectious Disease Workshop, Madrid, Spain
15th CRG-Centre for Genomic Regulation Symposium, Barcelona, Spain
Keynote Speaker, MSGERC Meeting, Asilomar, CA
Society for Glycobiology, New Orleans
Retreat Keynote Speaker, Department of Microbiology, U Maryland
Student Invited Speaker, McMaster University, Ontario, Portland
Reed College, Portland, Oregon
Merck Sharp and Dohme
Keynote Speaker (student invited), McMaster University, Ontario, Canada
Reed College, Portland, Oregon
Merck Sharp and Dohme
Boston University, Boston, MA
Plenty Speaker, 2016 Society for Glycobiology, New Orleans, LA
University of Pittsburgh, Pittsburgh, PA

2017 Westmere Lecture, Birmingham UK
Harry Smith Lecture, Birmingham UK
Boston University, Boston, MA
Queens College, New York, NY
University of Wisconsin-Madison, Madison, WI
University of Kansas, Manhattan, KS
Plenary Speaker, 2017 International Mtg of Microbiological Society of Korea, Seoul
5th International Symposium of the Collaborative Research Centre, Tubingen, Germany
GAP Summit 2017, Georgetown University, Washington, DC
Food & Drug Administration, Silver Spring, MD
Keynote Speaker, 2017-2018 Icahn SOM at Mount Sinai Annual Retreat, Ellenville, NY
Mahmoud Ghannoum 20th Anniversay Symposium, University Hospitals Cleveland Medical Ctr, Ohio
Middle Tennessee State University, Murfreesboro, TN
National Research Council of the Swiss Nation, Berne, Switzerland
Columbia Law School, New York, New York

2018 SPRIG Speaker, National Institutes of Health, Bethesda, MD
Columbia Law School, New York, New York
Plenary Speaker, 14th European Conference on Fungal Genetics, Haifa, Israel
Speaker, Biosecurity Luncheon, The National Academies of Science, Engineering and Medicine, Washington, DC
Speaker, Israel Society for Medical Mycology, Tel Aviv, Israel
Speaker, United States Uniformed Health Services, Bethesda, MD
Speaker, University of Connecticut, Storrs, CT
Speaker, Signals of Trust Science Communicaiton, Cold Spring Harbor, Lloyd Harbor, NY
Speaker, University of Nebraska Medical Center, Omaha, NE
Speaker, Broad Institute, Cambridge, MA
Keynote Speaker, Kelsey Lecture, The University of Texas MD Anderson Cancer Center, Houston, Texas

Keynote Speaker, Van Andel Institute, Grand Rapids, MI
Speaker, Gordon Research Conference Extracellular Vesicles, Newry, ME
Speaker, Duke University MGM annual retreat, Durham, NC
Speaker,8th BMMC Conference, Dublin, Ireland
Speaker Fungal CIFAR Workshop, Toronto, Canada
Speaker, Center for Valley Fever Symposium, Sacramento, California
Speaker, Tulane University School of Medicine, New Orleans, LA
Speaker, University of Pittsburgh, Pittsburgh, PA
Speaker, Columbia Law, New York, NY
Speaker, Albert Einstein College of Medicine, New York, NY

2019 Speaker, University of Alabama, Birmingham, Alabama
Speaker, University of Maryland Baltimore, Baltimore, Maryland
Speaker, Johns Hopkins School of Medicine, Baltimore, Maryland
Speaker, Columbia Law, New York, NY
Speaker, University of Arizona, Tucson, Arizona
Speaker, Baruch College CUNY, New York, NY
Speaker, APSA, Chicago, Il
Speaker, World Vaccine Congress, Washington, DC
Speaker, University of Buffalo, Buffalo, New York
Speaker, UT Southwestern Medical Center, Dallas, TX
Speaker, Merck Research Laboratories, Boston, MA
Speaker, Rocky Mountain Laboratories, Hamilton, MT
Speaker, Melanin Workshop, Silver Spring, MD
Speaker, Cancer Biology Training Consortium, Baltimore, MD
Keynote Speaker, Queen's University of Belfast, Belfast
Speaker, Cornell University, New York, New York
Speaker, NASA Glenn Research Center, Cleveland, Ohio
Speaker, National Academies of Sciences, Engineering and Medicine, Washington, DC
Speaker, Rockefeller University, New York, New York

Appendix B

APPENDIX B

Exh. No.	Description
AMG1001	U.S. Patent No. 9,732,149 to Bell et al.
AMG1002	Declaration of Joseph P. Balthasar, Ph.D.
AMG1003	Curriculum Vitae of Joseph P. Balthasar, Ph.D.
AMG1004	Hillmen, P., et al., “Effect of Eculizumab on Hemolysis and Transfusion Requirements in Patients with Paroxysmal Nocturnal Hemoglobinuria,” N. Engl. J. Med. 350:552-559 (2004) ("Hillmen '04")
AMG1005	Bell, L. and Rother, R., “Method of Treating Hemolytic Disease,” U.S. Patent Application Publication No. 2005/0191298 A1 (filed February 3,2005; published September 1, 2005)
AMG1006	Bowdish, K., et al., “Rationally Designed Antibodies,” U.S. Patent Application Publication No. 2003/0232972 A1 (filed December 2, 2002; published December 18, 2003)
AMG1007	Evans, M., et al., “C5-Specific Antibodies for The Treatment of Inflammatory Diseases,” U.S. Patent No. 6,355,245 B1 (filed June 7, 1995; issued March 12, 2002)
AMG1008	Mueller, J., et al., "Porcine Cell Interaction Proteins," International Patent Application Publication No. WO 97/11971 A1 (filed September 27, 1996; published April 3, 1997)
AMG1012	Hillmen, P., et al., “The Complement Inhibitor Eculizumab in Paroxysmal Nocturnal Hemoglobinuria,” N. Engl. J. Med. 355:1233-1243 (2006)
AMG1014	File History for U.S. Patent No. 9,725,504 B2
AMG1015	File History for U.S. Patent No. 9,732,149 B2
AMG1016	File History for U.S. Patent No. 9,718,880 B2
AMG1018	Harlow and Lane, Chapter 2: Antibody Molecules, in Antibodies, A Laboratory Manual (1988)
AMG1019	Brekke, O. and Sandlie, I., “Therapeutic antibodies for human diseases at the dawn of the twenty-first century,” Nature Reviews Drug Discovery 2: 52-62 (2003)
AMG1020	Pierangeli, S., et al., “Requirement of activation of complement C3 and C5 for antiphospholipid antibody-mediated thrombophilia,” Arthritis & Rheumatism 52: 2120-2124 (2005)
AMG1021	Kaplan, M., “Eculizumab (Alexion),” Curr. Opin. Investig. Drugs 3:1017-1023 (2002)

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AMG1023	Thomas, T., et al., “Inhibition of Complement Activity By Humanized Anti-C5 Antibody and Single-Chain Fv.,” Molecular Immunology, 33: 1389- 1401 (1996)
AMG1028	Wang, Y., "Nebulization of Monoclonal Antibodies for Treating Pulmonary Diseases," U.S. Patent Application Publication No. 2005/0271660 A1 (filed May 11, 2005; published December 8, 2005)
AMG1029	Wang, W., et al., “Antibody Structure, Instability, and Formulation,” Journal of Pharmaceutical Sciences 96: 1-26 (2007)
AMG1031	Mueller, P., et al., “Humanized Porcine VCAM-Specific Monoclonal Antibodies With Chimeric IgG2/G4 Constant Regions Block Human Leukocyte Binding To Porcine Endothelial Cells,” Molecular Immunology 34: 441 -452 (1997)
AMG1032	Rother, R., et al., “Antibodies and Fusion Proteins That Include Engineered Constant Regions,” International Patent Application Publication No. WO 2005/007809 A2 (filed May 28 2004; published January 27, 2005)
AMG1033	Rother, R., et al., “Discovery and development of the complement inhibitor eculizumab for the treatment of paroxysmal nocturnal hemoglobinuria,” Nature Biotechnology 25: 1256-1264 (2007)
AMG1034	Tacken, P., et al., “Effective induction of naive and recall T-cell responses by targeting antigen to human dendritic cells via a humanized anti–DC-SIGN antibody,” Blood 106: 1278-1285 (2005)
AMG1039	Matis, L. and Rollins, S., “Complement-specific antibodies: Designing novel anti-inflammatories,” Nature Medicine 1: 839-842 (1995)
AMG1042	Hillmen, P., et al., "Eculizumab, a C5 complement blocking antibody, is the first therapy to reduce transfusion requirements in patients with paroxysmal nocturnal haemoglobinuria (PNH)," British Journal of Haematology - Supplement 121:87, Abstract 257 (2003)
AMG1047	Hill, A., et al., “Sustained response and long-term safety of eculizumab in paroxysmal nocturnal Hemoglobinuria,” Blood 106: 2559-2565 (2005) ("Hill '05")
ALXN2005	Original SOLIRIS® Label (2005-2007)
ALXN2006	Dmytrijuk et al., FDA Report: Eculizumab (SOLIRIS®) for the Treatment of Patients with Paroxysmal Nocturnal Hemoglobinuria, THE ONCOLOGIST, 13:993-1000 (2008)
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ALXN2008	McCloskey et al., Human Constant Regions Influence the Antibody Binding Characteristics of Mouse-Human Chimeric IgG Subclasses, IMMUNOLOGY, 88: 169-173 (1996)
ALXN2009	Torres et al., The Immunoglobulin Heavy Chain Constant Region Affects Kinetic and Thermodynamic Parameters of Antibody Variable Region Interactions with Antigen, J. OF BIOL. CHEM., 282(18): 13917–27 (2007)
ALXN2010	Janda et al., Ig Constant Region Effects on Variable Region Structure and Function, FRONT.MICROBIOL., 7(22): 1-10 (2016)
ALXN2011	Pritsch et al., Can Immunoglobulin CH1 Constant Region Domain Modulate Antigen Binding Affinity of Antibodies?, J. CLIN. INVEST., 98(10): 2235-43 (1996)
ALXN2012	Pritsch et al., Can Isotype Switch Modulate Antigen-Binding Affinity and Influence Clonal Selection?, EUR. J. IMMUNOL., 30: 3387-95 (2000)
ALXN2013	McLean et al., Isotype Can Affect the Fine Specificity of an Antibody for a Polysaccharide Antigen, J. OF IMMUNOLOGY, 169: 1379–86 (2002)
ALXN2014	Greenspan et al., Complementarity, Specificity and the Nature of Epitopes and Paratopes in Multivalent Interactions, IMMUNOL. TODAY, 16(5): 226-30 (1995)
ALXN2015	Radbruch, et al., Drastic Change in Idiotypic but Not Antigen-Binding Specificity of an Antibody by a Single Amino-Acid Substitution, NATURE, 315(6): 506-508 (1985)
ALXN2017	Hawkins et al., The Contribution of Contact and Non-contact Residues of Antibody in the Affinity of Biding to Antigen: The Interaction of Mutant D1.3 Antibodies with Lysozyme, J.MOL. BIO., 234: 958-964 (1993)
ALXN2019	Ricklin & Lambris, Complement-Targeted Therapeutics, NATURE BIOTECHNOLOGY, 25(11); 1265-1275 (2007)
ALXN2020	Alexion Press Release, Alexion's Soliris® Receives 2008 Prix Galien USA Award for Best Biotechnology Product, September 25, 2008, available at https://news.alexion.com/press-release/company-news/alexions-soliris-receives-2008-prix-galien-usa-award-best-biotechnology-p (last visited May 15, 2019)

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ALXN2021	BusinessWire, Alexion's Soliris® Receives 2009 Prix Galien France for Most Innovative Drug for Rare Disease, June 10, 2009, available at https://www.businesswire.com/news/home/ 20090610005826/en/Alexions-Soliris®-Receives-2009-Prix-Galien-France (last visited May 15, 2019)
ALXN2023	Curriculum Vitae of Arturo Casadevall
ALXN2028	Hill, et al., Erythropoietin treatment during complement inhibition with eculizumab in a patient with paroxysmal nocturnal hemoglobinuria, THE HEMATOLOGY JOURNAL, 31-33, 2007
ALXN2029	Points to Consider in the Manufacture and Testing of Monoclonal Antibody Products for Human Use, U.S. Dept. of Health and Human Services, Food and Drug Admin., 1997
ALXN2030	3/16/2007 FDA Approves Alexion's Soliris™ for all Patients with PNH
ALXN2031	Janeway, et al.,Immunobiology, The Immune System in Health and Disease, Appendix I: Immunologists' Toolbox, 6th ed. 2005
ALXN2032	Deposition Transcript of Joseph P. Balthasar, Ph.D., Amgen, Inc. v. Alexion Pharmaceuticals, Inc., IPR No. 2019-00740 (Oct. 23, 2019)
ALXN2033	Kim, et al., Antibody Engineering for the Development of therapeutic Antibodies, MOLECULES AND CELLS, Vol. 20, No. 1, pp. 17-29, 2005
ALXN2034	Hwang, et al., Immunogenicity of engineered antibodies, SCIENCE DIRECT, 17 Jan. 2005
ALXN2035	Shepherd, et al., Monoclonal Antibodies, Oxford University Press, pp. 58-5 (Appendix) 2000
ALXN2036	Lo, Benny K., Antibody Engineering Methods and Protocols, METHODS IN MOLECULAR BIOLOGY, Vol. 248 2004
ALXN2037	Welt, et al., Phase I Study of Anticolon Cancer Humanized Antibody A33, CLINICAL CANCER RESEARCH, 2003
ALXN2038	Haller, et al., Safety Issues Specific to Clinical Development of Protein Therapeutics, NATURE PUBLISHING GROUP, 2008
ALXN2039	Torres, et al, Exchanging Murine and Human Immunoglobulin Constant Chains Affects the Kinetics and Thermodynamics of Antigen Binding and Chimeric Antibody Autoreactivity, PLOS ONE, 2007
ALXN2040	Torres, et al., Variable-Region-Identical Antibodies Differing in Isotype Demonstrate Differences in Fine Specificity and Idiotype, JOURNAL OF IMMUNOLOGY, 2005

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ALXN2042	Mathieu, Barbara G., Clinical Testing of Biologically Derived Therapeutics, Biologics Development: A Regulatory Overview, 3d ed., 2004
ALXN2043	Andersen, et al,, Production technologies for monoclonal antibodies and their fragments, SCIENCE DIRECT, 2004
ALXN2044	Chadd, et al., Therapeutic antibody expression technology, 2001
ALXN2045	2007 USP Dictionary of USAN and International Drug Names
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ALXN2049	HemOnc Today, Eculizumab's triumph over PNH, https://www.healio.com/hematology-oncology/news/print/hemonc-today/%7B01f97d7b-36b4-4462-aab4-02918370caa1%7D/eculizumabs-triumph-over-pnh (Aug. 25, 2008)
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ALXN2051	Foote, Jefferson and Winter, Greg, "Antibody Framework Residues Affecting the Coformation of the Hypervariable Loops," J. Mol. Biol., 224:487-449 (1992)
ALXN2052	Xiang, Jim et al., Framework Residues 71 and 93 of the Chimeric B72.3 Antibody are Major Determinants of the Conformation of Heavy-chain Hypervariable Loops," J. Mol. Biol. 253:385-390 (1995)
ALXN2053	June 2019 Soliris Label
ALXN2054	Alexion Press Release, "Alexion Pharmaceuticals Submits Biologics License Application for Soliris(TM) (eculizumab)," (Sept. 20, 2006)
ALXN2055	Alexion Press Release, "Alexion Submits Market Authorization Application for Soliris(TM) (eculizumab) in the Treatment of Paroxysmal Nocturnal Hemoglobinuria to the European Medicines Agency," (Sept. 26, 2006)
ALXN2075	GenScript, "Final Report – Antibody Full Length Sequencing of Hybridoma 5G1.1 T175," Order Number: U856UEK140-1 (Nov. 15, 2019)
ALXN2086	Stebbings, R., *et al.,*"After TGN1412: Recent developments in cytokine release assays," J. of Immunotoxicology, 10(1):75-82 (2013)
ALXN2088	Amgen Biosimilar Pipeline Approved Products (2019)

Exh. No.	Description
ALXN2089	Generium Pharmaceutical, "Elizaria" Product (2019)
ALXN2090	Samsung Bioepis - Biosimilar candidates and Novel biologic (2019)
ALXN2091	Harlow and Lane, Chapter 15: Antibody Molecules, in Antibodies, A Laboratory Manual, 622-25 (1988)