

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

AMGEN INC.
Petitioner,

v.

ALEXION PHARMACEUTICALS, INC.
Patent Owner.

Case No. IPR2019-00739
Patent: 9,725,504

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

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ALXN2022
IPR2023-00999

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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 claims 1-10 of United States Patent No. 9,725,504 (“the ’504 patent”) on seven “Grounds” alleging that claims 1-10 of the ’504 patent are unpatentable as anticipated or obvious. I understand that the PTAB’s Institution Decision regarding the ’504 patent (Paper No. 15) is not a final decision, and is based on the PTAB’s “preliminary review of the

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.

challenged claims, the asserted prior art, and the opinions set forth in the as-yet-unrebutted Balthasar Declaration.” (Institution Decision, Paper No. 15, at 64.)

4. I have reviewed and considered Amgen’s Petition regarding the ’504 patent (Paper No. 2) (“Amgen’s Petition”), the Declaration of Dr. Joseph P. Balthasar regarding the ’504 patent (AMG1002) (“Balthasar Declaration”), the Institution Decision regarding the ’504 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 claims 1-10 of the ’504 patent are anticipated or obvious in view of any of Amgen’s seven “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 on at least one claim under one Ground: alleged obviousness of claims 1 in view of Bell (AMG1005), Bowdish (AMG1006), and Evans (AMG1007) (“Ground 4”).² (Paper No. 15 at 37-48.) For the reasons I explain in

² I understand that Amgen’s Ground 4 is directed to claims 1-5 and 7-10 of the ’504 patent – but, for in its decision to institute this IPR in view of Ground 4, the Board “focus[ed] on claim 1,” and noted that Alexion had “non-trivial

this Declaration, it is my opinion that Amgen has failed to show that claims 1-5 or 7-10 of the '504 patent are unpatentable under this Ground, or that claim 6 is unpatentable under the combination of Bell, Wang (AMG1028), Bowdish, and Evans ("Ground 5").

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 five other Grounds: (1) alleged anticipation of claims 1-3 and 7-10 by Hillmen '04 (AMG1004) ("Ground 1"), (2) alleged obviousness of claims 4 and 5 in view of Hillmen '04 in combination with Bell ("Ground 2"), (3) alleged obviousness of claim 6 in view of Hillmen '04 in combination with Bell and Wang ("Ground 3"); (4) alleged obviousness of claims 1-5 and 7-10 in view of Bell, Evans, and Mueller (AMG1008) ("Ground 6"); and (5) alleged obviousness of claim 6 in view of Bell, Evans, Mueller (AMG1008) and Wang ("Ground 7"). (Paper No. 15 at 28-36, 52-54.) For the reasons I explain in this Declaration, it is my opinion that Amgen has failed to show that claims 1-10 of the '504 patent are unpatentable under any of these Grounds.

arguments" regarding the nonobviousness of claim 5 under Ground 4 and claim 6 under Ground 5. (Paper No. 15 at 37, 48 & n.20.)

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) (ALXN 2013), 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), 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 experienced discussed above, and further reflected in my curriculum vitae, I am an expert in the design, development, evaluation, and testing (including biological and physicochemical 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** (ALXN2023.)

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 in 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 ’504 patent.

26. I understand that, in its Institution Decision, the Board accepted that a POSA in the field of the ’504 patent would typically have “an M.D. and/or Ph.D. in immunology, biochemistry, cell biology, molecular biology, pharmaceuticals, 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 15 at 20-21.) 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 therein. I submit this Declaration in order to respond to opinions offered by Dr. Balthasar.

28. It is my opinion that claims 1-10 of the '504 patent are not anticipated by, or obvious in view of, any of the alleged prior art or combinations of prior art at issue in Amgen's seven "Grounds" in this proceeding.

29. I disagree with Dr. Balthasar's conclusions that claims 1-3 and 7-10 of the '504 patent was anticipated by Hillmen '04 (AMG1004) (as alleged in "Ground 1"). In my opinion, Hillmen '04 did not disclose each and every element recited in claim 2 as arranged in the claim, whether expressly or inherently.

30. I further disagree with Dr. Balthasar's conclusions that (1) claims 4 and 5 were obvious in view of the combination of Hillmen and Bell (AMG1005) ("Ground 2"); (2) that claims 1-5 and 7-10 were obvious in view of the combinations of Bell, Bowdish (AMG1006) and Evans (AMG1007) ("Ground 4") or the combination of Bell, Evans, and Mueller (AMG1008) ("Ground 5"), or (3) that claim 6 was obvious in view of the combinations of Hillmen '04, Bell, and Wang (AMG1028) ("Ground 3"), the combination of Bell, Bowdish, Evans, and Wang ("Ground 5"), or the combination of Bell, Evans, Mueller, and Wang ("Ground 7"). 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 claims 1-10 of the ’504 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 ’504 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 ’504 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

'504 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 '504 Patent

48. In forming my opinions, I have reviewed the '504 patent, titled "Treatment of Paroxysmal Nocturnal Hemoglobinuria Patients by an Inhibitor of Complement."

49. I understand from counsel that the '504 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 is the earliest priority date for the '504 patent.

50. I understand that the '504 patent reflects the work of Alexion scientists in developing SOLIRIS[®] as a safe and effective treatment for paroxysmal nocturnal hemoglobinuria ("PNH"). The '504 patent has ten claims directed to methods of treating a patient suffering from PNH by administering a pharmaceutical composition, as follows:

1. A method of treating a patient suffering from paroxysmal nocturnal hemoglobinuria (PNH) comprising administering to the patient a pharmaceutical composition comprising an antibody that binds C5, wherein the antibody comprises a heavy chain consisting of SEQ ID NO: 2 and a light chain consisting of SEQ ID NO: 4.

2. The method of claim 1, wherein the pharmaceutical composition is administered by intravenous infusion.
3. The method of claim 1, wherein the antibody is administered to the patient at a dosage level of between 5 mg per kg and 50 mg per kg per patient per treatment.
4. The method of claim 1, wherein the pharmaceutical composition is in a single unit dosage form.
5. The method of claim 4, wherein the single unit dosage form is a 300 mg single unit dosage form.
6. The method of claim 1, wherein the pharmaceutical composition comprises a 300 mg single-use formulation of 30 ml of a 10 mg/ml sterile, preservative free solution.
7. The method of claim 1, wherein the patient is anemic.
8. The method of claim 1, wherein the patient is dosed as follows: 600 mg of the antibody via intravenous infusion every 7 ± 1 days for 4 doses; followed by 900 mg of the antibody via intravenous infusion 7 ± 1 days later; followed by a maintenance dose of 900 mg of the antibody via intravenous infusion every 14 ± 2 days.
9. The method of claim 1, wherein administration of the antibody results in an immediate and sustained decrease in mean levels of lactate dehydrogenase (LDH).
10. The method of claim 9, wherein the immediate decrease occurs within one week of administration of the antibody.

(AMG1001 at 39:1-32.)

51. Claims 1-10 of the '504 patent recite 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 claims 1-10, and would not have known of any other monoclonal antibody having that specific sequence.

52. The '504 patent also provides data from the Phase III, placebo-controlled “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.) One of the efficacy parameters assessed in the TRIUMPH study as reported in the '504 patent was mean levels of lactate dehydrogenase (“LDH”) – which the '504 patent describes as “a biochemical marker of hemolysis in PNH.” As reported in the '504 patent, patients receiving the claimed antibody (which the '504 patent identified as eculizumab) showed an “immediate (one week) and sustained decrease in mean levels of LDH.” (AMG1001 at 22:23-26; *see also* AMG1001 at 27:1-6 (“Lactate dehydrogenase, a biochemical marker of hemolysis in PNH, was immediately and consistently decreased in all eculizumab-treated patients.”).) The '504 patent

points to Figure 1A as illustrating the “immediate and sustained decrease” in mean levels of LDH achieved by the specific claimed antibody of the '504 patent:

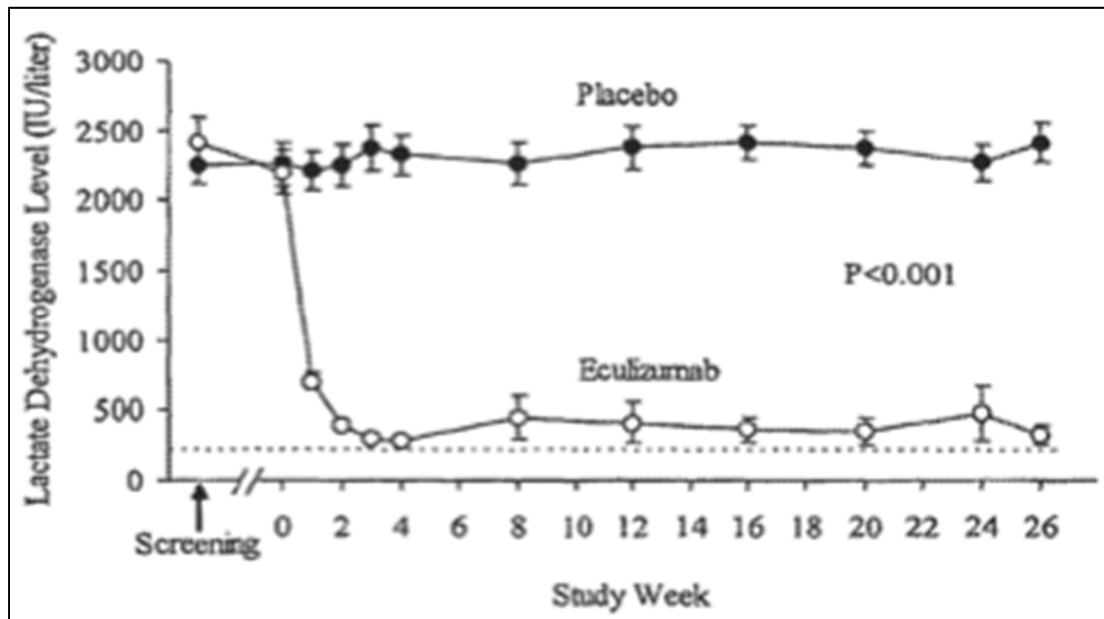


Figure 1: Figure 1A from the '504 patent (AMG1001)

53. The '504 patent also describes use of eculizumab in pharmaceutical compositions, including a “300 mg single-use formulation of 30 ml of a 10 mg/ml sterile, preservative free solution.” (AMG1001 at 4:21-24, 5:21-25, 16:30-33.).)

54. Claims 1-10 of the '504 patent reflect the purpose of the '504 patent's invention: the development of a humanized monoclonal antibody, and pharmaceutical compositions of that antibody, that can block cleavage of C5 and be used as a safe and effective therapy for patients with PNH.

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

55. 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.)

56. 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.”).) 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.)

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

58. 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

59. 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.

60. 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.)

61. 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.)

62. 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. (*Id.*)

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

1. General Antibody Structure

63. 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.)

64. 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.

65. 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.)

66. 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.)

67. 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.)

68. 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.)

69. Figure 1 (adopted from Amgen’s Petition) depicts the basic structure of a full-length, intact IgG antibody in a simplified, 2-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).

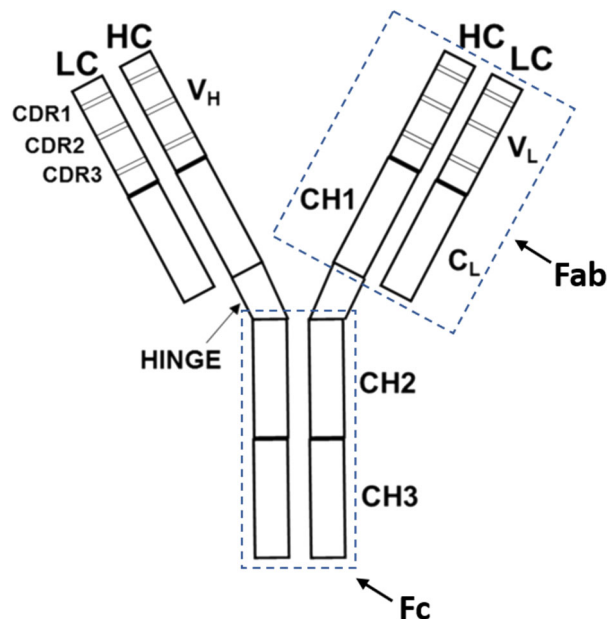


Figure 2: Basic structure of an IgG antibody (simplified 2-dimensional depiction)

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

70. 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.)

71. 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.)

72. 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.)

73. 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.)

74. 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, (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).)

75. 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.)

76. 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. (ALXN2023 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.)

77. 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.)

78. 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.”); *see also*; 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%).)

79. 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.)

80. 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.

81. 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).)

82. 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.)

83. 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.

84. 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 1310.) 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 reactivity with host tissues. (ALXN2009 at 13917, 13924-25; ALXN2039 at 4; *see also* ALXN2038 at 626.)

85. 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.

86. 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.

87. 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 1997 FDA Points to Consider 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.

88. 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.)

89. 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 to recruit 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. But such clinical trials were necessary, because as of that date, there was no way to reasonably predict a monoclonal antibody's therapeutic effects or safety in humans without actually performing human administration in a controlled setting.

90. 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.)

91. And, even for use in an experimental monoclonal antibody 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 the likely FDA would not even permit experimental human testing to go forward.

92. 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.)

93. 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.) An “Fab” fragment, containing the complete light chain, but

only the V_H 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 2-dimensional diagram.

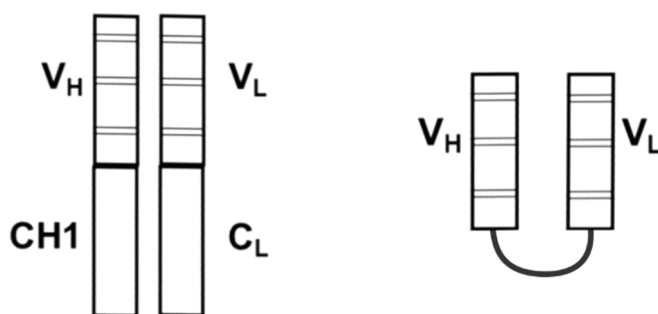


Figure 3: Left: Basic structure of an “Fab” (fragment antigen binding)

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

94. 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; AMG2007 at 107; ALXN2044 at 189; ALXN2043 at 456.) Further, as discussed in Section VI.D.4 below, 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

95. 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.

96. 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.)

97. 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.)

98. 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.

99. 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.)

100. 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." (*Id.*)

101. 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.)

102. 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 '504 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 of the pharmaceutical compositions recited in claims 1-10 of the '504 patent.

103. 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.

104. 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

105. 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.)

106. 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 ’504 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.

107. 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.*, ALXN2051 at 487; ALXN2052 at 253.) As discussed in Section IV.B.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.)

108. 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.) As discussed below in this Section, 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. (ALXN2010.)

109. 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.)

110. 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.)

111. 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.)

112. 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 fused to different human IgG constant regions. (*Id.*) 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.)

113. 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. (ALXN2040 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.”).)

114. Based on publications such as McClean, Greenspan, Pritsch 1996, and McCloskey, 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.)

115. 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). (*Id.*) 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.

116. 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-idiotypic” 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”); *see also* ALXN2037 at 1343-44; ALXN2038 at 624-26).)

117. 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.)

118. 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

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 at 1111-12, 1117-18.)

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”); *see also* ALXN2037 at 1343-44; ALXN2038 at 624-26.)

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

119. 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.)

120. 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.

121. 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).

122. 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 ¶¶ [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. (6/20/2006 Alexion Press Release; *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.

123. 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

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 ¶ 47; ALXN2032 at 242:21-243:4.)

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 <i>Thomas</i> , 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. . . .”
Hill 2005 (AMG1047) at 2559, reporting on a Phase II clinical trial for PNH, and citing <i>Thomas</i> , 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 <i>Thomas</i> , 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 <i>Thomas</i> , Ref No. 6	“Eculizumab is a novel humanized monoclonal antibody directed against the complement protein C5. ^{6”}

Exhibit	Statement Identifying “Eculizumab” as the IgG4 Humanized Antibody of Thomas
Bell (AMG1005) at [0052], in a patent application describing results of Phase II clinical trials for PNH, citing <i>Thomas</i>	“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 [<i>Thomas</i>], 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.”
Kaplan (AMG1021) at 1018, in a review article discussing development of “eculizumab,” citing <i>Thomas</i> , 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 <i>Thomas</i>	“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 <i>Thomas</i>	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).”

124. 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.)

125. 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.)

126. 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.)

127. 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.)

Evans

(15) United States Patent
Evans et al.

(15) Patent No.: US 6,355,245 B1
(15) Date of Patent: Mar. 12, 2002

(35) CLASSIFICATION: C07K 16/00, C07K 231/00, C07K 231/05, C07K 231/10, C07K 231/15, C07K 231/20, C07K 231/25, C07K 231/30, C07K 231/35, C07K 231/40, C07K 231/45, C07K 231/50, C07K 231/55, C07K 231/60, C07K 231/65, C07K 231/70, C07K 231/75, C07K 231/80, C07K 231/85, C07K 231/90, C07K 231/95, C07K 231/100, C07K 231/105, C07K 231/110, C07K 231/115, C07K 231/120, C07K 231/125, C07K 231/130, C07K 231/135, C07K 231/140, C07K 231/145, C07K 231/150, C07K 231/155, C07K 231/160, C07K 231/165, C07K 231/170, C07K 231/175, C07K 231/180, C07K 231/185, C07K 231/190, C07K 231/195, C07K 231/200, C07K 231/205, C07K 231/210, C07K 231/215, C07K 231/220, C07K 231/225, C07K 231/230, C07K 231/235, C07K 231/240, C07K 231/245, C07K 231/250, C07K 231/255, C07K 231/260, C07K 231/265, C07K 231/270, C07K 231/275, C07K 231/280, C07K 231/285, C07K 231/290, C07K 231/295, C07K 231/300, C07K 231/305, C07K 231/310, C07K 231/315, C07K 231/320, C07K 231/325, C07K 231/330, C07K 231/335, C07K 231/340, C07K 231/345, C07K 231/350, C07K 231/355, C07K 231/360, C07K 231/365, C07K 231/370, C07K 231/375, C07K 231/380, C07K 231/385, C07K 231/390, C07K 231/395, C07K 231/400, C07K 231/405, C07K 231/410, C07K 231/415, C07K 231/420, C07K 231/425, C07K 231/430, C07K 231/435, C07K 231/440, C07K 231/445, C07K 231/450, C07K 231/455, C07K 231/460, C07K 231/465, C07K 231/470, C07K 231/475, C07K 231/480, C07K 231/485, C07K 231/490, C07K 231/495, C07K 231/500, C07K 231/505, C07K 231/510, C07K 231/515, C07K 231/520, C07K 231/525, C07K 231/530, C07K 231/535, C07K 231/540, C07K 231/545, C07K 231/550, C07K 231/555, C07K 231/560, C07K 231/565, C07K 231/570, C07K 231/575, C07K 231/580, C07K 231/585, C07K 231/590, C07K 231/595, C07K 231/600, C07K 231/605, C07K 231/610, C07K 231/615, C07K 231/620, C07K 231/625, C07K 231/630, C07K 231/635, C07K 231/640, C07K 231/645, C07K 231/650, C07K 231/655, C07K 231/660, C07K 231/665, C07K 231/670, C07K 231/675, C07K 231/680, C07K 231/685, C07K 231/690, C07K 231/695, C07K 231/700, C07K 231/705, C07K 231/710, C07K 231/715, C07K 231/720, C07K 231/725, C07K 231/730, C07K 231/735, C07K 231/740, C07K 231/745, C07K 231/750, C07K 231/755, C07K 231/760, C07K 231/765, C07K 231/770, C07K 231/775, C07K 231/780, C07K 231/785, C07K 231/790, C07K 231/795, C07K 231/800, C07K 231/805, C07K 231/810, C07K 231/815, C07K 231/820, C07K 231/825, C07K 231/830, C07K 231/835, C07K 231/840, C07K 231/845, C07K 231/850, C07K 231/855, C07K 231/860, C07K 231/865, C07K 231/870, C07K 231/875, C07K 231/880, C07K 231/885, C07K 231/890, C07K 231/895, C07K 231/900, C07K 231/905, C07K 231/910, C07K 231/915, C07K 231/920, C07K 231/925, C07K 231/930, C07K 231/935, C07K 231/940, C07K 231/945, C07K 231/950, C07K 231/955, C07K 231/960, C07K 231/965, C07K 231/970, C07K 231/975, C07K 231/980, C07K 231/985, C07K 231/990, C07K 231/995, C07K 231/1000, C07K 231/1005, C07K 231/1010, C07K 231/1015, C07K 231/1020, C07K 231/1025, C07K 231/1030, C07K 231/1035, C07K 231/1040, C07K 231/1045, C07K 231/1050, C07K 231/1055, C07K 231/1060, C07K 231/1065, C07K 231/1070, C07K 231/1075, C07K 231/1080, C07K 231/1085, C07K 231/1090, C07K 231/1095, C07K 231/1100, C07K 231/1105, C07K 231/1110, C07K 231/1115, C07K 231/1120, C07K 231/1125, C07K 231/1130, C07K 231/1135, C07K 231/1140, C07K 231/1145, C07K 231/1150, C07K 231/1155, C07K 231/1160, C07K 231/1165, C07K 231/1170, C07K 231/1175, C07K 231/1180, C07K 231/1185, C07K 231/1190, C07K 231/1195, C07K 231/1200, C07K 231/1205, C07K 231/1210, C07K 231/1215, C07K 231/1220, C07K 231/1225, C07K 231/1230, C07K 231/1235, C07K 231/1240, C07K 231/1245, C07K 231/1250, C07K 231/1255, C07K 231/1260, C07K 231/1265, C07K 231/1270, C07K 231/1275, C07K 231/1280, C07K 231/1285, C07K 231/1290, C07K 231/1295, C07K 231/1300, C07K 231/1305, C07K 231/1310, C07K 231/1315, C07K 231/1320, C07K 231/1325, C07K 231/1330, C07K 231/1335, C07K 231/1340, C07K 231/1345, C07K 231/1350, C07K 231/1355, C07K 231/1360, C07K 231/1365, C07K 231/1370, C07K 231/1375, C07K 231/1380, C07K 231/1385, C07K 231/1390, C07K 231/1395, C07K 231/1400, C07K 231/1405, C07K 231/1410, C07K 231/1415, C07K 231/1420, C07K 231/1425, C07K 231/1430, C07K 231/1435, C07K 231/1440, C07K 231/1445, C07K 231/1450, C07K 231/1455, C07K 231/1460, C07K 231/1465, C07K 231/1470, C07K 231/1475, C07K 2

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129. 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.

130. 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 '504 patent (*see* AMG1002 ¶ 55, Figs. 6 and 7), that is only because he used his hindsight knowledge of the sequences disclosed in the '504 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 a 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 '504 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 '504 patent:

504-2:	-----QVQLVQSGAEVKKPGASVKVSCKASGYIFSN
Evans11:	MKWSWVILFLLSVTAGVHSQVQLVQSGAEVKKPGASVKVSCKASGYIFSN
504-2:	YWIQWVRQAPGQGLEWMGEILPGSGSTEY TENFKDRVTMT TRDTSTSTVYM
Evans11:	YWIQWVRQAPGQGLEWMGEILPGSGSTEY AQKFQGRVTMT ADTSTSTAYM
504-2:	ELSSLRSED TAVYYCARYFFGSSPNWYFDVWGQGT LVTVSSASTKGPSVF
Evans11:	ELSSLRSED TAVYYCARYFFGSSPNWYFDVWGQGT LVTVSSASTKGPSVF
504-2:	PLAP CSRSTSE STAALGCLVKDYFPEPVT VSWNSGALTSGVHTFPAVLQS
Evans11:	PLAP SSKSTSGG TAALGCLVKDYFPEPVT VSWNSGALTSGVHTFPAVLQS
504-2:	SGLYSLSSVVTVPSS NFGTQTYTCNV DHKPSNTKVDK TV ERKCC VE CPP
Evans11:	SGLYSLSSVVTVPSS SLGTQTYICNV NHKPSNTKVDK KV EPKSCDKTHT

Figure 5: '504 patent SEQ ID No. 2 compared with Evans SEQ ID No. 11

504-2:	-----QVQLVQSGAEVKKPGASVKVSCKASGYIFSN
Evans12:	MKWSWVILFLLSVTAGVHSQVQLVQSGAEVKKPGASVKVSCKASGYIFSN
504-2:	YWIQWVRQAPGQGLEWMGEILPGSGSTEY TENFKDRVTMT TRDTSTSTVYM
Evans12:	YWIQWVRQAPGQGLEWMGEILPGSGSTEY TENFKDRVTMT TRDTSTSTVYM
504-2:	ELSSLRSED TAVYYCARYFFGSSPNWYFDVWGQGT LVTVSSASTKGPSVF
Evans12:	ELSSLRSED TAVYYCARYFFGSSPNWYFDV WGQGT LVTVSSASTKGPSVF
504-2:	PLAP CSRSTSE STAALGCLVKDYFPEPVT VSWNSGALTSGVHTFPAVLQS
Evans12:	PLAP SSKSTSGG TAALGCLVKDYFPEPVT VSWNSGALTSGVHTFPAVLQS
504-2:	SGLYSLSSVVTVPSS NFGTQTYTCNV DHKPSNTKVDK TV ERKCC VE CPP
Evans12:	SGLYSLSSVVTVPSS SLGTQTYICNV NHKPSNTKVDK KV EPKSCDKTHT

Figure 6: '504 patent SEQ ID No. 2 compared with Evans SEQ ID No. 12

131. 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, as a POSA would have understood from clinical study publications.

132. 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.

133. 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

134. 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 '504 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.

135. ***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.

136. 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

137. The structure of the active molecule in SOLIRIS[®] that is claimed in the '504 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.

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 ¶¶23, 47 (citing AMG1031, AMG1032).) As I explain below, a POSA would have 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.

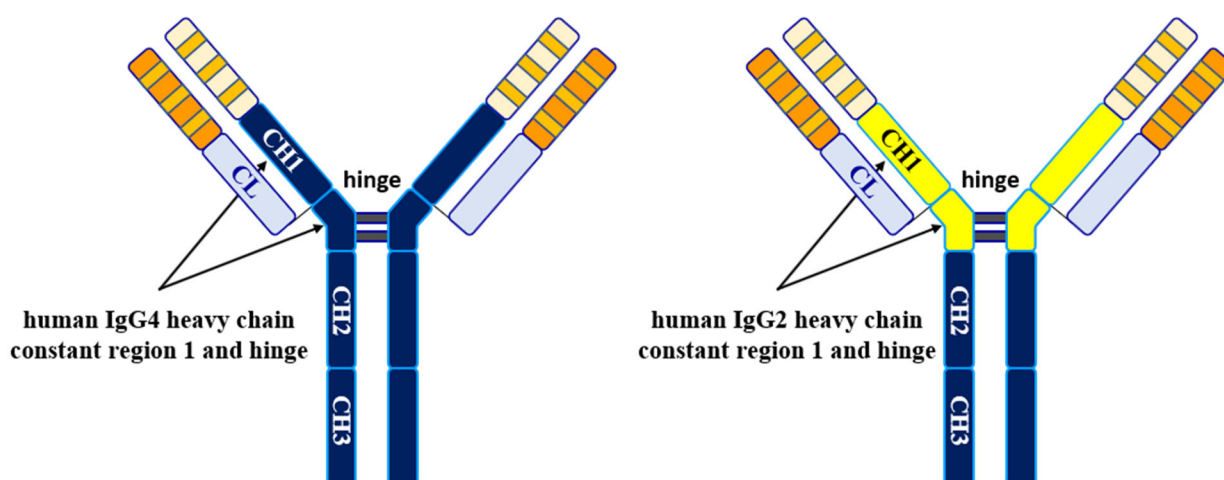


Figure 7: Left – Structure of the IgG4 isotype antibody referenced to as “eculizumab” in the literature as of March 15, 2007

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

VII. OPINIONS

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

138. 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 ’504 Patent

139. 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 . . .
.” (See AMG1002 ¶43.) 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.)

140. 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 (AMG1005), and Hillmen ’06 (AMG1012) all cite to Thomas in statements identifying what “eculizumab” is (ALXN2032 at 125:13-126:9; 128:20-129:10; 130:0-22)
- Bell (AMG1005) cites to Thomas and Evans (AMG1007) for “methods 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)

- 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.)

141. 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, Tacke (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 ¶¶ 46-47.) At his deposition, I understand that Dr. Balthasar admitted that Tacke 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.)

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

An isotype control antibody, h5G1.1-mAb (5G1.1, eculizumab [*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.)

143. 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 Tacke 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 Tacke 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.

144. 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 Tacke *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. (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.

145. 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. (*Id.*) 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.

146. 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) (emphasis added); ALXN2032 at 116:16-22.) 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 ¶ [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.

147. 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.

148. 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 ¶ 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 Tacke to Mueller is for description of the “human hybrid IgG2/IgG4 constant domain” described in Tacke; Mueller is not cited as describing “eculizumab.”

149. 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 ¶ 45.) I have been informed that these statements, made after the priority date and in an unrelated patent application, are not prior art to the ’504 patent. (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.

150. 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 ’504 patent for his understanding of “eculizumab’s heavy chain.” (AMG1002 ¶ 56 (citing AMG1033); AMG1002 ¶ 11 (citing AMG1014 at 767 (Boone Declaration ¶ 6).) 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.

151. Figure 8 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:

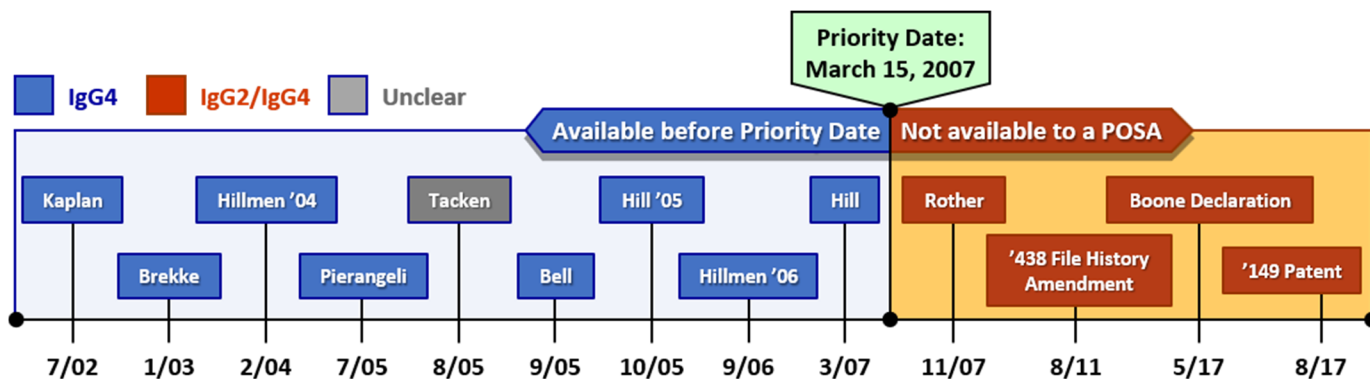


Figure 8: Documents referring to “eculizumab” before and after March 15, 2007

2. The Antibody Sequence Recited in the '504 Patent, and Methods of Treatment and Pharmaceutical Compositions of an Antibody Comprising the Sequence Recited in the '504 Patent, Were Not Publicly Known Before March 15, 2007

152. 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 ¶50.) Before March 15, 2007, a POSA would not have known the complete, full-length amino acid sequence of SOLIRIS® (eculizumab) – now claimed in the '504 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 '504 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.

153. Likewise, none of Dr. Balthasar's references dated prior to March 15, 2007 would have disclosed to a POSA that an antibody with the specific sequence recited in claims 1-10 of the '504 patent had ever been formulated into a pharmaceutical composition suitable for human or administration, or that such an antibody had ever been administered to any human patients. From the perspective of a POSA before March 15, 2007, the claimed antibody of the '504 patent was, for all they could tell, never characterized for C5 binding, never tested for any *in vitro* activity, never studied in any animal models or tested for toxicity in animals,

never grown in cells suitable to make quantities needed for clinical trials, never formulated into a pharmaceutical composition that was suitably stable to administer to humans, and never actually studied in humans for therapeutic effects or safety, including potential immunogenicity.

154. Dr. Balthasar first cites a declaration by an Alexion employee, submitted during prosecution of the '504 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 ¶49 (citing the Boone Declaration, AMG1014 at 764-766).) 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. 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.

155. 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 sequence of the antibody used in the pharmaceutical compositions claimed in the '504 patent, as described more fully in Sections VII.D and VII.E below.

156. First, Evans does not teach or suggest the specific, full-length antibody sequence described in claims 1-10 of the '504 patent, or that an antibody having that sequence would bind C5 or be safe and effective in human patients.

157. 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.) 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.

158. 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.)

159. 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. (AMG1007 at 45:24-33.) Evans does not suggest or disclose the hybrid IgG2/IgG4 corresponding to SEQ ID NO:2 of the ’504 patent, or teach that an antibody incorporating that sequence would be an “antibody that binds C5,” or that such an antibody could be suitable for “a method of treating a patient suffering from [PNH],” as claims 1-10 require. 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/IgG4.⁶ (*See* Section VI.D.5 above.)

160. Bowdish, Mueller, and Mueller II also did not disclose (1) the specific, full-length antibody described in claims 1-10 of the ’504 patent; (2) whether an antibody with the claimed sequence would be “an antibody that binds C5,” (3) whether an antibody with the claimed sequence would be suitable for use in “treating a patient suffering from [PNH],” or (4) whether that an antibody was

⁶ Evans refers to the chimeric version of its “Fd” series of compounds as “5G1.1M1 VH HuG1.” (AMG1007 at 43:18-20.)

suitable for formulation “pharmaceutical composition” for use in treating human patients suffering from PNH.

161. The subject matter of Bowdish was unrelated to “eculizumab,” C5 binding or the of PNH. 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 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].)

162. 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].)

163. I disagree with Dr. Balthasar’s characterization of Bowdish as disclosing sequences of “eculizumab” or an “eculizumab-based immunoglobulin.” (*See, e.g.*, AMG1002 ¶¶ 50-51, 55.) Bowdish never uses the term “eculizumab.” 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.”

164. A POSA would have understood Bowdish’s incorporation by reference of Evans to be more limited than is depicted in Dr. Balthasar’s report. For example, in his report, Dr. Balthasar states, “Bowdish references U.S. Pat. No. 6,355,245 (AMG1007; ‘Evans’) as describing the generation of the h5G1.1 antibody.” (AMG1002 ¶ 53.) 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 ¶ [0191].) A POSA would have understood that Evans,⁷ in turn, used

⁷ I understand from counsel that Bowdish cites 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

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 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.

165. 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 “construction 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.

166. 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-

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.)

human” assay reagent in a FACS experiment with the TPO-mimetic peptide compound. (AMG1002 ¶ 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. (ALXN2091 at 623.) Particularly given Bowdish’s earlier reference to the mouse “5G1.1” antibody Evans in ¶ [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.

167. 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 describes 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. (ALXN2032 at 232:17-21.)

168. I disagree with Dr. Balthasar's characterization of Mueller as disclosing "eculizumab's hybrid IgG2/IgG4 heavy chain constant region." (AMG1002 at 56.) Neither Mueller nor Mueller II use the term "eculizumab" or disclose the full-length antibody sequence claimed in the '504 patent. To support his assertions, Dr. Balthasar references Mueller's use of "h5G1.1 CO12 HuG2/G4 mAb" as a control antibody. 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 12:1-2; AMG1023 at 1396, 1399.)

169. 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,⁸ and would have been too ambiguous to have led a POSA to any particular variable region sequence. (See Section VII.E.1 below.)

170. I further disagree with Dr. Balthasar that, as of March 15, 2007, a POSA would have understood the full-length, specific sequence described in claims 1-10 of the '504 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 '504 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.

⁸ 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.

171. 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; AMG) 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* Balthasar Dep. Tr. at 97:23-99:20, 100:3-12, 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.)

172. As discussed above, as of March 15, 2007, a POSA would have understood that the design of monoclonal antibodies for human clinical therapy, as well as pharmaceutical compositions of such antibodies, and development of their use in treating human patients, was a complex and unpredictable process. (*See* Sections VI.D.2 and VI.D.4 above.) 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* Section 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 ’504 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 binds C5,” would be suitable for “treating a patient suffering from [PNH],” or would be suitable for formulation in a “pharmaceutical composition” for use in treating PNH, as claims 1-10 all require.

173. 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 (where presumably it was also formulated into a pharmaceutical composition suitable for such clinical use), 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 been reasonably been predicted.

**B. Claims 1-3 and 7-10 of the '504 Patent
Were Not Anticipated by Hillmen '04 (Ground 1)**

174. Amgen's Ground 1 contends that claims 1-3 and 7-10 of the '504 patent would have been anticipated by the clinical trial publication Hillmen '04 (AMG1004).

175. In my opinion, Amgen's Ground 1 fails because, among other things, Amgen cannot show that Hillmen disclosed each element of the claimed invention, either expressly or inherently. Specifically, Hillmen did not disclose the full-length sequence recited in claims 1-3 and 7-10 of the '504 patent.

176. Hillmen was a journal publication reporting on the successful use of "eculizumab," a humanized monoclonal antibody targeting C5, to treat PNH in a human clinical trial. (AMG1004 at 2.) Hillmen did not disclose any amino acid sequences for "eculizumab."

177. 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).

178. In my opinion, Hillmen did not disclose the claimed sequence of the '504 patent (SEQ ID NOs: 2 and 4) by its mention of "eculizumab," because a

POSA prior to March 15, 2007 would not know from reading Hillmen 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 ’504 patent was not publicly known prior to March 15, 2007. (See Section VI.E above.) And in fact, a POSA reading Hillmen would have understood that “eculizumab” had a *different* structure and sequence than the antibody with SEQ ID NOs: 2 and 4 claimed in the ’504 patent.

179. In particular, a POSA reading Hillmen and the other literature available as of March 15, 2007 would have understood “eculizumab” to have been the ***IgG4*** isotype antibody described in Thomas (AMG1023). (See Section VI.D.5 above.) As I discuss above, Hillmen cites to Thomas for a disclosure of what “eculizumab is.” (AMG1004 at 553 (Ref. No. 15).) 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 contained an IgG4 isotype, as taught by Thomas. (See Section VI.D.5 above.)

180. 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 to 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.

181. A POSA would not have been able to independently determine the amino acid sequence of the antibody clinically tested in Hillmen 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 '504 patent.

182. I disagree with Dr. Balthasar's assertions that Hillmen was enabling – *i.e.*, that it 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 ¶¶ 75, 85.) First, Hillmen did not 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, Hillmen did not contain any indication that the “eculizumab” antibody used in that

study would have the sequences that Dr. Balthasar selects from Bowdish, Evans, and Mueller. Hillmen cites 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; AMG1047 at 2559.) Finally, there is nothing in Bowdish, Evans, and Mueller that disclosed the specific amino acid claimed in the ’504 patent in any case, for the reasons stated in Section VI.E.

183. 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 ’504 patent, a POSA would not have been able to create an antibody that binds C5, with the specific amino acid claimed in the ’504 patent, based on the disclosures of Hillmen without significant experimentation.

184. Also, in my opinion, Hillmen did not disclose, and would not have enabled a POSA to make without undue experimentation, (1) a method of using the specific claimed antibody of the ’504 patent for treating a patient suffering from PNH, of (2) any “pharmaceutical composition” of the specific claimed antibody of the ’504 patent suitable for use in the claimed method of treating PNH patients recited in claims 1-3 and 7-10 of the ’504 patent. Nothing in Hillmen would have provided a POSA with any guidance on how to carry out such a method of

treatment or make such a pharmaceutical composition, or whether it would have even been possible to do so, because there is simply no information at all in Hillmen regarding an antibody with the claimed sequence of the '504 patent.

C. Claims 4 and 5 of the '504 Patent Would Not Have Been Obvious In View Of Hillmen Combined with Bell (AMG1005) (Ground 2), and Claim 6 Would Not Have Been Obvious in View of Hillmen, Bell, and Wang (AMG1028) (Ground 3)

185. Amgen contends that claims 4 and 5 of the '504 patent would have been obvious over the combination of Hillmen and Bell (AMG1005) (Ground 2), and that claim 6 would have been obvious in view of Hillmen, Bell and Wang (AMG1028) (Ground 3). As Grounds 2 and 3 raise overlapping issues, I disagree with both for the same reasons, I will address them both together here.

186. In my opinion, Amgen's Grounds 2 and 3 fail, because, among other things, Amgen cannot show that each element of the claimed invention was known or obvious in view of Hillmen in combination with Bell (and Wang, for claim 6).

187. First, none of Hillmen, Bell, nor Wang, when read alone or in combination, disclosed the specific amino acid sequence claimed in the '504 patent. For Grounds 2 and 3, Dr. Balthasar relies solely on Hillmen as providing the claimed amino acid sequence. (AMG1002, ¶97.) But as discussed above, from the perspective of a POSA prior to March 15, 2007, Hillmen did not disclose an antibody having the specific sequence claimed in the '504 patent, or any

pharmaceutical compositions of that antibody for use in treating PNH, or any other complement-mediated condition. (*See* Section VII.B above.)

188. Likewise, nothing in Bell (AMG1005) or Wang (AMG1028) disclosed the claimed amino acid sequence recited in the '504 patent. I understand Dr. Balthasar agrees. (AMG1002 at ¶ 130; ALXN2032 at 151:4-12, 160:7-10, 194:17-20, 257:13-18.) Like Hillmen and Hill, Bell and Wang discuss the antibody “eculizumab,” but neither reference provides the specific amino acid sequence recited in claims 4-6. Further, Bell, like Hillmen and Hill, would have suggested to a POSA that “eculizumab” was Thomas’s IgG4 isotype, and therefore would have pointed a POSA to an antibody structure and sequence that is different from the hybrid, non-naturally occurring isotype of claimed antibody of the '504 patent. (AMG1005 ¶[0052] (citing Thomas)); *see* Section VII.D.1 below.)

189. A POSA prior to March 15, 2007 would have had no reason or motivation to deviate from the IgG4 antibody structure of Thomas that Hillmen and Bell associated with the therapeutically useful “eculizumab” antibody. And, a POSA provided with Hillmen and Bell would not have been motivated to make a new, untested antibody using a clinically-untested non-naturally occurring hybrid constant region – or to make pharmaceutical compositions of such an antibody for the treatment of PNH – when Hillmen and Bell taught that “eculizumab,”

identified as an IgG4 antibody, was safe and effective for human use. (See Section VI.D.5 above.)

190. Wang (AMG1028) would not have taught a POSA otherwise. Wang provided no structural information at all regarding “eculizumab,” and only described experiments testing what happens when a 30 mg/ml solution of “eculizumab” is passed through a nebulizer device. (AMG1028 at [0169]-[0173].) Nothing in Wang, even combined with Hillmen and Bell, would have motivated a POSA to make the pharmaceutical compositions of claim 6 of the ’504 patent for use in treating patients suffering from PNH, or would have given a POSA a reasonable expectation of success in doing so.

191. I also note that nothing in Bell (AMG1005) or Wang (AMG1028), even together, disclosed the specific pharmaceutical composition recited in claim 6: “a 300 mg single-use formulation of 30 ml of a 10 mg/ml sterile, preservative free solution.” Neither Bell nor Wang describes any pharmaceutical compositions of the claimed antibody of the ’504 patent, let alone the specific composition of claims 6. And even with respect to “eculizumab” – which a POSA prior to March 15, 2007 would *not* have thought to be the claimed antibody – Bell and Wang did not disclose a 300 mg single-use dosage form, or any single-use dosage form comprising a 10 mg/ml antibody solution.

D. Claims 1-5 and 7-10 of the '504 Patent Would Not Have Been Obvious Over Bell, Bowdish, and Evans (Ground 4), and Claim 6 Would Not Have Been Obvious Over Bell, Wang, Bowdish and Evans (Ground 5)

192. Amgen contends that claims 1-5 and 7-10 of the '504 patent would have been obvious over the combination of Bell (AMG1005), Bowdish (AMG1006) and Evans (AMG1007) (Ground 4), and that claim 6 would have been obvious in view of Bell, Wang (AMG1028), Bowdish, and Evans (Ground 5). As Grounds 4 and 5 raise overlapping issues, I disagree with both for the same reasons, I will address them both together here.

193. In my opinion, Amgen's Grounds 4 and 5 fail, 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, or in further combination with Wang for claim 6. None of Bell, Wang, Bowdish, nor Evans, when read alone or in combination, disclosed the specific amino acid sequence claimed in the '504 patent. Nothing in Bell (or Wang) would have motivated a POSA to look to Bowdish or Evans to create the claimed sequence. And even if a POSA were to have made the exact, untaught combination of sequences from Bowdish and Evans in the way that Dr. Balthasar does in hindsight, a POSA would have had no motivation or reasonable expectation of success in using such an antibody to treat patients suffering from PNH as required by claims 1-10. A POSA also would not have been motivated or reasonably expected to succeed in making any

pharmaceutical compositions of an antibody with the claimed sequence (including the specific composition of claim 6) that would be suitable for use in the claimed method of treating patients suffering from PNH.

1. Bell (and Wang) Did Not Disclose the Specific Sequence of Claims 1-10, and Would Not Have Motivated a POSA to Make An Antibody With the Claimed Sequence

194. Dr. Balthasar relies on Bell (and Wang for claim 6) for their disclosures regarding “eculizumab” – but he admits that Bell and Wang did *not* disclose the claimed amino acid sequence of the ’504 patent. (AMG1002 at ¶ 130; ALXN2032 at 151:4-12, 160:7-10, 194:17-20, 257:13-18.)

195. Bell, in fact, would have guided a POSA towards use of an IgG4 isotype that is different from the claimed antibody of the ’504 patent, which has a different, uniquely-engineered amino acid sequence corresponding to a hybrid IgG2/IgG4 constant region.

196. 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].

197. 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 human heavy chain constant regions described in Evans are the

CH1 regions of “Fd” fragments⁹ (SEQ ID NOs: 11 and 12) that do not align with the constant regions of the claimed sequence. (*See* Section VI.D.5 above.)

198. 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 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. Figure 9 below 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:

⁹ 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.)

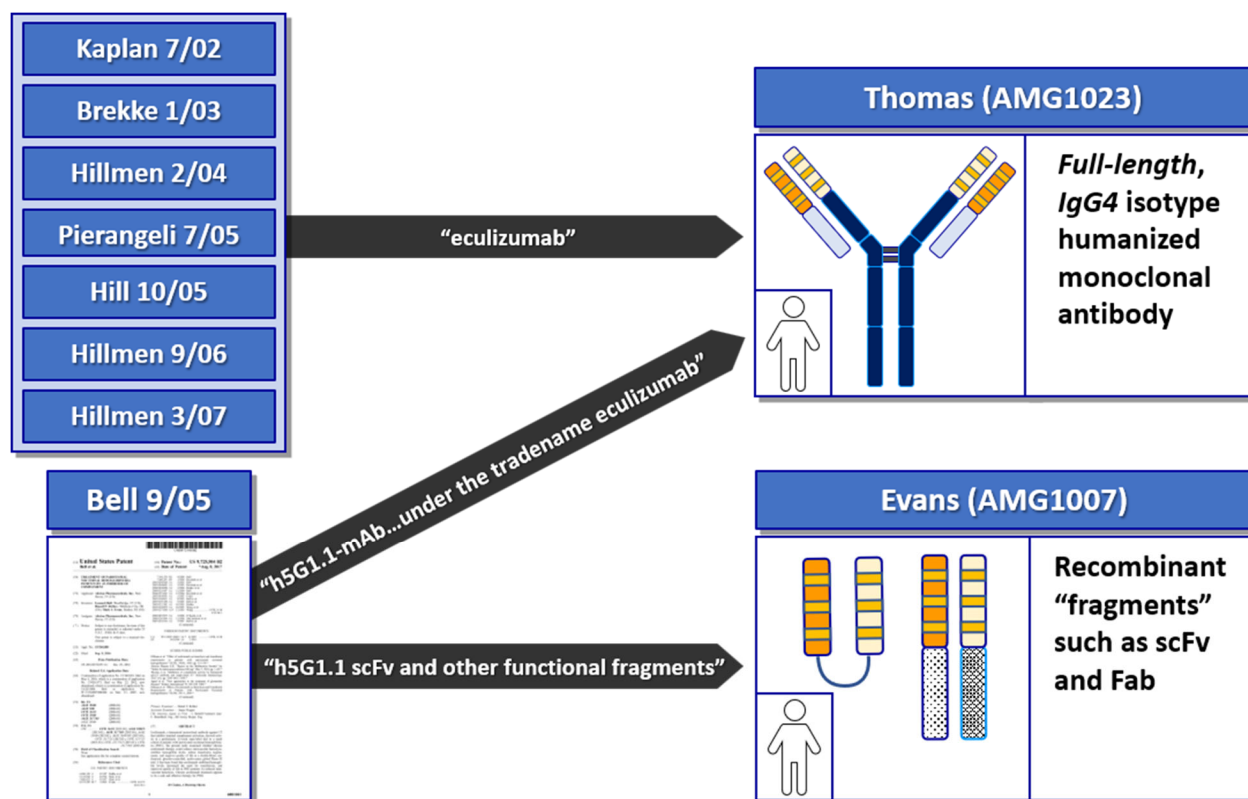


Figure 9: A POSA’s understanding of Bell’s teaching regarding “eculizumab,” “h5G1.1 scFv,” and “other function fragments

199. 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 at 115:16-23.)

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

200. 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 (*see* Section VII.A.2 above); 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.

201. I disagree with Dr. Balthasar’s arguments regarding why he claims a POSA would have been motivated to combine Bell, Wang, 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 ¶ 114.)

202. 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.

203. 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 refer specifically to the antibody “eculizumab,” and could refer to a variety of antibodies depending on the context. (*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.

204. 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 ¶¶ 139-140; 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.)

205. 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.)

206. 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 ¶ 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.

207. 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.

208. A POSA further would not have combined Bell and Bowdish based on Bell's reference to Evans. (See AMG1005 ¶ [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 IV.D.3, a POSA would have understood that the term “5G1.1” and its derivatives (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.

3. A POSA Would Not Have Been Motivated Make the Specific Claimed Antibody that Dr. Balthasar Assembles in Hindsight from Bowdish and Evans

209. Even if a POSA were to have turned from Bell and Wang to Bowdish and Evans – despite there being no reason for a POSA without hindsight to have done so – nothing in the combination of these four documents would have motivated a POSA to make the specific amino acid sequence recited in claims 1-3 of the ’504 patent.

210. There is no dispute that Bowdish did not disclose the entire amino acid sequence recited in claims 1-10 of the ’504 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 claims 1-10 of the '504 patent. (ALXN2032 at 184:10-16.) Dr. Balthasar also admits that neither Bowdish nor Evans uses the term “eculizumab.” (ALXN2032 at 199:9-17.)

211. 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.

212. The statement at issue appears in Example 4 of Bowdish, which states:

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.

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.

AMG1006 at [0191].

213. 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 "5G1.1" antibody, and that Evans does 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 context¹¹ – and nothing in that statement would indicate to a POSA any intent to incorporate the disclosures of Evans beyond what it states: "construction of 5G1.1," a mouse antibody. Accordingly, a POSA would not have read the statement in Bowdish as

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.

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 ¶ [0001].)

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.)

214. A POSA reading Bowdish, and seeing its incorporation by reference of Evans's mouse "5G1.1" antibody, would not have understood that it disclosed the claimed antibody of the '504 patent, which is a humanized antibody. If a POSA were to consider the sequence of Evans's mouse "5G1.1" antibody in view of Bowdish's Figs. 13A and 13B sequences, they would see misalignment beyond the region of Bowdish's "TPO-mimetic" peptide, and would not have further envisioned any combination of sequences that would result in the claimed antibody of the '504 patent.

215. 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 ’504 patent:

Bowdish13A:	QVQLVQSGAEVKKPGASVKVSKASGYIFSNIYWIQWVRQAPGQGLEWMGE
Evans19:	QVQLQQSGAELMKPGASVKMSCKATGYIFSNIYWIQWIKRPGHGLEWIGE
Bowdish13A:	ILPGSGSTEYTENFKDRVMTTRDTSTSTVYMESSLRSEDTAVYYCARLP
Evans19:	ILPGSGSTEYTENFKDKAAFTADTSSNTAYMQLSSLTSEDSAVYYCAR--
Bowdish13A:	IEGPTLRQWLAARAP-----VWGQGLTVTVSS
Evans19:	-----YFFGSSPNWYFDVWGAGTTTVTVSS

Bowdish13B:	DIQMTQSPSSLSASVGDRTITCGASENIYGALNWIQQKPGKAPKLLIYG
Evans18:	DIQMTQSPASLSASVGETVTITCGASENIYGALNWIQRKQKSPQLLIYG
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

216. 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 ’504 patent:

Bowdish13A:	-----QVQLVQSGAEVKKPGASVKVSCKASGYIFSN
5G1.1HC:	MEWTWVFLFLSVTAGVHSQVQLQQSGAELMKPGASVKMSCKATGYIFSN
Bowdish13A:	YWIQWVRQAPGQGLEWMGEILPGSGSTEYTENFKDRVTMTRDTSTSTVYM
5G1.1HC:	YWIQWIKQRPBGHGLEWIGEILPGSGSTEYTENFKDKAAFTADTSSNTAYM
Bowdish13A:	ELSSLRSED TAVYYCARLP IEGPTLRQWLAARAP-----VWGQGTLLVTVS
5G1.1HC:	QLSSLTSEDSAVYYCAR-----YFFGSSPNWYFDVWGAGTTTVTS
Bowdish13A:	SASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSG
5G1.1HC:	SAKTTAPSVYPLAPVCGDTTGSSVTLGCLVKGYFPEPVTLTWNSGSLSSG
Bowdish13A:	VHTFPAVLQSSGLYSLSSVTVTPSSNFGTQTYTCNV DHKPSNTKVDKTVE
5G1.1HC:	VHTFPAVLQSD-LYTLSSSVTVTSSTWPSQSITCNVAHPASSTKVDKKIE
Bowdish13A:	RK--CCVECPP--CPAPP-VAGPSVFLFPPKPKDTLMISRTPEVTCVVVD
5G1.1HC:	PRGPTIKPCPPCKCPAPNLLGGPSVFIFPPKIKDVLMI SLSPIVTCVVVD
Bowdish13A:	VSQEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLN
5G1.1HC:	VSEDDPDVQISW FVNNEVHTAQTQTHREDYNSTLRVVSALPIQH QDWMS
Bowdish13A:	GKEYKCKVSNKGLPSSIEKTISKAKGQPREPQVYTLPPSQEEMTKNQVSL
5G1.1HC:	GKEFKCKVNNKDLPAPIERTISKPKG SVRAPQVYVLPPEEEMTKKQVTL
Bowdish13A:	TCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSRLTVDKS
5G1.1HC:	TCMVTDFMPEDIYVEWTNNGKTELNYKNTEPVLDSDGSYFMYSKLRVEKK
Bowdish13A:	RWQEGNVFSCSV MHEALHNHYTQKSLSLGLGK
5G1.1HC:	NWVERNSYSCSVVHEGLHNHHTTKSFSRTPGK

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

217. And even if Bowdish and Evans were combined in full, they did not disclose or render obvious uniquely engineered amino acid sequence recited in claims 1-10 of the '504 patent. For example, if a POSA were to look 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 does not describe *any* full-length antibody (including Bowdish’s “scaffold” antibody), aside from the “5G1.1” mouse antibody, which does not align with the sequences disclosed in Bowdish. (ALXN2032 at 163:12-15, 169:6-23, 221:14-16.)

218. 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 Sections VI.D.2 and VI.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. Again, I note that Dr. Balthasar’s figures are misleading in this regard, because a POSA would not have envisaged Evans’s scFv sequences as 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 compounds different from the full-length structures described in Bowdish.

219. The following figure 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.

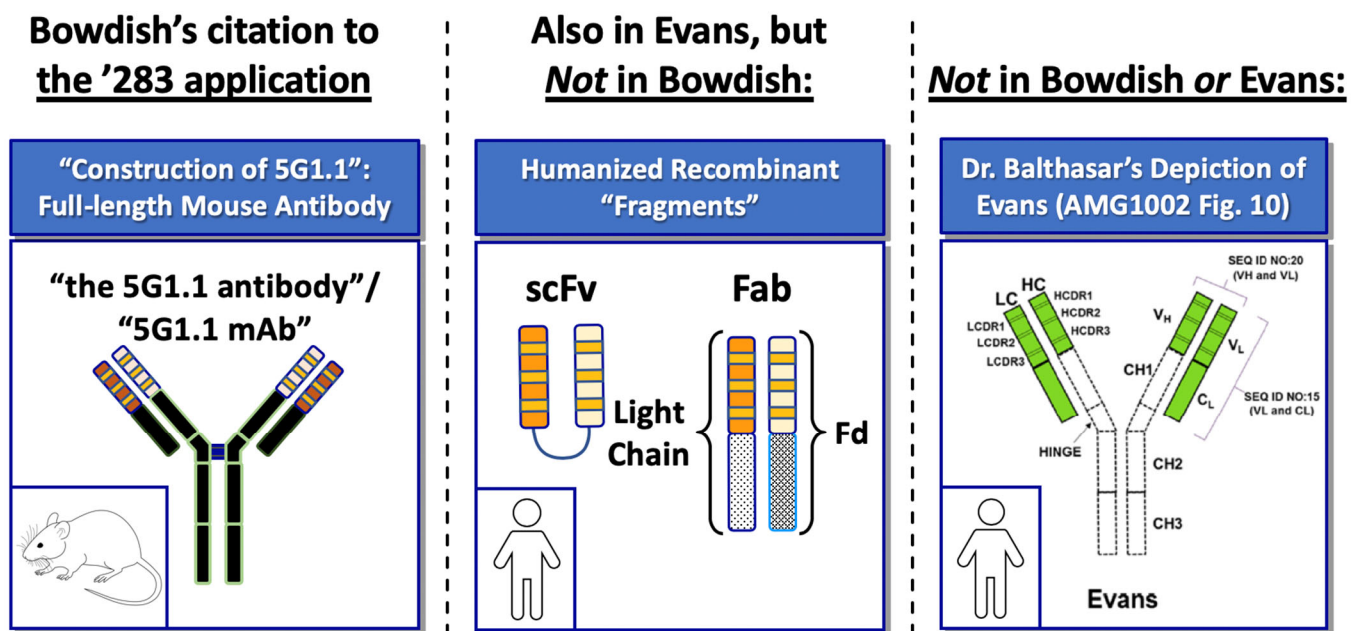


Figure 12: A POSA’s understanding of Bowdish’s reference to the ‘283 application, and what material was outside the referenced subject matter

220. Further, even if Dr. Balthasar were correct to combine Bowdish’s TPO-mimetic sequences with CDR sequences from Evans, he ignores that Evans refers 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 discloses 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.)

221. 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 ’504 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 ’504 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 been able to envisage the claimed sequence from the vague disclosures in Bowdish.

222. 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 ¶ 134.) This is not correct. Bowdish does 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.

223. I also disagree with Dr. Balthasar’s depiction in Figure 12.
(AMG1002 at 96.) As I discussed above (*see* Section VI.D.5), I disagree with Dr. Balthasar’s depiction of the disclosure from Evans, because Evans does 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.

224. 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, there is no evidence that the antibody described in Example 4 of Bowdish was in fact humanized, and Evans does 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 is 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 undertake to arrive at the claimed full-length sequence from the disclosures of Bowdish.

4. A POSA Without the Benefit of Hindsight Would Not Have Been Motivated to Make, and Would Not Have Reasonably Expected Success in Making, the Claimed Pharmaceutical Compositions for Treatment of PNH from Bell, Bowdish and Evans (or Wang for Claim 6)

225. Even if Dr. Balthasar were correct that a POSA could have assembled the specific amino acid sequence of the claimed antibody in the exact way he does from Bowdish and Evans, he still has not shown:

- How a POSA would have been motivated to use the claimed antibody in a “method of treating a patient suffering from [PNH]” (as the claims require), or would have reasonably expected to succeed in doing so;
- How a POSA would have reasonably expected to achieve success in using the claimed antibody to obtain the “immediate and sustained decrease in mean levels of lactate dehydrogenase (LDH)” recited in claims 9 and 10; and

- How a POSA would have further been motivated to make, or reasonably expected to succeed in making, the claimed *pharmaceutical compositions* of the specific amino acid sequence recited in claims 1-10 of the '504 patent, that would be suitable for use in the claimed methods of treating patients suffering from PNH.

226. 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 challenges, expenses, and unpredictability of clinical research of such monoclonal antibodies; and the design of pharmaceutical compositions of such antibodies suitable for human therapeutic use to treat PNH without undue harm to the patient. (See Sections VI.D.2 and VI.D.4 above.)

227. Dr. Balthasar conclusively states that “[a] POSA would have had a reasonable expectation of success in making the claimed pharmaceutical compositions because of the history of success with using eculizumab to treat PNH, and because generating the claimed antibody and anti-C5 antibody-containing compositions would have required only routine techniques.” (AMG1002 ¶ 123.) He further states that success with pharmaceutical compositions and treatment of PNH with the antibody he assembles in hindsight from Bowdish and Evans would be reasonably expected because of the preparation

of “eculizumab” compositions by Bell and Wang, and the success of “eculizumab” in published human clinical trials. (AMG1002 ¶ 143.)

228. 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 and Wang, would have taught or given a POSA a reasonable expectation of success that a different antibody with the specific amino acid sequence of claims 1-10 of the ’504 patent would even be “an antibody that binds C5,” let alone whether it would be suitable for “treating a patient suffering from [PNH]” (as all of the claims provide).

229. 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 ’504 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.)

230. 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.¹² 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):

¹² As I discuss below in Section VII.F.2, I note that, despite the publication of this review and other information as early as 1995 expressing interest in therapeutic development of anti-C5 monoclonal antibodies to treat PNH and other complement-mediated conditions, no one else succeeded in bringing any anti-C5 antibody to market before the approval of SOLIRIS® on March 16, 2007.

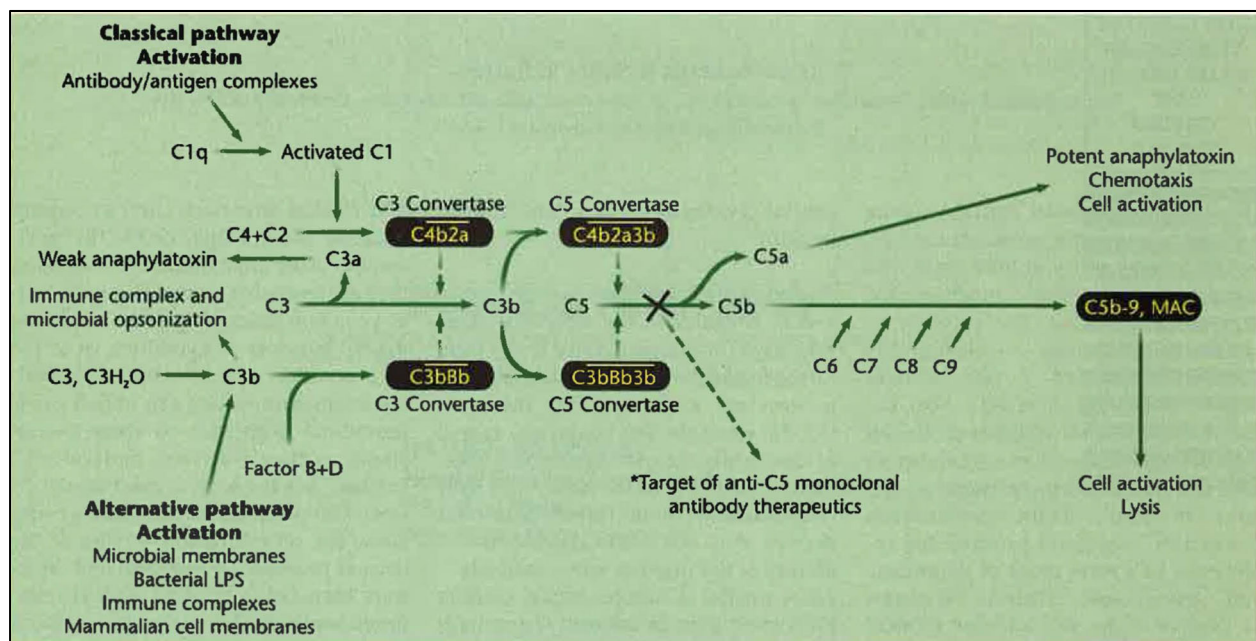


Figure 13: Mattis & Rollins (1995), Fig. 1 (AMG1039 at 840)

231. 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.)

232. 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 (let alone the specific 300 mg single unit dosage form, 10 mg/ml concentration antibody solution formulation of claim 6), or usefulness of the antibody or a pharmaceutical composition of the antibody in treating PNH or any other condition.

233. 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 '504 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

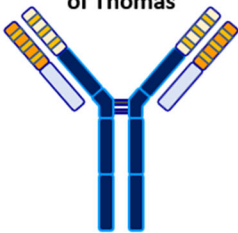
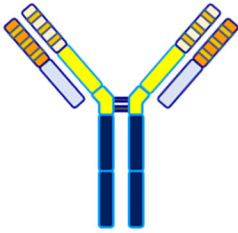
	Identified as "Eculizumab"?	Binds to C5?	Blocks C5 activity in vitro?	Treats PNH?	Suitable for formulation and human administration?
 "h5G1.1 HuG4" of Thomas	YES	YES Similar binding to mouse 5G1.1	YES Same <i>in vitro</i> activity as mouse 5G1.1	YES Efficacy reported in Phase II/Phase III studies	YES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

Figure 14: 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 '880 patent

234. Accordingly, even if a POSA provided with Bell ,Wang, 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 to use that antibody for the pharmaceutical compositions claimed in the '504 patent, and would not have reasonably expected to succeed in doing so.

E. Claims 1-5 and 7-10 of the '504 Patent Would Not Have Been Obvious Over Bell, Evans, and Mueller (Ground 6), and Claim 6 Would Not Have Been Obvious Over Bell, Wang, Evans and Mueller (Ground 7)

235. Amgen contends that claims 1-5 and 7-10 of the '504 patent would have been obvious over the combination of Bell (AMG1005), Evans (AMG1007) and Mueller (AMG1008) (Ground 6), and that claim 6 would have been obvious in view of Bell, Wang (AMG1028), Evans, and Mueller (Ground 7). As Grounds 6 and 7 raise overlapping issues, I disagree with both for the same reasons, I will address them both together here.

236. In my opinion, Amgen's Ground 6 and 7 fail, because, among other things, Amgen cannot show that each element of the claimed invention was known or obvious in view of Bell, Evans and Mueller (or further in view of Wang, for claim 6).

237. As with Grounds 4 and 5, Dr. Balthasar's arguments in Grounds 6 and 7 starts with the premise that Bell (and Wang, for claim 6) taught all of the claim elements except for the unique claimed amino acid sequence – which Dr. Balthasar concedes was not cited in Bell or Wang. (AMG1002 ¶ 176, ALXN2032 at 151:4-12, 160:7-10, 194:17-20, 257:13-18.) With respect to Bell and Wang, Dr. Balthasar again focuses on a POSA being motivated by their teachings regarding “eculizumab,” and with Bell in particular, its teachings that “eculizumab” was an

anti-C5 antibody what was clinically tested and shown to be safe and effective in treating PNH. (AMG1002 ¶¶ 176-178.)

**1. A POSA Without the Benefit of Hindsight
Would Not Have Been Motivated to Combine Bell
(and Wang) with Evans and Mueller, or to Make the
Specific Claimed Antibody of the '504 Patent**

238. For the same reasons as stated above with respect to Bowdish and Evans in Grounds 4 and 5, a POSA would not have had any motivation to jump from Bell – which taught that “eculizumab” was a therapeutically effective and safe IgG4 isotype antibody – to Evans and Mueller to look for a *different*, uncharacterized antibody with a different, hybrid IgG2/IgG4 constant region. (See Section VI.D.2 above.) Nothing in Bell, or the Thomas and Evans documents that Bell cites, cited or directed a POSA to look at Mueller. And a POSA in particular would have had no motivation to look to Mueller for methods of treating patients with PNH, or pharmaceutical compositions suitable for use in such a treatment. Bell already confirmed to a POSA as of March 15, 2007 that Thomas’s IgG4 antibody could be used to treat PNH (and sufficiently formulated to be suitable for such treatment in a clinical study); and a POSA would not have reasonably expected that a different antibody with a different, non-natural hybrid constant region that had never been reported as being tested in people, or even studied for C5 binding, would be useful for compositions as claimed in the '504 patent.

239. And even if a POSA had considered Evans and Mueller simultaneously, neither Evans nor Mueller, alone or in combination, would have disclosed to a POSA prior to March 15, 2007 the specific, full-length antibody sequence claimed in the '504 patent. (*See* Section VII.A.2 above.)

240. 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 is not related to C5-binding or treatment of PNH, the subject of Evans. Mueller has no experiments or data on C5 binding or blocking complement. Mueller only references “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 442 443, 448.)

241. 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.

242. 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* Section 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.

243. Even if a POSA had chosen to adopt an IgG2/IgG4 hybrid isotype – which a POSA would not have consider, 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.

244. I disagree with Dr. Balthasar's suggestion that Evans and Mueller would have been linked because both allegedly disclosed "humanized 5G1.1" or "h5G1.1." (AMG1002 ¶¶ 178-179.) First, this statement is inaccurate because Evans does 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. Evans'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.)

245. 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.

246. 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 in the name of an scFv, whereas in Mueller it is used in the name of 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.”

247. I disagree with Dr. Balthasar that “[o]verlapping sequences” would have caused a POSA to combine sequences from Mueller and Evans. (AMG1002 ¶ 168.) 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 discloses 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.

248. 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 ’504 patent.

249. For example, as Dr. Balthasar admitted at his deposition, Mueller does not indicate exactly where the IgG2/IgG4 heavy chain sequences in its anti-VCAM antibodies begins or ends. (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 ¶¶ 132-135; ALXN2032 at 233:3-234:4.) As Dr. Balthasar further testified, Mueller does 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.

250. 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 provide 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.

251. 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 region from Evans, rather than Thomas, to combine with

those constant regions. The light chain variable region sequences described in Thomas differ from the variable regions of Evans's "5G1.1-scFv-CO12" construct – and from SEQ ID NO: 4 of the '504 patent – at position 38. (*See* AMG1023 at 1396 (Fig. 4); AMG1007 at Certificate of Correction, p. 42-44.) 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 '504 patent.

252. A POSA as of March 15, 2007 would have had no motivation to select any of the variable regions disclosed in Evans and combine it 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.

253. Even if a POSA had sought to combine variable sequences from Evans with constant regions from Mueller, there is no guidance in either Evans or Mueller as to how to do so – for example, neither reference provides 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 (AMG1008) contains an extra amino acid (alanine) at the beginning of what Dr. Balthasar identifies as the IgG2/G4 constant region, but that does *not* appear in the “HuG2/G4” construct described in Mueller II (AMG1031). (*See* AMG1008 at 59 (“3F4 Human G2/G4 Expression Plasmid Insert Sequence” at position 138); AMG1031 at 449 (Fig. 9).)

254. 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 16-17 of his declaration (*see* AMG1002 at 122-123), which compare sequences from Mueller and Evans against SEQ ID NO: 2 and SEQ ID NO: 4 recited in the ’504 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 ’504 patent to help select sequences to combine from Evans and Mueller, and accordingly would not have reached the claimed full length sequence of the ’504 patent.

2. A POSA Without the Benefit of Hindsight Would Not Have Been Motivated to Make, and Would Not Have Reasonably Expected Success in Making, the Claimed Pharmaceutical Compositions for Treatment of PNH Conditions from Bell, Wang, Mueller and Evans

255. As with Grounds 4 and 5, it is my opinion that, even if a POSA had followed Dr. Balthasar's exact combination of sequences from Evans and Mueller that he assembles in hindsight, despite there being no motivation or teaching to do so in the specific way leading to the claimed antibody sequence, the claimed pharmaceutical compositions of the '504 patent would still be nonobvious.

256. In particular, Dr. Balthasar still has not shown:

- How a POSA would have been motivated to use the claimed antibody in a “method of treating a patient suffering from [PNH]” (as the claims require), or would have reasonably expected to succeed in doing so;
- How a POSA would have reasonably expected to achieve success in using the claimed antibody to obtain the “immediate and sustained decrease in mean levels of lactate dehydrogenase (LDH)” recited in claims 9 and 10; and
- How a POSA would have further been motivated to make, or reasonably expected to succeed in making, the claimed *pharmaceutical compositions* of the specific amino acid sequence recited in claims 1-10

of the '504 patent, that would be suitable for use in the claimed methods of treating patients suffering from PNH.

257. Again, Dr. Balthasar ignores the known complexity and unpredictability in antibody design as of March 15, 2007, including the design of humanized monoclonal antibodies; the challenges, expenses, and unpredictability of clinical research of such monoclonal antibodies; and the design of pharmaceutical compositions of such antibodies suitable for human therapeutic use to treat PNH without undue harm to the patient. (*See* Sections VI.D.2 and VI.D.4 above.)

258. 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 ¶ 192.) He further states that success with pharmaceutical compositions and treatment of PNH with the antibody he assembles in hindsight from Evans and Mueller would be reasonably expected because of the preparation of “eculizumab” compositions by Bell and Wang, and the success of “eculizumab” in published human clinical trials. (AMG1002 ¶ 191.)

259. 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 Evans and Mueller, or Bell and Wang, would have taught or given a POSA a reasonable expectation of success that a different antibody with the specific amino acid sequence of claims 1-10 of the ’504 patent would even be “an antibody that binds C5,” let alone whether it would be suitable for use in “treating a patient suffering from [PNH],” as is required by all of claims 1-10.

260. 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 ’504 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, VI.D.4 and VII.D.4 above.)

261. For the antibody that Dr. Balthasar constructs in hindsight from Evans and Mueller 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 (let alone the specific 300 mg single unit dosage form, 10 mg/ml concentration antibody solution formulation of claim 6), or usefulness of the antibody or a pharmaceutical composition of the antibody in treating PNH.

262. Accordingly, even if a POSA provided with Bell, Evans and Mueller (and Wang) 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 to use that antibody for the specific methods of treating PNH and pharmaceutical compositions claimed in the '504 patent, and would not have reasonably expected to succeed in doing so.

**F. Objective Indicia Support the
Nonobviousness of Claims 1-10 of the '504 Patent**

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

264. In my opinion, objective evidence supports the nonobviousness of the invention claimed in the '504 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 ¶ 215.)

**1. SOLIRIS[®] is the Commercial Embodiment
of the '504 Patent**

265. 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.

266. In my opinion, the commercial product SOLIRIS[®] embodies the claimed features of claims 1-10 of the '504 patent. Claims 1-10 of the '504 patent each cover methods of treating PNH using pharmaceutical compositions comprising 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; ALXN2032 at 262:2-19.)

267. 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 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 ’504 patent. (ALXN2005 at 1, 5 (Section 11); ALXN2053 at 1, 21.)

268. 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 ’504 patent. The specially engineered anti-C5 antibody claimed by its unique amino acid sequence in claims 1-10 of the ’504 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.)

269. While the claims of the ’504 patent are limited to methods of treating PNH, I further note that the claimed antibody recited in the ’504 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**

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

271. 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 to medicine.” (ALXN2050 at 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.” (*Id.*)

272. 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.)

273. 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.)

274. 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.)

275. 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.)

276. 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) (“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.”).)

277. In sum, there is no question that the invention claims 1-10 of the ’504 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.

278. In my opinion, the nonobviousness of the ’504 patent is also supported by the failure of others to solve the problem that was addressed by the claimed invention of the ’504 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.

279. 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 '504 patent in particular.

3. SOLIRIS® Is A Commercial Success

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

281. 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.

282. In my opinion, the commercial success of SOLIRIS® is directly linked to the claimed invention of the '504 patent. As I explain in Section VII.F.1 above, the invention of claims 1-10 of the '504 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

283. Praise in the industry for SOLIRIS[®] further supports my opinions on the nonobviousness of the '504 patent. As shown above in Section VII.F.2, SOLIRIS[®], the commercial embodiment of the claimed invention of the '504 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[®].

284. 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. Copying

285. I am also aware that Amgen, who is challenging the '504 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 '504 patent. (ALXN2088 at 1; ALXN2090 at 2; ALXN2089 at 1.)

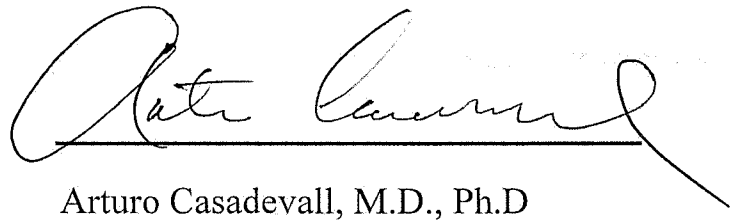
286. The copying by others of the claimed antibody comprising SEQ ID NOs: 2 and 4 is, in my view, further objective evidence of the nonobviousness of the '504 patent's invention. If it were simple to recreate the clinical benefits of properties of SOLIRIS without using the specific amino acid sequence of eculizumab (as known today) claimed in the '504 patent, then these companies could have tried to develop their own antibodies with different amino acid sequences not recited in the '504 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 '504 patent, and have tried to copy it in an effort to provide patients with the same clinical benefits provided by SOLIRIS®.

287. This supports my opinion, as explained above, that 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

288. For the reasons stated above, claims 1-10 of the '504 patent were 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.

A handwritten signature in black ink, appearing to read 'Arturo Casadevall', is written over a horizontal line. The signature is fluid and cursive, with a large initial 'A' and a long, sweeping tail that extends to the right.

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
615 N. Wolfe Street, E5132
Baltimore, MD 21205
Phone: 410-955-3457
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	2015-Present	JH Bloomberg Sch. of Public Health Dept of Molecular, Microbiol. & Immunol
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 21 st 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 six 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 Livermore National 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; Chair 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, NIAID 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	Commencement 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	14 th Farness Lecturer, U. Arizona
2010	Marshall S. Horwitz Faculty Achievement Award
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, lKe, 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) Silver (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 York 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* Glucuronoxylomannan. *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 Immunoglobulin 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.
45. Brosnan CF, Battistini L, Raine CS, Dickson DW, **Casadevall A**, Lee SC. (1994). Reactive nitrogen intermediates in human neuropathology: an overview. *Developmental Neuroscience* 16:152-161.

46. Cleare W, Mukherjee J, Spitzer ED, **Casadevall A** (1994) Prevalence in *Cryptococcus neoformans* strains of a polysaccharide epitope which can elicit protective antibodies. Clin. Diagn. Lab. Immunol. 1:737-740.
47. Wang, Y. and **Casadevall A** (1994) Decreased susceptibility of melanized *C. neoformans* to ultraviolet light. Appl.Environ.Microbiol. 60:3864-3866.
48. Spira, G, Ruirong, Y, Paizi, M, Weisendal M, **Casadevall A** (1994) Simultaneous expression of kappa and lambda light chains in a murine IgG3 anti-*Cryptococcus neoformans* hybridoma cell line. Hybridoma 13:531-535.
49. Mukherjee J, Scharff MD, **Casadevall A** (1994) *Cryptococcus neoformans* infection can elicit protective antibodies in mice. Can.J.Microbiol. 40:888-892.
50. Wang Y, **Casadevall A** (1994) Growth of *Cryptococcus neoformans* in the presence of L-dopa decreases its susceptibility to Amphotericin B. Antimicrobial Agents Chemoth. 38:2648-2650.
51. Goldman D, Lee SC, **Casadevall A** (1994) Pathogenesis of pulmonary cryptococcosis in the rat Infect. Immun. 62:4755-4761.
52. Mukherjee J, Nussbaum G, Scharff MD, **Casadevall A** (1995) Protective and non-protective antibodies to *C. neoformans* originating from one B cell. J. Exp. Med. 181:405-409.
53. Mukherjee S, Lee SC, **Casadevall A** (1995) Antibodies to *Cryptococcus neoformans* glucuronoxylomannan enhance antifungal activity of murine macrophages. Infect. Immun. 63:573-579.
54. Ruirong Y, **Casadevall A**, Spira G, Scharff MD (1995) Isotype switching from IgG3 to IgG1 converts a non-protective murine antibody to *Cryptococcus neoformans* to a protective antibody. J. Immunol. 154:1810-1816.
55. Mukherjee S, **Casadevall A** (1995) Sensitivity of sandwich ELISAs for *Cryptococcus neoformans* polysaccharide antigen is dependent on the isotype of the capture and detection antibodies. J. Clin. Microbiol. 33:765-768.
56. Mozaffarian N, Berman JW, **Casadevall A** (1995) Crosslinking of Fc-gamma receptors increases nitric oxide production by interferon-gamma-stimulated murine macrophage-like J774.16 cells. J.Leukocyte Biol. 57:657-662.
57. Cherniak R, Morris LC, Belay T, Spitzer ED, **Casadevall A** (1995) Variation in the structure of glucuronoxylomannan in isolates from patients with recurrent Cryptococcal Meningitis. Infect. Immun. 63:1899-1905
58. **Casadevall A** (1995) Antibody Immunity and *Cryptococcus neoformans*. Can.J.Bot. 73:s1180-1186.
59. **Casadevall A**, Scharff MD (1995) Return to the past: the case for the re-introduction of passive antibody therapy. Clin. Infect. Dis. 21:150-161.
60. Nussbaum G, Yuan R, **Casadevall A**, Valadon P, Scharff MD (1995) Vaccination elicits protective and non-protective antibodies to *Cryptococcus neoformans*. Vaccines 95. Cold Spring Harbor Press. Cold Spring Harbor, NY. p.231-235.

61. Kristensson K, Glasser SM, **Casadevall A**, Scharff MD, Zebedee SL, Huse WD (1995) Humanization of a murine antibody against *Cryptococcus neoformans* polysaccharide using a novel approach. *Vaccines* 95. Cold Spring Harbor Laboratory Press, Cold Spring Harbor, NY. p.39-43.
62. Mukherjee J, Cleare W, **Casadevall A** (1995) Monoclonal antibody mediated capsular reactions (quellung) in *Cryptococcus neoformans*. *J. Immunol. Methods* 184:139-143.
63. Currie BP, Ghannoum M, **Casadevall A** (1995) Decreased fluconazole susceptibility of a relapse *Cryptococcus neoformans* isolated after fluconazole treatment. *Infect.Dis.Clin.Pract.* 4:318-319.
64. Fan M, Chen L.-C, Ragan MA, Guttell RR, Warner JR, Currie BP, **Casadevall A** (1995) The 5S rRNA and the rDNA intergenic spacer of the two varieties of *Cryptococcus neoformans*. *J. Med. Vet. Mycology* 33:215-221.
65. Mukherjee J, Scharff MD, Feldmesser M, **Casadevall A** (1995) Monoclonal antibodies to *Cryptococcus neoformans* glucuronoxylomannan enhance fluconazole efficacy. *Antimicrob. Agents. Chemotherap.* 39:1398-1405.
66. Wang Y, Aisen P, **Casadevall A** (1995) *Cryptococcus neoformans* melanin and Fungal Virulence: Mechanism of Action. *Infect. Immun.* 63:3131-3136.
67. Goldman D, Lee SC, **Casadevall A** (1995) Tissue localization of *Cryptococcus neoformans* glucuronoxylomannan in the presence and absence of specific antibody. *Infection and Immunity* 63:3448-3453.
68. Lee SC, Kress Y, Dickson DW, and **Casadevall A** (1995) Human microglia mediate anti-*Cryptococcus neoformans* activity in the presence of specific antibody. *J. Neuroimmunology* 62:43-52.
69. Edelman M, Birkenhauer MC, Steinberg JJ, Dickson DW, **Casadevall A**, Lee SC. (1996) Microglial nodule encephalitis: limited CNS infection despite disseminated systemic Cryptococcosis. *Clinical Neuropathology* 15:30-33.
70. Mukherjee J., Scharff MD, and **Casadevall A** (1995) Variable efficacy of passive antibody administration against diverse *Cryptococcus neoformans* strains. *Infection and Immunity* 63:3353-3359.
71. Currie BC, Sanati H, Ibrahim AS, Edwards JE, **Casadevall A** and Ghannoum MA. (1995) The sterol composition and susceptibility to amphotericin B of environmental *Cryptococcus neoformans* are changed by murine passage. *Antimicrob. Agents Chemotherap.* 39:1934-1937.
72. Gordon M. and **Casadevall A** (1995) Serum therapy for cryptococcal meningitis. *Clin. Infect. Dis.* 21:1477-9.
73. Chen F, Currie BP, Chen L, Spitzer S, Spitzer ED, **Casadevall A** (1995) Genetic relatedness of *Cryptococcus neoformans* clinical isolates Grouped with repetitive DNA Probe CNRE-1. *J. Clin. Microbiol* 33:2818-2822.
74. **Casadevall A** (1995) Antibody immunity and fungal infections. *Infection and Immunity* 63:4211-4218.
75. Lee SC, Kress Y, Zhao ML, Dickson DW, **Casadevall A** (1995) *Cryptococcus neoformans* survive and replicate in human microglia. *Laboratory Investigation* 73:871-879.

76. Feldmesser M, Mukherjee J, **Casadevall A** (1996) Combination of 5-flucytosine and capsule binding monoclonal antibody in therapy of murine *Cryptococcus neoformans* infections and *in vitro*. J. Antimicrobial. Therap. 37:617-622.
77. Lee SC, **Casadevall A**, and Dickson, DW (1996) Immunohistochemical localization of capsular polysaccharide antigen in the central nervous system cells in cryptococcal meningitis. Amer. J. of Pathol. 148:1267-1274.
78. Pirofski L, **Casadevall A** (1996). *Cryptococcus neoformans*: Paradigm for the role of antibody immunity against fungi? Zentralblatt fur Bakteriologie 284:475-495.
79. Goldman D, Chao Y, Zhao M-L, **Casadevall A**, Lee, S.C. (1996) Expression of inducible nitric oxide synthase in rat pulmonary *Cryptococcus neoformans* granuloma. Amer. J. Pathol 148:1275-1282.
80. Nussbaum G, Yuan R, **Casadevall A**, Scharff MD. (1996) Immunoglobulin G3 to the Fungal Pathogen *Cryptococcus neoformans*. J. Exp. Med. 183:1905-1909.
81. Mukherjee S, Feldmesser M, **Casadevall A** (1996) J774 Murine macrophage cell interactions with *C. neoformans* in the presence and absence of opsonins. J. Infect. Dis. 173:1222-1231.
82. Lee SC, **Casadevall A** (1996) Polysaccharide antigen in brain tissue of patients with cryptococcal meningitis. Clin. Infect. Dis. 23:194-195.
83. Wang Y, **Casadevall A** (1996) Susceptibility of melanized and non-melanized *Cryptococcus neoformans* to the melanin-binding compounds trifluoperazine and chloroquine. Antimicrobial Agents and Chemotherapy 40:541-545.
84. Lee SC, Dickson DW, **Casadevall A** (1996) Pathology of cryptococcal meningoencephalitis. Analysis of 27 patients with pathogenic implications. Human Pathology 27:839-847.
85. Fries BC, Chen F, Currie BP, and **Casadevall A** (1996) Karyotype instability in *C. neoformans* J. Clin. Microbiol. 34:1531-1534.
86. **Casadevall A** Antibody-based therapies for emergent pathogens (1996) Emergent Infectious Diseases. Emergent Infectious Diseases 2:200-208.
87. Wang Y, Aisen P, and **Casadevall A** (1996) Melanin, melanin ghosts, and melanin composition of *Cryptococcus neoformans*. Infection and Immunity 64:2420-2424.
88. Spira G, Paizi M, Nussbaum G, Mukherjee S, **Casadevall A** (1996) Generation of biologically active anti *Cryptococcus neoformans* IgG, IgE, and IgA isotype-switch variant antibodies by acridine orange mutagenesis. Clin. Exp. Immunol. 105:436-442.
89. Chen L, Blank E, **Casadevall A** (1996) Extracellular proteinase activity of *C. neoformans*. Clin. Diagn. Lab. Immunol. 3:570-574.
90. **Casadevall A** (1996) Crisis in Infectious disease: Time for a new paradigm? Clin. Infect. Dis. 1996:23:790-794.
91. Feldmesser M, Harris C, Reichberg S, Khan S, and **Casadevall A** (1996) Serum Cryptococcal antigen in Patients with AIDS. Clin. Infect. Dis. 23:827-30.

92. Glatman-Freedman A, Martin JM, Riska, PF, Bloom BR, **Casadevall A** (1996) Monoclonal antibodies to surface antigens of *Mycobacterium tuberculosis* and their use in a modified ELISA spot assay for the detection of mycobacteria. J. Clin. Microbiol. 34:2795-2802.
93. Goldman DL, **Casadevall A**, ChoY, Lee SC (1996) Cryptococcus meningitis in the rat. Laboratory Investigation 75:759-770.
94. **Casadevall A** (1997) Antibodies and fungi: an evolving paradigm with opportunities for the development of new antifungal therapies and vaccines. Revista Iberoamericana de Micologia 14:2-3.
95. Feldmesser M, **Casadevall A** (1997) Effect of Serum IgG1 to *Cryptococcus neoformans* glucuronoxylomannan alters the course of murine pulmonary infection J. Immunol. 158:790-799.
96. Belay T, Cherniak R, Kozel T.R., **Casadevall A** (1997) Reactivity patterns and epitope specificities of anti-*Cryptococcus neoformans* antibodies by Enzyme-linked immunosorbent assay and dot blot assay. Infection and Immunity 65:718-728.
97. Nussbaum G, Cleare W, **Casadevall A**, Scharff MD, Valadon P (1997) Epitope location in the *Cryptococcus neoformans* capsule is a determinant of antibody efficacy. J. Exp. Med 185:685-694.
98. Franzot S and **Casadevall A** (1997) Pneumocandin L-743,872 enhances the activity of amphotericin b and fluconazole against *Cryptococcus neoformans in vitro*. Antimicrob. Agents Chemotherap. 41:331-336.
99. Lukashok S, **Casadevall A** (1997) Persistent vancomycin-resistant *Enterococcus faecium* bacteremia. Infect. Dis. Clin. Pract. 6:250-255.
100. Nosanchuck J and **Casadevall A** (1997) The cellular charge of *C. neoformans*: contributions from polysaccharide capsule, melanin, and monoclonal antibody binding. Infect. Immun. 65:1836-1841.
101. Ruirong Y, **Casadevall A**, Scharff MD (1997) T cells cooperate with passive antibody to modify *Cryptococcus neoformans* infective in mice. PNAS 94:2483-2488.
102. Feldmesser M, **Casadevall A**, Kress Y, Spira G, and Orlofsky A (1997) Eosinophil-*Cryptococcus neoformans* interactions *in vitro* and *in vivo*. Infection and Immunity 65:1899-1907.
103. Goldman DL, **Casadevall A**, Zuckier LS (1997) Pharmacokinetics and biodistribution of a monoclonal antibody to *Cryptococcus neoformans* capsular polysaccharide antigen in a rat model of cryptococcal meningitis: implications for passive immunotherapy. J. Med. Vet. Mycol. 35:271-8.
104. Chen L-L, Pirofski L, **Casadevall A** (1997) Extracellular proteins of *C. neoformans* and the host antibody response. Infection and Immunity 65:2599-2605.
105. Rosas AL, **Casadevall A** (1997) Melanization affects susceptibility of *Cryptococcus neoformans* to heat and cold stress. FEMS Microbiology Letters 153:265-272.
106. Franzot S, Hamdan J, Currie BP, **Casadevall A** (1997). Molecular epidemiology of *Cryptococcus neoformans* in Brazil and the United States: evidence for both local genetic differences and a global clonal population structure. J. Clin. Microbiol. 35:2243-2251.

107. Mozaffarian N, Berman JW, **Casadevall A** (1997) Enhancement of macrophage nitric oxide synthesis represents an additional mechanism of action for amphotericin B. *Antimicrob. Agents Chemotherap.* 41:1825-1829.
108. Blackstock R and **Casadevall A** (1997) Presentation of Cryptococcal Capsular polysaccharide (GXM) on activated antigen-presenting cells inhibits the T suppressor response and enhances delayed-type hypersensitivity and survival. *Immunology* 92:334-339.
109. **Casadevall A**, Goldman DL, Feldmesser MF (1997) Antibody-based therapies for infectious diseases: Renaissance for an abandoned arsenal? *Ann. Pasteur. Inst.* 95:247-257.
110. Pirofski L and **Casadevall A** (1998) The use of licenced vaccines for active immunization of the immunocompromised host. *Clin. Microbiol. Rev.* 11:1-26.
111. Podwall D, Yador E, Mille, S, Pena J, Franzot SP, **Casadevall A**, Steinberg JJ (1998) Interstrain variation in the deoxynucleotide composition of *Cryptococcus neoformans*. *J. Med. Vet. Mycol.* 36:1-5.
112. Young A, Valadon P, **Casadevall A**, Scharff MD, Sacchatini J (1997) The three dimensional structures of a polysaccharide binding antibody to *Cryptococcus neoformans* and its complex with a peptide from a phage display library: implications for the identification of peptide epitopes. *J. Mol. Biol.* 274:622-634.
113. Vecchiarelli A, Monan C, Retini C, Pietrella D, Palazetti B, Pitzurra L, and **Casadevall A** (1998) *Cryptococcus neoformans* differently regulates B7-1 (CD80) and B7-2 (CD86) expression on human monocytes. *Eur. J. Immunol.* 28:114-121.
114. Franzot SP, Mukherjee J, Cherniak R, Chen L, Hamdam JS, and **Casadevall A** (1998) Microevolution of a standard strain of *Cryptococcus neoformans* resulting in differences in virulence and other phenotypes. *Infect. Immun.* 66:89-97.
115. Vecchiarelli A, Retini C, Monari C and **Casadevall A** (1998) Specific antibody to *Cryptococcus neoformans* alters human leukocyte cytokine expression and promotes T cell proliferation. *Infect. Immun.* 66:1244-1247.
116. Glattman-Freedman A and **Casadevall A** (1998) Serum therapy for tuberculosis revisited: A critical reappraisal of the role of antibody-mediated immunity against *Mycobacterium tuberculosis*. *Clin. Microbiol. Rev.* 11:514-542.
117. Yuan R, Spira G, Oh J, Paizi M, **Casadevall A**, Scharff MD, (1998). Isotype switching increases antibody protective efficacy to *Cryptococcus neoformans* infection in mice. *Infect. Immun.* 66:1057-1062.
118. Lendvai N, **Casadevall A**, Liang Z, Goldman DL, Mukherjee J, Zuckier L, (1998) Effect of immune mechanisms on the pharmacokinetics and organ distribution of cryptococcal polysaccharide. *J. Infect. Dis.* 177:1647-1659.
119. Feldmesser M, Kress Y, **Casadevall A** (1998) Effect of antibody to capsular polysaccharide on eosinophilic pneumonia in murine infection with *Cryptococcus neoformans*. *J. Infect. Dis.* 177:1639-1646.

120. Murphy JW, Schafer F, **Casadevall A** (1998) Antigen-induces protective and nonprotective cell-mediated immune components against *Cryptococcus neoformans*. *Infection and Immunity* 66:2632-2639.
121. Cleare W and **Casadevall A** (1998) The different binding patterns of two immunoglobulin M monoclonal antibodies to *Cryptococcus neoformans* serotype A and D strains correlate with serotype classification and differences in functional assays. *Clin. Diagn. Lab. Immunol.* 5:125-128.
122. **Casadevall A** (1998) Antibody-mediated protection against intracellular pathogens. *Trends in Microbiology* 6:102-107.
123. Feldmesser M and **Casadevall A** (1998) Mechanism of action of antibody to capsular polysaccharide in *Cryptococcus neoformans* infection *Frontiers in Bioscience*, 3:d136-151.
124. **Casadevall A** (1998) Antibody-based therapies as anti-infective agents *Expert Opinion on Investigational Drugs*, 7:307-321.
125. **Casadevall A**, Cleare W, Feldmesser M, Glatman-Freedman A, Goldman DL, Kozel TR, Lendvai N, Mukherjee J, Pirofski L, Rivera J, Rosas AL, Scharff MD, Valadon P, Westin K, Zhong Z (1998) Characterization of a murine monoclonal antibody to *Cryptococcus neoformans* polysaccharide that is a candidate for human therapeutic studies. *Antimicrob. Agents Chemotherap.* 42:1437-1446.
126. **Casadevall A.** (1998) Cryptococcosis in Alabama. *Ann. Epidemiol.* 8:209-211.
127. Dixon DM, **Casadevall A**, Klein B, Mendoza L, Travassos L, Deepe GS (1998) Development of vaccines and their use in prevention of fungal infections *Medical Mycology* 36 (suppl):57-67.
128. **Casadevall A**, Cassone A, Bistoni, F., Cutler, J.E., Magliani, W., Murphy, J.W., Polonelli, L., Romani, L. Antibody - and/or cell mediated immunity - protective mechanisms in fungal disease: and ongoing dilemma or an unnecessary dispute? (1998) *Medical Mycology* 36 (suppl):95-105.
129. Franzot SP, Fries BC, Cleare W, **Casadevall A** (1998) Genetic relationship between *Cryptococcus neoformans* var. *neoformans* strains of serotypes A and D. *J. Clin. Microbiol.* 36 :2200-2204.
130. Nosanchuk JD, Rosas AL, **Casadevall A** (1998) The antibody response to fungal melanin in mice *J. Immunol.* 160:6026-6031.
131. Vecchiarelli A, Retini C, **Casadevall A**, Monari C, Pietrella D, Kozel TR (1998) Involvement of C3a and C5a in Interleukin-8 secretion by human polymorphonuclear cells in response to capsular polysaccharide material of *Cryptococcus neoformans*. *Infect. Immun.* 66:4324-4330,.
132. Dong F, Feldmesser M, **Casadevall A**, Rubin CS (1998) Molecular characterization of a cDNA that encodes six isoforms of a novel murine A kinase anchor protein. *J.Biol.Chem.* 273:6533-6541.
133. Vecchiarelli A and **Casadevall A** (1998) Antibody-mediated effects against *Cryptococcus neoformans*: evidence for interdependency and collaboration between humoral and cellular immunity. *Res.Immunol.* 149:321-333.
134. Mukherjee J, Kozel TR, **Casadevall A** (1998) Monoclonal antibodies Reveal Additional Epitopes of Serotype D *Cryptococcus neoformans* capsular Glucuronoxylomannan that Elicit Protective Antibodies. *J. Immunol.* 161:3557-3568.

135. Rivera J, Feldmesser M, Cammer M, **Casadevall A** (1998) Organ dependent variation of capsule thickness in *Cryptococcus neoformans* during experimental murine infection. Infect. Immun. 66:5027-5030.
136. Fries BC and **Casadevall A** (1998) Serial isolates of *Cryptococcus neoformans* from patients with AIDS differ in virulence for mice. J. Infect. Dis. 178:1761-1766
137. Goldman DL, Fries, BC, Franzot SP, Montella L, **Casadevall A** (1998) Phenotypic switching in the human pathogenic fungus *Cryptococcus neoformans* is associated with changes in virulence and pulmonary inflammatory responses in rodents. PNAS 95:14967-14972.
138. Teitelbaum R, Glatman-Freedman A, Chen B, Robbins JB, Unanue E, **Casadevall A**, Bloom BR (1998) A Mab recognizing a surface antigen of *Mycobacterium tuberculosis* enhances host survival. PNAS 95:15688-15693.
139. Heitman J, **Casadevall A**, Lodge JK, and Perfect JR (1999) The *Cryptococcus neoformans* genome sequencing project. Mycopathologia 148:1-7.
140. Nosanchuk J, Valadon P, Feldmesser M, **Casadevall A** (1999) Melanization of *Cryptococcus neoformans* in murine infection. Mol.Cell Biol. 19:745-750.
141. Cleare W and **Casadevall A** (1999) Scanning electron microscopy of encapsulated and non-encapsulated *Cryptococcus neoformans* and the effect of glucose on capsular polysaccharide release. Medical Mycology 7(4):235-43.
142. Retini C, **Casadevall A**, Pietrella D, Monari C, Palazatti B, Vecchiarelli A (1999) Specific activated T cells regulate interleukin-12 production by human monocytes stimulated with *Cryptococcus neoformans*. J. Immunol. 162:1618-1623.
143. Nosanchuk J, Cleare W, Franzot SP, **Casadevall A** (1999) Amphotericin B and fluconazole affect cellular charge, macrophage phagocytosis, and cellular morphology of *Cryptococcus neoformans* at subinhibitory concentrations. Antimicrob. Agents Chemother. 43:233-239.
144. Franzot SP, Salkin IF, **Casadevall A** (1999) *Cryptococcus neoformans* var. *grubii*: separate varietal status for *Cryptococcus neoformans* serotype A isolates. J. Clin. Microbiol. 37:838-840.
145. Chen LC and **Casadevall A** (1999) Labeling of proteins with [³⁵S]-methionine and/or [³⁵S]-cysteine in the absence of cells. Analytical Biochem. 269:179-188.
146. Chen LC and **Casadevall A** (1999) Variants of a *Cryptococcus neoformans* strain elicit different inflammatory responses in mice. Clin.Diagn.Lab.Immunol.6:266-268.
147. Doering TL, Nosanchuk KD, Roberts KW **Casadevall A** (1999) Melanin as a potential cryptococcal defense against microbicidal proteins. Med.Mycol. 7(3):175-81.
148. Chen L, Goldman DA, Doering TL, Pirofski L, **Casadevall A** (1999) The antibody response to *Cryptococcus neoformans* in rodents and humans. Infect. Immun. 67:2218-2224.

149. Monari C, **Casadevall** A, Retini C, Baldelli F, Bistoni F, Vecchiarelli A (1999) Antibody to capsular polysaccharide enhances the function of neutrophils from patients with AIDS against *Cryptococcus neoformans*. *AIDS* 13:653-660.
150. Cleare W, Cherniak RL, **Casadevall** A (1999). In vitro and in vivo stability of a *Cryptococcus neoformans* glucuronoxylomannan epitope that elicits protective antibodies. *Infect. Immun.* 67(6):3096-107.
151. Lendvai N, **Casadevall** A (1999) Monoclonal Antibody-mediated toxicity in *Cryptococcus neoformans* infection: mechanism and relationship to antibody isotype. *J. Infect. Dis.* 180:791-801.
152. **Casadevall** A, Pirofski L (1999) Host-pathogen interactions: redefining the basic concepts of virulence and pathogenicity. *Infect. Immun.* 67:3703-3713.
153. Monari C, Kozel TR, **Casadevall** A, Pietrella D, Palazzetti B, Vecchiarelli A (1999) B7 co-stimulatory ligand regulates development of the T cell response to *Cryptococcus neoformans*. *Immunology* 98:27-35.
154. Nussbaum GJ, Anadasabapthy S, Mukherjee J, Fan M, **Casadevall** A, Scharff MD (1999) Molecular and idiotypic analysis of the antibody response to *Cryptococcus neoformans* glucuronoxylomannan-protein conjugate vaccine in autoimmune and nonautoimmune mice. *Infect. Immun.* 67(9):4469-76.
155. Cleare W, Brandt ME, **Casadevall** A (1999) Monoclonal antibody 13F1 produces annular immunofluorescence patterns on *Cryptococcus neoformans* serotype AD isolates. *J. Clin. Microbiol.* 37:3080.
156. **Casadevall** A (1999) Passive antibody therapies: progress and continuing challenges. *Clin. Immunol.* 93(1):5-15.
157. Nosanchuk J, Rudolf J, Rosas AL, **Casadevall** A (1999) Evidence that *Cryptococcus neoformans* is melanized in pigeon excreta: implications for pathogenesis. *Infect. Immun.* 67:5477-9.
158. Monari C, **Casadevall** A, Pietrella D, Bistoni F, Vecchiarelli A (1999) Neutrophils from Patients with Advanced Human Immunodeficiency Virus Infection have impaired complement receptor function and preserved FCY Receptor Function. *J. Infect. Dis.* 180:1542-9.
159. Fries BC, Goldman DL, Cherniak R, Ju R, **Casadevall** A (1999) Phenotypic Switching in *Cryptococcus neoformans* strain 24067A is associated with changes in virulence, polysaccharide structure and cellular morphology. *Infect. Immun.* 67:6076-83.
160. Goldman DL, Lee SC, Mednick AJ, Montell L, **Casadevall** A (2000) Persistent *Cryptococcus neoformans* pulmonary infection in the rat is associated with intracellular parasitism, decreased inducible nitric oxide expression and altered antibody responsiveness to cryptococcal polysaccharide. *Infect. Immun.* 68:832-838.
161. Glatman-Freeman, Mednick A, Lendvai N, **Casadevall** A (2000) Clearance and organ distribution of *Mycobacterium tuberculosis* lipoarabinomannan (LAM) in the presence and absence of LAM-specific Immunoglobulin M. *Infect. Immun.* 68:335-341.
162. Cox GM, Mukherjee J, Cole GT, **Casadevall** A, Perfect JR (2000). Urease as a virulence factor in experimental cryptococcosis. *Infect. Immun.* 68:443-8.

163. Nosanchuk JD, Shoham S, Fries BC, Shapiro DS, Levitz SM, **Casadevall A** (2000) Evidence for zoonotic transmission of *Cryptococcus neoformans* from a pet cockatoo to an immunocompromised patient. *Ann.Intern.Med.*2000: 132; 205-208.

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<http://partners.nytimes.com/library/national/science/health/020800hth-animal-fungus.html>

164. Rosas A, Nosanchuk JD, Feldmesser M, Cox, McDade HC, and **Casadevall A** (2000) Synthesis of polymerized melanin by *Cryptococcus neoformans* in rodents. *Infect. Immun.* 68:2845-2853.

165. Lendvai N, Xiao-Wu Q, Hsueh W, **Casadevall** (2000) Mechanism for the isotype dependence of antibody-mediated toxicity in *Cryptococcus neoformans* infected mice. *J. Immunol.* 164:4367-4374.

166. Feldmesser M, Rivera J, Kress Y, Kozel TR, **Casadevall A** (2000) Antibody interactions with the capsule of *Cryptococcus neoformans*. *Infect. Immun.* 68:3642-3650.

167. Steenbergen J and **Casadevall A** (2000) Prevalence of *cryptococcus neoformans* var. *neoformans* (Serotype D) and *cryptococcus neoformans* var. *grubii* (Serotype A) isolates in New York City. *J. Clin. Microbiol.* 38:1974-1976.

168. Nosanchuk JD, Rosas AL, Lee SC, **Casadevall A** (2000) Melanization of *Cryptococcus neoformans* in human brain tissue. *Lancet* 355:2049-2050.

169. Tracy C, MacGill RS, MacGill A, **Casadevall A**, Kozel TR (2000) Biological correlates of capsular (quellung) reactions of *Cryptococcus neoformans*. *J. Immunol.* 164:4835-4842.

170. **Casadevall A**, Rosas AL, Nosanchuk JD (2000) Melanin and virulence in *Cryptococcus neoformans*. *Current Opinion in Microbiology* 3:354-358



171. Feldmesser M, Kress Y, Novikoff P **Casadevall A** (2000). *Cryptococcus neoformans* is a facultative intracellular pathogen in murine pulmonary infection. *Infect. Immun.* 68:4225-4237.

172. Mozaffarian N, **Casadevall A**, Berman JW (2000) Inhibition of human endothelial cell chemokine production by the opportunistic fungal pathogen *Cryptococcus neoformans*. *J. Immunol.* 165:1541-1547.

173. Rosas AL, Nosanchuk JD, Gomez BL, Edens WA, Henson JM, **Casadevall A** (2000) Isolation and serological analyses of fungal melanins. *J. Immunol. Methods* 244:69-80.

174. **Casadevall A** (2000) Host-microbe interactions: fungi. *Recent Progress in understanding host-fungal interactions. Current Opinion in Microbiology* 3:337-338.

175. Monari C, **Casadevall A**, Baldelli F, Francisci D, Pietrella D, Bistoni F, Vecchiarelli A (2000) Normalization of anti-cryptococcal activity and interleukin-12 secretory function of polymorphonuclear leukocytes from HIV-infected patients after highly active antiretroviral therapy. *AIDS* 14:2699-2708.

176. Vecchiarelli A, Monari C, Palazzetti B, Bistoni F, **Casadevall A** (2000) Dysregulation of IL-12 secretion by neutrophils from infected patients. *Clin.Exp.Immunol.* 121:311-319.
177. **Casadevall A**, Pirofski L (2000) Host-Pathogen Interactions. The basic concepts of microbial commensalism, colonization, infection and disease. *Infect. Immun.* 68:6511-6518.
178. Feldmesser M, Kress Y, **Casadevall A** (2000) The Effect of the Echinocandin Analog Caspofungin on Cell Wall Glucan Synthesis by *Cryptococcus neoformans*. *J. Infect. Dis.* 182:1791-1795.
179. Cox GM, McDade HC, Chen SC, Tucker SC, Gottfredsson M, Wright LC, Sorrell T, Leidich SD, **Casadevall A**, Ghannoum MS, Perfect JR (2001) Extracellular Phospholipase Activity is a Virulence Factor for *Cryptococcus neoformans* *Mol.Micro.* 39:166-175.
180. Garcia-Rivera J, **Casadevall A** (2001) Melanization of *Cryptococcus neoformans* reduces its susceptibility to the antimicrobial effects of Silver Nitrate. *Medical Mycology* 39:353-357.
181. Tabora C, **Casadevall A** (2001). Immunoglobulin M efficacy against *Cryptococcus neoformans*: mechanism, dose dependence and prozone-like effects in passive protection experiments. *J. Immunol.* 166:2100-2107.
182. Luberto C, Toffaletti DL, Wills EA, Tucker SC, **Casadevall A**, Perfect JR, Hannun YU, Del Poeta M (2001). Roles for inositol-phosphoryl ceramide synthase 1 (*IPC1*) in pathogenesis of *Cryptococcus neoformans*. *Genes & Development* 15:201-212.
183. Schwebach JR, Jacobs WR Jr, **Casadevall A** (2001) Sterilization of *Mycobacterium tuberculosis* Erdman Samples by Antimicrobial Fixation in the BSL-3 Laboratory. *J. Clin. Microbiol.* 39:769-771.
184. Goldman DL, Khine H, Abadi J, Lindenberg DJ, Pirofski L, Niang R, **Casadevall A** (2001) Serologic Evidence for *Cryptococcus neoformans* Infection in Early Childhood. *Pediatrics* 107; E66. (Published in electronic pages - full text at <http://www.pediatrics.org/cgi/content/full/107/5/e66>)
185. McClean GR, Nakouzi A, **Casadevall A**, Green NS (2000). Human and murine immunoglobulin expression vector cassettes. *Mol.Immunol.* 37:837-845.
186. Nosanchuk JD, Ovalle R, **Casadevall A** (2001). Glyphosate Inhibits Melanization of *Cryptococcus neoformans* and Prolongs Survival of Mice following Systemic Infection. *J. Infect. Dis.* 183:1093-1099.
187. Goldman D, Song X, Kitai R, **Casadevall A**, Zhao M, and Lee SC (2001) *Cryptococcus neoformans* induces MIP-1alpha and MIP-1alpha in human microglia: The role of specific antibody and soluble capsular polysaccharide. *Infect. Immun.* 69:1808-1815.
188. San-Blas G, Travassos LR, Fries BC, Goldman DS, **Casadevall A**, Carmona AK, Barros TF, Puccia R, Hostetter MK, Shanks SG, Copping VMS, Knox Y, Gow NAR (2001) Fungal morphogenesis and virulence. *Med.Mycol.* 38(Suppl 1):79-86.
189. Stevens DA, Kullberg BJ, Brummer E, **Casadevall A**, Netea MG (2001) Combined treatment: antifungal drugs with antibodies and cytokines. *Med Mycol* 38(Suppl 1):305-315.
190. Polonelli L, **Casadevall A**, Adriani D, Bernardis F, Boccanera M, Burnie JP, Cassone A, Conti S, Cutler JE, Frazzi R, Gregory C, Han Y, Hodgetts S, Illidge C, Kirkland TN, Magliani W, Matthews RC, Rigg G, Santoni G (2001) The efficacy of acquired humoral and cellular immunity in the prevention and

therapy of experimental fungal infections. *Med. Mycol.* 38(Suppl 1):281-292.

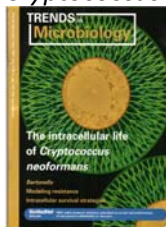
191. Feldmesser M, Kress Y, **Casadevall** A (2001) Intracellular crystal formation as a mechanism of cytotoxicity in murine pulmonary *Cryptococcus neoformans* infection. *Infect. Immun.* 69:2723-2727.

192. Wills EA, Roberts IS, del Poeta M, Cox GM, Rivera J, **Casadevall** A, Perfect JR (2001) Identification and characterization of the *Cryptococcus neoformans* phosphomannose isomerase-encoding gene, *MAN1*, and its impact on pathogenicity. *Mol. Micro.* 40:610-620.

193. Nakouzi A, Valadon P, Nosanchuk J, Green N, **Casadevall** A (2001) Molecular basis for IgM specificity to epitopes in *Cryptococcus neoformans* that elicit protective and non-protective antibodies. *Infect. Immun.* 69:3398-3409.

194. Rosas AL, Nosanchuk J, **Casadevall** A (2001) Passive Immunization with Melanin-Binding Monoclonal Antibodies Prolongs Survival in Mice with Lethal *Cryptococcus neoformans* Infection *Infect. Immun.* 69:3410-3412.

195. Feldmesser M, Tucker S, **Casadevall** A (2001) Intracellular parasitism of macrophages by *Cryptococcus neoformans*. *Trends in Microbiology* 9:273-278.



196. **Casadevall** A, Pirofski L (2001) Host-pathogen interactions: the attributes of virulence. *J. Infect. Dis.* 184:337-344.

197. Feldmesser M, Kress Y, **Casadevall** A (2001) Dynamic changes in the morphology of *Cryptococcus neoformans* during infection. *Microbiology* 147:2355-2365.

198. **Casadevall** A, Pirofski L (2001) Adjunctive immune therapy for fungal infections. *Clin. Infect. Dis.* 33:1048-1056.

199. Gomez BL, Nosanchuk JD, Diez S, Youngchim S, Aisen P, Cano LE, Restrepo A, **Casadevall** A, Hamilton AJ (2001) Detection of melanin-like pigments in the dimorphic fungal pathogen *Paracoccidioides brasiliensis* *in vitro* and during infection. *Infect. Immun.* 69:5760-5767.

200. Schwebach JR, **Casadevall** A, Schneerson R, Dai Z, Wang Z, Robbins JB, Glatman-Freedman A (2001) Expression of a *Mycobacterium tuberculosis* arabinomannan antigen *in vitro* and *in vivo*. *Infect. Immun.* 69:5671-5678.

201. Zhu X, Gibbons J, Garcia-Rivera J, **Casadevall** A, Williamson PR (2001) Laccase of *Cryptococcus neoformans* is a cell wall associated virulence factor. *Infect. Immun.* 69:5589-5596.
F1000 Recommended <http://f1000.com/prime/1052866#recommendations>

202. Rosas AL, **Casadevall** A (2001) Melanization decreases the susceptibility of *Cryptococcus neoformans* to enzymatic degradation. *Mycopathologia* 151:53-56.

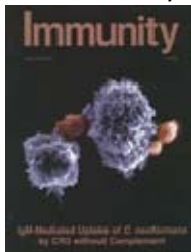
203. Martinez LR, Garcia-Rivera J, **Casadevall A** (2001) *C. neoformans* serotype D strains are more susceptible to heat than serotype A strains. J. Clin. Microbiol. 39:3365-3367.
204. Beenhouwer DO, Shapiro S, Feldmesser M, **Casadevall A**, Scharff MD (2001) Th1 and Th2 cytokines affect the ability of monoclonal antibodies to protect mice against *Cryptococcus neoformans*. Infect.Immun.69:10) 6445-6455
205. McFadden DC, **Casadevall A** (2001) Capsule and melanin synthesis in *Cryptococcus neoformans*. Med. Mycol. 39:19-30.
206. Fries BC, Tarborda CP, Serfass E, **Casadevall A** (2001) Phenotypic switching of *Cryptococcus neoformans* occurs in vivo and influences the outcome of infection. J. Clin. Invest. 108:1639-1648.
207. Steenbergen J, Shuman H, **Casadevall A** (2001). *Cryptococcus neoformans* interactions with amoebae suggest an explanation for its virulence and intracellular pathogenic strategy in macrophages. PNAS 98:15245-15250.
F1000 Recommended Must read <http://f1000.com/prime/1004027#recommendations>
Paper was discussed in PNAS commentary <http://www.pnas.org/content/98/26/14760.extract>
Editor's choice. Science, <http://www.sciencemag.org/content/295/5553/235.2.full.pdf?sid=3c9abfcd-cf2e-42a1-a014-c5fe82017a7b>
208. Rosas AL, McGill RS, Nosanchuk JD, Kozel TR, **Casadevall A** (2002) Activation of the alternative complement pathway by fungal melanins. Clin.Dian.Lab.Immunol. 9:144-148
209. Westin Kwon K, Lendvai N, Morrison S, Trinh KR, **Casadevall A** (2002) Biological activity of a mouse-human chimeric immunoglobulin G2 antibody to *Cryptococcus neoformans* polysaccharide. Clin. Diagn. Lab. Immunol. 9:201-204.
210. Feldmesser M, Mednick A, **Casadevall A** (2002). Antibody-mediated protection in murine *Cryptococcus neoformans* infection is associated with subtle pleiotrophic effects on cytokine and leukocyte response. Infect. Immun. 70:1571-1580.
211. **Casadevall A**, Pirofski L (2002) What is a pathogen? Annals of Medicine 34:2-4.
212. Tucker SC, **Casadevall A** (2002) Replication of *Cryptococcus neoformans* in macrophages is accompanied by phagosomal permeabilization and accumulation of vesicles containing polysaccharide in the cytoplasm. PNAS 99:3165-3170.
213. Schwebach JR, Glatman-Freedman A, Gunther-Cummins L, Dai Z, Robbins JB, Schneerson R and **Casadevall A** (2002) Glucan is a Component of the *Mycobacterium tuberculosis* Surface That is Expressed *in vitro* and *in vivo*. Infect. Immun. 70:2566-2577.
214. Shapiro S, Beenhouwer DO, Feldmesser M, Taborda C, Carroll MC, **Casadevall A**, Scharff MD (2002) Immunoglobulin G monoclonal antibodies to *Cryptococcus neoformans* protects mice deficient in complement component C3. Infect. Immun. 70:2598-2604.
215. **Casadevall A** (2002) Antibodies for defense against biological attack. Nature Biotechnology 20:114.
216. Rivera J, Mukherjee J, Weiss LM, **Casadevall A** (2002) Antibody efficacy in murine pulmonary *Cryptococcus neoformans* infection: a role for nitric oxide. J. Immunol. 168:3419-3427.

217. Vecchiarelli A, Pietrella D, Bistoni F, Kozel TR, **Casadevall** A (2002) Antibody to *Cryptococcus neoformans* capsular glucuronoxylomannan promotes expression of IL2Rbeta2 subunit on human T cells in vitro through effects mediated by antigen-presenting cells. Immunology 106:267-72.

218. **Casadevall** A, Feldmesser M, and Pirofski L (2002) Induced humoral immunity and vaccination against major human fungal pathogens. Curr. Opin. Microbiol. 5:386.

219. **Casadevall** A (2002) Passive antibody administration ('immediate immunity') as a specific defense against biological weapons. Emerg. Infect. Dis. 8:833-41

220. McLean G, Torres M, Elguezabal N, Nakouzi A, **Casadevall** A (2002) Isotype can affect the specificity of an antibody for a polysaccharide antigen. J. Immunol. 169:1379-86.



221. Taborda C, **Casadevall** A (2002) CR3 (CD11b/CD18) and CR4 (CD11c/CD18) are involved in complement independent antibody-mediated phagocytosis of *Cryptococcus neoformans*. Immunity 16:791-802 *F1000 Must Read* <http://f1000.com/prime/1030371#recommendations>

222. Schwebach JR, Chen B, Glatman-Freedman, **Casadevall** A, McKinney J, Bloom BR, Jacobs WR Jr. (2002) Infection in mice with aerosolized *Mycobacterium tuberculosis*: use of a nose-only apparatus for delivery of low-innocula and design of an ultra-safe facility. Applied Environ. Microbiol. 68:4646-4649

223. Song X, Shapiro S, Goldman DL, **Casadevall** A, Scharff M, Lee SC (2002) FcgammaRI_ and FcgammaRIII_ mediated MIP_1alpha induction in primary human and murine microglia. Infect. Immun. 70:5177-84

224. Nosanchuk JD, Gomez BL, Diez S, Youngchim S, Aisen P, Restrepo A, **Casadevall** A, Hamilton AJ (2002). *Histoplasma capsulatum* synthesizes melanin_like pigments in vitro and during mammalian infection. Infect. Immun. 70:5124-31 **A. Casadevall** And A.J. Hamilton shared senior authorship

225. Van Duin D, **Casadevall** A, Nosanchuk JD (2002) Melanization of *Cryptococcus neoformans* and *Histoplasma capsulatum* Reduces Their Susceptibilities to Amphotericin B and Caspofungin. Antimicrob. Agents Chemotherap. 46:3394-400.

226. Pirofski L, **Casadevall** A (2002). The meaning of microbial exposure, infection, colonization, and disease in clinical practice. Lancet Infect. Dis. 2(10):628-35.

227. Fries BC, Goldman DL, **Casadevall** A (2002) Phenotypic switching in *Cryptococcus neoformans*. Microbes Infect. 4:1345-1352.

228. Perfect JR, **Casadevall** A (2002) Cryptococcosis. Infect. Dis. Clin. North Am. 16(4):837-74, v-vi.

229. Cox GM, Harrison, TS, McDade HC, Taborda CP, Heinrich G, **Casadevall A**, Perfect, JR (2003) Superoxide dismutase influences the virulence of *Cryptococcus neoformans* by affecting growth within macrophages. Infect. Immun. 71:173-80.
230. He W, **Casadevall A**, Lee SC, Goldman MD (2003) Phagocytic activity and monocyte chemotactic protein (MCP-1) expression by pulmonary macrophages in persistent pulmonary cryptococcosis. Infect. Immun. 71(2):930-6.
231. Wang F, Nakouzi A, Angeletti RH, **Casadevall A** (2003) Site-specific characterization of the N-linked oligosaccharides of a murine immunoglobulin M by high-performance liquid chromatography/electrospray mass spectrometry. Anal. Biochem. 314:266-280.
232. Nosanchuk JD, **Casadevall A** (2003) 'The contribution of melanin in microbial pathogenesis. Cell. Microbiol 5:203-205.
233. Navoa JA, Laal S, Pirofski LA, McLean GR, Dai Z, Robbins JB, Schneerson R, **Casadevall A**, Glatman-Freedman A. (2003) Specificity and diversity of antibodies to Mycobacterium tuberculosis arabinomannan. Clin. Diagn. Lab. Immunol. 2003:88-94.
234. Taborda C, Rivera J, Zaragoza O, **Casadevall A** (2003) More is not necessarily better: 'prozone-like' effects in passive immunization with immunoglobulin. G. J. Immunol. 170:3621-3630.
235. **Casadevall A**, Pirofski L (2003) Virulence is an outcome of the host-interaction. Trends in Microbiol. 11:157-8.
236. Steenbergen JN and **Casadevall A** (2003) The origin and maintenance of virulence for the human pathogenic fungus *Cryptococcus neoformans*. Microbes Infect. 5:667-675.
237. Nosanchuk JD, Mednick A, Shi L, **Casadevall A** (2003). Experimental murine infection results in contamination of bedding with *Cryptococcus neoformans*. Contemporary Trends in Laboratory and Animal Sciences 42:9-12.
238. Morris-Jones R, Youngchim S, Gomez B, Aisen P, Hay R, Nosanchuk, J, **Casadevall A**, Hamilton AJ (2003) Synthesis of melanin-like pigments by *Sporothrix schenckii* *in vitro* and during mammalian infection. Infection and Immunity 71:4026-33.
239. Mednick AJ, Feldmesser M, Rivera J, **Casadevall A** (2003). Neutropenia alters lung cytokine production in mice and reduces their susceptibility to murine cryptococcosis. Eur. J. Immunol. 33:1744-53.
240. Monari C, Retini C, **Casadevall A**, Netski D, Bistoni F, Kozel TR, Vecchiarelli A (2003) Differences in outcome of the interaction between *Cryptococcus neoformans* glucuronoxylomannan and human monocytes and neutrophils. Eur J Immunol. 33:1041-1051.
241. Nosanchuk JD, **Casadevall A** (2003) Budding of melanized *Cryptococcus neoformans* in the presence or absence of L-dopa. Microbiology 149:1945-1951
242. Zaragoza, O., Taborda, C., **Casadevall A** (2003) Localization of C3 affects complement-mediated phagocytosis of C. neoformans. Eur. J. Immunol. 33:1957-67.

243. **Casadevall A** (2003) Antibody-mediated immunity against intracellular pathogens; two dimensional thinking comes full circle. *Infect. Immun.* 71:4225-8.

244. **Casadevall A**, Nosanchuk JD, Steenbergen JN (2003) 'Ready-made' virulence and 'dual-use' virulence factors in pathogenic environmental fungi - the *Cryptococcus neoformans* paradigm. *Current Opinion in Microbiol.* 6:332-337.

245. Tian S, Garcia-Rivera J, Yan B, **Casadevall A**, Stark RE (2003) Unlocking the Molecular Structure of Fungal Melanin Using ¹³C Biosynthetic Labeling and Solid-State NMR. *Biochem.* 42:8105-9.

246. **Casadevall A** and Pirofski L (2003) Exploiting the redundancy of the immune system: vaccines can mediate protection by eliciting 'unnatural' immunity. *J. Exp. Med.* 197:1401-1404.

247. Nakouzi A and **Casadevall A** (2003) The function of conserved amino acids in or near the complementarity determining regions for related antibodies to *Cryptococcus neoformans* glucuronoxylomannan. *Mol. Immunol.* 40:351-361.

248. Steenbergen J, Nosanchuk JD, Malliaris S, and **Casadevall A** (2003) *Cryptococcus neoformans* virulence is enhanced after intracellular growth in the genetically malleable host *Dictyostelium discoideum*. *Infect. Immun.* 71:4862-72.

249. **Casadevall A** and Pirofski L (2003) Antibody-mediated regulation of cellular immunity and the inflammatory response. *Trends Immunol.* 24:474-478.

250. Dadachova E, Nakouzi A, Ryan RA, **Casadevall A** (2003) Ionizing radiation delivered by specific antibody is therapeutic against a fungal infection. *PNAS* 100:10942-10947.
[F1000 Recommended] <http://f1000.com/prime/1015868#recommendations>

251. **Casadevall A** and Pirofski L (2003) The 'damage-response' framework of microbial pathogenesis. *Nature Microbiology Reviews* 1:17-24.

252. Pietrella D, Fries B, Lupo P, Bistoni F, **Casadevall A**, Vecchiarelli A (2003) Phenotypic switching of *Cryptococcus neoformans* can influence the outcome of the human immune response. *Cell Microbiol.* 5:513-22.

253. Vecchiarelli A, Pietrella D, Lupo P, Bistoni F, McFadden D, **Casadevall A** (2003) The polysaccharide capsule of *Cryptococcus neoformans* interferes with human dendritic cell maturation and activation. *J. Leukoc. Biol.* 74:370-378.

254. Datta K, Jain N, Sethi S, Rattan A, **Casadevall A**, Banerjee U. (2003) Fluconazole and itraconazole susceptibility of clinical isolates of *Cryptococcus neoformans* at a tertiary care centre in India: a need for care. *J. Antimicrob. Agents Chemotherap.* 52:682-683.

255. Sweeney DA, Caserta, MT, Kornoos D, **Casadevall A**, Goldman DL. (2003) A 10 year old boy with a pulmonary nodule secondary to *Cryptococcus neoformans*: A case report and review of the literature. *Ped. Infect. Dis.* 1089-1093.

256. **Casadevall A**, Pirofski L (2003) 'Anti-virulence' genes – further muddling the lexicon? *Trends Microbiol.* 11:413-5.

257. Nosanchuk JD, Steenbergen JN, Deepe GS, **Casadevall A** (2003) Antibodies to a cell surface histone-like protein protect against *Histoplasma capsulatum*. J. Clin. Invest. 112:1164-1175.
258. Zaragoza O, Fries BC, **Casadevall A** (2003). Induction of capsule growth in *Cryptococcus neoformans* by mammalian serum and CO₂. Infect. Immun. 71:6155-6164.
259. Hassani M, Tanowitz HB, Levi MH, Smolkin M, Wasi F, **Casadevall A**, (2004) Extrapulmonary Nonmeningela Coccidioidomycosis. Infections in Medicine 21:245-248.
260. Dadachova E, Howell RW, Bryan RA, Frenkel A, Nosanchuk JD, **Casadevall A** (2004) Susceptibility of human pathogens *Cryptococcus neoformans* and *Histoplasma capsulatum* to gamma radiation versus radioimmunotherapy with alpha- and beta-emitting radioisotopes. J. Nuclear Med. 45:313-320.
261. Garcia-Rivera J, Chang YC, Kwon-Chung KJ, **Casadevall A** (2004) *Cryptococcus neoformans* CAP59 (or Cap59p) is involved in the extracellular trafficking of capsular glucuronoxylomannan. Eukaryotic Cell 3:385-392.
262. McFadden D. **Casadevall A** (2004) Unexpected diversity in the fine specificity of monoclonal antibodies that use the same variable region gene to glucuronoxylomannan of *Cryptococcus neoformans*. J. Immunol. 172:3670-3677.
263. Dadachova E, Burns T, Bryan RA, Apostolidis C, Brechbiel MW, Nosanchuk JD, **Casadevall A**, Pirofski L. (2004) Feasibility of radioimmunotherapy of experimental pneumococcal infection. Antimicrob. Agents Chemotherap. 48:1624-1629.
264. Dadachova E, Bryan RA, Frenkel A, Zhang T, Apostolidis C, Nosanchuk JS, Nosanchuk JD, **Casadevall A** (2004) Evaluation of acute hematological and long-term pulmonary toxicity of radioimmunotherapy of *Cryptococcus neoformans* infection in murine models. Antimicrob. Agents Chemotherap. 48:1004-1006.
265. Pirofski L, **Casadevall A** (2004) 'Good', 'bad', and 'neutral' antibodies – the adjective depends on the context of the host-microbe interaction. Trends in Immunology 25:167-168.
266. Steenbergen J, Nosanchuk JD, Malliaris S, **Casadevall A** (2004). The interaction of *Blastomyces dermatitidis*, *Sporothrix schenckii*, and *Histoplasma capsulatum* with *Acanthamoeba castellanii*. Infect. Immun 72:3478-88.
267. Malliaris S, Steenbergen J and **Casadevall A**(2004) *Cryptococcus neoformans* variety *gattii* can exploit *Acanthamoeba castellanii* for growth. Med. Mycol. 42:149-158.
268. Martinez L, Moussai D, **Casadevall A** (2004) Antibody to *Cryptococcus neoformans* glucuronoxylomannan inhibits the release of capsular antigen. Infect. Immun. 72:3674-9.
269. **Casadevall A** (2004) What is the latest approach to pulmonary cryptococcosis? J. Resp. Dis. 25:5:188-199.
270. Zaragoza O and **Casadevall A** (2004) Experimental modulation of capsule size in *Cryptococcus neoformans*. Biol. Proc. Online 6:10-15.
271. van Duin D, Cleare W, Zaragoza O, **Casadevall A**, Nosanchuk J (2004) Effects of Voriconazole on *Cryptococcus neoformans*. Antimicrob. Agents Chemotherap. 48:2014-2020.
F1000 Recommended <http://f1000.com/prime/1020742#recommendations>

272. McFadden DC, Zaragoza O, **Casadevall A** (2004) The immunoreactivity of cryptococcal antigen is not stable under prolonged incubations in human serum. *J. Clin. Microbiol.* 42:2786-8.
273. **Casadevall A**, Pirofski L (2004). The weapon potential of a microbe. *Trends Microbiol.* 12:259-263.
274. Morris-Jones R, Hextall JM, Youngchim S, Morris-Jones SD, Hay RJ, Nosanchuk JD, **Casadevall A**, Hamilton AJ (2004) *Scytalidium dimidiatum* causing recalcitrant subcutaneous lesions produces melanin. *J. Clin. Microbiol.* 42:3789-94.
275. Glatman-Freedman A, **Casadevall A**, Dai Z, Jacobs Jr, WR Li A, Morris SL, Navoa JAD, Piperdi S, Robbins JB, Schneerson R, Schwebach JR, Shapiro M. (2004) Antigenic evidence of prevalence and diversity of *Mycobacterium tuberculosis* arabinomannan. *J. Clin. Microbiol.* 42:3225-31.
276. Zaragoza O, **Casadevall A** (2004) Antibodies produced in response to *Cryptococcus neoformans* pulmonary infection in mice have characteristics of non-protective antibodies. *Infect. Immun* 42:2786-8
277. Banerjee U, Datta K, **Casadevall A** (2004) Serotype distribution of *Cryptococcus neoformans* in patients in a tertiary care center in India. *Med. Mycol* 181-186.
278. **Casadevall A** (2004) The methodology for determining the efficacy of antibody-mediated immunity. *J. Immunol. Methods.* 291:1-10.
279. **Casadevall A**, Dadachova E, Pirofski L (2004) Passive antibody therapy for infectious diseases. *Nature Microbiol. Rev.* 2:695-703.
280. **Casadevall A**, Pirofski L. New concepts in antibody-mediated immunity (2004) *Infect. Immun.* 72:6191-6196.
281. Monari C, Bistoni F, **Casadevall A**, Pericolini E, Pietrella D, Kozel TR, Vecchiarelli A (2004) Glucuronylmannan, a microbial compound, regulates expression of co-stimulatory molecules and cytokines in macrophages. *J. Infect. Dis.* 191:127-137.
282. Nosanchuk JD, van Duin D, Mandal P, Aisen P, Legendre AM, **Casadevall A** (2004) *Blastomyces dermatitidis* produces melanin in vitro and during infection. *FEMS Microbiol. Lett.* 239:187-93.
283. Dadachova E, Nosanchuk JD, Shi L, Schweitzer AD, Frenkel A, Nosanchuk JS, **Casadevall A** (2004) Dead cells in melanoma tumors provide abundant antigen for targeted delivery of ionizing radiation by a mAb to melanin. *PNAS* 101:14865-70.
Paper featured in Science daily <http://www.sciencedaily.com/releases/2006/12/061208101603.htm>
284. Fries BD, Cook E, Wang C, **Casadevall A** (2005) Effects of antifungal interventions on the outcome of experimental infections with phenotypic switch variants of *Cryptococcus neoformans*. *Antimicrob. Agents. Chemotherap.* 49:350-7.
285. Capitelli F, Vicini S, Piaggio P, Abbruscato P, Princi E, **Casadevall A**, Nosanchuk JD, Zanardini E (2005) Investigation of fungal deterioration of synthetic paint binders using vibrational spectroscopic techniques. *Macromolec. Biosci.* 5:49-57.
286. Rivera J, **Casadevall A** (2005) 'Antibody-mediated protection against *Cryptococcus neoformans* pulmonary infection is dependent on B cells. *Infect. Immun.* 73:1141-50.

287. Larsen RA, Pappas PG, Perfect J, Aberg J, **Casadevall A**, Cloud GA, James R, Filler S, Dismukes WE. (2005) A Phase I evaluation of the safety and activity of a murine derived anti-cryptococcal antibody in subjects with treated cryptococcal meningitis. *Antimicrob. Agents Chemotherap.* 49:952-8.

288. **Casadevall A** (2005). Fungal virulence, vertebrate endothermy and dinosaur extinction: is there a connection? *Fungal Genetics and Biol* 42:98-106.

F1000 Must read <http://f1000.com/prime/13578958#recommendations>

Boston Globe interview

http://www.boston.com/news/globe/health_science/articles/2005/02/22/were_the_dinosaurs_done_in_by_fungus/

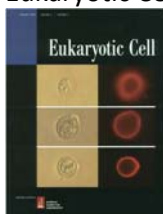
Live Science Interview

<http://www.livescience.com/11705-theory-mammals-fungus-explains-bat-plague.html>

289. McLean GR, Torres M, Trotter B, Nosedá M, Bryson S, Pai EF, **Casadevall A** (2005) A point mutation in the CH3 domain of human IgG3 inhibits antibody secretion without affecting antigen specificity. *Mol. Immunol.* 42:1111-1119.

290. Fries B, **Casadevall A**, Goldman DA (2005) Phenotypic switching of *Cryptococcus neoformans* can produce variants that elicit increased intracranial pressure in a rat model of cryptococcal meningoencephalitis. *Infect. Immun.* 73:1779-1787.

291. Bryan RA, Zaragoza O, Zhang T, Ortiz G, **Casadevall A**, Dadachova E (2005) Radiological studies reveal radial differences in the architecture of the polysaccharide capsule of *Cryptococcus neoformans*. *Eukaryotic Cell* 4:465-475.



292. Mednick A, Nosanchuk JD, **Casadevall A** (2005) Melanization of *Cryptococcus neoformans* affects lung inflammatory responses during cryptococcal infection. *Infect. Immun.* 73:2012-2019.

293. Eisenman HC, Nosanchuk JD, Webber JBW, Emerson RJE, Camesano TA, **Casadevall A** (2005). The microstructure of cell-wall associated melanin in the human pathogenic fungus *Cryptococcus neoformans*. *Biochem.* 44:3683-3693.

294. Torres M, May R, Scharff MD, **Casadevall A** (2005) Variable region identical antibodies differing in isotype demonstrate differences in fine specificity and isotype. *J. Immunol.* 174:2132-2142.

295. Monari C, Pericolini E, Bistoni G, **Casadevall A**, Kozel TR, Vecchiarelli, A (2005) *Cryptococcus neoformans* capsular glucuronoxylomannan induces expression of Fas ligand in macrophages. *J. Immunol* 174:3461-3468. *F1000 Recommended*

296. Garcia-Rivera J, Tucker SC, Feldmesser M, Williamson PR, **Casadevall A** (2005) Laccase Expression in Murine Pulmonary *Cryptococcus neoformans* infection. *Infect. Immun.* 73:3124-7.

297. Luo, Y, Tucker, SC, **Casadevall A** (2005) Fc- and Complement-Receptor Activation Stimulates Cell Cycle Progression of Macrophage Cells from G1 to S. *J. Immunol.* 174:7226-7233.

298. Oscarson S, Alpe M, Svahnberg P, Nakouzi A, and **Casadevall A** (2005) Synthesis and immunological studies of glycoconjugates of *Cryptococcus neoformans* capsular glucuronoxylomannan oligosaccharide structures. *Vaccine* 23:3961-3972.
299. Rivera, J, **Casadevall A** (2005) Mouse genetic background is a major determinant of isotype-related differences for antibody-mediated protective efficacy against *C. neoformans*. *J. Immunol.* 174:8017-8026.
300. **Casadevall A** (2005) The host as a variable: model hosts approach the immunological asymptote. *Infect. Immun.* 73:3829-3832.
301. **Casadevall A**, Pirofski, L (2005) Insights into mechanisms of antibody-mediated immunity from studies with *Cryptococcus neoformans*. *Current Molecular Medicine.* 5:421-433.
302. Nielsen, K, Cox GM, Litvintseva AP, Mylonakis E, Malliaris SD, Benjamin DK Jr, Giles SS, Mitchell TG, **Casadevall A**, Perfect, JR, Heitman J (2005) *C. neoformans* alpha strains preferentially disseminate to the central nervous system during co-infection. *Infect. Immun* 73:4922-33.
303. Wang W, Nakouzi A, Alvarez M, Zaragoza O, Angeletti RH, **Casadevall A** (2005) Structural and functional characterization of glycosylation in an immunoglobulin G1 to *Cryptococcus neoformans* glucuronoxylomannan. *Mol. Immunol.* 43:987-998.
304. Morris-Jones R, Gomez BL, Diez S, Uran M, Morris-Jones SD, **Casadevall A**, Nosanchuk JD, Hamilton AJ (2005). Synthesis of melanin pigment by *Candida albicans* in vitro and during infection. *Infect. Immun.* 73:6147-6150.
305. Shao X, Mednick A, Alvarez M, van Rooijen N, **Casadevall A**, Goldman DL (2005) An innate immune system cell is a major determinant of species-related susceptibility differences to fungal pneumonia. *J. Immunol.* 175:3244-3251.
306. Mandal, P, Banerjee U, **Casadevall A**, Nosanchuk JD (2005) Dual infections with pigmented and albino strains of *Cryptococcus neoformans* in patients with and without human immunodeficiency virus infection in India. *J. Clin. Microbiol.* 43:4766-4772.
307. Martinez LR, **Casadevall A** (2005) Specific antibody can prevent fungal biofilm formation and this effect correlates with protective efficacy. *Infect. Immun.* 73:6350-6362.
308. McClellan EE, Perrine WT, Potts WK, **Casadevall A** (2005) The relationship of virulence factor expression to evolved virulence in mouse-passaged *Cryptococcus neoformans* strains. *Infect. Immun.* 73:7047-50.
309. Zaragoza O, Mihu C, **Casadevall A**, and Nosanchuk JD (2005) Effect of amphotericin B on capsule and cell size in *Cryptococcus neoformans* during murine infection. *Antimicrobial Agents Chemotherap.* 49:4358-61.
310. **Casadevall A** and Pirofski L (2005) The potential of antibody-mediated humoral immunity against biological weapons. *Expert Opinion on Biological Therapy* 5:1359-1372.
311. Da Silva MB, Marques AF, Nosanchuk JD, **Casadevall A**, Travassos LR, Taborda CP (2005) Melanin in the dimorphic fungal pathogen *Paracoccidioides brasiliensis*: effects on phagocytosis, intracellular resistance, and drug susceptibility. *Microbes Infect.* 8:197-205.

312. Shao X, Rivera J, Niang R, **Casadevall A**, Goldman DL (2005) A dual role for TGF-beta1 in the control of fungal pneumonia. J. Immunol. 175:6757-63.

313. Jain N, Wickes BL, Keller SM, Fu J, **Casadevall A**, Jain P, Ragan MA, Banerjee U, Fries BC (2005) The molecular epidemiology of clinical *Cryptococcus neoformans* strains from India. J. Clin. Microbiol. 43:5733-5742.

314. Garcia-Rivera J, Nosanchuk JD, Aisen P, Zaragoza O, Moadel T, Dadachova E, **Casadevall A** (2005) Comparative analysis of *Cryptococcus neoformans* acid-resistant particles generated from pigmented cells grown in different laccase substrates. Fungal Genetics and Biol. 42:989-998.



315. Dadachova E, **Casadevall A** (2005) Antibodies as delivery vehicles for radioimmunotherapy of infectious diseases. Exp. Opin. Drug. Deliv. 2:1075-1084.

316. **Casadevall A**, Pirofski L (2005) Feasibility and prospects for a vaccine to prevent cryptococcosis. Med. Mycol 43:667-80.

317. Pericolini E, Cenci E, Monari C, DeJesus M, Bistoni F, **Casadevall A**, Vecchiarelli A (2005) *Cryptococcus neoformans* capsular polysaccharide component galactoxylomannan induces apoptosis of human T cells through caspase 8 activation. Cellular Microbiology 8:267-75.

318. Dadachova E, **Casadevall A** (2005) Melanin as a potential target for radionuclide therapy of metastatic melanoma. Future Oncology 1:541-9.

319. **Casadevall A** (2006) The cards of virulence and the global virulome. Microbe 1:359-364.

320. McFadden D, DeJesus M, **Casadevall A** (2006) The physical properties of the capsular polysaccharides from *Cryptococcus neoformans* suggest features for capsule construction. J. Biol. Chem. 281:1868-75.

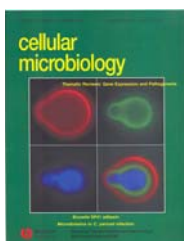
321. **Casadevall A**, Pirofski L (2006) Polysaccharide-containing conjugate vaccines for fungal diseases. Trends in Molecular Medicine 12:6-9.

322. Zaragoza O, Telzak A, Bryan R, Dadachova E, **Casadevall A** (2006) The polysaccharide capsule of the pathogenic fungus *Cryptococcus neoformans* enlarges by distal growth and is rearranged during budding. Mol.Microbiol. 59:67-83.
F1000 Recommended <http://f1000.com/prime/1030371#recommendations>

323. Frases S, Chaskes S, Dadachova E, **Casadevall A** (2006) Induction by *Klebsiella aerogenes* of a melanin-like pigment in *Cryptococcus neoformans*. Applied and Environmental Microbiol. 72:1542-50.

324. Martinez L, **Casadevall A** (2006) Susceptibility of *Cryptococcus neoformans* biofilms to antifungal agents in vitro. Antimicrob. Agents Chemotherap. 50:1021-33.

325. McClellan E, Bernhardt D, **Casadevall A** (2006) Estimating the relative contribution of virulence factors for pathogenic microbes. *Infect. Immun.* 74:1500-1504.
326. Goldman D, Davis J, Bommartio F, Shao X, **Casadevall A** (2006) Enhanced allergic inflammation and airway responsiveness in rats with chronic *Cryptococcus neoformans* infection suggests a potential role for fungal pulmonary infection in the pathogenesis of asthma. *J. Infect. Dis.* 193:1178-86.
F1000 Recommended 'Must Read' <http://f1000.com/prime/1069772#recommendations>
327. **Casadevall A** (2006) The third age of antimicrobial therapy. *Clin. Infect. Dis.* 42:1414-6.
328. Dadachova E, Bryan RA, Apostolidis C, Morgenstern A, Zhang T, Moadel T, Torres M, Huang X, Revskaya E, **Casadevall A** (2006) Interaction of radiolabeled antibodies with fungal cells and components of the immune system in vitro and during radioimmunotherapy of experimental infection. *J. Infect. Dis.* 193:1427-1436.
329. Zaragoza O, McClelland E, Telzak A, **Casadevall A** (2006) Equatorial ring-like channels in the *Cryptococcus neoformans* polysaccharide capsule. *FEMS Yeast Research* 6:662-666.
330. Dadachova E, Moadel T, Schweitzer AD, Bryan RA, Zhang T, Mints L, Revskaya E, Huang X, Ortiz G, Nosanchuk JS, **Casadevall A** (2006). Radiolabeled melanin-binding peptides are safe and effective in treatment of human pigmented melanoma in a mouse model of disease. *Cancer Biother Radiopharm* 21:117-29.
331. Martinez LR, Bryan RA, Apostolidis C, Morgenstern A, **Casadevall A**, Dadachova E (2006) Antibody-guided alpha radiation effectively damages fungal biofilms. *Antimicrob Agents Chemother* 50:2132-6.
332. McClelland E, Bernhardt D, **Casadevall A** (2006) Coping with multiple virulence factors: which is most important? *PLOS Pathogens* 1:4:287-288.
333. Li L, Zaragoza O, **Casadevall A**, Fries B (2006) Characterization of a flocculation-like phenotype in *Cryptococcus neoformans* and its effect on pathogenesis. *Cellular Microbiol.* 8(11):1730-1739.
334. Martinez, L, Christaki E, **Casadevall A** (2006) Specific antibody to *Cryptococcus neoformans* glucuronoxylomannan antagonizes antifungal drug action against cryptococcal biofilms in vitro. *J. Infect. Dis.* 194:261-266
335. Paolo WF, Jr, Mandal P, Dadachova E, **Casadevall A**, Szaniszlo PJ and Nosanchuk JD (2006) Effects of disrupting the polyketide synthase gene WdPKS1 in *Wangiella [Exophiala] dermatitidis* on melanin production and resistance to killing by antifungal compounds, enzymatic degradation, and extremes in temperature. *BMC Microbiology* 6(1):55.
336. Rivera J, Nakouzi A, Abboud N, Revskaya E, Goldman D, Collier RJ, Dadachova E, **Casadevall A** (2006) A monoclonal antibody to *Bacillus anthracis* protective antigen defines a neutralizing epitope on domain one. *Infect. Immun.* 74(7):4149-4156.
337. Zaragoza O, **Casadevall A** (2006) Monoclonal antibodies can affect complement deposition on the capsule of the pathogenic fungus *Cryptococcus neoformans* by both classical pathway activation and steric hindrance. *Cell Microbiol* 8:1862-1876.



338. Dadachova E, **Casadevall A** (2006) Treatment of infection with radiolabeled antibodies. QJ Nucl.Med Mol. Imaging 50:193-204.
339. Luo Y, Cook E, Fries BC, **Casadevall A** (2006) Phagocytic efficacy of macrophage-like cells as a function of cell cycle and Fcgamma receptors (FcgammaR) and complement receptor (CR)3 expression. Clin Exp Immunol. 145:380-7.
340. Mavrogiorgos N, Zaragoza O, **Casadevall A**, and Nosanchuk JD (2006) Efficacy of voriconazole in experimental *Cryptococcus neoformans* infection. Mycopathologia 162:111-114.
341. Pirofski LA, **Casadevall A**. (2006) Immunomodulators as an antimicrobial tool. Curr Opin Microbiol. Oct;9(5):489-95. Epub 2006 Aug 22. Review. PMID: 16931122
342. **Casadevall A**, Pirofski L (2006) A reappraisal of humoral immunity based on mechanism of antibody-mediated protection against intracellular pathogens. Advances in Immunology 91:1-44.
343. Maxson MM, Cook E, **Casadevall A** (2006). The volume and hydration of the *Cryptococcus neoformans* polysaccharide capsule. Fungal Genetics and Biology 44(3):180-6.



344. Anaissie EJ, Segal BH, Graybill JR, Arndt C, Perfect JR, Kleinberg M, Pappas P, Benjamin D, Rubin R, Aberg JA, Adderson EE, Adler-Shohet FC, Akan H, Akova M, Almyroudis NG, Alexander BD, Andes D, Arrieta A, Baddley JW, Barron MA, Belzberg H, Boucher HW, Boyce TG, **Casadevall A**, Chandrasekar PH, Cleary JD, Cordonnier C, Cornely OA, Cuenca-Estrella M, Daly JS, Daoura N, Denning DW, dePauw B, de Repentigny L, Dignani MC, Dismukes WE, Donnelly JP, Donowitz GR, Dupont B, Drusano G, Ellis M, Espinel-Ingroff A, Fishman JA, Fleming R, Forrest G, Ghannoum M, Goldman M, Graziutti M, Greene JN, Greenberg RN, Gubbins PO, Hadley S, Herbrecht R, Hiemenz JW, Hope W, Hospenthal DR, Husain S, Ito JI, Jacobson RM, Johnson M, Keating MR, Kett DH, Knapp K, Kontoyiannis DP, Krcmery VC, Larsen R, Laverdiere M, Ljungman P, Lortholary O, Maertens J, Marriott D, Mattiuzzi G, McGinnis MR, Morris M, Nucci M, Odds FC, Pankey GA, Patterson T, Pfaller M, Razonable RR, Reboli AC, Rinaldi MG, Roberts GD, Rodriguez Tudela JL, Rotstein C, Ruhnke M, Schuster M, Shoham S, Sia IG, Siebel N, Silviera F, Singh N, Sobel J, Solomkin JS, Sorrell TC, Steinbach WJ, Temesgen Z, Tortorano A, Vartivarian S, VerWeij P, Viscoli C, Viviani MA, Walker RC, Wheat JL, Wiley J, Williamson P, Wingard JR, Yu VL, Zaoutis T. (2006) Clinical research in the lay press: irresponsible journalism raises a huge dose of doubt. Clin Infect Dis. Oct 15;43(8):1031-9. Epub Sep 13. Clin Infect Dis. 2007 Mar 15;44(6):894. PMID: 16983616.

345. McFadden D, Zaragoza O, **Casadevall A** (2006) The capsular dynamics of *Cryptococcus neoformans*. *Trends in Microbiol.* 14:497-505.
346. Okoli I, Oyeka C, Kwon-Chung K, Theelen B, Robert V, Groenewald J, McFadden D, **Casadevall A**, Boekhout T (2006) *Cryptotrichosporon anacardii* gen. nov., sp. nov., a new trichosporonoid capsulate basidiomycetous yeast from Nigeria that is able to form melanin on niger seed agar. *FEMS Yeast Research.* 7(2):339-50.
347. Martinez L, **Casadevall A** (2006) *Cryptococcus neoformans* cells in biofilms are less susceptible to antimicrobial molecules produced by the innate immune system than planktonic cells. *Infec. Immun.* 74(11):6118-6123.
348. Nosanchuk J, **Casadevall A** (2006). Impact of melanin on microbial virulence and clinical resistance to antimicrobial compounds. *Antimicrob. Agents Chemotherap.* 50(11):3519-3528.
349. Capittelli F, Nosanchuk JD, **Casadevall A**, Toniolo L, Brusetti L, Florio S, Principi P, Borin S, Sorlini C (2006) Synthetic consolidants attacked by melanin-producing fungi: the study case of biodeterioration of the Milan Cathedral (Italy) marble treated with acrylics. *Appl Environ Microbiol* 72:271-277.
350. Nosanchuk JD, Yu J, Hung C, **Casadevall A**, Cole GT (2006). *Coccidioides posadasii* produces melanin in vitro and during infection. *Fungal Genetics and Biology* 44(6):517-20.
351. Monari C, Kozel TR, Paganelli F, Pericolini E, Perito S, Bistoni F, **Casadevall A**, Vecchiarelli A (2006). Microbial immune suppression mediated by direct engagement of inhibitory Fc receptor. *J. Immunol.* 177:6842-6851.
352. Alvarez M, Casadevall A (2006) Phagosome extrusion and host cell survival after *Cryptococcus neoformans* phagocytosis by macrophages. *Current Biology* 16:2161-2165.
F1000 Recommended Must Read <http://f1000.com/prime/1069772#recommendations>
353. Dadachova E, Patel MC, Toussi S, Apostolidis C, Morgenstern A, Brechbiel MW, Gorny MK, Zolla-Pazner S, **Casadevall A**, Goldstein H (2006) Targeted killing of virally infected cells by radiolabeled antibodies to viral proteins. *PLOS Medicine* 3:e427. [*Drs Casadevall and Goldstein shared senior authorship*]
F1000 Recommended <http://f1000.com/prime/1052866#recommendations>
Featured in Science Daily <http://www.sciencedaily.com/releases/2008/06/080616115744.htm>
Featured in Scientific American <http://www.scientificamerican.com/article.cfm?id=kill-the-virus-stop-the-cancer>
354. Barbosa FM, Fonseca FL, Figueiredo RT, Bozza MT, **Casadevall A**, Nimrichter L, Rodrigues ML (2007) Binding of glucuronoxylomannan to CD14 receptor in human A549 alveolar cells induces IL-8. *Clin. Vaccine Immunol.* 14:94-98.
355. Frases S, **Casadevall A** (2007) *Cryptococcus neoformans* can utilize the bacterial melanin precursor homogentisic acid for fungal melanogenesis. *Appl Environ Microbiol.* 73:615-621.
356. Maxon MM, Dadachova E, **Casadevall A**, Zaragoza O (2007) Radial mass density, charge, and epitope distribution in the *Cryptococcus neoformans* capsule. *Eukaryotic cell* 6:95-109.

357. Rodrigues ML, Nimrichter L, Oliveira DL, Frases S, Miranda K, Zaragoza O, Alvarez M, Nakouzi A, Feldmesser M, **Casadevall A** (2007) Vesicular polysaccharide export in *Cryptococcus neoformans* is an eukaryotic solution to the problem of fungal trans-cell wall transport. *Eukaryotic Cell* 6:48-59.
F1000 Recommended <http://f1000.com/prime/1069772#recommendations>
358. **Casadevall A**, Pirofski L (2006) The weapon potential of human pathogenic fungi. *Medical Mycology* 44:689-696.
359. Dadachova E., **Casadevall A** (2007) Renaissance of targeting molecules for melanoma. *Cancer Radiother. Biopharm* 21:545-52.
360. Macura N, Zhang T, **Casadevall A** (2007) The dependence of macrophage phagocytic efficacy on antibody concentration. *Infect. Immun.* 75:1904-15.
361. Torres M, Fernandez-Fuentes N, Fiser A, **Casadevall A** (2007) The immunoglobulin heavy chain constant region affects kinetic and thermodynamic parameters of antibody variable region interactions with antigen. *J. Biol. Chem* 282:13917-27.
F1000 Recommended <http://f1000.com/prime/1082953#recommendations>
362. De Jesus M, Hackett E, Durkin M, Connolly P, **Casadevall A**, Petraitiene R, Walsh, TJ, Wheat LJ (2007) Galactoxylomannan (GalXM) does not Exhibit Cross-Reactivity with *Aspergillus* Galactomannans. *Clin. Vaccine Immunol.* 14:624-7.
F1000 Recommended <http://f1000.com/prime/1086020#recommendations>
363. Zaragoza O, Alvarez M, Telzak A, Rivera J, **Casadevall A** (2007). The relative susceptibility of mouse strains to pulmonary *Cryptococcus neoformans* infection is associated with pleiotropic differences in immune response. *Infect. Immun.* 75:2729-39.
364. **Casadevall A**, Goldstein H, Dadachova E (2007) Targeting host cells harboring viruses with radiolabeled antibodies. *Expert Opinion in Biological Therapy* 7:595-7.
365. Martinez LR, **Casadevall A** (2007) Biofilm formation depends on surface support and carbon source and reduces fungal cell susceptibility to heat, cold, and ultraviolet light. *Appl Environ Microbiol* 73(14):4592-601.
366. Dadachova E, Bryan RA, Huang X, Moadel T, Schweitzer AD, Aisen P, Nosanchuk JD, **Casadevall A** (2007) Ionizing radiation changes the electronic properties of melanin and enhances the growth of melanized fungi. *PLoS ONE*. 2:e457.
F1000 Rated Exceptional <http://f1000.com/prime/1086966#recommendations>
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Fox News <http://www.foxnews.com/story/0,2933,276196,00.html>
Scientific American <http://www.scientificamerican.com/article.cfm?id=radiation-helps-fungi-grow>
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Yahoo Voices <http://voices.yahoo.com/scientists-discover-radiation-eating-fungi-362074.html>
Nasa http://solarsystem.nasa.gov/news/display.cfm?News_ID=21175
Nature <http://www.nature.com/news/2007/070521/full/news070521-5.html>
Nature Micro Rev O'Connell D, Fungal Physiology: Radiation Jukes Nature Reviews Microbiology5, 475-475 doi:10.1038/nrmicro1694

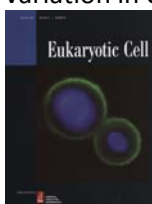
Natural History <http://www.naturalhistorymag.com/samplings/141343/radiation-its-whats-for-dinner>

367. Davis, J, Zheng WY, Glatman-Freedman A, Ng JN, Pagcatipunan MR, Lessin H, **Casadevall A**, Goldman, DL. (2007) Serological evidence for differences in cryptococcal infection. *Ped. Infect. Dis* 26:549-51.

368. Achkar JM, **Casadevall A**, Glatman-Freedman A (2007) Immunological options for the treatment of tuberculosis: evaluation of novel therapeutic approaches. *Expert Rev. Anti. Infect. Ther.* 5:461-7.

369. Nimrichter L, Frases S, Cinelli LP, Viana NB, Nakouzi A, Travassos LR, **Casadevall A**, Rodriguez ML (2007) Self-aggregation of *Cryptococcus neoformans* capsular polysaccharide is dependent of divalent ions. *Eukaryotic Cell* 16:1400-10. [Drs **Casadevall** and Rodriguez shared senior authorships]

370. McFadden D, Fries BC, Wang F, **Casadevall A** (2007) Capsule structural heterogeneity and antigenic variation in *Cryptococcus neoformans*. *Eukaryotic Cell* 6:1464-73.



372. Dadachova E, Wang XG, **Casadevall A** (2007) Targeting the virus with radioimmunotherapy in virus-associated cancers. *Cancer Biother. Radiopharm.* 22:303-308.

372. Mylonakis E., **Casadevall A**, Ausubel FM (2007) Exploiting amoeboid and non-vertebrate animal model systems to study the virulence of human pathogenic fungi. *PLoS Pathog.* 3:e101.

373. Alvarez M, **Casadevall A** (2007) Cell-to-cell spread and massive vacuole formation after *Cryptococcus neoformans* and infection of murine macrophages. *BMC Immunology* 8:16.
F1000 Recommended <http://f1000.com/prime/1086966#recommendations>

374. **Casadevall A**, Pirofski L, (2007) Antibody-mediated protection through cross-reactivity introduces a fungal heresy into immunological dogma. *Infect. Immun.* 75(11):5074-8.

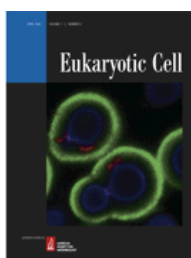
375. Dadachova, E, Bryan RA, Huang X, Ortiz G, Moadel T, **Casadevall A** (2007) Comparative evaluation of capsular polysaccharide-specific IgM and IgG antibodies and F(ab')₂ and Fab fragments as delivery vehicles for radioimmunotherapy of fungal infection. *Clin Cancer Res.* 13:5629s-5635s.

376. Al-Sayyed B, Piperdi S, Yuan X, Li A, Besra GS, Jacobs WR, **Casadevall A**, Glatman-Freedman A (2007). Monoclonal antibodies to *Mycobacterium tuberculosis* CDC 1551 reveal subcellular localization of MPT51. *Tuberculosis (Edinb).* 87:489-97.

377. Schweitzer AD, Rakesh V, Revskaya E, Datta A, **Casadevall A**, Dadachova E. (2007) Computational model predicts effective delivery of 188-Re-labeled melanin-binding antibody to the metastatic melanoma tumors with wide range of melanin concentrations. *Melanoma Res.* 17:291-303.

378. Martinez LR, Ntiamoah P, **Casadevall A**, Nosanchuk JD (2007) Caspofungin reduces the incidence of fungal contamination in cell culture. *Mycopathologia.* 164(6):279-86.

379. Howell RC, Revskaya E, Pazo V, Nosanchuk JD, **Casadevall A**, Dadachova E (2007) Phage display library derived peptides that bind to human tumor melanin as potential vehicles for targeted radionuclide therapy of metastatic melanoma. *Bioconjug Chem.* 18(6):1739-48.
380. Martinez LR, Ntiamoah P, Gacser A, **Casadevall A**, Nosanchuk JD (2007) Voriconazole Inhibits Melanization in *Cryptococcus neoformans*. *Antimicrob Agents Chemother.* 51:4396-400.
381. **Casadevall A**, Pirofski L (2007) Accidental Virulence, cryptic pathogenesis, martians, lost hosts, and the pathogenicity of environmental microbes. *Eukaryotic Cell* 6:2169-74.
F1000 Recommended 'Must Read' <http://f1000.com/prime/1098373#recommendations>
382. Saha Dc, Goldman DL, Shao X, **Casadevall A**, Husain S, Limaye AP, Lyon M, Somani J, Pursell K, Pruett TL, Singh N (2007) Voriconazole Inhibits Melanization in *Cryptococcus neoformans*. *Antimicrob Agents Chemother.* 51:4396-400.
383. **Casadevall A** (2007) Determinants of virulence in the pathogenic fungi. *Fungal Biology Reviews* 21(4):130-132.
384. Wang XG, Revskaya E, Bryan RA, Strickler HD, Burk RD, **Casadevall A**, Dadachova E (2007) Treating cancer as an infectious disease-viral antigens as novel targets for treatment and potential prevention of tumors of viral etiology. *PLoS ONE.* 2(10):e1114.
385. Chaskes S, Frases S, Cammer M, Gerfen G, **Casadevall A** (2008) Growth and Pigment Production by *Cryptococcus gattii*, *Cryptococcus neoformans*, and *Candida albicans* from D-Tryptophan. *J Clin Microbiol.* 46:255-64.
386. Eisenman HC, **Casadevall A**, McClellan EE (2007) New Insights on the Pathogenesis of Invasive *Cryptococcus neoformans* Infection. *Curr. Infect. Dis. Rep.* 9:457-64.
387. Rodrigues ML, Nakayasu ES, Oliveira DL, Nimrichter L, Nosanchuk JD, Almeida IC, **Casadevall A** (2007) Extracellular vesicles produced by *Cryptococcus neoformans* contain protein components associated with virulence. *Eukaryot Cell.* 7:58-67.
388. Eisenman HC, Mues M, Weber SE, Chaskes S, Frases S, **Casadevall A** (2007) *Cryptococcus neoformans* laccase catalyzes melanin synthesis from both D- and L-DOPA. *Microbiology* 153(Pt 12):3954-62.
389. Torres M, Fernandez-Fuentes N, Fiser A, **Casadevall A**. (2007) Exchanging murine and human immunoglobulin constant chains affects the kinetics and thermodynamics of antigen binding and chimeric antibody autoreactivity.
PLoS One. Dec 12;2(12):e1310. PMID: 18074033
390. Zhuang D, Hage C, DeJesus M, Hackett M, Durkin M, Davis TE, **Casadevall A**, Wheat LJ (2007) Cryptococcal glucuronoxylomannan does not exhibit cross reactivity in the MVista™ *Histoplasma* antigen assay immunoassay. *Clin Vaccine Immunol* 15:392-3.
391. Rodrigues ML, Alvarez M, Fonseca FL, **Casadevall A** (2008) Binding of the wheat germ lectin to *Cryptococcus neoformans* suggests an association of chitin-like structures with yeast budding and capsular glucuronoxylomannan. *Eukaryot Cell.* 7:602-9.



392. Frases S, Nimrichter L, Viana NB, Nakouzi A, **Casadevall A** (2008) *Cryptococcus neoformans* capsular polysaccharide and exopolysaccharide fractions manifest physical, chemical, and antigenic differences. *Eukaryot. Cell* 7:319-27.
393. Torres M, **Casadevall A** (2008) The immunoglobulin constant region contributes to affinity and specificity. *Trends in Immunology* 29:91-7.
394. Dadachova E, **Casadevall A**. (2008) Host and microbial cells as targets for armed antibodies in the treatment of infectious diseases. *Curr Opin Investiga Drugs*. Feb: 9(2):184-8. PMID: 18246521
395. Zarebski LM, Vaughan K, Sidney J, Peters B, Grey H, Janda KD, **Casadevall A**, Sette A. (2008) Analysis of epitope information related to *Bacillus anthracis* and *Clostridium botulinum*. *Expert Rev Vaccines*. Feb;7(1):55-74. doi: 10.1586/14760584.7.1.55. PMID: 18251694
396. Maglione P.J., Xu J., **Casadevall A**, Chan J (2008) Fcγ receptors regulate immune activation and susceptibility during *M. tuberculosis* infection. *J. Immunol* 180:3329-38.
397. De Jesus M; Park CG, Su Y; Goldman D; Steinman RM; **Casadevall A** (2008) Spleen deposition of *Cryptococcus neoformans* capsular Glucuronoxylomannan in rodents occurs in red pulp macrophages and not marginal zone macrophages expressing the C-type lectin SIGN-R1. *Med. Mycol* 46:153-62.
398. Howell RC, Schweitzer AD, **Casadevall A**, Dadachova EA (2008) Chemosorption of radiometals of interest to nuclear medicine by synthetic melanins. *Nucl Med. Biol* 35:335-7.
399. Zhong J, Frases-Carvajal S, Hsin W, **Casadevall A**, Stark RE (2008) Following Fungal Melanin Biosynthesis with Solid-State NMR: biopolymer molecular structures and possible connections to cell-wall polysaccharides. *Biochem.* 47:4701-10.
400. Bryan RA, Huang X, Morgenstern A, Bruchertseifer F, **Casadevall A**, Dadachova E. (2008) Radiofungicidal effects of external gamma radiation and antibody-targeted beta and alpha radiation on *Cryptococcus neoformans*. *Antimicrob Agents Chemother.* 52(6):2232-5.
401. Alvarez M, Saylor C, **Casadevall A** (2008) Antibody action after phagocytosis promotes *Cryptococcus neoformans* and *Cryptococcus gattii* macrophage exocytosis with biofilm-like microcolony formation. *Cell Microbiol* 10:1622-33.
402. Albuquerque PC, Nakayasu ES, Rodrigues ML, Frases S, **Casadevall A**, Zancoppe-Oliveira RM, Almeida IC, Nosanchuk JD. (2008) Vesicular transport in *Histoplasma capsulatum*: an effective mechanism for trans-cell wall transfer of proteins and lipids in ascomycetes. *Cell Microbiol.* 10:1695-710.

403. Dadachova E, Bryan RA, Howell RC, Schweitzer AD, Aisen P, Nosanchuk JD, **Casadevall A** (2008) The radioprotective properties of fungal melanin are a function of its chemical composition, stable radical presence and spatial arrangement. *Pigment Cell Melanoma Res.* 21(2):192-9
404. Goldman DL, Zeng W, Rivera J, Nakouzi A, **Casadevall A** (2008) Human serum contains a protease that protects against cytotoxic activity of *Bacillus anthracis* lethal toxin in vitro. *Clin Vaccine Immunol.* Jun 15(6):970-3.
405. Abboud N, **Casadevall A** (2008) The Immunogenicity of *Bacillus Anthracis* Protective Antigen Domains and the Efficacy of Elicited Antibody Responses Depend on host Genetic Background. *Clin Vaccine Immunol.* 15:1115-23.
406. Vicencio AG, Narain S, Du Z, Zeng WY, Ritch J, **Casadevall A**, Goldman DL (2008) Pulmonary cryptococcosis induces chitinase in the rat. *Respir Res.* 15:9:40.
407. Goldman DL, **Casadevall A** (2008) Anthrax-associated shock. *Front Biosci.* May 1(13):4009-14.
408. Dadachova E, Revskaya E, Sesay MA, Damania H, Boucher R, Sellers RS, Howell RC, Burns L, Thornton GB, Natarajan A, Mirick GR, Denardo SJ, Denardo GL, **Casadevall A** (2008) Pre-clinical evaluation and efficacy studies of a melanin-binding IgM antibody labeled with (188)Re against experimental human metastatic melanoma in nude mice. *Cancer Biol Ther.* 9:1116-27.
409. Zaragoza O, Chrisman CJ, Castelli MV, Frases S, Cuenca-Estrella M, Rodriguez-Tudela JL, **Casadevall A** (2008) 'Capsule enlargement in *C. neoformans* confers resistance to oxidative stress suggesting a mechanism for intracellular survival'. *Cell Microbiol* 10:2043-57.
410. Martinez LR, Ibom DC, **Casadevall A**, Fries BC (2008) Characterization of phenotypic switching in *Cryptococcus neoformans* biofilms. *Mycopathologia* 66:175-80.
411. Nicola A, **Casadevall A**, Goldman DA (2008) Fungal killing by mammalian phagocytic cells. *Current Opinion in Microbiology* 11:313-7.
412. Rakesh V, Schweitzer, A, Zaragoza O, Bryan R, Wong, K, Ashim, D, **Casadevall A**, Dadachova E (2008) 'Finite-element model of interaction between fungal polysaccharide and monoclonal antibody in the capsule of *Cryptococcus neoformans*. *J. Phys. Chem. B*: 8514-22.
413. **Casadevall A**, Fang FC (2008) Descriptive Science. *Infect. Immun.* 76:3835-6.
414. Rodriguez ML, Nimrichter L, Oliveira DL, Nosanchuk JD, **Casadevall A** (2008). Vesicular trans cell wall transport in fungi: a mechanism for delivery of virulence-associated macromolecules? *Lipid Insights* 2:27-40.
415. **Casadevall A** (2008) Evolution of intracellular pathogens. *Annual Reviews in Microbiology* 62:19-33
416. Luo Y, Alvarez M, **Casadevall A** (2008) The Outcome of Phagocytic Cell Division with Infectious Cargo Depends on Single Phagosome Formation. *PlosOne* e3219.
417. Dam TK, Torres M, Brewer CD, **Casadevall A** (2008) Isothermal titration calorimetry reveals differential binding thermodynamics of variable region-identical antibodies differing in constant region for a univalent ligand. *J. Biol. Chem.* 283:31366-70.

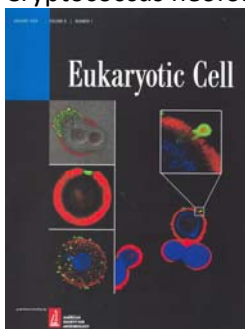
418. Nakouzi A, Rivera J, Rest RF, **Casadevall A** (2008) Passive administration of monoclonal antibodies to Anthrolysin O prolong survival in mice lethally infected with *Bacillus anthracis*. *BMC Microbiology* 8:159.

419. Pirofski L, **Casadevall A** (2008) The damage-response framework of microbial pathogenesis and infectious diseases. *Adv Exp Med Biol* 635:135-46.

420. Dadachova E, Rivera J, Revskaya E, Nakouzi A, Cahill SM, Blumenstein M, Xiao D, **Casadevall A** (2008) In vitro evaluation, biodistribution and scintigraphic imaging in mice of radiolabeled anthrax toxins. *Nuclear Medicine and Biology* 35:755-61.

421. Dadachova E, **Casadevall A** (2008) Ionizing radiation: how fungi cope, adapt and exploit with the help of melanin. *Curr Opin Microbiol.* 11:525-31.

422. De Jesus M, Nicola AM, Rodrigues ML, Janbon G, **Casadevall A** (2008) Capsular localization of the *Cryptococcus neoformans* polysaccharide component galactoxylomannan. *Eukaryotic Cell* 8:96-103.



423. **Casadevall A**, Ehrlich SA, Franz DR, Imperiale MJ, Keim PS. (2008) Biosecur Bioterror. 2008 Dec;6(4):291-2. doi: 10.1089/bsp.2008.1114. PMID: 19090664

424. Bliska JB, **Casadevall A** (2009) Intracellular pathogenic bacteria and fungi – a case of convergent evolution? *Nat. Rev. Microbiol.* 7:165-171.

425. Bryan, RA, Jiang Z, Huang X, Morgestem A, Bruchertseifer F, Sellers R, **Casadevall A**, Dadachova E. (2009) Radioimmunotherapy is effective against high-inoculum *Cryptococcus neoformans* infection in mice and does not select for radiation-resistant cryptococcal cells. *Antimicrob. Agents Chemother.* 53:1679-82.

426. Frases S, Pontes B, Nimrichter L, Viana NB, Rodrigues ML, **Casadevall A** (2009) The capsule of *Cryptococcus neoformans* grows by enlargement of polysaccharide molecules. *PNAS* 106:1228-33.

427. Fang FC, **Casadevall A** (2009) NIH Peer Review Reform – Change we need, or Lipstick on a Pig. *Infect. Immun.* 77:929-32

428. Nosanchuk JD, Nimrichter L, **Casadevall A**, Rodrigues ML (2009) A role for vesicular transport of macromolecules across cell walls in fungal pathogenesis. *Commun. Integr. Biol* 1:37-39.

429. Dadachova E, **Casadevall A** (2009) Radioimmunotherapy of Infectious Diseases *Semin Nucl Med* 39:146-53.

430. Pirofski L, **Casadevall A** (2009) Rethinking T cell immunity in oral candidiasis. *J. Exp. Med* 206:269-73.

431. Panepinto J, Komperda K, Frases S, Park Y, Djordjevic JT, **Casadevall A**, Williamson PR (2009) Sec6-dependent sorting of fungal extracellular exosomes and laccase of *Cryptococcus neoformans*. *Mol. Micro* 71:1165-76.
432. **Casadevall A**, Fang FC (2009) Is peer review censorship. *Infect. Immun.* 77:1273-4.
433. Robertson EJ, **Casadevall A** (2009) Antibody-mediated immobilization of *Cryptococcus neoformans* promotes biofilm formation. *Appl. Environ. Microbiol* 75:2528-33.
434. Alvarez, Burns T, Luo Y, Pirofski L, **Casadevall A** (2009) The outcome of *Cryptococcus neoformans* intracellular pathogenesis in human monocytes. *BMC Microbiology* 5:51.
435. Fonseca F, Frases S, **Casadevall A**, Fischman-Gompertz O, Nimrichter L. (2009) The Structural and functional properties of the *Trichosporon asahii* glucuronoxylomannan. *Fungal Genet. Biol.* 46:496-505.
436. Revskaya E, Jongco AM, Sellers RS, Howell RC, Koba W, Guimaraes AJ, Nosanchuk JD, **Casadevall A**, Dadachova E. (2009) Radioimmunotherapy of experimental human metastatic melanoma with melanin-binding antibodies and in combination with dacarbazine. *Clin Cancer Res.* Apr 1;15(7):2373-9. doi: 10.1158/1078-0432.CCR-08-2376. Epub 2009 Mar 17. PMID: 19293257
437. **Casadevall A**, Nosanchuk JD, Williamson P, Rodrigues ML. (2009) Vesicular transport across the fungal cell wall. *Trends Microbiol.* Apr;17(4):158-62. doi: 10.1016/j.tim.2008.12.005. Epub 2009 Mar 18. PMID: 19299133
438. Rodrigues ML, Fonseca FL, Frases S, **Casadevall A**, Nimrichter L. (2009) The still obscure attributes of cryptococcal glucuronoxylomannan. *Med Mycol.* Dec;47(8):783-8. doi: 10.3109/13693780902788621. PMID: 19343609
439. Pericolini E, Gabrielli E, Cenci E, De Jesus M, Bistoni F, **Casadevall A**, Vecchiarelli A (2009) Involvement of glyco-receptors in galactoxylomannan-induced T cell death. *J. Immunol.* 182:6003-10.
440. Zaragoza O, Rodrigues ML, De Jesus MD, Frases S, Dadachova E, **Casadevall A** (2009) The Capsule of fungal pathogen *Cryptococcus neoformans*. *Adv Appl. Microbiol.* 68:133-216.
441. Nakouzi A, Zhang T, Oscarson S, **Casadevall A** (2009) The common *Cryptococcus neoformans* glucuronoxylomannan M2 motifs elicits non-protective antibodies. *Vaccine* 27:3513-9.
442. Nicola A, Frases S, **Casadevall A** (2009) Lipophilic dye staining of *Cryptococcus neoformans* extracellular vesicles and capsule. *Eukaryotic Cell* 8:1373-80.
443. **Casadevall A** (2009) The case for pathogen specific therapy. *Expert Opinion of emerging drugs* 10:1699-703.
444. **Casadevall A**, Fang F (2009). Mechanistic science. *Infect. Immun.* 77:3717-19.
F1000 Recommended 'Must Read' <http://f1000.com/prime/1163707#recommendations>
445. Fonseca FL, Nimrichter L, Cordero RJB, Frases S, De Siqueira JR, Goldman DL, Andruszkiewicz R, Milewski S, Travassos LR, **Casadevall A**, Rodrigues ML (2009). A role for chitin and chito oligomers in the capsular architecture of *Cryptococcus neoformans*. *Eukaryotic Cell* 8:1543-53.

446. Abboud N, DeJesus M, Nakouzi A, Cordero RJB, Puhato M, Fiser A, Rivera J, and **Casadevall A** (2009) Identification of linear epitopes in *Bacillus anthracis* protective antigen bound by neutralizing antibodies. *J. Biol. Chem.* 284:25077-86.
447. Luo Y, Isaac BM, **Casadevall A**, Cox D (2009) Phagocytosis inhibits F-actin enriched membrane protrusions stimulated by fractalkine (CX3CL1) and colony-stimulating factor-1. *Infect. Immun.* 77:4487-95.
448. **Casadevall A**, Fang F (2009). Important Science. *Infect. Immun* 77:4177-80.
449. DeJesus M, Nicola AM, Frases S, Lee IR, Mieses S, **Casadevall A** (2009) Galactoxylomannan-mediated immunological paralysis results from specific B cell depletion in the context of widespread immune system damage. *J. Immunol* 183:3885-94.
450. Frases S, Pontes B, Nimrichter L, Rodrigues ML, Viana NB, **Casadevall A** (2009) The elastic properties of the *Cryptococcus neoformans* capsule. *Biophysical J.* 97:937-45.
451. Rivera J, Nakouzi AS, Morgenstern A, Bruchertseifer F, Dadachova E, **Casadevall A** (2009). Radiolabeled antibodies to *Bacillus anthracis* toxins are bactericidal and partially therapeutic in experimental murine anthrax. *Antimicrobiol. Agents. Chemotherapy.* 53:4860-8.
452. **Casadevall A**, Pirofski L (2009) Virulence factors and their mechanisms of action: the view from a damage-response framework. *J Water Health* 7 Suppl 1:S2-S18. doi: 10.2166/wh.2009.036. Review. PMID: 19717929
453. Silva MB, Thomaz L, Marques AF, Svidzinski AR, Nosanchuk JD, **Casadevall A**, Travassos LR, Taborda CP (2009) Resistance of melanized yeast cells of *Paracoccidioides brasiliensis* to antimicrobial oxidants and inhibition of phagocytosis using carbohydrates and monoclonal antibody to CD18. *Mem Inst Oswaldo Cruz* 104:644-8.
454. Eisenman H, Frases S, Nicola AM, Rodrigues ML, **Casadevall A** (2009) Vesicle-associated melanization in *Cryptococcus neoformans*. *Microbiology* 155:3860-7. PMCID: PMC2889422
455. Oliveira D, Nimrichter L, Miranda K, Frases S, Faull K, **Casadevall A** (2009) *Cryptococcus neoformans* cryoimmunoelectronmicroscopy and vesicle fractionation reveals an intimate association between membrane lipids and glucuronoxylomannan. *Fungal Genetics Biol* 46:956-63.
456. Schweitzer AD, Howell RC, Jiang Z, Bryan RA, Gerfen G, Chen CC, Mah D, Cahill S, **Casadevall A**, Dadachova E. (2009) Physico-chemical evaluation of rationally designed melanins as novel nature-inspired radioprotectors. *PLOS One* e7229 PMCID: PMC2749938
457. Martinez LR, Mihi MR, Han G, Frases S, Cordero RJB, **Casadevall A**, Friedman AJ, Friedman JM, and Nosanchuk (2009) The use of chitosan to damage *Cryptococcus neoformans* biofilms. *Biomaterials* 31:669-79. PMCID: PMC2783412
458. Robert VA, **Casadevall A**. (2009) Vertebrate endothermy restricts most fungi as potential pathogens. *J Infect Dis.* 2009 Nov 15;200(10):1623-6. doi: 10.1086/644642. PMID: 19827944
459. Saylor C, Dadachova E, **Casadevall A**. (2009) Monoclonal antibody-based therapies for microbial diseases.

Vaccine. 2009 Dec 30;27 Suppl 6:G38-46. doi: 10.1016/j.vaccine.2009.09.105. Review. PMID: 20006139

460. Franz DR, Ehrlich SA, **Casadevall A**, Imperiale MJ, Keim PS (2010) The 'nuclearization' of biology is a threat to health and security. *Biosecur. Bioterror.* 7:243-4.

461. Saylor C, Dadachova E, **Casadevall A** (2010) Murine IgG1 and IgG3 isotype switch variants promote phagocytosis of *Cryptococcus neoformans* through different receptors. *J. Immunol.* 184:336-43.

462. Luo Y, Pollard JW, **Casadevall A** (2010) Fcγ receptor crosslinking stimulates cell proliferation of macrophages via the ERK pathway. *J. Biol. Chem* 285:4232-42.

463. Fang FC, **Casadevall A** (2010) Lost in translation – basic science in the era of translational research. *Infect. Immun.* 78:563-6. PMCID: PMC2812192

464. Biron CA, **Casadevall A.** (2010) On immunologists and microbiologists: ground zero in the battle for interdisciplinary knowledge. *MBio.* 1(5). pii: e00260-10. PMID: 21714147

465. De Jesus M, Chow S., Cordero R.J.B., Frases S, **Casadevall A** (2010) Galactoxylomannans from *Cryptococcus neoformans* varieties *neoformans* and *grubii* are structurally and antigenically variable. *Eukaryotic Cell* 9:1018-28.

466. **Casadevall A**, Relman DA (2010) Microbial threat lists: obstacles in the quest for biosecurity? *Nature Micro. Reviews* 8:149-54.

467. Guimaraes AJ, Frases S, Cordero RJB, Nimrichter L, **Casadevall A**, Nosanchuk JD (2010). *Cryptococcus neoformans* responds to mannitol by increasing capsule size in vitro and in vivo. *Cell. Microbiol.* 12:740-53. PMCID: PMC289187

468. Achkar JM, Jenny-Avital E, Yu X, Burger S, Leibert E, Bilder PW, Almo SC, **Casadevall A**, Laal S (2010) Antibodies against immunodominant antigens of *M. tuberculosis* in tuberculosis suspects in the US: a comparison by HIV status. *Clin.Vaccine Immunol* 17:384-92. PMCID: PMC2837951

469. Phaeton R, Wang XG, Einstein MH, Goldberg GL, **Casadevall A**, Dadachova E (2010). The influence of proteasome inhibitor MG132, external radiation, and unlabeled antibody on the tumor uptake and biodistribution of 188Re-labeled anti-E6 C1P5 antibody in cervical cancer in mice. *Cancer* 20:1067-1074. PMCID: PMC2820134

470. Oliveira DC, Freire-de-Lima CG, Nosanchuk JD, **Casadevall A**, Rodrigues ML, Nimrichter L. (2010) Extracellular vesicles from *Cryptococcus neoformans* modulate macrophage functions. *Infect. Immun.* 78:1601-9. PMCID: PMC2849392

471. Luke TC, **Casadevall A**, Watowich SJ, Hoffman SL, Beigel JH, Burgess TH. (2010) Hark back: passive immunotherapy for influenza and other serious infections. *Crit. Care Med.* 38 (4 Suppl), e66-73.

472. Frager SZ, Chrisman CJ, Shakked R, **Casadevall A** (2010) Paramecium species ingest and kill the cells of the human pathogenic fungus *Cryptococcus neoformans*. *Med Mycol.* 48:775-9.

473. Janda A, **Casadevall A** (2010) Circular Dichroism Reveals Evidence of Coupling between Immunoglobulin Constant and Variable Region Secondary Structure. *Molecular Immunology* 47:1421-5. PMCID: PMC2872143

474. McClelland EE, Nicola AM, Prados-Rosales, R, **Casadevall A** (2010). Humoral immunity can modulate fungal metabolism. *J. Clin. Invest.* 120:1355-61.
Paper was accompanied by a JCI commentary: <http://www.ncbi.nlm.nih.gov/pubmed/20335652>
475. Winterroth L, Rivera J, Nakouzi AS, Dadachova E, **Casadevall A** (2010). A neutralizing monoclonal antibody to edema toxin and its effect on murine anthrax. *Infection and Immunity* 78(6):2890-8 .
476. Scheweitzer AS, Revskaya E, Chu P, Pazo V, Friedman M, Nosanchuk JK, Cahill S, Frases S, **Casadevall A**, Dadachova E. (2010) Melanin-covered nanoparticles for protection of bone marrow during radiation therapy of cancer. *Int J. Radiat. Oncol. Biol. Phys* 78(5):1494-502.
Paper was featured in Science Daily
<http://www.sciencedaily.com/releases/2010/04/100426182022.htm>
477. **Casadevall A** (2010) Cryptococci at the brain gate: break and enter or use a Trojan horse. *J. Clin. Invest* 210:1689-92. PMCID: PMC2860912
478. Fonseca FL, Nohara LL, Cordero JB, Frases S, **Casadevall A**, Almeida I, Nimrichter L, Rodrigues ML (2010) Immunomodulatory effects of serotype B glucuronoxylomannan from *Cryptococcus gattii* correlate with polysaccharide diameter. *Infect. Immun.* 78:3861-70.
479. Oliveria DL, Nakayasu ES, Joffe LS, Guimaraes AJ, Sobreira TJ, Nosanchuk JD, Cordero RJ, Frases S, **Casadevall A**, Almeida IC, Nimrichter L, Rodrigues ML (2010) Characterization of yeast extracellular vesicles: evidence for the participation of different pathways of cellular traffic in vesicle biogenesis. *PLOS One* e11113. PMCID: PMC2885426
480. **Casadevall A**, Imperiale MJ (2010). Destruction of Microbial Collections in Response to Select Agent and Toxin List Regulations. *Biosecurity and Bioterrorism: Biodefense Strategy, Practice and Science*. Vol 8:151-4.
This paper was the subject of an NPR Morning Edition program
<http://www.npr.org/player/v2/mediaPlayer.html?action=1&t=1&islist=false&id=133066108&m=133071625>
481. Zaragoza O, Garcia-Rodas R, Nosanchuk JD, Cuenca-Estrella M, Rodriguez-Tudela JL, **Casadevall A** (2010) Fungal cell gigantism during mammalian infection. *PLOS Pathogens* e1000945. PMCID: PMC2887474 *F1000 Recommended 'Must Read'* <http://f1000.com/prime/7063956#recommendations>
482. Bryan RA, Jiang Z, Howell RC, Morgenstern A, Bruchertseifer R, **Casadevall A**, Dadachova E. (2010) Radioimmunotherapy is more effective than antifungal treatment in experimental cryptococcal infection. *J. Infect. Dis.* 202:633-7.
F1000 Recommended <http://f1000.com/prime/4145956#recommendations>
483. Muehlbauer SM, Lima Hr Jr, Goldman DL, Jacobson L, Rivera J, Goldberg MF, Palladino MA, **Casadevall A**, Brojatsch J (2010) Proteosome inhibitors prevent caspase-1-mediated disease in rodents challenged with anthrax lethal toxin. *Am. J. Pathol* 177(2):735-43.
484. Chrisman CJ, Alvarez M, **Casadevall A** (2010). Phagocytosis and non-lytic exocytosis of *Cryptococcus neoformans* by and from *Acanthamoeba castellanii*. *Appl Environ Microbiol.* 76:6065-62.
485. **Casadevall A**. (2010) ASM Launches mBio. *MBio*. 2010 May 18;1(1). pii: e00120-10. doi: 10.1128/mBio.00120-10.
PMID: 20689741

486. Garcia-Solache MA, **Casadevall A** (2010) Global warming will bring new fungal diseases for mammals. *mBio* 1:e00061-10.

In 2016 this paper was the subject of a Wall Street Op Ed raising the specter that fungi could cause devastating epidemics. <http://www.wsj.com/articles/what-comes-after-zika-1457132252>

487. Ostrosky-Zeichner L, **Casadevall A**, Galgiani JN, Odds FC, Rex JH (2010) An insight into the antifungal pipeline: selected molecules and beyond. *Nat. Rev. Drug. Discov.* 9:719-27.

488. Luo Y, **Casadevall A** (2010). Intracellular cryptococci suppress Fc-mediated cyclin D1 elevation. *Commun. Intergr. Biol.* 3:390-1.

489. Pericolini E, Gabrielle E, Bistoni G, Cenci E, Perito S, Chow SK, Riuzzi F, Donato R, **Casadevall A**, Vecchiarelli A (2010) Role for CD45 signalling pathway in galactoxylomannan-induced T cell damage. *PLOS One* e12720.

490. Phaeton R, Harris M, Jiang Z, Wang XG, Einstein MH, Goldberg GL, **Casadevall A**, Dadachova E. (2010) Radioimmunotherapy with antibody to HPV16 E6 oncoprotein is effective in experimental cervical tumor expressing low levels of E6. *Cancer Biol Ther.* 10:1041-7.

491. Casadevall A, Fang F (2010) Reproducible Science. *Infect. Immun* 78:4972-5.

492. Lye LF, Kang SO, Nosanchuk JD, **Casadevall A**, Beverley SM (2010) Phenylalanine hydroxylase (PAH) from the lower eukaryote *Leishmania major*. *Mol. Biochem. Parasitol.* 175:58-67.

493. Abboud N, Chow S, Ravetch J, Scharff MD, **Casadevall A** (2010). A requirement for FcR in antibody-mediated bacterial toxin neutralization. *J. Exp. Med* 2010:207; 2395-405.

494. Rivera J, Cordero RJB, Nakouzi AS, Frases S, Nicola A, **Casadevall A** (2010) *Bacillus anthracis* produces membrane-derived vesicles containing biologically active toxins. *PNAS* 107:19002-7. *This paper was rated F1000 Must Read* <http://f1000.com/prime/717992089#recommendations>

495. Siev M, Yu X, Prados-Rosales R, Martiniuk FT, **Casadevall A**, Achkar JM. (2011) Correlation between serum and plasma antibody titers to mycobacterial antigens. *Clin Vaccine Immunol.* 2011 Jan;18(1):173-5. doi: 10.1128/CVI.00325-10. Epub 2010 Nov 3. PMID: 21047999

496. Bergman A, **Casadevall A** (2010) Mammalian endothermy optimally restricts fungi and metabolic costs. *mBio* r00212-10.

Featured in Science News

http://www.sciencenews.org/view/generic/id/67029/title/Just_warm_enough

Featured in Scientific American <http://www.scientificamerican.com/podcast/episode.cfm?id=986-trades-metabolic-cost-for-funga-10-12-27>

497. Biron CA, **Casadevall A**. (2010) On immunologists and microbiologists: ground zero in the battle for interdisciplinary knowledge. *MBio.* Nov 2;1(5). pii: e00260-10. doi: 10.1128/mBio.00260-10. PMID: 21103040

498. Miller JF, McFall-Ngai M, **Casadevall A** (2010) A new design for the ASM general meeting. *MBio.* 2010 Nov 23;1(5). pii: e00240-10. doi: 10.1128/mBio.00240-10. PMID:21151775

499. Jesus M, Nicola AM, Chow S, Lee IR, Nong S, Spech CA, Levitz SM, **Casadevall A** (2010). Glucuronoxylomannan, galactoxylomannan, and mannoprotein occupy spatially separate and discrete regions in the capsule of *Cryptococcus neoformans*. *Virulence* 1:500-8.
500. Cordero RJB, Frases S, Guimaraes AJ, Rivera J, **Casadevall A** (2011) Evidence for branching in cryptococcal capsular polysaccharides and consequences on its biological activity. *Mol. Micro* 79;1101-17.
501. Chow, S, **Casadevall A** (2011) Evaluation of a *Cryptococcus neoformans* galactoxylomanna-protein conjugate vaccine candidate against murine cryptococcosis. *Vaccine* 29:1891-8.
502. Harris M, Wang X-G, Jiang X, Goldberg GL, **Casadevall A** and Dadachova E. (2011). Radioimmunotherapy of experimental head and neck squamous cell carcinoma (HNSCC) with E6-specific antibody using a novel HPV-16 positive HNSCC cell line. *Head Neck Oncol.* 3;9.
This paper was highlighted in the Jan. 2011 Journal of Nuclear Medicine
503. Fang FC, **Casadevall A** (2011) Reductionistic and Holistic Science. *Infect. Immun.* 79:1401-4.
504. Oliveira DL, Nakayasu ES, Joffe LS, Guimaraes AJ, Sobreira TJ, Nosanchuk JD, Cordero RJ, Frases S, **Casadevall A**, Almeida IC, Nimrichter L, Rodrigues ML. (2011) Biogenesis of extracellular vesicles in yeast: many questions with few answers. *Commun. Intergr Biol.* 3:533-535.
505. Prados-Rosales R, Baena A, Martinez L, Luque-Garcia J, Kalscheuer R, Veeraraghavan U, Camara C, Nosanchuk JD, Guryal SB, Chen B, Jimenez J, Glatman-Freedman A, Jacobes WR, Porcelli SA, **Casadevall A** (2011). Mycobacteria release active membrane vesicles that modulate immune responses in a TLR2-dependent manner. *J. Clin. Invest.* 121;1471-83.
506. Liu, T, Wang Y, Stukes S, Chen Q, **Casadevall A**, Xue C (2011) The F-box protein Fbp1 regulates sexual reproduction and virulence in *Cryptococcus neoformans*. *Eukaryotic Cell* 10:791-802.
507. Kmetzsch L, Joffe LS, Staats CC, de Oliveira DL, Fonseca FL, Cordero RJB, **Casadevall A**, Nimrichter L, Schrank A, Vainstein MH, Rodrigues ML (2011). Role for Golgi reassembly and stacking protein (Grasp) in polysaccharide secretion and fungal virulence. *Mol. Microbiol.* 81:206-18.
508. Turick CE, Milliken C, Ekechukwu, A, **Casadevall A**, Dadachova E. (2011) Gamma Radiation Interacts with Melanin to Alter its oxidation-reduction potential and results in electric current production. *Bioelectrochemistry* 82:69-73.
509. Chrisman CJ, Andrade PA, Guimaraes AJ, **Casadevall A** (2011) Phospholipids trigger *Cryptococcus neoformans* capsular enlargement during interactions with amoebae and macrophages. *PLOS Pathogens* e1002047.
510. Eisenman H, Chow S, **Casadevall A** (2011) The effect of L-DOPA on *Cryptococcus neoformans* growth and gene expression. *Virulence* 2:329-36.
511. Dadachova E, **Casadevall A** (2011) *Cryptococcus neoformans* as a model for radioimmunotherapy of infections. *Interdisciplinary Perspectives on Infectious Diseases* 2011:830286.
512. **Casadevall A**, Fang FC, Pirofski L (2011) Microbial Virulence as an emergent property: consequences and opportunities. *PLoS Pathogens* e1002136

513. Fang FC, **Casadevall A** (2011) Retracted Science and the Retraction Index. *Infect. Immun.* 79:3855-9.

This paper was featured in Science News of the Week and several online magazines

<http://www.timeshighereducation.co.uk/story.asp?sectioncode=26&storycode=417226&c=1>

Paper was featured in Science Magazine News of the week

<http://www.sciencemag.org/content/333/6045/923.2.full.pdf?sid=4fb4481d-9df8-427e-bffb-15e01e1b0634>

The Scientist News and Opinion

<http://the-scientist.com/2011/08/11/qa-the-impact-of-retractions/>

514. Nicola AM, Robertson EJ, Albuquerque P, Silveira-Derongowski L, **Casadevall A** (2011) Non-lytic exocytosis of *Cryptococcus neoformans* from macrophages occurs in vivo and is influenced by phagosomal pH. *mBio* 2, e00167-11.

515. Vecchiarelli A, Pericolini E, Gabrielli E, Chow SK, Bistoni F, Cenci E, **Casadevall A** (2011) *Cryptococcus neoformans* galactoxylomannan is a potent negative immunomodulator, inspiring new approaches in anti-inflammatory therapy. *Immunotherapy* 3:997-1005

516. Rodrigues ML, Nimrichter L, Cordero RJ, **Casadevall A** (2011) Fungal polysaccharides: biological activity beyond the usual structural properties. *Front Microbiol.* 2:171.

517. Garcia-Rodas R, **Casadevall A**, Rodrigues-Tudela JL, Cuenca-Estrella M, Zaragoza O (2011) *Cryptococcus neoformans* capsular enlargement and cellular gigantism during *Galleria mellonella* infection. *Plos ONE* 6(9) e24485.

518. Del Poeta M, **Casadevall A** (2011). Ten Challenges on *Cryptococcus* and cryptococcosis. *Mycopathologia* 173(5-6):303-10.

519. Khajo A, Bryan RA, Friedman M, Burger RM, Levitsky Y, **Casadevall A**, Magliozzo RS, Dadachova E (2011) Protection of melanized *Cryptococcus neoformans* from lethal dose gamma radiation involves changes in melanin's chemical structure and paramagnetism. *PLoS One* 6:e25092.

520. Tsirilakis K, Kim C, Vicencio AG, Andrade C, **Casadevall A**, Goldman DL (2012) Methylxanthine inhibit Fungal Chitinases and exhibit antifungal activity. *Mycopathologia* 172:83-91.

521. Cordero RJB, Pontes B, Guimaraes AJ, Martinez LR, Rivera J, Fries BC, Nimrichter L, Rodrigues ML, Viana NM, **Casadevall A** (2011) Chronological aging is associated with biophysical and biochemical changes in the capsule of *Cryptococcus neoformans*. *Infect. Immun.* 79:4990-5000. *This paper was the highlighted in the journal Infection and Immunity*

522. Jiang Z, Bryan RA, Morgenstern A, Bruchertseifer F, **Casadevall A**, Dadachova E (2011) Treatment of early and established *Cryptococcus neoformans* infection with radiolabeled antibodies in immunocompetent mice. *Antimicrob Agents Chemother.* 56:552-4.

523. Frases S, Viana NB, **Casadevall A** (2011) Biophysical methods for the study of microbial surfaces. *Front Microbiol* 2:207

524. Imperiale MJ, **Casadevall A** (2011) Bioterrorism: lessons learned since the anthrax mailings. *mBio* 2, e00232.

525. Bryan RA, Guimaraes AJ, Hopcraft S, Jiang Z, Bonilla K, Morgenstern A, Bruchertseifer F, Del Poeta M, Torosantucci A, Cassone A, Nosanchuk KD, **Casadevall A**, Dadachova E. (2011) Toward developing a universal strategy for fungal disease using radioimmunotherapy targeting common fungal antigens. *Mycopathologia* 173(5-6):463-71.

526. Rodrigues ML, Nosanchuk JD, Schrank A, Vainstein MH, **Casadevall A**, Nimrichter L (2011) Vesicular transport systems in fungi. *Future Microbiol.* 2011;6:1371-81.

527. **Casadevall A**, Pirofski L (2011) A new synthesis for antibody mediated immunity. *Nature Immunology* 13:21-8.

F1000 recommended <http://f1000.com/prime/13578958#recommendations>

528. Goldman DL, Li X, Tsirilakis K, Andrade C. **Casadevall A**, Vicencio AG (2012) Increased chitinase expression and fungal-specific antibodies in the bronchoalveolar lavage fluid of asthmatic children. *Clin Exp Allergy* 42(4):523-30.

529. **Casadevall A** (2012) Amoeba can provide insight into the origin of virulence in pathogenic fungi. *Adv Exp Med Biol* 710:1-10.

530. Yu X, Prados-Rosales R, Jenny-Avital ER, Sosa K, **Casadevall A**, Achkar JM. (2012) Comparative evaluation of antibody profiles to mycobacterial capsular polysaccharides in tuberculosis patients and controls stratified by HIB status. *Clin. Vaccine Immunol.* 19:198-208.

531. Eisenman HC, **Casadevall A** (2012). Synthesis and assembly of fungal melanin. *Appl. Microbiol. Biotechnol.* 93:931-40.

532. **Casadevall A**, Fang FC. (2012) Reforming Science I. Methodological and cultural reforms. *Infect. Immun.* 80(3):891-6.

533. Fang FC, **Casadevall A** (2012). Reforming Science II. Structural reforms. *Infect. Immun.* 80(3):897-901.

The above two papers led to a New York Times article by Carl Zimmer

<http://www.nytimes.com/2012/04/17/science/rise-in-scientific-journal-retractions-prompts-calls-for-reform.html>

These efforts led to Drs. Casadevall and Fang being profiled in Science magazine:

<http://www.ncbi.nlm.nih.gov/pubmed/23349264>

534. Coelho C, Tesfa L, Zhang J, Rivera J, Gongalves T, **Casadevall A** (2012). Analysis of cell cycle and replication of mouse macrophages after in vivo and in vitro *Cryptococcus neoformans* infection using laser scanning cytometry. *Infect. Immun* 80(4):1467-78.

535. Araujo GS, Fonseca FL, Pontes B, Torres A, Cordero RJ, Zoncope-Oliveria RM, **Casadevall A**, Viana NB, Nimrichter L, Rodrigues ML, Garcia ES, de Souza W, Frases S. (2012) Capsules from pathogenic and non-pathogenic *Cryptococcus* spp. Manifest significant differences in structure and ability to protect against phagocytic cells. *PLoS One* e29561.

536. Nicola AM, **Casadevall A** (2012) In vitro measurement of phagocytosis and killing of *Cryptococcus neoformans* by macrophages. *Methods Mol. Biol* 844:189-197.

537. Albuquerque P, **Casadevall A** (2012). Quorum sensing in fungi – a review. *Med Mycol* 50(4):337-45.

538. Wolf J, Rivera J, **Casadevall A** (2012). Serum albumin disrupts *Cryptococcus neoformans* and *Bacillus anthracis* extracellular vesicles. *Cell Microbiol* 14(5):762-73.

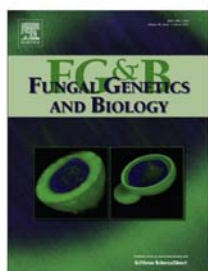
539. Pirofski L, **Casadevall A** (2012). What is a pathogen? A question that begs the point. *BMC Biology* 10:6.

540. Berns KI, **Casadevall A**, Cohen MI, Ehrlich SA, Enquist LW, Fitch JP, Franz DR, Fraser-Liggett CM, Grant CM, Imperiale MJ, Kanabrocki J, Keim PS, Lemon SM, Levy SB, Lumpkin JR, Miller JF, Murch R, Nance ME, Osterholm MT, Relman DA, Roth JA, Vidaver AK (2012) Policy: Adaptations of avian flu virus are a cause for concern. *Nature* 482:153-154.

541. **Casadevall A**, Shenk T (2012) The H5N1 manuscript redaction controversy. *mBio* 3(1). pii: e00022-12.

542. Berns KI, **Casadevall A**, Cohen MI, Ehrlich SA, Enquist LW, Fitch JP, Franz DR, Fraser-Liggett CM, Grant CM, Imperiale MJ, Kanabrocki J, Keim PS, Lemon SM, Levy SB, Lumpkin JR, Miller JF, Murch R, Nance ME, Osterholm MT, Relman DA, Roth JA, Vidaver AK (2012) Public Health and biosecurity: Adaptation of Avian flu virus area cause for concern. *Science* 335(6069):660-1.

543. McClellan, EE, **Casadevall A** (2012). Strain-related differences in antibody-mediated changes gene expression are associated with differences in capsule and location of binding. *Fungal Gen Bio* 149(3):227-34.



544. **Casadevall A**, Nakouzi A, Crippa PR, Eisner M (2012) Fungal melanins differ in planar stacking distances. *PLoS One* 7(2):e30299. PMID:PMC3281024

545. **Casadevall A** and Shenk T (2012) Mammalian transmissible H5N1 virus: containment level and case fatality ratio. *mBio* 6;3(2):e00054-12.

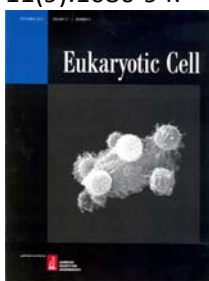
546. Dadachova E, Kitchen SG, Bristol G, Baldwin GC, Revskaya E, Empig C, Thornton GB, Gorny MK, Zolla-Pazner S, **Casadevall A**. (2012) Pre-Clinical evaluation of a Bi-labeled 2556 antibody to HIV-1 gp41 glycoprotein in HIV-1 mouse models as a reagent for HIV eradication. *PLoS One* 7(3):e31866.

547. **Casadevall A** (2012) The future of biological warfare. *Microbial Biotechnology* 5(5):584-7 .

548. Muhammed M, Feldmesser M, Shubitz LJ, Lionakis MS, Sil A, Wang Y, Glavis-Blom, Lewis RE, Galgiani J, **Casadevall A**, Konoyannis DP, Mylonakis E. (2012) Mouse models for the study of fungal pneumonia: a collection of detailed protocols for the study of *Coccidioides*, *Cryptococcus*, *Fusarium*, *Histoplasma* and combined infection due to *Aspergillus-Rhizopus*. *Virulence* 3(3):329-38.

549. Ramos C, Fonseca F, Rodrigues J, Guimaraes A, Cinelli L, Miranda K, Nimrichter L, **Casadevall A**, Travassos L, Rodrigues M (2012) Chitin-like molecules associate with *Cryptococcus neoformans*

glucuronoxylomannan to form a glycan complex with previously unknown properties. *Eukaryotic Cell* 11(9):1086-94.



550. Cassone A, **Casadevall A** (2012) Recent progress in vaccines against fungal diseases. *Current Opin. Microbiol.* 15(4):427-33.

551. **Casadevall A** and Pirofski L (2012) Immunoglobulins in defense, pathogenesis, and therapy of fungal diseases. *Cell Host and Microbe* 11:445-56.

552. Nicola AM, Albuquerque P, Martinez LR, Dal-Rosso RA, Saylor C, De Jesus, M, Nosanchuk JD, **Casadevall A** (2012) Macrophage autophagy in immunity to *Cryptococcus neoformans* and *Candida albicans*. *Infect. Immun.* 80(9):3065-76.

553. Chatterjee S, Prados-Rosales R, Frases S, Itin B, **Casadevall A**, Stark RE (2012). Using solid-state NMR to monitor the molecular consequences of *Cryptococcus neoformans* melanization with different catecholamine precursors. *Biochem.* 7;51(31):6080-8 PMID:PMC3448835

554. Chow S, **Casadevall A** (2012) Monoclonal antibodies and toxins – a perspective on function and isotype. *Toxins* 4(6):430-54.

555. **Casadevall A**, Janda A (2012) Immunoglobulin isotype influences affinity and specificity. *PNAS* 109(31):12272-3.

556. Xia Y, Rawar R, Nokouz AS, Monestier M, Fan M, Wang L, **Casadevall A**, Putterman C (2012) The constant region contributes to the antigenic specificity and renal pathogenicity of anti-DNA antibodies. *J. Autoimmunity* 56(1-2):28-37.

557. **Casadevall A**, Fang FC (2012) Winner takes all. *Scientific American* 307(2):13.

558. **Casadevall A** (2012) Fungi and the rise of mammals. *PLoS Pathogens* Aug;8(8):e1002808
F1000 recommended: <http://f1000.com/prime/718006239#recommendations>

559. Janda A, Eryilmaz E, Nakouzi A, Cowburn D, **Casadevall A** (2012) Variable region identical immunoglobulins differing in isotype express different paratopes. *J Biol Chem.* 287(42):35409-17.

560. Robertson EJ, Wolf JM, **Casadevall A** (2012) EDTA inhibits *Cryptococcus neoformans* biofilm formation, extracellular vesicular secretion and shedding of the capsular polysaccharide glucuronoxylomannan. *Appl Environ Microbiol* 78(22):7977-84.

561. Albuquerque PC, B Cordero RJ, Fonseca FL, Peres R, Ramos CL, Miranda KR, **Casadevall A**, Puccia R, Nosanchuk JD, Nimrichter L, Guimaraes AJ, Rodrigues ML. (2012) A *Paracoccidioides brasiliensis* glycan shares serologic and functional properties with cryptococcal glucuronoxylomannan. *Fungal Genet Biol.* (11):943-54.

562. **Casadevall A**, Shenk T (2012) The H5N1 moratorium controversy and debate. *Mbio* e00379-12

563. Fang FC, Steen RC, **Casadevall A** (2013) Misconduct accounts for the majority of retracted scientific publications. *PNAS* 109(42):17028-33.

F1000 Recommended <http://f1000.com/prime/4145956#recommendations>

This paper received intense media coverage. Here are some links

<http://news.sciencemag.org/scienceinsider/2012/10/misconduct-not-mistakes-causes-m.html>

http://www.sciencenews.org/view/generic/id/345465/description/Misconduct_prompts_most_retractions

<http://www.the-scientist.com/?articles.view/articleNo/32687/title/Fraud-Breeds-Retractions/>

<http://www.guardian.co.uk/science/2012/oct/01/tenfold-increase-science-paper-retracted-fraud>

http://carlzimmer.com/articles/index.php?subaction=showfull&id=1356631997&archive=&start_from=&ucat=15&

564. Revskaya E, Chu P, Howell RC, Schweitzer AD, Bryan RA, Harris M, Gerfen G, Jiang Z, Jandl T, Kim K, Ting LM, Sellers RS, Dadachova E, **Casadevall A** (2013) Compton scattering by internal shields based on melanin-containing mushrooms provides protection of gastrointestinal tract from ionizing radiation. *Cancer Biother Radiopharm* 27(9):570-6. PMID:PMC3484786.

This paper was covered by ASM blog Small things considered:

<http://schaechter.asmblog.org/schaechter/2013/11/radiation-ahead-eat-a-black-mushroom.html>

Also covered by This Week in Microbiology

TwIM #67 (<http://www.microbeworld.org/podcasts/this-week-in-microbiology/archives/1501-twim-67>)

565. Jandl T, Revskaya E, Jiang Z, Harris M, Dorokhova O, Tsukrov D, **Casadevall A**, Dadachova E. (2013) Melanoma stem cells in experimental melanoma are killed by radioimmunotherapy. *Nucl Med Biol.* 40(2):177-81.

566. Fang, FC, **Casadevall A**. (2013). Why We Cheat. *Scientific American Mind*, 24(2), 30-37.



567. Cordero RBJ, Pontes B, Frases S, Nakouzi AS, Nimrichter L, Rodrigues ML, Viana NB, **Casadevall A** (2013) Antibody binding to *Cryptococcus neoformans* impairs budding by altering capsular mechanical properties. *J. Immunol.* 190(1):317-23.

568. Pericolini E, Alunno A, Gabrielli E, Bartoloni E, Cenci E, Chow SK, Bistoni G, **Casadevall A**, Gerli R, Vecchiarelli A (2013). The Microbial Capsular Polysaccharide Galactoxylomannan Inhibits IL-17A Production in Circulating T Cells from Rheumatoid Arthritis Patients. *Plos One* 8(1):e53336.

569. Fang FC, Bennett JW, **Casadevall A**. (2013) Males are overrepresented among life science researchers committing scientific misconduct. *Mbio* 4(1):e00640-12.

This paper received considerable media coverage. Here are some links

<http://www.sciencedaily.com/releases/2013/01/130122101905.htm>

<http://news.sciencemag.org/2013/01/male-scientists-more-prone-misconduct-study-concludes>

<http://www.biotechniques.com/news/Men-Commit-More-Misconduct/biotechniques-339315.html>

<http://www.nature.com/scitable/forums/women-in-science/do-men-commit-more-scientific-misconduct-102166616>

570. Klein M, Lotem M, Peretz T, Zwas ST, Mizrahi S, Liberman Y, Chisin R, Schachter J, Ron IG, Iosilevsky G, Kennedy JA, Revskaya E, de Kater AW, Banaga E, Klutzaritz V, Friedmann N, Galun E, Denardo GL, Denardo SJ, **Casadevall A**, Dadachova E, Thornton GB. (2013) Safety and efficacy of 188-rhenium-labeled antibody to melanin in patients with metastatic melanoma. *J. Skin. Cancer* 2013:828329

571. **Casadevall A**, Pirofski L (2013) Exserohilum rostrum fungal meningitis associated with methylprenilolone injections. *Future Microbiol.* 8:135-7.

572. Harris M, Wang XG, Jiang Z, Phaeton R, Koba W, Goldberg GL, **Casadevall A**, Dadachova E. (2013) Combined treatment of the experimental human papilloma virus-16-positive cervical and head and neck cancers with cisplatin and radioimmunotherapy targeting viral E6 oncoprotein. *Br. J. Cancer.* 108(4):859-65.

573. Achkar J, **Casadevall A** (2013) Antibody-mediated immunity against tuberculosis: implications for vaccine development. *Cell Host Microbe* 13;13(3):250-62.

574. Pohl MA, Rivera J, Nakouzi A, Chow SK, **Casadevall A** (2013) Combinations of antibodies to anthrax toxin manifest new properties in neutralization assays. *Infect. Immun.* 81(6):1880-8.

575. Derengowski L, Costa Paes H, Tavares AHFP, Albuquerque P, Fernandes L, Silva-Pereira I, **Casadevall A** (2013) The transcriptional response of *Cryptococcus neoformans* to *Acanthamoeba castellanii* and macrophages provides insights into the evolutionary adaptation to the mammalian host. *Eukaryotic Cell* 12(5):761-74.

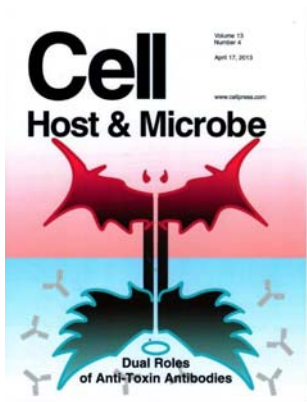
F1000 Recommended <http://f1000.com/prime/717992089#recommendations>

576. Jandl T, Revskaya E, Jiang Z, Bryan RA, **Casadevall A**, Dadachova E (2013) Complement-dependent cytotoxicity of an antibody to melanin in radioimmunotherapy of metastatic melanoma. *Immunotherapy* 5(4):357-64.

577. Ziegenbalg A, Prados-Rosales R, Jenny-Avital ER, Kim RS, **Casadevall A**, Achkar JM (2013) Immunogenicity of mycobacterial vesicles in humans: identification of a new biomarker. *Tuberculosis* S1472-9792(13)00061-9.

578. Jain N, Cordero RJB, **Casadevall A**, Fries BC (2013) Allergen1 Regulates Polysaccharide Structure in *Cryptococcus neoformans*. *Mol. Micro* 88(4):713-27.

579. Chow SK, Smith C, MacCarthy T, Pohl MA, Bergman A, **Casadevall A**. (2013) Disease-enhancing antibodies improve the activity of toxin-neutralizing antibodies. *Cell Host Microbe* 13(4):417-28.



580. Fonseca FL, Guimarães AJ, Kmetzsch L, Dutra FF, Silva FD, Taborda CP, Araujo GD, Frases S, Staats CC, Bozza MT, Schrank A, Vainstein MH, Nimrichter L, **Casadevall A**, Rodrigues ML (2013) Binding of the wheat germ lectin to *Cryptococcus neoformans* chitooligomers affects multiple mechanisms required for fungal pathogenesis. *Fungal Genet Biol.* ;60:64-73.

581. Quispe-Tintaya W, Chandra D, Jahangir A, Harris M, **Casadevall A**, Dadachova E, and Gravekamp C (2013) Non-toxic radioactive *Listeria* is a highly effective therapy against metastatic pancreatic cancer. *PNAS* 110(21):8668-73.

This manuscript received considerable media attention and was the object of an NIH Press release

<http://www.nih.gov/researchmatters/may2013/05062013radioactive.htm>

<http://www.sciencedaily.com/releases/2013/04/130422154753.htm>

<http://www.nature.com/news/radioactive-bacteria-attack-cancer-1.12841>

<http://news.sciencemag.org/sciencenow/2013/04/radioactive-microbes-nuke-tumor-.html>

The paper was also accompanied by an editorial in *PNAS*

<http://www.ncbi.nlm.nih.gov/pubmed/23667150>

582. Garcia-Solache MA, Izquierdo-Garcia D, Smith C, Bergman A, **Casadevall A**. (2013) Fungal virulence in a lepidopteran model is an emergent property with deterministic features. *MBio.* 2013 Apr 30;4(3). pii: e00100-13.

This paper was chosen for the journal 'Editor picks'

F1000 recommended <http://f1000.com/prime/718006239#recommendations>

583. Xia Y, Janda A, Eryilmaz E, **Casadevall A**, Putterman C. (2013). The constant region affects antigen binding of antibodies to DNA by altering secondary structure. *Mol. Immunol* 56(1-2):28-37.

584. Kania G, Siegert S, Behnke S, Prados-Rosales R, **Casadevall A**, Lüscher TF, Luther SA, Kopf M, Eriksson U, Blyszczuk P (2013) Innate Signalling Promotes Formation of Regulatory Nitric Oxide-Producing Dendritic Cells Limiting T Cell Expansion in Experimental Autoimmune Myocarditis. *Circulation* 127(23):2285-94

585. McClelland EE, Hobbs LM, Rivera J, **Casadevall A**, Potts WK, Smith JM, Ory JJ (2013) The Role of Host Gender in the Pathogenesis of *Cryptococcus neoformans* Infections. *PLoS One.* 2013 May 31;8(5):e63632.

586. Steen RG, **Casadevall A**, Fang FC. (2013) Why has the number of scientific retractions increased? *PLoS One* e68397.

587. Eryilmaz E, Janda A, Kim J, Cordero RJ, Cowburn D, **Casadevall A**. (2013) Global structures of IgG isotypes expressing identical variable regions. *Mol. Immunol.* 56(4):588-598.

588. **Casadevall A** (2013) Progress in understanding fungal pathogenesis. *Curr Opin Microbiol.* 16(4):375-6.
589. Cordero RJ, Bergman A, **Casadevall A** (2013). Temporal Behavior of Capsule Enlargement for *Cryptococcus neoformans*. *Eukaryot Cell* 12(10):1383-8.
590. **Casadevall A**, Fang FC (2013) Is the Nobel Prize good for Science? *FASEB J.* 27(12):4682-90. <http://www.laborjournal.de/blog/?p=8514>
591. Andes D, **Casadevall A** (2013) Insights into fungal pathogenesis from the iatrogenic epidemic of *Exserohilum rostratum* fungal meningitis. *Fungal Genet Bio*161:143-5 .
592. Bryan RA, Jiang Z, Morgenstern A, Bruchertseifer F, **Casadevall A**, Dadachova E. (2013) Radioimmunotherapy of *Cryptococcus neoformans* spares bystander mammalian cells. *Future Microbiol. Sep*;8(9):1081-9.
593. Coelho C, Bocca A, **Casadevall A.** (2013) The Intracellular Life of *Cryptococcus neoformans*. *Annu Rev Pathol.* 2014 9:219-38. doi: 10.1146/annurev-pathol-012513-104653,
594. **Casadevall A** (2013) Progress in understanding fungal pathogenesis. *Curr Opin Microbiol.* 16(4):375-6.
595. Rath P, Huang C, Wang T, Wang T, Li H, Prados-Rosales R, Elemento O, **Casadevall A** and Nathan C. (2013) Genetic Regulation of Vesiculogenesis and Immunomodulation in *Mycobacterium tuberculosis*. *PNAS* 110(49):E4790-7.
596. Silva BMA, Prados-Rosales R, Espadas-Moreno J, Wolf JM, Luque-Gracia JL, Gongalves T, **Casadevall A** (2013) Characterization of *Alternaria infectoria* extracellular vesicles. *Med Mycol*, 52(2):202-10.
597. **Casadevall A**, Enquist L, Imperiale MJ, Keim P, Relman DA (2013) Redaction of Sensitive Data in the Publication of Dual Use Research of Concern. *mBio* e00991-13 .
598. Albuquerque P, Nicola AM, Nieves E, Williamson PR, **Casadevall A** (2013) Quorum Sensing Mediated-Cell-Density Dependent Regulation of Growth and Virulence in *Cryptococcus neoformans*. *mBio* e00986-13.
599. Alunno A, Pericolini E, Gabrielli E, Bistoni O, Caterbi S, Bartoloni E, Terenzi R, Valentini E, La Paolia E, Chow SK, **Casadevall A**, Vechiarelli A, Gerli R (2014) Purified microbial capsular polysaccharide Galactoxylomannan (GalXM) inhibits the effector T lymphocyte arm and potentiates the regulatory counterpart in rheumatoid arthritis. *Ann Rheum Dis.* 2014;73:Suppl 1 A71.
600. Prados-Rosales R, Brown L, **Casadevall A**, Montalvo-Quirós S, Luque-Garcia JL. (2014) Isolation and identification of membrane vesicle-associated proteins in Gram-positive bacteria and mycobacteria. *MethodsX.* Aug 19;1:124-9. doi: 10.1016/j.mex.2014.08.001. eCollection 2014. PMID: PMC4472924
601. Rivera J, Morgenstern A, Bruchertseifer F, Kearney JF, Turnbough CL Jr, Dadachova E, **Casadevall A.** (2014) Microbicidal power of alpha radiation in sterilizing germinating *Bacillus anthracis* spores. *Antimicrob. Agents Chemotheap.* 58(3):1813-5. doi: 10.1128/AAC.01266-13.

602. Brotjatsch J, **Casadevall A**, Goldman DL (2014) Molecular determinants for a cardiovascular collapse in anthrax. *Front Biosci (Elite Ed)* 6:139-47.

603. **Casadevall A**, Handelsman J (2014) The presence of women conveners correlates with a higher proportion of female speakers at scientific symposia. *mBio* 5(1):e00846-13.

This article attracted considerable media attention and was featured in *The Scientist*, *Nature*, *The Atlantic*, *The chronicle of higher education* and numerous other journals and sites.

<http://www.theatlantic.com/technology/archive/2014/01/the-easiest-possible-way-to-increase-female-speakers-at-conferences/282858/>

<http://www.the-scientist.com/?articles.view/articleNo/38795/title/Speaker-Selection-Bias/>

<http://www.livescience.com/42362-encouraging-women-science.html>

<http://chronicle.com/blogs/ticker/include-women-on-meeting-teams-to-help-careers-of-female-scientists-study-suggests/71045>

<http://www.nature.com/naturejobs/science/articles/10.1038/nj7483-445a>

http://www.huffingtonpost.com/2014/01/08/women-in-science-stem-leaky-pipeline_n_4561084.html

604. Bournazos S, Chow S, Abboud N, **Casadevall A**, Ravetch JV (2014) Human IgG Fc domain engineering enhances anti-toxin neutralizing antibody activity. *J. Clin. Invest* 124(2):725-9. doi: 10.1172/JCI72676.

JV Ravetch and A Casadevall shared senior authorship

605. Prados-Rosales R, Weinrick BC, Pique DG, Jacobs WR Jr, **Casadevall A**, Rodrigues GM (2014) Role for *Mycobacterium tuberculosis* vesicles in iron acquisition. *J. Bacteriol.* 196:1250-6.

606. **Casadevall A**, Fang FC (2014) Specialized Science. *Infect. Immun* 82(4):1355-60. doi: 10.1128/IAI.01530-13.

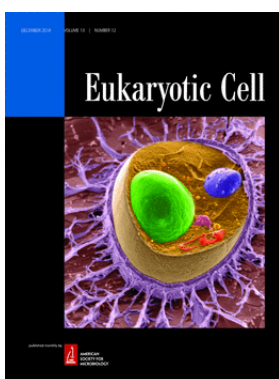
607. Rivera J, Sellers RS, Zeng W, van Rooijen N, **Casadevall A**, Goldman DL (2014) Platelet-activating factor contributes to *Bacillus anthracis* lethal toxin-associated damage. *J. Biol. Chem* 289(10):7131-41. *DL Goldman and A Casadevall shared senior authorship.*

608. Albuquerque PC, Fonseca FL, Dutra FF, Bozza MT, Frases S, **Casadevall A**, Rodrigues ML (2014) *Cryptococcus neoformans* glucuronoxylomannan fractions of different molecular masses are functionally distinct. *Future Microbiol.* 2014 Feb;9(2):147-61. PMID: PMC4294706

609. Coelho C, Bocca AL, **Casadevall A** (2014). The tools for virulence of *Cryptococcus neoformans*. *Adv Appl Microbiol.* 2014;87:1-41. doi: 10.1016/B978-0-12-800261-2.00001-3. PMID: PMC4132287

610. Brown GD, Meintjes G, Kolls JK, Gray C, Horsnell W; Working Group from the EMBO-AIDS Related Mycoses Workshop, Achan B, Alber G, Aloisi M, Armstrong-James D, Beale M, Bicanic T, Black J, Bohjanen P, Botes A, Boulware DR, Brown G, Bunjun R, Carr W, **Casadevall A**, Chang C, Chivero E, Corcoran C, Cross A, Dawood H, Day J, De Bernardis F, De Jager V, De Repentigny L, Denning D, Eschke M, Finkelman M, Govender N, Gow N, Graham L, Grysczek R, Hammond-Aryee K, Harrison T, Heard N, Hill M, Hoving JC, Janoff E, Jarvis J, Kayuni S, King K, Kolls J, Kullberg BJ, Lalloo DG, Letang E, Levitz S, Limper A, Longley N, Machiridza TR, Mahabeer Y, Martinsons N, Meiring S, Meya D, Miller R, Molloy S, Morris L, Mukaremera L, Musubire AK, Muzoora C, Nair A, Nakiwala Kimbowa J, Netea M, Nielsen K, O'hern J, Okurut S, Parker A, Patterson T, Pennap G, Perfect J, Prinsloo C, Rhein J, Rolfes MA, Samuel C, Schutz C, Scriven J, Sebolai OM, Sojane K, Sriruttan C, Stead D, Steyn A, Thawer NK, Thienemann F, Von Hohenberg M, Vreulink JM, Wessels J, Wood K, Yang YL. (2014) AIDS-related mycoses: the way forward. *Trends Microbiol.* Mar;22(3):107-9. doi: 10.1016/j.tim.2013.12.008. PMID: PMC4129449

611. Stukes S, Cohen HW, **Casadevall A** (2014) Temporal Kinetics and Quantitative Analysis of *Cryptococcus neoformans* Non-Lytic Exocytosis. *Infect. Immun.* 82(5):2059-67.
612. **Casadevall A**, Fang FC. (2014) Causes for the persistence of impact factor mania. *MBio.* 5(2):e00064-14. doi: 10.1128/mBio.00064-14.
613. **Casadevall A**, Dermody TS, Imperiale MJ, Sandri-Goldin RM, Shenk T. (2014) On the need for a national board to assess dual use research of concern (DURC). *J Virol.* 88(12):6535-7.
614. Chaskes S, Cammer M, Nieves E, **Casadevall A** (2014) Pigment Production on L-Tryptophan Medium by *Cryptococcus gattii* and *Cryptococcus neoformans*. *PLOS One* 9(4):e91901.
615. Olaya-Abril A, Prados-Rosales R, McConnell MJ, Martín-Peña R, González-Reyes JA, Jiménez-Munguía I, Gómez-Gascón L, Fernández J, Luque-García JL, García-Lidón C, Estévez H, Pachón J, Obando I, **Casadevall A**, Pirofski LA, Rodríguez-Ortega MJ (2014). Characterization of protective extracellular membrane-derived vesicles produced by *Streptococcus pneumoniae*. *J Proteomics.* 106:46-60.
616. Park Y-D, Shin S, Panepinto J, Ramos J, Qiu J, Frases S, Albuquerque P, Cordero RJB, Himmelreich W, Beenhouwer D, Bennett JE, **Casadevall A**, Williamson PR (2014) A role for LHC1 in higher order structure and complement binding of the *Cryptococcus neoformans* capsule. *PLOS Pathogens* 10(5):e1004037.
617. Brown L, Kessler A, Cabezas-Sanchez P, Luque-Garcia JL, **Casadevall A.** (2014) Extracellular vesicles produced by the Gram-positive bacterium *Bacillus subtilis* are disrupted by the lipopeptide surfactin. *Mol Microbiol.* 93(1):183-98. doi: 10.1111/mmi.12650
618. Wolf J, Espadas-Moreno J, Luque-Garcia JL, **Casadevall A** (2014) Interaction of *Cryptococcus neoformans* extracellular vesicles with the cell wall. *Eukaryotic Cell* 13:1484-93. doi: 10.1128/EC.00111-14.



619. **Casadevall A**, Steen RG, Fang FC (2014) Sources of error in the retracted scientific literature. *FASEB J* 28(9):3847-55.
620. García-Rodas R, Cordero RJ, Trevijano-Contador N, Janbon G, Moyrand F, **Casadevall A**, Zaragoza O. (2014) Capsule Growth in *Cryptococcus neoformans* Is Coordinated with Cell Cycle Progression. *mBio* 5(3):e00945-14. doi: 10.1128/mBio.00945-14.

621. **Casadevall A**, Fang FC (2014) Diseased Science. *Microbe*. See http://www.microbemagazine.org/index.php?option=com_content&view=article&id=6814:diseased-science&catid=1373&Itemid=1652



Poster given out by ASM Publications Board at the ASM 2015 General Meeting.

622. Chatterjee S, Prados-Rosales R, Tan S, Itin B, **Casadevall A**, Stark RE (2014). Demonstration of a common indole-based aromatic core in natural and synthetic eumelanins by solid-state NMR. *Org Biomol Chem*. 12(34):6730-6. doi: 10.1039/c4ob01066c.

623. **Casadevall A**, Imperiale MJ (2014) Risks and Benefits of Gain-of-Function Experiments with Pathogens of Pandemic Potential, Such as Influenza Virus: a Call for a Science-Based Discussion. *mBio* doi:10.1128/mBio.01730-14.

624. Stern AM, **Casadevall A**, Steen RG, Fang FC (2014). Financial costs and personal consequences of research misconduct resulting in retracted publications. *Elife*. 2014 Aug 14;3:e02956. doi: 10.7554/eLife.02956.

625. **Casadevall A**, Howard D, Imperiale MJ (2014) An epistemological perspective on the value of gain-of-function (GOF) experiments involving pathogens with pandemic potential (PPP). *mBio* pii: e01875-14. doi: 10.1128/mBio.01875-14. PMCID: PMC4172079

626. **Casadevall A**, Imperiale MJ. (2014) Reply to "a brain drain due to increased regulation of influenza virus research is highly speculative". *MBio*. Sep 23;5(5):e01860-14. doi: 10.1128/mBio.01860-14. PMCID: PMC4173769

627. Prados-Rosales R, Carreño LJ, Batista-Gonzalez A, Baena A, Venkataswamy MM, Xu J, Yu X, Wallstrom G, Magee DM, LaBaer J, Achkar JA, Jacobs Jr WR, Chan J, Porcelli SA, **Casadevall A** (2014) Mycobacterial membrane vesicles induce a protective immune response directed to the surface compartments of *Mycobacterium tuberculosis* when applied systemically in mice. *mBio* e01921-14. doi: 10.1128/mBio.01921-14. PMID: 25287304

628. Achkar JM, Chan J, **Casadevall A**. (2014) Role of B Cells and Antibodies in Acquired Immunity against *Mycobacterium tuberculosis*. *Cold Spring Harb Perspect Med*. 2014 Oct 9. pii: a018432. PMCID: PMC4355258

629. Dermody TS, **Casadevall A**, Imperiale MJ, Sandri-Goldin RM, Shenk T (2014) The Decision to Publish an Avian H7N1 Influenza Virus Gain-of-Function Experiment. *MBio*. 2014 Oct 14;5(5). pii: e01985-14. PMCID: PMC4205794

630. **Casadevall A**, Howard D, Imperiale MJ. (2014) Reply to "Can limited scientific value of potential pandemic pathogen experiments justify the risks?". MBio. Oct 14;5(5):e02053-14. doi: 10.1128/mBio.02053-14. PMCID: PMC4205797

631. **Casadevall A**, Howard D, Imperiale MJ. (2014) Reply to "Valuing knowledge: a reply to the epistemological perspective on the value of gain-of-function experiments". MBio. Oct 14;5(5):e02054-14. doi: 10.1128/mBio.02054-14. PMCID: PMC4205798

632. **Casadevall A**, Howard D, Imperiale MJ (2014) The Apocalypse as a Rhetorical Device in the Influenza Virus Gain-of-Function Debate. MBio. 2014 Oct 14;5(5). pii: e02062-14. PMCID: PMC4205799

633. Pericolini E, Gabrielli E, Alunno A, Bartoloni Bocci E, Perito S, Chow SK, Cenci E, **Casadevall A**, Gerli R, Vecchiarelli A. (2014) Functional improvement of regulatory T cells from rheumatoid arthritis subjects induced by capsular polysaccharide glucuronoxylomannogalactan. PLoS One Oct 22;9(10):e111163. doi: 10.1371/journal.pone.0111163. eCollection 2014. PMCID: PMC4206502

634. Stukes S, **Casadevall A** (2014) Visualizing non-lytic exocytosis of *Cryptococcus neoformans* from macrophages using digital light microscopy. J Vis Exp. 2014 Oct 21;(92). doi: 10.3791/52084. PMCID: PMC4353314

635. Kohler JR, **Casadevall A**, Perfect JR (2014) The spectrum of pathogenic fungi. Cold Spring Harb Perspect Med. 2014 Nov 3. pii: a019273. doi: 10.1101. PMCID: PMC4292074

636. Vargas G, Rocha JD, Oliveira D, Albuquerque PC, Frases S, Santos SS, Nosanchuk JD, Soares Medeiros LC, Miranda KR, Sobreira T, Nakayasu ES, Agiri EA, Almeida IC, **Casadevall A**, Rodrigues M, Freire-de-Lima CG, Nimrichter L (2015) Compositional and immunobiological analyses of extracellular vesicles released by *Candida albicans* Cell Microbiol. Mar;17(3):389-407. doi: 10.1111/cmi.12374. PMID: 25287304

637. **Casadevall A**, Pirofski L (2015) What is a host? Incorporating the microbiota to the 'damage response framework' of microbial pathogenesis. Infect. Immun. Jan;83(1):2-7. doi: 10.1128/IAI.02627-14. PMCID: PMC4288903

638. Chan J, Mehta S, Bharrhan S, Chen Y, Achkar JM, **Casadevall A**, Flynn J. (2014) The role of B cells and humoral immunity in *Mycobacterium tuberculosis* infection. Semin Immunol. 2014 Oct 28;26(6):588-600. doi: 10.1016/j.smim.2014.10.005. PMCID: PMC4314354

639. Wolf JM, **Casadevall A** (2014) Challenges posed by extracellular vesicles from eukaryotic microbes. Curr Opin Microbiol. 2014 Oct 17;22C:73-78. doi: 10.1016/j.mib.2014.09.012. PMCID: PMC4359756

640. **Casadevall A**, Pirofski LA (2014) Microbiology: Ditch the term pathogen. Nature 516(7530):165-6. doi: 10.1038/516165a. PMID: 25503219

641. Imperiale MJ, **Casadevall A** (2014) Vagueness and Costs of the Pause on Gain-of-Function (GOF) Experiments on Pathogens with Pandemic Potential, Including Influenza Virus. MBio pii: e02292-14. doi: 10.1128/mBio.02292-14. PMCID: PMC4278541

642. Duprex WP, **Casadevall A** (2014) Falling down the Rabbit Hole: aTRIP Toward Lexiconic Precision in the "Gain-of-Function" Debate. MBio pii: e02421-14. doi: 10.1128/mBio.02421-14. PMCID: PMC4271557

643. **Casadevall A**, Shenk T. (2014) mBio addresses the pause in gain-of-function (GOF) experiments involving pathogens with pandemic potential (PPP). MBio. Dec 12;5(6). pii: e02434-14. doi: 10.1128/mBio.02434-14. PMID: PMC4271558
644. Dadachova E, **Casadevall A**. (2014) Radiolabeled antibodies for therapy of infectious diseases. Microbiol Spectr. 2014 Nov;2(6):0023. PMID: PMC4294273
645. Fang FC, **Casadevall A** (2015) Competitive Science: Is Competition Ruining Science. Infect. Immun. Jan 20. pii: IAI.02939-14. PMID: PMC4363426
646. Coelho C, Oliveira Souza AC, Derengowski L, de Leon-Rodriguez C, Wang B, Leon-Rivera R, Bocca, AL, Gonçalves T, **Casadevall A** (2015) Macrophage mitochondrial and stress response to ingestion of *Cryptococcus neoformans*. J. Immunol. 194(5):2345-57. PMID: PMC3647765
647. Majlessi L, Prados-Rosales R, **Casadevall A**, Brosch R. (2015) Release of mycobacterial antigens. Immunol Rev. 264(1):25-45. PMID: 25703550
648. Achkar JM, Chan J, **Casadevall A** (2015) B cells and antibodies in the defense against *Mycobacterium tuberculosis* infection. Immunol. Rev. 264(1):167-81. PMID: PMC4629253
649. Imperiale MJ, **Casadevall A** (2015) The importance of virology at a time of great need and great jeopardy. mBio 6(2). pii: e00236-15. doi: 10.1128/mBio.00236-15. PMID: PMC4453524
650. Robert V, Cardinali G, **Casadevall A** (2015) Distribution and impact of yeast thermal tolerance permissive for mammalian infection. BMC Biology Feb 26;13:18. doi: 10.1186/s12915-015-0127-3. PMID: PMC4381509
651. Janda A, Eryilmaz E, Nakouzi A, Pohl MA, Bowen A, **Casadevall A** (2015) Variable region identical IgA and IgE to *Cryptococcus neoformans* capsular polysaccharide manifest specificity differences. J. Biol. Chem 290(19):12090-100. PMID: PMC4424345
652. Chatterjee S, Prados-Rosales R, Itin B, **Casadevall A**, Stark RE (2015) Solid-state NMR Reveals the Carbon-based Molecular Architecture of *Cryptococcus neoformans* Fungal Eumelanins in the Cell Wall. J. Biol. Chem 290(22):13779-90. PMID: PMC4447955
653. Imperiale MJ, **Casadevall A** (2015) A new synthesis for dual use research of concern. PLoS Med. Apr 14;12(4):e1001813. doi: 10.1371/journal.pmed.1001813. PMID: PMC4397073
654. Pirofski L, **Casadevall A** (2015) What is infectiveness? BMC Immunology Mar 26;16:13. doi: 10.1186/s12865-015-0076-1. PMID: PMC4374184
655. **Casadevall A**, Pirofski L (2015) The Ebola epidemic crystallizes the potential of passive antibody therapy for infectious diseases. Plos Pathogens 11(4):e1004717. PMID: PMC4408073
656. Zolla V, Nizamutdinova IT, Scharf B, Clement CC, Maejima D, Akl T, Nagai T, Luciani P, Leroux JC, Halin C, Stukes S, Tiwari S, **Casadevall A**, Jacobs WR Jr, Entenberg D, Zawieja DC, Condeelis J, Fooksman DR, Gashev AA, Santambrogio L (2015). Aging-related anatomical and biochemical changes in lymphatic collectors impair lymph transport, fluid homeostasis, and pathogen clearance. Aging Cell. May 15. doi: 10.1111/ace.12330. PMID: PMC4531072

657. Wolf JM, Espadas J, Luque-Garcia J, Reynolds T, **Casadevall A** (2015) Lipid biosynthetic genes affect *Candida albicans* extracellular vesicle morphology, cargo, and immunostimulatory properties. Eukaryotic Cell May 29. pii: EC.00054-15. PMCID: PMC4519749

658. Martinez LR, **Casadevall A** (2015) Biofilm formation by *Cryptococcus neoformans*. Microbiol Spectr. 2015 Jun;3(3). doi: 10.1128/microbiolspec.MB-0006-2014. PMID: 26185073

659. **Casadevall A** (2015) Achieving gender equity at the American Society for Microbiology General Meeting. mBio doi: 10.1128/mBio.01146-15. PMCID:PMC4526716

This study received media coverage

http://sciencecareers.sciencemag.org/career_magazine/previous_issues/articles/2015_07_29/caredit.a1500189

<https://www.insidehighered.com/news/2015/08/05/microbiologists-show-its-possible-achieve-gender-equity-scholarly-presentations>

<http://mbioblog.asm.org/mbiosphere/2015/08/toward-gender-parity-in-conference-presentation.html>

<https://www.genomeweb.com/scan/asm-reports-near-gender-parity-speakers-meeting>

660. Prados-Rosales R, Toriola S, Nakouzi A, Chatterjee S, Stark R, Gerfen G, Tumpowsky P, Dadachova E, **Casadevall A**. (2015) Structural Characterization of Melanin Pigments from Commercial Preparations of the Edible Mushroom *Auricularia auricula*. J Agric Food Chem 26;63(33):7326-32. doi: 10.1021/acs.jafc.5b02713. PMCID: PMC4862413

661. **Casadevall A**, Dermody TS, Imperiale MJ, Sandri-Goldin RM, Shenk T (2015) Dual-Use Research of Concern (DURC) Review at American Society for Microbiology Journals. MBio. 2015 Aug 11;6(4). pii: e01236-15. doi:10.1128/mBio.01236-15. PMCID: PMC4542189

662. Bowen A, **Casadevall A** (2015) Increasing disparities between resource inputs and outcomes, as measured by certain health deliverables, in biomedical research. PNAS 112(36):11335-40. PMCID: PMC4568675

Article feature in 'this issue' in PNAS

<http://www.pnas.org/content/112/36/11139.full>

This study received media coverage

<http://www.washingtonpost.com/news/wonkblog/wp/2015/08/17/scientists-are-trying-to-figure-out-the-best-ways-to-spend-money-on-science/>

<http://www.sciencedaily.com/releases/2015/08/150817160617.htm>

<http://news.yahoo.com/more-money-fewer-cures-us-medical-research-faces-201526110.html>

<http://news.sciencemag.org/scientific-community/2015/08/effort-c-impact-u-s-biomedical-research-study-concludes>

See also correspondence:

663. **Casadevall A**, Shenk T. (2015) The Justification for the Academy Track in mBio. MBio. Aug 18;6(4). pii: e01222-15. doi: 10.1128/mBio.01222-15. PMCID: PMC4542184

664. García-Rodas R, Trevijano-Contador N, Román E, Janbon G, Moyrand F, Pla J, **Casadevall A**, Zaragoza O (2015) Role of Cln1 during melanization of *Cryptococcus neoformans* Frontiers Microbiol. 6:798. doi: 10.3389/fmicb.2015.00798. PMCID: PMC4532930

665. Brown L, Wolf JM, Prados-Rosales R, **Casadevall A** (2015) Through the wall: extracellular vesicles in Gram-positive bacteria, mycobacteria and fungi. Nature Micro Rev 13(10):620-30. PMCID: PMC4860279

666. **Casadevall A**, Fang FC (2015) Field Science: The Nature and Utility of Scientific Fields. *Mbio* e01259-15. doi: 10.1128/mBio.01259-15. PMCID: PMC4600110
667. **Casadevall A**, Fang FC (2015) A Historical Science. *Infect. Immun.* 83(12):4460-4. PMCID: PMC4645372
668. Frank GM, Adalja A, Barbour A, **Casadevall A**, Dormitzer PR, Duchin J, Hayden FG, Hirsch MS, Hynes NA, Lipsitch M, Pavia AT, Relman DA (2015) Infectious Diseases Society of America and Gain-of-Function Experiments With Pathogens Having Pandemic Potential. *J. Infect. Dis.* 213(9):1359-61. doi: 10.1093/infdis/jiv474. PMID: 26416656
669. Fang FC, **Casadevall A**. (2015) Correction for Fang and Casadevall, Competitive Science: Is Competition Ruining Science? *Infect. Immun.* 2015 Nov;83(11):4452. doi: 10.1128/IAI.01031-15. PMCID:PMC4598405
670. Almeida F, Wolf JM, **Casadevall A** (2015) Virulence-Associated Enzymes of *Cryptococcus neoformans*. *Eukaryotic Cell* 14(12):1173-85. PMCID: PMC4664877
671. **Casadevall A**, Fang FC (2015) Impacted science: impact is not importance. *mBio* e01593-15. doi: 10.1128/mBio.01593-15. PMCID:PMC4620476
672. Bowen A, **Casadevall A**. (2015) Reply to Fiscella: the phases of biomedical science should be studied to optimize health outcomes. *Proc Natl Acad Sci U S A.* Nov 24;112(47):E6413. PMCID: PMC4664302
673. Fernandes C, Prados-Rosales R, Silva BM, Nakouzi-Naranjo A, Zuzarte M, Chatterjee S, Stark RE, **Casadevall A**, Gonçalves T. (2015) Activation of Melanin Synthesis in *Alternaria infectoria* by Antifungal Drugs. *Antimicrob Agents Chemother.* Dec 28;60(3):1646-55. PMCID: PMC4775914
674. Nosanchuk JD, Stark RE, **Casadevall A**. (2015) Fungal Melanin: What do We Know About Structure? *Front Microbiol.* 6:1463. doi: 10.3389/fmicb.2015.01463. PMCID: PMC4687393
675. Fang FC, **Casadevall A** (2016) The illusion of self correction. *Chemistry World* <http://www.rsc.org/chemistryworld/2015/12/self-correction-illusion-misconduct-retraction>
676. Janda A, Bowen A, Greenspan NS, **Casadevall A** (2016) Ig Constant Region Effects on Variable Region Structure and Function. *Front Microbiol.* 4;7:22. doi: 10.3389/fmicb.2016.00022. PMCID: PMC4740385
677. Fang FC, Bowen A, **Casadevall A**. (2016) NIH peer review percentile scores are poorly predictive of grant productivity (2016). *Elife pii: e13323*. doi: 10.7554/eLife.13323. PMCID: PMC4769156
The Scientist <http://www.the-scientist.com/?articles.view/articleNo/45379/title/NIH-Grant-Reviews-Don-t-Predict-Success/>
F1000 <http://f1000.com/prime/726150583>
678. Cordero RJ, Liedke SC, de S Araújo GR, Martinez LR, Nimrichter L, Frases S, Peralta JM, **Casadevall A**, Rodrigues ML, Nosanchuk JD, Guimaraes AJ (2016). Enhanced virulence of *Histoplasma capsulatum* through transfer and surface incorporation of glycans from *Cryptococcus neoformans* during co-infection. *Sci Rep.* 6:21765. doi: 10.1038/srep21765. PMCID: PMC4764860

679. DeLeon-Rodriguez CM, **Casadevall A.** (2016) *Cryptococcus neoformans*: Tripping on Acid in the Phagolysosome. *Front Microbiol.* doi: 10.3389/fmicb.2016.00164. PMID: PMC4756110

680. **Casadevall A**, Fang FC. (2016) Revolutionary Science. *mBio.* pii: e00158-16. doi: 10.1128/mBio.00158-16. PMID: PMC4810483

681. Coelho C, **Casadevall A** (2016) Cryptococcal therapies and drug targets: the old, the new and the promising. *Cell Microbiol.* 18(6):792-9. doi: 10.1111/cmi.12590. PMID: 26990050

682. Chen T, Blanc C, Eder AZ, Prados-Rosales R, Souza AC, Kim RS, Glatman-Freedman A, Joe M, Bai Y, Lowary TL, Tanner R, Brennan MJ, Fletcher HA, McShane H, **Casadevall A**, Achkar JM (2016) Association of Human Antibodies to Arabinomannan with enhanced mycobacterial Opsonophagocytosis and intracellular growth reduction. *J. Infect. Dis.* 241(2):300-10 doi: 10.1093/infdis/jiw141. Epub April 7. PMID: PMC4918826

683. Fang FC, **Casadevall A.** (2016) Research funding: the case for a modified lottery. *mBio* e00422-16. doi: 10.1128/mBio.00422-16. PMID: PMC4959526

684. Collier RJ, **Casadevall A.** (2016) The Holobiont/Hologenome Concept Series. *MBio.* Apr 14;7(2). pii: e00605-16. doi: 10.1128/mBio.00605-16. PMID: PMC4850271

685. Fang FC, **Casadevall A** (2016) Grant funding – playing the odds. *Science.* 352(6282):158. doi: 10.1126/Science 352.6282.158-a. PMID: 27124444

686. **Casadevall A** (2016) Thermal restriction as an antimicrobial function of fever. *PLoS Pathog.* 2016 May 5;12(5):e1005577. doi: 10.1371/journal.ppat.1005577. PMID: PMC4858228

687. Fang FC, **Casadevall A.** (2016) Erratum for Fang and Casadevall, Research Funding: the Case for a Modified Lottery *MBio.* May 17;7(3). pii: e00694-16. doi: 10.1128/mBio.00694-16. PMID: PMC4895113

688. Prados-Rosales R, Carreño LJ, Weinrick B, Batista-Gonzalez A, Glatman-Freedman A, Xu J, Chan J, Jacobs WR Jr, Porcelli SA, **Casadevall A** (2016) The Type of Growth Medium Affects the Presence of a Mycobacterial Capsule and Is Associated With Differences in Protective Efficacy of BCG Vaccination Against *Mycobacterium tuberculosis*. *J. Infect. Dis.* 214(3):426-37. PMID: PMC4936643

689. Bik EM, **Casadevall A**, Fang FC (2016). The Prevalence of Inappropriate Image Duplication in Biomedical Research Publications. *mBio* pii: e00809-16. doi: 10.1128/mBio.00809-16. (AC and FCF contributed equally). PMID: PMC4941872

This article received wide coverage:

Retraction watch

<http://retractionwatch.com/2016/04/19/one-in-25-papers-contains-inappropriately-duplicated-images-screen-finds/>

The Scholarly Kitchen

<https://scholarlykitchen.sspnet.org/2016/05/02/image-manipulation-cleaning-up-the-scholarly-record/>

Nature <http://www.nature.com/news/problematic-images-found-in-4-of-biomedical-papers-1.19802>

Stat News <https://www.statnews.com/2016/04/29/duplicated-images-research-papers/>

690. Imperiale MJ, **Casadevall A** (2016) Zika virus focuses the gain-of-function debate (2016) *mSphere* DOI: 10.1128/mSphere.00069-16. PMID: PMC4894681

691. Matos Baltazar LM, Nakayasu ES, Sobreira TJP, Choi H, **Casadevall A**, Nimrichter L, Nosanchuk JD (2016) Antibody Binding Alters the Characteristics and Contents of Extracellular Vesicles Released by *Histoplasma capsulatum*. *mSphere* DOI: 10.1128/mSphere.00085-15. PMID: PMC4894687

692. Cordero RJB, De Leon-Rodriguez C, Alvarado-Torres J, Rodz A, **Casadevall A** (2016) Life Science's Average Publishable Unit (APU) has increased over the past two decades. *PLOS One* 11(6):e0156983. doi: 10.1371/journal.pone.0156983. PMID: PMC4911092

693. Stukes S, Coelho C, Rivera J, Jedlicka AE, Hajjar KA, **Casadevall A** (2016) The Membrane Phospholipid Binding Protein Annexin A2 Promotes Phagocytosis and Non-lytic Exocytosis of *Cryptococcus neoformans* and Impacts Survival in Fungal Infection. *J Immunol.* Jul 1. pii: 1501855. [Epub ahead of print]. PMID: PMC5160961

694. **Casadevall A**, Bertuzzi S, Buchmeier MJ, Davis RJ, Drake H, Fang FC, Gilbert J, Goldman BM, Imperiale MJ, Matsumura P, McAdam AJ, Pasetti MF, Sandri-Goldin RM, Silhavy T, Rice L, Young JA, Shenk T. (2016) ASM Journals Eliminate Impact Factor Information from Journal Websites. *MBio.* Jul 11;7(4). pii: e01150-16. doi: 10.1128/mBio.01150-16. PMID: PMC5069964

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<http://europeanscienceediting.eu/articles/good-practice-asm-journals-eliminate-impact-factor-information-from-their-journals-websites/>

695. **Casadevall A**, Ellis LM, Davies EW, McFall-Ngai M, Fang FC. (2016) A Framework for Improving the Quality of Research in the Biological Sciences. *MBio.* Aug 30;7(4). pii: e01256-16. doi: 10.1128/mBio.01256-16.

Related correspondence:

Casadevall A, Ellis LM, Davies EW, McFall-Ngai M, Fang FC. (2016) Reply to "Improving Microbiology Research: the Problems Are Less Statistical and More Biological". *MBio.* 2016 Oct 18;7(5). pii: e01680-16. doi: 10.1128/mBio.01680-16. PMID: PMC5082904

696. **Casadevall A**, Fang FC. (2016) Moonshot Science-Risks and Benefits. *MBio.* Aug 30;7(4). pii: e01381-16. doi: 10.1128/mBio.01381-16. PMID: PMC4999559

697. **Casadevall A**, Fang FC. (2016) Reply to "Funding by Lottery: Political Problems and Research Opportunities". *MBio.* Aug 30;7(4). pii: e01401-16. doi: 10.1128/mBio.01401-16. PMID: PMC27578762

698. McClelland EE, Ramagopal UA, Rivera J, Cox J, Nakouzi A, Prabu MM, Almo SC, **Casadevall A**. (2016) A Small Protein Associated with Fungal Energy Metabolism Affects the Virulence of *Cryptococcus neoformans* in Mammals. *PLoS Pathog.* Sep 1;12(9):e1005849. doi: 10.1371/journal.ppat.1005849. PMID: PMC5008624

699. Bowen A, **Casadevall A**. (2016) Revisiting the Immunoglobulin Intramolecular Signaling Hypothesis. *Trends Immunol.* Sep 14. pii: S1471-4906(16)30118-1. doi: 10.1016/j.it.2016.08.014. PMID: PMC5287420

700. **Casadevall A.** (2016) To Be or Not Be a (Functional) Antibody Against TB. *Cell*. Oct 6;167(2):306-307. doi: 10.1016/j.cell.2016.09.041. PMID: 27716502

701. Tsukrov D, McFarren A, Morgenstern A, Bruchertseifer F, Dolce E, Gorny MK, Zolla-Pazner S, Berman JW, Schoenbaum E, Zingman BS, **Casadevall A**, Dadachova E. (2016) Combination of Antiretroviral Drugs and Radioimmunotherapy Specifically Kills Infected Cells from HIV-Infected Individuals. *Front Med (Lausanne)*. Sep 26;3:41. PMCID: PMC5035742

702. da Silva TA, Roque-Barreira MC, **Casadevall A**, Almeida F. (2016) Extracellular vesicles from *Paracoccidioides brasiliensis* induced M1 polarization in vitro. *Sci Rep*. Oct 24;6:35867. doi: 10.1038/srep35867. PMCID: PMC5075875

703. Saks MJ, Albright T, Bohan TL, Bierer BE, Bowers CM, Bush MA, Bush PJ, **Casadevall A**, Cole SA, Denton MD, Diamond SS, Dioso-Villa R, Epstein J, Faigman D, Faigman L, Fienberg SE, Garrett BL, Giannelli PC, Greely HT, Imwinkelried E, Jamieson A, Kafadar K, Kassirer JP, Koehler JJ, Korn D, Mnookin J, Morrison AB, Murph E, Peerwani N, Peterson JL, Risinger DM, Sensabaugh GF, Spiegelman C, Stern H, Thompson WC, Wayman JL, Zabel S, Zumwalt RE (2016) Forensic bite mark identification: weak foundations, exaggerated claims. *Journal of Law and the Biosciences*, 1–38. doi:10.1093/jlb/lsw045

704. **Casadevall A**, Fang FC. Rigorous Science: a how to guide. *MBio*. 2016 Nov 8;7(6). pii: e01902-16. doi: 10.1128/mBio.01902-16. PMCID: PMC5111411

705. Bowen A, Wear MP, Cordero R, Oscarson S, **Casadevall A** (2016) A monoclonal antibody to *Cryptococcus neoformans* glucuronoxylomannan manifests hydrolytic activity for both peptides and polysaccharides. *J Biol Chem*. Nov 21. pii: jbc.M116.767582. PMCID: PMC5241721

706. Grossman NT, **Casadevall A.** (2016) Physiological Differences in *C. neoformans* in vitro versus in vivo and Their Effects on Antifungal Susceptibility. *Antimicrob Agents Chemother*. Dec 28. pii: AAC.02108-16. doi: 10.1128/AAC.02108-16. PMCID: PMC5328578

707. **Casadevall A** (2016) Acknowledgment of Reviewers. *MBio* Dec 30;8(1). pii: e02303-16. doi: 10.1128/mBio.02303-16. PMID: 28039306

708. Saks MJ, Albright T, Bohan TL, Bierer BE, Bowers CM, Bush MA, Bush PJ, **Casadevall A**, Cole SA, Denton MB, Diamond SS, Dioso-Villa R, Epstein J, Faigman D, Faigman L, Fienberg SE, Garrett BL, Giannelli PC, Greely HT, Imwinkelried E, Jamieson A, Kafadar K, Kassirer JP, Koehler J, Korn D, Mnookin J, Morrison AB, Murphy E, Peerwani N, Peterson JL, Risinger DM, Sensabaugh GF, Spiegelman C, Stern H, Thompson WC, Wayman JL, Zabel S, Zumwalt RE (2016) Forensic bite mark identification: weak foundations, exaggerated claims. *J Law Biosci*. 6 Nov 23;3(3):538-575. doi: 10.1093/jlb/lsw045. PMID: 28852538

709. Prados-Rosales R, Carreño L, Cheng T, Blanc C, Weinrick B, Malek A, Lowary TL, Baena A, Joe M, Bai Y, Kalscheuer R, Batista-Gonzalez A, Saavedra NA, Sampedro L, Tomás J, Anguita J, Hung SC, Tripathi A, Xu J, Glatman-Freedman A, Jacobs WR Jr, Chan J, Porcelli SA, Achkar JM, **Casadevall A.** (2017) Enhanced control of *Mycobacterium tuberculosis* extrapulmonary dissemination in mice by an arabinomannan-protein conjugate vaccine. *PLoS Pathog*. Mar 9;13(3):e1006250. doi: 10.1371/journal.ppat.1006250. PMCID: PMC5360349

710. **Casadevall A**, Cordero RJ, Bryan R, Nosanchuk J, Dadachova E. (2017) Melanin, Radiation, and Energy Transduction in Fungi. *Microbiol Spectr*. Mar;5(2). doi: 10.1128/microbiolspec.FUNK-0037-2016. PMID: 28256187

711. **Casadevall A.** (2017) The Pathogenic Potential of a Microbe. *mSphere*. Feb 22;2(1). pii: e00015-17. doi: 10.1128/mSphere.00015-17. PMCID: PMC5322344

712. Chandra D, Selvanesan BC, Yuan Z, Libutti SK, Koba W, Beck A, Zhu K, **Casadevall A**, Dadachova E, Gravekamp C. (2017) 32-Phosphorus selectively delivered by listeria to pancreatic cancer demonstrates a strong therapeutic effect. *Oncotarget*. Feb 6. doi: 10.18632/oncotarget.15117. [Epub ahead of print] PMCID: PMC5400540

713. **Casadevall A**, Shenk T. (2017) The mBio American Academy of Microbiology Submission Track in 2017. *MBio*. Feb 7;8(1). pii: e00050-17. doi: 10.1128/mBio.00050-17. PMCID: PMC5296597

714. Fang FC, **Casadevall A.** (2017) Reply to "On the Impact Factor and the ASM Editorial Policy". *Infect Immun*. 2017 Jan 26;85(2). pii: e00989-16. doi: 10.1128/IAI.00989-16. PMCID: PMC5278168

715. Kwon-Chung KJ, Bennett JE, Wickes BL, Meyer W, Cuomo CA, Wollenburg KR, Bicanic TA, Castañeda E, Chang YC, Chen J, Cogliati M, Dromer F, Ellis D, Filler SG, Fisher MC, Harrison TS, Holland SM, Kohno S, Kronstad JW, Lazera M, Levitz SM, Lionakis MS, May RC, Ngamskulrongsroj P, Pappas PG, Perfect JR, Rickerts V, Sorrell TC, Walsh TJ, Williamson PR, Xu J, Zelazny AM, **Casadevall A.** (2017) The Case for Adopting the "Species Complex" Nomenclature for the Etiologic Agents of Cryptococcosis. *mSphere*. Jan 11;2(1). pii: e00357-16. doi: 10.1128/mSphere.00357-16. PMCID: PMC5227069

716. **Casadevall A.** (2017) Antibodies to *Mycobacterium tuberculosis*. *N Engl J Med*. Jan 19;376(3):283-285. doi: 10.1056/NEJMcibr1613268. PMID: 28099836

717. Grossman NT, **Casadevall A.** (2017) Physiological Differences in *Cryptococcus neoformans* Strains *In Vitro* versus *In Vivo* and Their Effects on Antifungal Susceptibility. *Antimicrob Agents Chemother*. Feb 23;61(3). pii: e02108-16. doi: 10.1128/AAC.02108-16. Review. PMCID: PMC5328578

718. Bowen A, Wear MP, Cordero RJ, Oscarson S, **Casadevall A.** (2017) A Monoclonal Antibody to *Cryptococcus neoformans* Glucuronoxylomannan Manifests Hydrolytic Activity for Both Peptides and Polysaccharides. *J Biol Chem*. Jan 13;292(2):417-434. doi: 10.1074/jbc.M116.767582. PMCID: PMC5241721

719. Grossman NT, **Casadevall A.** (2017) Physiological Differences in *Cryptococcus neoformans* Strains *In Vitro* versus *In Vivo* and Their Effects on Antifungal Susceptibility. *Antimicrob Agents Chemother*. Feb 23;61(3). pii: e02108-16. doi: 10.1128/AAC.02108-16. PMCID: PMC5328578

720. Kwon-Chung KJ, Bennett JE, Wickes BL, Meyer W, Cuomo CA, Wollenburg KR, Bicanic TA, Castañeda E, Chang YC, Chen J, Cogliati M, Dromer F, Ellis D, Filler SG, Fisher MC, Harrison TS, Holland SM, Kohno S, Kronstad JW, Lazera M, Levitz SM, Lionakis MS, May RC, Ngamskulrongsroj P, Pappas PG, Perfect JR, Rickerts V, Sorrell TC, Walsh TJ, Williamson PR, Xu J, Zelazny AM, **Casadevall A.** (2017) The Case for Adopting the "Species Complex" Nomenclature for the Etiologic Agents of Cryptococcosis. *mSphere*. Jan 11;2(1). pii: e00357-16. doi: 10.1128/mSphere.00357-16. eCollection Jan-Feb. PMCID: PMC5227069

721. Fang FC, **Casadevall A.** (2017) Reply to "On the Impact Factor and the ASM Editorial Policy". *Infect Immun*. Jan 26;85(2). pii: e00989-16. doi: 10.1128/IAI.00989-16. Print Feb. PMCID: PMC5278168

722. **Casadevall A**, Shenk T. (2017) The mBio American Academy of Microbiology Submission Track in 2017. MBio. Feb 7;8(1). pii: e00050-17. doi: 10.1128/mBio.00050-17. PMCID: PMC5296597
723. Chandra D, Selvanesan BC, Yuan Z, Libutti SK, Koba W, Beck A, Zhu K, **Casadevall A**, Dadachova E, Gravekamp C. (2017) 32-Phosphorus selectively delivered by listeria to pancreatic cancer demonstrates a strong therapeutic effect. Oncotarget. Mar 28;8(13):20729-20740. doi: 10.18632/oncotarget.15117. PMCID: PMC5400540
724. **Casadevall A**. (2017) The Pathogenic Potential of a Microbe. mSphere. Feb 22;2(1). pii: e00015-17. doi: 10.1128/mSphere.00015-17. eCollection Jan-Feb. PMCID: PMC5322344
725. **Casadevall A**, Cordero RJ, Bryan R, Nosanchuk J, Dadachova E. (2017) Melanin, Radiation, and Energy Transduction in Fungi. Microbiol Spectr. Mar;5(2). doi: 10.1128/microbiolspec.FUNK-0037-2016. PMID: 28256187
726. Prados-Rosales R, Carreño L, Cheng T, Blanc C, Weinrick B, Malek A, Lowary TL, Baena A, Joe M, Bai Y, Kalscheuer R, Batista-Gonzalez A, Saavedra NA, Sampedro L, Tomás J, Anguita J, Hung SC, Tripathi A, Xu J, Glatman-Freedman A, Jacobs WR Jr, Chan J, Porcelli SA, Achkar JM, **Casadevall A**. (2017) Enhanced control of Mycobacterium tuberculosis extrapulmonary dissemination in mice by an arabinomannan-protein conjugate vaccine. PLoS Pathog. Mar 9;13(3):e1006250. doi: 10.1371/journal.ppat.1006250. eCollection Mar. PMCID: PMC5360349
727. **Casadevall A**. (2017) Crisis in Infectious Diseases: 2 Decades Later. Clin Infect Dis. Apr 1;64(7):823-828. doi: 10.1093/cid/cix067. PMID: 28362950
728. **Casadevall A**. (2017) Acknowledgment of Invited Editors. MBio. Apr 4;8(2). pii: e00455-17. doi: 10.1128/mBio.00455-17. PMCID: PMC5380845
729. **Casadevall A**, Freij JB, Hann-Soden C, Taylor J. (2017) Continental Drift and Speciation of the Cryptococcus neoformans and Cryptococcus gattii Species Complexes. mSphere. Apr 19;2(2). pii: e00103-17. doi: 10.1128/mSphere.00103-17. eCollection Mar-Apr. PMCID: PMC5397565
730. Kohler JR, Hube B, Puccia R, **Casadevall A**, Perfect JR (2017) Fungi that infect humans. Microbiol Spectr. 2017 Jun;5(3). doi: 10.1128/microbiolspec.FUNK-0014-2016. PMID: 28597822
731. **Casadevall A**, Freij JB, Hann-Soden C, Taylor J. (2017) Reply to Engelthaler and Meyer, "Furthering the Continental Drift Speciation Hypothesis in the Pathogenic Cryptococcus Species Complexes". mSphere Jun 14;2(3). pii: e00242-17. doi: 10.1128/mSphere.00242-17. PMID: 28635996 PMCID: PMC5471351
732. Bowen A, Wear M, **Casadevall A** (2017) Antibody-mediated Catalysis in Infection and Immunity. Infect Immun. Jul 3. pii: IAI.00202-17. doi: 10.1128/IAI.00202-17. PMCID: PMC5563562
733. **Casadevall A** (2017) Don't forget the fungi when considering global catastrophic biorisks. Health Secur Jul 25. doi: 10.1089/hs.2017.0048. PMCID: PMC5576259
734. Cordero RJB, Vij R, **Casadevall A** (2017) Microbial melanins for radioprotection and bioremediation. Microb Biotechnol. Aug 14. doi: 10.1111/1751-7915.12807. PMCID: PMC5609342
735. Coelho C, Oliveira Souza AC, da Silveira Derengowski L, de Leon-Rodriguez C, Wang B, Leon-Rivera R, Bocca AL, Gonçalves T, **Casadevall A** (2017) Correction: Macrophage Mitochondrial and Stress

Response to Ingestion of *Cryptococcus neoformans*. *J Immunol.* Sep 1;199(5):1944. doi: 10.4049/jimmunol.1700948. PMID: 28827389

736. Saks MJ, Albright T, Bohan TL, Bierer BE, Bowers CM, Bush MA, Bush PJ, **Casadevall A**, Cole SA, Denton MB, Diamond SS, Dioso-Villa R, Epstein J, Faigman D, Faigman L, Fienberg SE, Garrett BL, Giannelli PC, Greely HT, Imwinkelried E, Jamieson A, Kafadar K, Kassirer JP, Koehler J', Korn D, Mnookin J, Morrison AB, Murphy E, Peerwani N, Peterson JL, Risinger DM, Sensabaugh GF, Spiegelman C, Stern H, Thompson WC, Wayman JL, Zabell S, Zumwalt RE. (2017) Forensic bite mark identification: weak foundations, exaggerated claims. *J Law Biosci.* Nov 23;3(3):538-575. doi: 10.1093/jlb/lsw045. PMID: PMC5570687

737. Nolan SJ, Fu MS, Coppens I, **Casadevall A** (2017) Lipids affect the *Cryptococcus neoformans*-macrophage interaction and promote non-lytic exocytosis. *Infect Immun.* Sep 25. pii: IAI.00564-17. doi: 10.1128/IAI.00564-17. PMID: PMC5615203

738. Schloss PD, Johnston M, **Casadevall A** (2017) Support Science by Publishing in Scientific Society Journals. *MBio.* Sep 26;8(5). pii: e01633-17. doi: 10.1128/mBio.01633-17.

739. Luo R, Zimin A, Workman R, Fan Y, Pertea G, Grossman N, Wear MP, Jia B, Miller H, **Casadevall A**, Timp W, Zhang SX, Salzberg SL. (2017) First Draft Genome Sequence of the Pathogenic Fungus *Lomentospora prolificans* (formerly *Scedosporium prolificans*). *G3 (Bethesda).* Sep 29. pii: g3.300107. doi: 10.1534/g3.117.300107. [Epub ahead of print] PMID: PMC5677167

740. Camacho E, Chrissian C, Cordero RJB, Liporagi-Lopes L, Stark RE, **Casadevall A** (2017) N-acetylglucosamine affects *Cryptococcus neoformans* cell-wall composition and melanin architecture. *Microbiology* Oct 18. doi: 10.1099/mic.0.000552. [Epub ahead of print] PMID: PMC5775898

741. Sah S, **Casadevall A**, Bell S, Gates SJ, Albright TD, Denton MB (2017) Forensic science must be scientific: A body created to set national standards is now in danger. *Scientific American* Oct. 317:12.

742. **Casadevall A**, Pirofski LA (2017) What is a host II: The attributes of individual susceptibility. *Infect Immun.* 2017 Oct 30. pii: IAI.00636-17. doi: 10.1128/IAI.00636-17. [Epub ahead of print] PMID: PMC5778373

743. Fu MS, **Casadevall A** (2017) Divalent metal cations potentiate the predatory capacity of amoeba for *Cryptococcus neoformans*. *Appl Environ Microbiol.* Nov 17. pii: AEM.01717-17. doi: 10.1128/AEM.01717-17. PMID: PMC5772251

744. Schloss PD, Johnston M, **Casadevall A** (2017) Erratum for Schloss et al., "Support Science by Publishing in Scientific Society Journals". *MBio.* Nov 21;8(6). pii: e01926-17. doi: 10.1128/mBio.01926-17. PMID: PMC5698558

745. Almeida F, Wolf JM, da Silva TA, DeLeon-Rodriguez CM, Rezende CP, Pessoni AM, Fernandes FF, Silva-Rocha R, Martinez R, Rodrigues ML, Roque-Barreira MC, **Casadevall A** (2017) Galectin-3 impacts *Cryptococcus neoformans* infection through direct antifungal effects. *Nat Commun.* Dec 6;8(1):1968. doi: 10.1038/s41467-017-02126-7. PMID: PMC5719036

746. Pirofski LA, **Casadevall A** (2017) Immune-Mediated Damage Completes the Parabola: *Cryptococcus neoformans* Pathogenesis Can Reflect the Outcome of a Weak or Strong Immune Response. *MBio.* Dec 12;8(6). pii: e02063-17. doi: 10.1128/mBio.02063-17. PMID: PMC5727418

747. Bosch G, **Casadevall A** (2017) Graduate Biomedical Science Education Needs a New Philosophy. MBio. Dec 19;8(6). pii: e01539-17. doi: 10.1128/mBio.01539-17. PMCID: PMC5736909

748. **Casadevall A**, Fang FC (2017) Reply to Argüelles and Argüelles-Prieto, "Are the Editors Responsible for Our Obsession with the Impact Factor?" MBio. Dec 19;8(6). pii: e02079-17. doi: 10.1128/mBio.02079-17. PMCID: PMC5736916

749. Rizzo J, Colombo AC, Zamith-Miranda D, Silva VKA, Allegood JC, **Casadevall A**, Del Poeta M, Nosanchuk JD, Kronstad JW, Rodrigues ML. (2017) The putative flippase Apt1 is required for intracellular membrane architecture and biosynthesis of polysaccharide and lipids in *Cryptococcus neoformans*. Biochim Biophys Acta. Dec 29;1865(3):532-541. doi: 10.1016/j.bbamcr.2017.12.007. PMCID: PMC6052768

750. Dragotakes Q, **Casadevall A** (2017) Automated Measurement of Cryptococcal Species Polysaccharide Capsule and Cell Body. J Vis Exp. 2018 Jan 11;(131). doi: 10.3791/56957. PMCID: PMC5908552

751. **Casadevall A**, Coelho C, Cordero RJB, Dragotakes Q, Jung E, Vij R, Wear MP (2018) The Capsule of *Cryptococcus neoformans*. Virulence Feb 13:0. doi: 10.1080/21505594.2018.1431087. PMID: 29436899

752. Walker L, Sood P, Lenardon MD, Milne G, Olson J, Jensen G, Wolf J, **Casadevall A**, Adler-Moore J, Gow NAR (2018) The Viscoelastic Properties of the Fungal Cell Wall Allow Traffic of AmBisome as Intact Liposome Vesicles. MBio. Feb 6;9(1). pii: e02383-17. doi: 10.1128/mBio.02383-17. PMCID:PMC5801470

753. Fanelli D, Costas R, Fang FC, **Casadevall A**, Bik EM (2018) Testing Hypotheses on Risk Factors for Scientific Misconduct via Matched-Control Analysis of Papers Containing Problematic Image Duplications. Sci Eng Ethics. Feb 19. doi: 10.1007/s11948-018-0023-7. PMID: 29460082

754. **Casadevall A**, Fang FC (2018) Elegant Science. MBio. Feb 20;9(1). pii: e00043-18. doi: 10.1128/mBio.00043-18. PMCID: PMC5821082

755. **Casadevall A**. (2018) Melanin triggers antifungal defences. Nature. Mar 15;555(7696):319-320. doi: 10.1038/d41586-018-02370-x. PMID: 29542711

756. Gonçalves DS, Ferreira MDS, Liedke SC, Gomes KX, de Oliveira GA, Leão PEL, Cesar GV, Seabra SH, Cortines JR, **Casadevall A**, Nimrichter L, Domont GB, Junqueira MR, Peralta JM, Guimaraes AJ (2018) Extracellular vesicles and vesicle-free secretome of the protozoa *Acanthamoeba castellanii* under homeostasis and nutritional stress and their damaging potential to host cells. Virulence Mar 21:0. doi: 10.1080/21505594.2018.1451184. PMID: 29560793

757. Jung EH, Meyers DJ, Bosch J, **Casadevall A** (2018) Novel Antifungal Compounds Discovered in Medicines for Malaria Venture's Malaria Box. Sphere Mar 14;3(2). pii: e00537-17. doi: 10.1128/mSphere.00537-17. eCollection 2018 Mar-Apr. PMCID: PMC5853493

758. Imperiale MJ, **Casadevall A** (2018) A New Approach to Evaluating the Risk-Benefit Equation for Dual-Use and Gain-of-Function Research of Concern. Front Bioeng Biotechnol. Mar 8;6:21. doi: 10.3389/fbioe.2018.00021. eCollection 2018. PMCID: PMC5853790

759. **Casadevall A**, Gow N (2018) Using Preprints for Journal Clubs. MBio. Apr 3;9(2). pii: e00516-18. doi: 10.1128/mBio.00516-18. PMCID: PMC5885029

760. Nosanchuk JD, Jeyakumar A, Ray A, Revskaya E, Jiang Z, Bryan RA, Allen KJH, Jiao R, Malo ME, Gómez BL, Morgenstern A, Bruchertseifer F, Rickles D, Thornton GB, Bowen A, **Casadevall A**, Dadachova E (2018) Structure-function analysis and therapeutic efficacy of antibodies to fungal melanin for melanoma radioimmunotherapy. *Sci Rep.* Apr 3;8(1):5466. doi: 10.1038/s41598-018-23889-z. PMCID: PMC5882926
761. Bell S, Sah S, Albright TD, Gates SJ Jr., Denton MB, **Casadevall A**. (2018) A call for more science in forensic science. *Proc Natl Acad Sci U S A.* Apr 12. pii: 201712161. doi: 10.1073/pnas.1712161115. PMCID:PMC5939058
762. **Casadevall A**. (2018) Acknowledgment of Invited Editors. *MBio.* Apr 24;9(2). pii: e00731-18. doi: 10.1128/mBio.00731-18. PMCID:PMC5915734
763. **Casadevall A**, Pirofski LA (2018) A Therapeutic Vaccine for Recurrent Vulvovaginal Candidiasis. *Clin Infect Dis.* 2018 Apr 25. doi: 10.1093/cid/ciy188. PMID: 29697770
764. **Casadevall A** (2018) Antibody-based vaccine strategies against intracellular pathogens. *Curr Opin Immunol.* Apr 25;53:74-80. doi: 10.1016/j.coi.2018.04.011. PMID: 29704764
765. Freij JB, Fu MS, De Leon Rodriguez CM, Dziedzic A, Jedlicka AE, Dragotakes Q, Rossi DCP, Jung EH, Coelho C, **Casadevall A** (2018) Conservation of Intracellular Pathogenic Strategy among Distantly Related Cryptococcal Species. *Infect Immun.* Jun 21;86(7). pii: e00946-17. doi: 10.1128/IAI.00946-17. PMCID:PMC60143651
766. **Casadevall A**, Coelho C, Alanio A (2018) Mechanisms of *Cryptococcus neoformans*-Mediated Host Damage. *Front Immunol.* Apr 30;9:855. doi: 10.3389/fimmu.2018.00855. PMCID: PMC5936990
767. Hommel B, Mukaremera L, Cordero RJB, Coelho C, Desjardins CA, Sturny-Leclère A, Janbon G, Perfect JR, Fraser JA, **Casadevall A**, Cuomo CA, Dromer F, Nielsen K, Alanio A (2018) Titan cells formation in *Cryptococcus neoformans* is finely tuned by environmental conditions and modulated by positive and negative genetic regulators. *PLoS Pathog.* May 18;14(5):e1006982. doi: 10.1371/journal.ppat.1006982. PMCID: PMC5959062
768. Martinez LR, Boucaud DW, **Casadevall A**, August A (2018) Factors Contributing to the Success of NIH-Designated Underrepresented Minorities in Academic and Nonacademic Research Positions. *CBE Life Sci Educ.* Jun;17(2):ar32. doi: 10.1187/cbe.16-09-0287. PMCID:PMC5998319
769. De Leon-Rodriguez CM, Rossi DCP, Fu MS, Dragotakes Q, Coelho C, Guerrero Ros I, Caballero B, Nolan SJ, **Casadevall A** (2018) The Outcome of the *Cryptococcus neoformans*-Macrophage Interaction Depends on Phagolysosomal Membrane Integrity. *J Immunol.* Jun 1. pii: ji1700958. doi: 10.4049/jimmunol.1700958. PMID: 29858266
770. Fu MS, Coelho C, De Leon-Rodriguez CM, Rossi DCP, Camacho E, Jung EH, Kulkarni M, **Casadevall A** (2018) *Cryptococcus neoformans* urease affects the outcome of intracellular pathogenesis by modulating phagolysosomal pH. *PLoS Pathog.* Jun 15;14(6):e1007144. doi: 10.1371/journal.ppat.1007144. PMCID:PMC6021110
771. Perez-Dulzaides R, Camacho E, Cordero RJB, **Casadevall A** (2018) Cell-wall dyes interfere with *Cryptococcus neoformans* melanin deposition. *Microbiology.* Jun 25. doi: 10.1099/mic.0.000682. PMID: 29939127

772. Goldman DL, Nieves E, Nakouzi A, Rivera J, Phyu EE, Win TH, Achkar JM, **Casadevall A** (2018) Serum-Mediated Cleavage of *Bacillus anthracis* Protective Antigen Is a Two-Step Process That Involves a Serum Carboxypeptidase. *mSphere* Jun 27;3(3). pii: e00091-18. doi: 10.1128/mSphere.00091-18. PMID: PMC6021598
773. Bik EM, Fang FC, Kullas AL, Davis R, **Casadevall A** (2018) Analysis and Correction of Inappropriate Image Duplication: The *Molecular and Cellular Biology* Experience. *Mol Cell Biol*. Jul 23. pii: MCB.00309-18. doi: 10.1128/MCB.00309-18. PMID: 30037982
774. Camacho E, **Casadevall A** (2018) Cryptococcal Traits Mediating Adherence to Biotic and Abiotic Surfaces. *J Fungi (Basel)*. Jul 29;4(3). pii: E88. doi: 10.3390/jof4030088. PMID: 30060601
775. Cordero RJB, Robert V, Cardinali G, Arinze ES, Thon SM, **Casadevall A** (2018) Impact of Yeast Pigmentation on Heat Capture and Latitudinal Distribution. *Curr Biol*. Aug 20;28(16):2657-2664.e3. doi: 10.1016/j.cub.2018.06.034. Epub 2018 Aug 2. PMID: 30078567
776. Rodrigues ML, **Casadevall A** (2018) A two-way road: novel roles for fungal extracellular vesicles. *Mol Microbiol*. 2018 Aug 5. doi: 10.1111/mmi.14095. [Epub ahead of print]. PMID: 30079549
777. Pirofski LA, **Casadevall A** (2018) The Damage-Response Framework as a Tool for the Physician-Scientist to Understand the Pathogenesis of Infectious Diseases. *J Infect Dis*. Aug 14;218(suppl_1):S7-S11. doi: 10.1093/infdis/jiy083. PMID: PMC6093430
778. Vij R, Cordero RJB, **Casadevall A** (2018) The Buoyancy of *Cryptococcus neoformans* Is Affected by Capsule Size. *mSphere*. Nov 7;3(6). pii: e00534-18. doi: 10.1128/mSphere.00534-18. PMID: PMC6222054
779. Chatterjee S, Prados-Rosales R, Tan S, Phan VC, Chrissian C, Itin B, Wang H, Khajo A, Magliozzo RS, **Casadevall A**, Stark RE (2018) The melanization road more traveled by: precursor substrate effects on melanin synthesis in cell-free and fungal cell systems. *J Biol Chem*. Nov 1. pii: jbc.RA118.005791. doi: 10.1074/jbc.RA118.005791. [Epub ahead of print] PMID: 30385508
780. De Leon-Rodriguez CM, Fu MS, Çorbali MO, Cordero RJB, **Casadevall A** (2018) The Capsule of *Cryptococcus neoformans* Modulates Phagosomal pH through Its Acid-Base Properties. *mSphere*. Oct 24;3(5). pii: e00437-18. doi: 10.1128/mSphere.00437-18. PMID: PMC6200979
781. May RC, **Casadevall A** (2018) In Fungal Intracellular Pathogenesis, Form Determines Fate. *MBio*. Oct 23;9(5). pii: e02092-18. doi: 10.1128/mBio.02092-18. PMID: PMC6199499
782. **Casadevall A**, Fang FC (2018) Making the scientific literature fail-safe. *J Clin Invest*. 2018 Oct 1;128(10): 4243-4244. doi: 10.1172/JCI123884. Epub 2018 Sep 4. PMID: PMC6159988
783. Paes HC, Frazão SO, Rosa CP, Albuquerque P, **Casadevall A**, Felipe MSS, Nicola AM (2018) Opsonin-free, real-time imaging of *Cryptococcus neoformans* capsule during budding. *Virulence* 9(1):1483-1488. doi: 10.1080/21505594.2018.1515610. PMID: PMC6177245
784. Imperiale MJ, Howard D, **Casadevall A** (2018) The Silver Lining in Gain-of-Function Experiments with Pathogens of Pandemic Potential. *Methods Mol Biol*. 1836:575-587. doi: 10.1007/978-1-4939-8678-1_28. PMID: 30151593

785. Paes HC, Frazão SO, Rosa CP, Albuquerque P, **Casadevall A**, Felipe MSS, Nicola AM (2018) Opsonin-free, real-time imaging of *Cryptococcus neoformans* capsule during budding. *Virulence*. 9(1):1483-1488. doi: 10.1080/21505594.2018.1515610. PMCID: PMC6177245

786. **Casadevall A**, Fang FC (2018) Making the scientific literature fail-safe. *J Clin Invest*. Oct 1;128(10):4243-4244. doi: 10.1172/JCI123884. Epub 2018 Sep 4. PMCID: PMC6159988

787. May RC, **Casadevall A** (2018) In Fungal Intracellular Pathogenesis, Form Determines Fate. *MBio*. Oct 23;9(5). pii: e02092-18. doi: 10.1128/mBio.02092-18. PMCID: PMC6199499

788. De Leon-Rodriguez CM, Fu MS, Çorbali MO, Cordero RJB, **Casadevall A** (2018) The Capsule of *Cryptococcus neoformans* Modulates Phagosomal pH through Its Acid-Base Properties. *mSphere*. Oct 24;3(5). pii: e00437-18. doi: 10.1128/mSphere.00437-18. PMCID: PMC6200979

789. Chatterjee S, Prados-Rosales R, Tan S, Phan VC, Chrissian C, Itin B, Wang H, Khajo A Magliozzo RS, **Casadevall A**, Stark RE (2018) The melanization road more traveled by: Precursor substrate effects on melanin synthesis in cell-free and fungal cell systems. *J Biol Chem*. Dec 28;293(52):20157-20168. doi: 10.1074/jbc.RA118.005791. Epub 2018 Nov 1. PMCID: PMC6311522

790. Vij R, Cordero RJB, **Casadevall A** (2018) The Buoyancy of *Cryptococcus neoformans* Is Affected by Capsule Size. *mSphere*. Nov 7;3(6). pii: e00534-18. doi: 10.1128/mSphere.00534-18. PMCID: PMC6222054

791. Guimarães AJ, de Cerqueira MD, Zamith-Miranda D, Lopez PH, Rodrigues ML, Pontes B, Viana NB, DeLeon-Rodriguez CM, Rossi DCP, **Casadevall A**, Gomes AMO, Martinez LR, Schnaar RL, Nosanchuk JD, Nimrichter L. (2018) Host membrane glycosphingolipids and lipid microdomains facilitate *Histoplasma capsulatum* internalisation by macrophages. *Cell Microbiol*. Nov 14:e12976. doi: 10.1111/cmi.12976. [Epub ahead of print] PMID: 30427108; DOI: 10.1111/cmi.12976

792. **Casadevall A** (2018) Fungal Diseases in the 21st Century: The Near and Far Horizons. *Pathog Immun*. 2018;3(2):183-196. doi: 10.20411/pai.v3i2.249. Epub Sep 25. PMCID: PMC6241320

793. Coelho C, Brown LC, Maryam M, Vij R, Smith DF, Burnet MC, Kyle JE, Heyman HM, Ramirez J, Prados-Rosales R, Lauvau G, Nakayasu ES, Brady NR, Hamacher-Brady A, Coppens I, **Casadevall A** (2018) *Listeria monocytogenes* virulence factors, including Listeriolysin O, are secreted in biologically active Extracellular Vesicles. *J Biol Chem*. Nov 30. pii: jbc.RA118.006472. doi: 10.1074/jbc.RA118.006472. [Epub ahead of print] PMCID: PMC6349127

794. Casadevall A (2018) Is the Pace of Biomedical Innovation Slowing? *Perspect Biol Med*. 61(4):584-593. doi: 10.1353/pbm.2018.0067. PMID: 30613040; DOI: 10.1353/pbm.2018.0067

795. **Casadevall A**, Fu MS, Guimaraes AJ, Albuquerque P (2019) The 'Amoeboid Predator-Fungal Animal Virulence' Hypothesis. *J Fungi (Basel)*. Jan 21;5(1). pii: E10. doi: 10.3390/jof5010010. PMID: 30669554; DOI: 10.3390/jof5010010

796. Broderick, NA, **Casadevall A** (2019) Gender inequalities among authors who contributed equally. *Elife*. Jan 29;8. pii: e36399. doi: 10.7554/eLife.36399. PMID: 30698140; DOI: 10.7554/eLife.36399

797. Dragotakes Q, Fu MS, **Casadevall A** (2019) Dragotcytosis: Elucidation of the Mechanism for *Cryptococcus neoformans* Macrophage-to-Macrophage Transfer. *J Immunol*. May 1;202(9):2661-2670. doi: 10.4049/jimmunol.1801118. Epub Mar 15.

798. Hawk CS, Coelho C, Oliveira DSL, Paredes V, Albuquerque P, Bocca AL, Correa Dos Santos A, Rusakova V, Holemon H, Silva-Pereira I, Felipe MSS, Yagita H, Nicola AM, **Casadevall A**. Integrin β 1 Promotes the Interaction of Murine IgG3 with Effector Cells. J Immunol. 2019 May 1;202(9):2782-2794. doi: 10.4049/jimmunol.1701795. Epub 2019 Mar 20.

799. Williams CL, **Casadevall A**, Jackson S. (2019) Figure errors, sloppy science, and fraud: keeping eyes on your data. J Clin Invest. Mar 25;129(5):1805-1807. doi: 10.1172/JCI128380. eCollection Mar 25.

800. Kumagai T, Palacios A, **Casadevall A**, García MJ, Toro C, Tiemeyer M, Prados-Rosales R (2019) Serum IgM Glycosylation Associated with Tuberculosis Infection in Mice. mSphere. Mar 27;4(2). pii: e00684-18. doi: 10.1128/mSphere.00684-18.

801. **Casadevall A**. (2019) Duke University's huge misconduct fine is a reminder to reward rigour. Nature Apr;568(7750):7. doi: 10.1038/d41586-019-01032-w.

802. Hatanaka O, Rezende CP, Moreno P, Freitas Fernandes F, Oliveira Brito PKM, Martinez R, Coelho C, Roque-Barreira MC, **Casadevall A**, Almeida F (2019) Galectin-3 Inhibits Paracoccidioides brasiliensis Growth and Impacts Paracoccidioidomycosis through Multiple Mechanisms. mSphere. Apr 24;4(2). pii: e00209-19. doi: 10.1128/mSphere.00209-19.

803. **Casadevall A**, Semenza GL, Jackson S, Tomaselli G, Ahima RS. (2019) Reducing bias: accounting for the order of co-first authors. J Clin Invest. Apr 29;129(6):2167-2168. doi: 10.1172/JCI128764. eCollection Apr 29.

804. Camacho E, Vij R, Chrissian C, Prados-Rosales R, Gil D, O'Meally RN, Cordero RJB, Cole RN, McCaffery JM, Stark RE, **Casadevall A** (2019) The structural unit of melanin in the cell wall of the fungal pathogen *Cryptococcus neoformans*. J Biol Chem. Jul 5;294(27):10471-10489. doi: 10.1074/jbc.RA119.008684. Epub May 22.

805. **Casadevall A** (2019) Global Catastrophic Threats from the Fungal Kingdom : Fungal Catastrophic Threats. Curr Top Microbiol Immunol. May 23. doi: 10.1007/82_161. [Epub ahead of print].

806. Maryam M, Fu MS, Alanio A, Camacho E, Goncalves DS, Faneuff EE, Grossman NT, **Casadevall A**, Coelho C (2019) The enigmatic role of fungal annexins: the case of *Cryptococcus neoformans*. Microbiology. Aug;165(8):852-862. doi: 10.1099/mic.0.000815. Epub May 29.

807. **Casadevall A**, Pirofski LA (2019) Benefits and Costs of Animal Virulence for Microbes. MBio. Jun 4;10(3). pii: e00863-19. doi: 10.1128/mBio.00863-19.

808. Gonçalves DS, Ferreira MDS, Gomes KX, Rodríguez-de La Noval C, Liedke SC, da Costa GCV, Albuquerque P, Cortines JR, Saramago Peralta RH, Peralta JM, **Casadevall A**, Guimarães AJ (2019) Unravelling the interactions of the environmental host *Acanthamoeba castellanii* with fungi through the recognition by mannose-binding proteins. Cell Microbiol. Oct;21(10):e13066. doi: 10.1111/cmi.13066. Epub Jun 19.

809. Smith DFQ, **Casadevall A** (2019) The Role of Melanin in Fungal Pathogenesis for Animal Hosts. Curr Top Microbiol Immunol. 422:1-30. doi: 10.1007/82_2019_173.

810. Coelho C, **Casadevall A** (2019) Answers to naysayers regarding microbial extracellular vesicles. Biochem Soc Trans. Aug 30;47(4):1005-1012. doi: 10.1042/BST20180252. Epub Jul 18.

811. **Casadevall A**, Kontoyiannis DP, Robert V (2019) On the Emergence of *Candida auris*: Climate Change, Azoles, Swamps, and Birds. *MBio*. Jul 23;10(4). pii: e01397-19. doi: 10.1128/mBio.01397-19.

812. Hommel B, Sturny-Leclère A, Volant S, Veluppillai N, Duchateau M, Yu CH, Hourdel V, Varet H, Matondo M, Perfect JR, **Casadevall A**, Dromer F, Alanio A (2019) *Cryptococcus neoformans* resists to drastic conditions by switching to viable but non-culturable cell phenotype. *PLoS Pathog*. Jul 29;15(7):e1007945. doi: 10.1371/journal.ppat.1007945. eCollection Jul.

813. Coelho C, Camacho E, Salas A, Alanio A, **Casadevall A** (2019) Intranasal Inoculation of *Cryptococcus neoformans* in Mice Produces Nasal Infection with Rapid Brain Dissemination. *mSphere*. Aug 7;4(4). pii: e00483-19. doi: 10.1128/mSphere.00483-19.

Editorials

Fang Fc, Casadevall A (2012) Why people cheat and what needs to change. *The Seattle Times* http://seattletimes.com/html/opinion/2020569681_ferricfangarturocasadevallopedxml.html

Casadevall A, Fang Fc (2013) Science Health Thyself. Carried by many newspapers <http://www.project-syndicate.org/commentary/using-science-to-address-threats-to-the-scientific-enterprise-by-arturo-casadevall-and-ferric-c--fang>

Fang Fc, Casadevall (2014) Taking the Powerball Approach to Funding Medical Research. Winning a government grant is already a crapshoot. Making it official by running a lottery would be an improvement. *The Wall Street Journal* <http://online.wsj.com/news/articles/SB10001424052702303532704579477530153771424>

Casadevall A (2015) Put the Ph back into PhD, *Johns Hopkins Public Health Magazine* <http://magazine.jhsph.edu/2015/summer/forum/rethinking-put-the-ph-back-in-phd/>

Casadevall A, Fang FC (2015) Is Science in Crisis? *The Baltimore Sun*. <http://www.baltimoresun.com/news/opinion/oped/bs-ed-science-crisis-20150725-story.html>

Casadevall A (2016) To fight superbugs, scientists are turning toward antibodies. *Newsweek*

Casadevall A, Fang FC (2017) Science is Society's best insurance policy. *Bloomberg*. <https://www.bloomberg.com/view/articles/2017-04-06/science-is-society-s-best-insurance-policy>

Book Chapters, Monographs

1. **Casadevall, A.** (2000). The return of antibody based therapies *MDVista*

1. Kobrin B, **Casadevall A**, Schiff C, Pirofski L, and Scharff MD (1990) Somatic Instability of Immunoglobulin Genes in Culture in Somatic Hypermutation in V-regions. Edited by J. Steele. *CRC Critical Review in Immunology*, 11-24.

2. Goldman, D.G., **Casadevall A.** (1998) Experimental pulmonary *cryptococcus* infection in rats. *Handbook of Animal Models of Infection*. Academic Press, London, U.K.

3. **Casadevall, A.** Immunity to fungi *Encyclopedia of Live Sciences*

4. **Casadevall, A.** Fungal infections, systemic, by Opportunistic agents *Encyclopedia of Microbiology* 2nd Edition.

5. Nosanchuk, J. and **Casadevall**, A. (1998) Amphotericin B: activity beyond fungal sterols. *Recent Research Developments in Antimicrobial Agents & Chemotherapy* 3:7-15.
6. **Casadevall**, A., Goldman, D.G., Lee, S. (1999) Cryptococcal meningoencephalitis New Concepts on the Immunopathogenesis of CNS infections.
7. **Casadevall** A. Resistance and Immunization to Infectious Diseases (2000) *Immunology: A Short Course*, 4th Edition, John Wiley and Sons, Inc pp 421-454.
8. **Casadevall**, A. Immunotherapy for fungal infections in *Immunotherapy for Infectious Diseases*. Humana Press.
9. **Casadevall**, A. Humoral immunity and *Cryptococcus neoformans*. Dekker Press. *Fungal Pathogenesis* 2001-14:293-324
10. Pirofski, L. and **Casadevall**, A. Antibody therapy for infectious diseases: a progress report at the start of the 3rd millennium
11. **Casadevall**, A. Acquired immunity against fungi. (Chapter 16) In *Immunology of Infectious Diseases* (2001). S.H.E. Kaufman, Sher, A., and Ahmed, R. eds. ASM Press, Washington, DC.
12. Pirofski, L. and **Casadevall**, A. (2001). Traitement anti-infectieux par anticorps. *Annales de L'Institut Pasteur/Actualites - Le retour de la serotherapie*. Cohen, G.N. and Alonso, J. (eds) Elsevier, Paris.
13. **Casadevall** A. Resistance and Immunization to Infectious Diseases (2003) *Immunology: A Short Course*, 5th Edition, John Wiley and Sons, Inc.
14. **Casadevall** A (2002) Acquired Immunity against fungi (Chapter 16; p 223-234). In *Immunology of Infectious Diseases*. Edited by SHE Kaufman, A Sher, and R Ahmed ASM Press. Washington
15. **Casadevall** A (2002) Humoral Immunity and *Cryptococcus neoformans* (Chapter 14, p293-324). In *Fungal Pathogenesis – Principles and Clinical Applications*. Ed. by RA Calderone, RL Cihlar. Marcel Dekker NY
16. **Casadevall** A (2002) Immunotherapy for fungal infections (Chapter 18, p303-322). In *Immunotherapy for Infectious Diseases*. Ed. JM Jacobson. Humana Press, Totowa, NJ
17. Pirofski L, **Casadevall** A (2006). Acquired Immunity to Fungi, In *Molecular Principles of Fungal Pathogenesis*. Ed J Heitman, S Filler, A Mitchell ASM Press, Washington.
18. Steenbergen JN and **Casadevall** A (2005). The evolution of human fungal pathogens. In *The evolution of Human Fungal Pathogens*. Ed. HS Seifert. ASM Press, Washington.
19. **Casadevall**, A (2006). Amoebae and slime mold: host of virulence evolution. In *Molecular Principles of Fungal Pathogenesis*. Ed J Heitman, S Filler, A Mitchell, ASM Press, Washington.
20. Macura N, Zhang T, **Casadevall** A (2006) Developing a mathematical model of phagocytosis: a learning process.
21. McLelland E, Heisenman H, **Casadevall** A (2007) 'Pathogenesis of *Cryptococcus neoformans*' in *New Insights in Fungal Pathogenesis*.

22. Zaragoza, O, Frases S, **Casadevall A** (2007) Pathogenicity of *Cryptococcus neoformans*: an evolutionary perspective. In *Introduction to Evolutionary Biology of Bacterial and Fungal Pathogens*. Eds. Baquero F, Nombela C, Cassell GH, Gutierrez JA. ASM Press.
23. Pirofski L, **Casadevall A**. (2007) 'The Damage-response framework of microbial pathogenesis in GI Microbiota and Regulation of the Immune System Landes Bioscience
24. Dadachova K, **Casadevall A** (2010) Melanin and resistance to ionizing radiation in fungi. *Extremophiles handbook*. Koki Horikoshi (Ed). Springer, Japan.
25. Perfect JR, **Casadevall A** (2010) The history of *Cryptococcus* and cryptococcosis, in *Cryptococcus: from human pathogen to model yeast*. Heitman J, Kozel TR, Kwon-Chung KJ, Perfect JR, **Casadevall A** (Eds). ASM Press. Washington DC.
26. Rodrigues ML, **Casadevall A**, Zaragoza O (2010) The architecture and antigenic composition of the polysaccharide capsule, in *Cryptococcus: from human pathogen to model yeast*. Heitman J, Kozel TR, Kwon-Chung KJ, Perfect JR, **Casadevall A** (Eds). ASM Press. Washington DC.
27. Trofa D, **Casadevall A**, Nosanchuk JD (2010) Melanin: structure, function, and biosynthesis in *Cryptococcus*. in *Cryptococcus: from human pathogen to model yeast*. Heitman J, Kozel TR, Kwon-Chung KJ, Perfect JR, **Casadevall A** (Eds). ASM Press. Washington DC.
28. Coleman JJ, Chrisman CJ, **Casadevall A**, Mylanakis E. (2010) *Cryptococcus neoformans*: nonvertebrate hosts and the emergence of virulence. in *Cryptococcus: from human pathogen to model yeast*. Heitman J, Kozel TR, Kwon-Chung KJ, Perfect JR, **Casadevall A** (Eds). ASM Press. Washington DC.
29. Pirofski L, **Casadevall A** (2010) Acquired Humoral Immunity to *Cryptococcus neoformans*. in *Cryptococcus: from human pathogen to model yeast*. Heitman J, Kozel TR, Kwon-Chung KJ, Perfect JR, **Casadevall A** (Eds). ASM Press. Washington DC.
30. Dromer F, **Casadevall A**, Perfect J, Sorrell T (2010) *Cryptococcus neoformans*: Latency and Disease. in *Cryptococcus: from human pathogen to model yeast*. Heitman J, Kozel TR, Kwon-Chung KJ, Perfect JR, **Casadevall A** (Eds). ASM Press. Washington DC.
31. **Casadevall A**, Dadachova E, Pirofski L (2010) Vaccine and antibody therapies from *Cryptococcus neoformans* to melanoma. in *Cryptococcus: from human pathogen to model yeast*. Heitman J, Kozel TR, Kwon-Chung KJ, Perfect JR, **Casadevall A** (Eds). ASM Press. Washington DC.
32. **Casadevall A** (2011) Changing the Therapeutic Paradigm in Antibacterial Drug Discovery. Alita A. Miller and Paul F. Miller (Eds) Caister Academic Press. Norfolk UK.
33. **Casadevall A** (2011) *Cryptococcus* (Chapter 202) in *Harrison's Principles of Internal Medicine 18th Edition* Edited by D. Longo, A. Fauci, D. Kasper, S. Hauser, J. Jameson, J. Loscalzo. McGraw Hill.
34. Nicola AM, Fabricant SA, Albuquerque P, Soares Felipe MS, **Casadevall A** (2016) Host Autophagy in Antifungal Immunity in Autophagy M.A. Hayat (ed), Volume 9. 317-330.

Books, Textbooks

Cryptococcus neoformans. Written by A. Casadevall and J. Perfect. ASM Press, Washington DC, 1998

Cryptococcus neoformans: from human pathogen to model yeast. Edited by J. Heitman, TR Kozel, KJ Kwon-Chung, JR Perfect, and A, Casadevall. ASM Press 2011

Recent Advances on Model Hosts. Edited by Mylonakis E, Ausubel F.M., Casadevall A, Gilmore, M Springer Verlag/Springer Science & Business. 2011

Human Fungal Pathogens. Edited by A. Casadevall, Aaron P. Mitchell, Judith Berman, KJ Kwon-Chung, John R. Perfect and Joseph Heitman. Cold Spring Harbor Press 2014

Letters, correspondence

Casadevall, A, Spitzer, E.D. (1995) Involvement of multiple *Cryptococcus neoformans* strains in a single episode of cryptococcus and reinfection with novel strains in recurrent infection as demonstrated by random amplification of polymorphic DNA and DNA fingerprinting [Letter]. J.Clin.Microbiol. 33:1682-1683.

Casadevall, A. (1997) Changing the focus of infectious diseases to pathogen-specific therapy Clin.Infect.Dis. 25:349-350.

Nosanchuk, J.D., **Casadevall**, A. Separated at birth. N Engl J Med. 1999 Feb 4;340:395

Casadevall, A. and Pirofski, L. 'On the definition of virulence' ASM News 69(5) 217

Casadevall, A. and Pirofski, L. 'Anti-virulence genes - further muddling the lexicon?' Trends Microbiol. 11:413-4.

Fang FC, **Casadevall A** (2016) A modified lottery can reduce bias in the allocation of research funds. Science April issue.

Fang FC, **Casadevall A** (2016) Grant funding: Playing the odds. Science Apr 8:352(6282) 158. doi: 10.1126/science 352.6282.158-a. Epub 2016 Apr 7

Other media

National Public Radio - <http://www.npr.org/templates/story/story.php?storyId=94563054&ft=1&f=5>
Boston Globe

http://www.boston.com/news/globe/health_science/articles/2005/02/22/were_the_dinosaurs_done_in_by_fungus/

BBC Interview

<http://www.bbc.co.uk/programmes/p005w29s>

NPR talk of the Nation – Fungi: the good, the bad and the edible.

<http://www.npr.org/templates/story/story.php?storyId=94563054>

NYT interview on retracted publication

<http://www.nytimes.com/2012/04/17/science/rise-in-scientific-journal-retractions-prompts-calls-for-reform.html>

NPR Interview on problems with science

<http://www.yourpublicmedia.org/content/wnpr/getting-psyched-about-science>

NPR All Things Considered about new botulinum toxin

<http://www.npr.org/blogs/health/2014/04/21/305650796/whos-protecting-whom-from-deadly-toxin>

NPR Biologist choose sides in safety debate over lab made pathogens

<http://www.npr.org/blogs/health/2014/08/13/339854400/biologists-choose-sides-in-safety-debate-over-lab-made-pathogens>

NPR Interview on the pause involving GOF experiments with pathogens of pandemic potential

<http://www.npr.org/blogs/health/2014/10/23/358122198/scientists-fight-for-superbug-research-as-u-s-pauses-funding>

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; Aharon, 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;
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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 Metrology, 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 Scientist, 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 Inflammation, 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, Istituto 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 Pittsburgh
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 Tennessee
University of Puerto Rico
Pasteur Institute
2012 Pugwash Conference
Symposium on fungal pathogenesis, Oviedo, Spain
ICAAC Lecture 2012
Translational Science 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 Carbohydrate 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 Medical Center
Snowmass Microbial Pathogenesis Meeting
Kynnon Lecture, NIAID

2014

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

Department 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 Molecular Fungal Biology
 Group on Research Advancement and Development (GRAND), AAM Colleges
 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 Republica, 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 Colloquium, 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 Tennessee 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, Tübingen, 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 Anniversary 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 Communication, 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 9,725,504 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)

Exh. No.	Description
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)
ALXN2007	Janeway and Travers, Immunobiology: The Immune System in Health and Disease (Garland Science, 6th ed. (2005))

Exh. No.	Description
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)

Exh. No.	Description
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 Anticlonal 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

Exh. No.	Description
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
ALXN2046	Guidelines on the Use of International Nonproprietary Names (INNs) for Pharmaceutical Substances, 1997
ALXN2047	McClellan, et al., A point mutation in the CH3 domain of human IgG3 inhibits antibody secretion without affecting antigen specificity, MOLECULAR IMMUNOLOGY, 2005
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)
ALXN2050	Fatimah Al-Ani et al., "Eculizumab in the management of paroxysmal nocturnal hemoglobinuria: patient selection and special considerations, Ther. Clin. Risk Manag.; 12: 1161–1170 (2016)
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	Stebbing, R., <i>et al.</i> , "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)