

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

XENCOR, INC.,

Petitioner

v.

MERUS N.V.,

Patent Owner

IPR2025-00604
Patent No. 9,358,286

**DECLARATION OF BRIAN J. SUTTON, Ph.D. IN SUPPORT OF PATENT
OWNER'S PRELIMINARY RESPONSE**

I. INTRODUCTION

1. I, Dr. Brian J. Sutton, Ph.D., declare as follows:

2. I have been retained by Merus N.V., (“Patent Owner”) as an independent expert in this proceeding brought by Xencor, Inc. (“Petitioner”) before the United States Patent and Trademark Office regarding U.S. Patent No. 9,358,286 (“the ’286 Patent”) (Ex. 1001).

3. I was asked to provide my opinions regarding whether: (1) Lazar (Ex. 1004) discloses all of the limitations of claims 1, 7, 21, 22, 24, 26, 28, 30, and 32 of the ’286 Patent; (2) the combination of Lazar (Ex. 1004) and Arathoon (Ex. 1006) discloses or suggests all of the limitations of claims 1-2, 7-24, 26-28, and 30-32 of the ’286 Patent; (3) Cabrera (Ex. 1005) discloses all of the limitations of claims 1-2, 7, 21, 22, 24, 26-28, and 30-32 of the ’286 Patent; and (4) the combination of Lazar (Ex. 1004), Cabrera (Ex. 1005), and Arathoon (Ex. 1006) discloses or suggests all of the limitations of claims 1-2, 7-24, 26-28, and 30-32 of the ’286 Patent.

4. I am compensated at my normal and customary hourly consulting rate of £350 for the time that I spend on this matter. My opinions are independent and my compensation is not contingent on my opinions in this matter. I have no interest in the outcome of this proceeding.

II. BACKGROUND AND QUALIFICATIONS

5. Below, I summarize my qualifications, which can be found in more detail in my *curriculum vitae*, which I understand is being submitted as Exhibit 2009.

6. I received both a B.A. in Chemistry and a Ph.D. in Molecular Biophysics from the University of Oxford in 1976 and 1980, respectively.

7. My doctoral work and early publications concerned the structure of the antibody combining site for antigen, the structure of the receptor-binding Fc region of IgG, and the mechanism of antibiotic resistance enzymes. I used spin-labels, ESR and NMR to probe the structure and mobility of antibody combining sites, and applied X-ray crystallography to determine the structure of the Fc region of IgG, at the same time initiating X-ray studies of the bacterial metallo- β -lactamases that are responsible for bacterial resistance to antibiotics.

8. The structure of the *B. cereus* zinc-dependent enzyme was one of the first of this class to be determined, and I worked with SmithKline Beecham (now GSK); this and other enzyme structures subsequently led to a programme of inhibitor design.

9. I completed my post-doctoral training at the Oxford University Laboratory of Molecular Biophysics in 1986, where I received the Royal Society Howe Junior Research Fellowship and a Royal Society University Research

Fellowship. In 1994, I was awarded a Nuffield Foundation Research Fellowship at King's College London.

10. I have spent more than 40 years in structural biology research, mainly using X-ray crystallography and studying proteins, principally antibodies, and with a focus on the Fc regions of IgE, IgG and other antibody classes.

11. Presently, I am Emeritus Professor of Molecular Biophysics at the Randall Centre for Cell & Molecular Biophysics, King's College London. Previously, I served as Head of Structural Biology and Director of the Centre for Biomolecular Spectroscopy at King's College London.

12. My current research focuses on IgE-Fc/receptor interactions and their inhibition, and tracing the evolution of antibody structure using X-ray crystallography and X-ray solution scattering.

13. I was a founding member and Programme Leader for *IgE Structure, Function and Regulation* in the MRC & Asthma UK Centre for Allergic Mechanisms of Asthma. I was also a member of the Asthma UK Research Grants Committee, and I was the co-organizer of the Federation of American Societies for Experimental Biology (FASEB) meeting IgE and Allergy – 50 Years and Onward.

14. I have received multiple major research grants, including from the UKRI Medical Research Council (including two Programme grants) and the

Biotechnology and Biological Sciences Research Council, the Wellcome Trust (including two Programme grants), and Asthma UK.

15. Over the course of my career, I have authored or co-authored about 175 peer-reviewed journal papers and 7 book chapters.

16. I am a named inventor on two patent families related to novel anti-IgE inhibitors.

III. PERSON OF ORDINARY SKILL IN THE ART

17. In my opinion, given the nature of the technology at issue, a person of ordinary skill in the art (“POSA”) would have a Ph.D. in biochemistry, chemistry, molecular or structural biology, molecular biophysics, antibody engineering, immunology, or related discipline and at least 2 years of related experience in academia or industry or a Master’s degree in any of the above fields with at least 4 years of related experience in academia or industry.

18. I am informed that all of my opinions in this Declaration should be from the perspective of a POSA as of April 20, 2012. None of my opinions in this Declaration would change if I used Dr. Presta’s definition of a POSA instead of the one set forth above.

IV. TECHNOLOGICAL OVERVIEW

19. Antibodies, which are also referred to as immunoglobulins or Igs, are naturally generated by the body and are an important defense for fighting infections; they are a key component of an immune response directed against a “foreign” invading organism or for eliminating cancer cells. Antibodies or Igs are complex proteins that are made from combinations of 20 amino acids.

20. Each amino acid has distinct properties based on their side chains. Some amino acids are positively charged because the side chains can accept protons at physiological pH (approximately pH 7.4). Some amino acids have negatively charged side chains which donate protons at physiological pH. Other amino acids are neutral, without any charge.

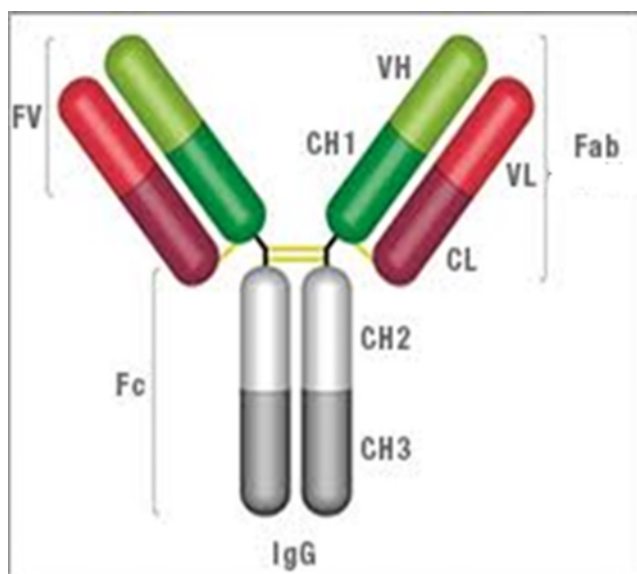
21. Additionally, some amino acids are hydrophobic because their side chains are mostly constituted of carbon and hydrogen atoms and cannot interact with water. Others are hydrophilic because their side chains can form hydrogen bonds with surrounding water molecules.

22. The charge, hydrophilicity and hydrophobicity of the amino acids are crucial to determining, among other things, the folding of a protein structure.

23. Natural or wild-type Igs have a Y shape that consists of two identical light (L) chains and two identical heavy (H) chains; this is typical of an IgG class of

antibody, and is the basic unit of antibodies of the other human classes (IgM, IgA, IgE and IgD) (See figure below).

24. Each IgG heavy chain consists of one variable domain (VH) and three constant domains (CH1, CH2, and CH3). Each light chain consists of one variable domain (VL) and one constant domain (CL). The CH2 and CH3 domains of the heavy chains interact to form the “fragment crystallizable” or Fc region. The VH and VL domains form the Fv fragment, which binds antigen, and together with the CL and CH1 domains forms the “fragment antigen-binding” or Fab region (See figure below).



25. The heavy chains are held together (dimerized) through covalent disulphide bridges in the “hinge” region between the Fab and Fc regions (See figure above), and by strong non-covalent interactions such as hydrophobic interactions,

salt bridges, van der Waals forces and hydrogen bonds between interacting surfaces of the two CH3 domains. The CH2 domains do not interact directly with each other and contain sites of glycosylation (not shown in figure).

26. The various Ig domains fold independently, and for Fc dimerization to occur, each CH3 domain must first fold. Once properly folded, the CH3 domain of one heavy chain can then interact with the CH3 domain of the other heavy chain to form a non-covalent dimer and maintain the dimeric structure of the antibody.

27. The folding of the CH3 domain is largely controlled by hydrophobic amino acid residues clustering together in the core of the protein domain to avoid contact with water. The surface of the CH3 domain is principally hydrophilic, the amino acid side-chains interacting with water molecules, but with a hydrophobic “patch”. The amino acids of the hydrophobic patch on the surface of the folded CH3 region will form hydrophobic and other non-covalent interactions with the amino acids of the hydrophobic patch on the CH3 domain of the other, identical heavy chain. These amino acids interact to form a principally hydrophobic CH3-CH3 dimer interface.

28. Nature has evolved the formation of four salt bridges, partially or almost fully buried around the edge of the principally hydrophobic CH3-CH3 dimer interface; these electrostatic interactions between oppositely charged amino acid

side chains (salt bridges) enhance the formation of the CH3 domain dimer. The salt bridges must remain at least partially buried within the hydrophobic CH3-CH3 dimer interface because the salt bridges will be weaker or may not form at all if exposed to water.

29. In addition, the amino acid residues in the CH3-CH3 dimer interface make van der Waals contact with each other. These van der Waals interactions occur only when side chains from different amino acids across the interface make very close contact, and this commonly occurs because of the high degree of shape complementarity at the CH3:CH3 interface.

30. Making modifications to the amino acids that make up the hydrophobic core of the CH3 domains may well affect their ability to fold, and this may also be the case for amino acids at the hydrophobic interface, which may affect folding and/or dimerization. Generally, it was well known in the art by a POSA at the relevant time period, that one should not make modifications to the hydrophobic core of the CH3 to introduce hydrophilic or charged residues, due to the likelihood of disrupting the CH3 interface and destabilizing the antibody's Fc.

31. Gunasekaran discloses to a POSA not to modify the neutral residues in the hydrophobic core of the CH3 region or in the hydrophobic region of the CH3-CH3 interface. According to Gunasekaran, "[i]t has long been established that the

hydrophobic core of protein domains plays an important role in protein folding and stability,” accordingly, it was understood to modify charged residues, not hydrophobic residues, to improve heterodimerization, as Gunasekaran stated. See Gunasekaran (EX1012) at 4.

32. Wild-type Igs can only bind one kind of antigen and are “monospecific” (although bivalent—meaning that they have two binding domains—by virtue of their two identical Fab regions) while bispecific Igs are engineered to bind two different antigens by bringing together two different heavy chains from two different wild-type antibodies, *i.e.*, heterodimerization.

33. Engineering a bispecific Ig with two different heavy chains is challenging for many reasons. For example, it is difficult to overcome the strong, natural affinity for the CH3 domains of identical heavy chains to interact with each other, as discussed above. Conversely, it is difficult to promote the interaction of the CH3 domains from two different heavy chains.

34. As of April 20, 2012, POSAs were aware of techniques such as “knobs-into-holes” and “charge reversal” or “electrostatic steering” to try to create bispecific antibodies; these approaches enhance heterodimerization of different heavy chains and reduce the homodimerization that occurs in the formation of the wild-type antibodies. However, POSAs also understood that these techniques had

shortcomings because they often resulted in insufficient yield of the desired heterodimer compared with that of the two homodimers, as well as reduced protein stability and consequent impaired functionality of the heterodimeric antibody, resulting in unstable proteins with poor half-life and shelf life, making them unsuitable for development.

35. Merus pursued a different approach that went against conventional wisdom by modifying a neutral residue in the hydrophobic interface of the CH3 dimer, one on each heavy chain, from an amino acid having a neutral side chain to an amino acid having a charged side chain, to create an interaction between two oppositely charged residues to enhance the stability of the CH3-CH3 dimer interface.

36. Surprisingly, Merus' heterodimerization technique achieves heterodimeric antibodies capable of higher yield and increased stability. Merus was granted the '286 Patent for its novel invention.

V. THE '286 PATENT

37. I am informed that Xencor challenges Claims 1-2, 7-24, 26-28, and 30-32 of the '286 Patent in its Petition.

38. Independent Claim 1 is directed to a method for producing a heterodimeric antibody from a single cell. Independent Claim 1 of the '286 Patent recites:

A method for producing a heterodimeric antibody from a single cell, wherein said antibody comprises two heavy chains with CH3 domains that are capable of forming an interface, said method comprising:

a. providing a host cell comprising

(i) a first nucleic acid molecule encoding a 1st antibody heavy chain comprising at least one substitution of a neutral amino acid residue in the CH3 domain by a positively charged amino acid residue, and

(ii) a second nucleic acid molecule encoding a 2nd antibody heavy chain comprising at least one substitution of a neutral amino acid residue in the CH3 domain by a negatively charged amino acid residue;

b. culturing said host cell and allowing for expression of said two nucleic acid molecules to produce said 1st antibody heavy chain and said 2nd antibody heavy chain, wherein the at least one positively charged amino acid residue substituted in the CH3 domain of said 1st antibody heavy chain interacts with the at least one negatively charged amino acid residue substituted in the CH3 domain of said 2nd antibody heavy chain in the interface between said 1st and 2nd antibody heavy chains to produce a heterodimeric antibody; and

c. harvesting said heterodimeric antibody from the culture.

39. Dependent Claims 2, 7-24, 28, and 32 depend from Independent Claim

1. Dependent Claims 2, 7-24, 28, and 32 include all of the elements of Independent Claim 1 and further require additional limitations, including a common light chain (Claim 2), a purity level (Claim 7), binding targets (Claims 8-20, and 23), a human IgG (Claim 21, 24, and 32), a heterodimeric antibody (Claim 22), and a pharmaceutical composition (Claim 28).

40. Independent Claim 26 is directed to a recombinant host cell that includes nucleic acid sequences encoding at least one substitution of a neutral amino acid residue by a positively charged amino acid residue in one heavy chain and at least one substitution of a neutral amino acid residue by a negatively charged amino acid residue in another heavy chain. Independent Claim 26 of the '286 Patent recites:

A recombinant host cell comprising nucleic acid sequences encoding at least a 1st and 2nd antibody heavy chain, wherein the CH3 domain of said 1st antibody heavy chain comprises at least one substitution of a neutral amino acid residue by a positively charged amino acid residue, and wherein the CH3 domain of said 2nd antibody heavy chain comprises at least one substitution of a neutral amino acid residue by a negatively charged amino acid residue.

41. Dependent Claim 27 depends from Independent Claim 26, includes all of the limitations of Independent Claim 26 and the additional common light chain limitation.

42. Independent Claim 30 is directed to a method for making a host cell for production of a heterodimeric antibody by introducing nucleic acid sequences claimed in other independent claims into a host cell consecutively or concomitantly. Independent Claim 30 of the '286 Patent recites:

A method for making a host cell for production of a heterodimeric antibody, the method comprising the step of introducing into said host cell nucleic acid molecules encoding at least a 1st and 2nd antibody heavy chain, wherein the CH3 domain of said 1st antibody heavy chain comprises at least one substitution of a neutral amino acid residue by a positively charged amino acid residue and wherein the CH3 domain of said 2nd antibody heavy chain comprises at least one substitution of a neutral amino acid residue by a

negatively charged amino acid residue, wherein said nucleic acid sequences are introduced consecutively or concomitantly.

43. Dependent Claim 31 directly depends from Independent Claim 30, includes all of the limitations of Independent Claim 30 and the additional common light chain limitation.

VI. LAZAR DOES NOT DISCLOSE ALL OF THE ELEMENTS OF THE CLAIMS OF THE '286 PATENT

44. Independent Claims 1, 26, and 30 of the '286 Patent require an antibody with a heavy chain comprising at least one substitution of a neutral amino acid residue in the CH3 domain by a positively charged amino acid, that interacts with at least one negatively charged amino acid residue substituted from a neutral amino acid residue in the CH3 domain of said 2nd antibody heavy chain, in the interface between said 1st and 2nd antibody heavy chains, to produce a heterodimeric antibody. The elements of Independent Claims 1, 26, and 30 are not disclosed in Lazar. First, Lazar does not disclose antibodies with heavy chains as defined in the Specification of the '286 Patent and as required by Independent Claims 1, 26, and 30. Second, Lazar does not disclose neutral to positive and neutral to negative substitutions of residues in heavy chains as defined in the Specification of the '286 Patent that interact to promote heterodimerization as required by Independent Claim 1 of the '286 Patent.

A. Lazar Does Not Disclose Claimed Heavy Chain and Heterodimeric Antibody

45. The Specification of the '286 Patent defines the claim term heavy chains:

The IgG structure has four chains, two light and two heavy chains; each light chain has two domains, the variable and the constant light chain (VL and CL) and **each heavy chain has four domains, the variable heavy chain (VH) and three constant heavy chain domains (CH1, CH2, CH3).**

(See '286 Patent (Ex. 1001), Col. 11, lines 58-66, emphasis added)

46. The Specification of the '286 Patent further requires that the heavy chains have different specificity. The Specification states that the: “bispecific dimers (also called heterodimers) contain two different paired heavy chains with different specificity.” See '286 Patent (Ex. 1001) at Col. 3, lines 27-31. A POSA would understand that the '286 Patent is directed to producing bispecific antibodies with two heavy chains each having VH, CH1, CH2, and CH3 domains and two Fab arms each with a different binding site specificity.

47. In contrast, Lazar discloses a binding moiety for screening purposes, namely scFv-Fc/empty-Fc format, which does **not** have the heavy chains with four domains as defined in the Specification of the '286 Patent. Lazar also discloses an alternative type of bispecific moiety in which the interaction with the first antigen [Ag 1] is bivalent and the interaction with the second antigen [Ag 2] is monovalent. In

this construct, the two chains are identical with respect to their antigen specificity [Ag 1] and the second specificity [Ag 2] is generated by fusion of Fv or Fab domains to the C termini of the two chains, separated by a linker region. One chain carries a fusion of VH or VH-CH1 while the other carries VL or VL-CL: these constructs are referred to as mAb-Fv and mAb-Fab, respectively.

48. The scFv-Fc/empty-Fc format of Lazar does not have heavy chains with four domains (*i.e.*, VH, CH1, CH2, and CH3) as defined in the Specification of the '286 Patent. According to Lazar, the scFv-Fc has a sequence of VH-linker-V κ -Hinge-CH2-CH3' and the empty-Fc has a sequence of Hinge-CH2-CH3''. Such sequences clearly show that the scFv-Fc lacks a CH1 domain, and the empty-Fc lacks VH and CH1 domains. See Lazar (EX1004) at ¶ 238 and Figure 1.

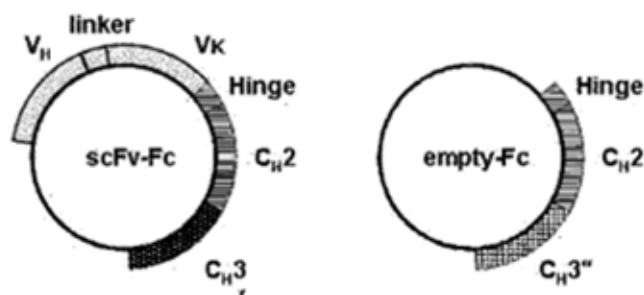


Figure 1

49. Further, the scFv-Fc/empty-Fc format does not include chains with different specificities. According to the disclosed sequences and Figure 1 in Lazar,

empty-Fc does not have any antigen-binding site and the chain in scFv-Fc has only one binding site (*i.e.*, a single-chain variable fragment (scFv)). Thus, the scFv-Fc/empty-Fc format is a monospecific antibody, lacking heavy chains as required by the '286 Patent claims.

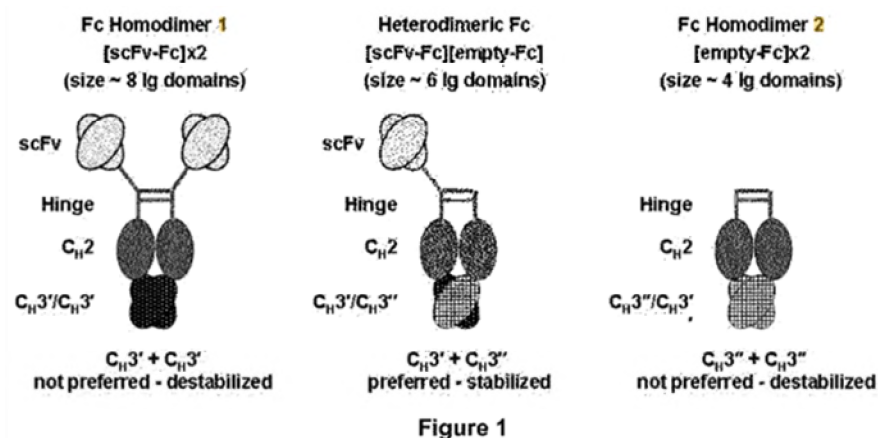


Figure 1

50. Therefore, Lazar's scFv-Fc/empty-Fc formats do not have "two different paired heavy chains with different specificity" as required by the claims and Specification of the '286 Patent.

51. Dr. Presta relies on variants disclosed in Tables 1-2 of Lazar to argue that Lazar discloses every limitation of Claim 1. Dr. Presta states "[i]n Tables 1 and 2, Lazar discloses substituting a neutral amino acid residue in the CH3 domain of one antibody heavy chain with a positive amino acid residue and substituting a neutral amino acid residue in the CH3 domain of a second antibody heavy chain with a

negative amino acid residue, as claim 1 requires.” See Presta Declaration (EX1002), at ¶ 115.

52. However, all of the variants in Tables 1-2 were tested in the scFv-Fc/empty-Fc format. Lazar states:

A DNA library encoding variant immunoglobulin polypeptides, designed as described above, was constructed in the scFv-Fc and empty-Fc constructs. Pairs of scFv-Fc and empty-Fc constructs were cotransfected into HEK293E cells for expression, and resulting proteins were purified using protein A affinity chromatography. Relative concentrations of the expressed protein species were determined using the Agilent 2100 Bioanalyzer microfluidics-based platform, as described above. Resulting gels are shown in FIG. 4. A quantitative summary of the results from this library is provided in FIG. 5. A number of designed variants increased the content of heterodimer relative to that of the native parent Fc region. Using the information obtained from the previous library, a new library was designed and screened as described above. Quantitative electrophoretic results are shown in FIGS. 6 and 7. **A number of designed variants increased the content of heterodimer relative to that of the native parent Fc region. Preferred and most preferred variants from this screen are listed in Tables 1 and 2 respectively.**

See Lazar (EX1004), at ¶¶ 240-241 (emphasis added).

53. The scFv-Fc/empty-Fc construct in Lazar was designed for testing the variants in Figures 5-7. Lazar made clear that the variants in Figures 5-7 were tested

on the empty-Fc/scFv-Fc format by the use of the headers: “Empty-Fc” and “scFv-Fc”, as shown below:

Figure 5

Lane	Empty-Fc	scFv-Fc	Empty -M	Empty -D	Hetero	scFv -D	scFv -M
1	IgG1 WT	IgG1 WT	2%	33%	42%	23%	0%
2	S364D	Y349K	0%	6%	73%	21%	0%
3	S364E	Y349K	0%	7%	75%	19%	0%

Figure 6

Empty-Fc	scFv-Fc	Empty -M	Empty -D	Hetero	scFv -D	scFv -M
F405A	T394F	3%	26%	66%	5%	0%
F405A	T394W	3%	31%	64%	2%	0%

Figure 7

Empty-Fc	scFv-Fc	Empty -M	Empty -D	Hetero	scFv -D	scFv -M
F405A	T394F	1%	19%	72%	8%	0%
F405S	T394Y	0%	3%	40%	57%	0%
K370C	S364C	0%	24%	0%	76%	0%

54. Lazar’s scFv-Fc/empty-Fc format does not have two heavy chains with four domains and different specificity. Therefore, the variants in Tables 1 and 2, which were used only for scFv-Fc/empty-Fc formats, do not disclose the subject matter claimed in Independent Claim 1.

55. Lazar’s alternative bispecific moieties (*i.e.*, mAb-Fv, mAb-Fab, Fab-Fv, and Fab-Fab) also do not have two different paired heavy chains with different specificity.

56. According to Lazar, the alternative moieties are created by adding a Fv or Fab at the C termini of wild-type IgG. See Lazar (EX1004) at ¶ 46. As shown in

Figure 8 of Lazar, the addition of a Fv or a Fab does not change the fact that the two chains have the same antigen specificity (for Ag1) in the Fab regions.

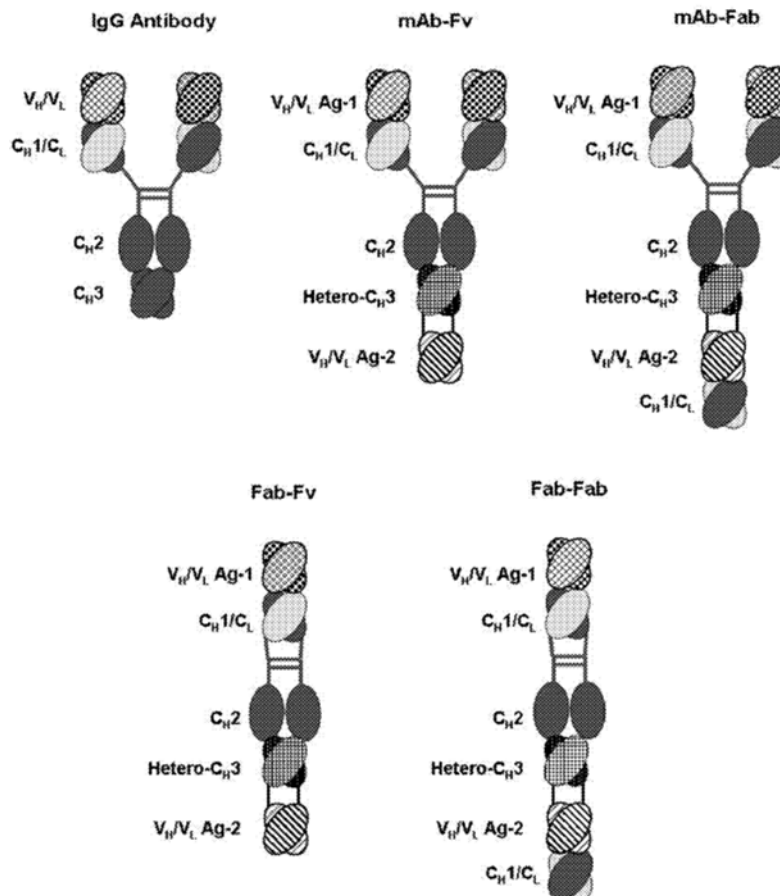


Figure 8

57. As shown in Fig 8, Fab-Fv and Fab-Fab are “analogues of the mAb-Fv and mAb-Fab that bind both antigen-1 and antigen-2 monovalently.” See Lazar (EX1004) at ¶ 48. Therefore, the alternative bispecific moieties are not the antibodies of the '286 Patent that have heavy chains as required by the Patent (“each heavy chain

has four domains, the variable heavy chain (VH) and three constant heavy chain domains (CH1, CH2, CH3)”) with different binding specificities.

58. Furthermore, Lazar does not disclose the claimed substitutions of neutral to charged residues with the alternative bispecific moiety. Indeed, Lazar used only one substitution (*i.e.*, Y349T/T394F and S364H/F405A) for the alternative bispecific moiety.

59. Therefore, it is my opinion that Lazar does not disclose the claimed heterodimeric antibody with heavy chains consisting of four domains and different specificity as defined in the Specification of the '286 Patent and required by Independent Claims 1, 26, and 30.

B. Lazar Does Not Show Interaction of Residues

60. Independent Claim 1 requires a heterodimeric antibody with substitutions of neutral to positive and neutral to negative residues on heavy chains as defined in the Specification of the '286 Patent that interact with each other to promote heterodimerization. Lazar fails to disclose the required “interacting” element of Independent Claim 1.

61. Discussion regarding interactions to promote heterodimerization in Lazar only relates to the overall CH3-CH3 interaction, not to interactions between individual residues. For example, Lazar states:

Such variants, referred to herein as hetero-Fc variants, comprise a pair of different variants such that one pair (referred to as variant') modifies one CH3 domain (referred to as CH3'), while the other pair (variant'') modifies another CH3 domain (CH3''). The variants are designed such that their interaction in a heterodimeric CH3 interface (variant'/variant'') is favorable, thus resulting in a stable heterodimeric Fc species (comprising CH3'/CH3''). In contrast, the pairing of each variant with itself across a homodimeric CH3 interface (variant'/variant' and variant''/variant'') is unfavorable, resulting in unstable homodimeric Fc species (comprising CH3'/CH3' and CH3''/CH3'').

See Lazar (EX1004) at ¶ 121.

Indeed, Dr. Presta does not identify any information in Lazar to support his opinions concerning residue to residue interactions. Critically, it is the interaction of the neutral to positive and neutral to negative substituted residues, which is a key component of the '286 Patent invention, and what went against the conventional wisdom of the POSA at the time of the invention. Lazar provides no disclosure or teaching of this required element. Dr. Presta, in my opinion, incorrectly assumes that the introduction of positive and negative charges would necessarily result in favorable electrostatic interactions within the CH3 interface. See Presta Declaration (EX1002), at ¶ 112. Lazar is silent in this regard, and nothing in Lazar demonstrates, nor does Dr. Presta provide, any evidence that the alterations of the chains of the bispecific moiety in Lazar interact to confer heterodimerization.

62. Therefore, it is my opinion that Lazar does not disclose a heterodimeric antibody with substitutions of neutral to positive and neutral to negative residues on heavy chains as defined in the Specification of the '286 Patent that interact with each other to promote heterodimerization as required by Independent Claims 1, 26 and 30.

63. Lazar also does not disclose the claimed limitations in Dependent Claims 7, 21, 22, 24, 26, 28, 30, and 32 of the '286 Patent. Dependent Claims 7, 21, 22, 24, 26, 28, 30, and 32 of the '286 Patent depend from Independent Claims 1, 26, or 30. For the reasons discussed above Lazar does not disclose a heterodimeric antibody with substitutions of neutral to positive and neutral to negative residues on heavy chains as defined in the Specification of the '286 Patent that interact with each other to promote heterodimerization. Therefore, Lazar also does not disclose the elements of the Dependent Claims.

VII. LAZAR AND ARATHOON DO NOT SUGGEST ALL THE ELEMENTS OF CLAIMS 1, 26, AND 30 OF THE '286 PATENT

64. It is my opinion that a POSA would not arrive at the inventions of Independent Claims 1, 26, and 30 based on the disclosures of Lazar alone or in combination with Arathoon.

65. Lazar does not disclose heavy chains, nor heavy chains with different specificity as defined in the Specification of the '286 Patent, nor substitutions of neutral to positive and neutral to negative residues that interact to promote

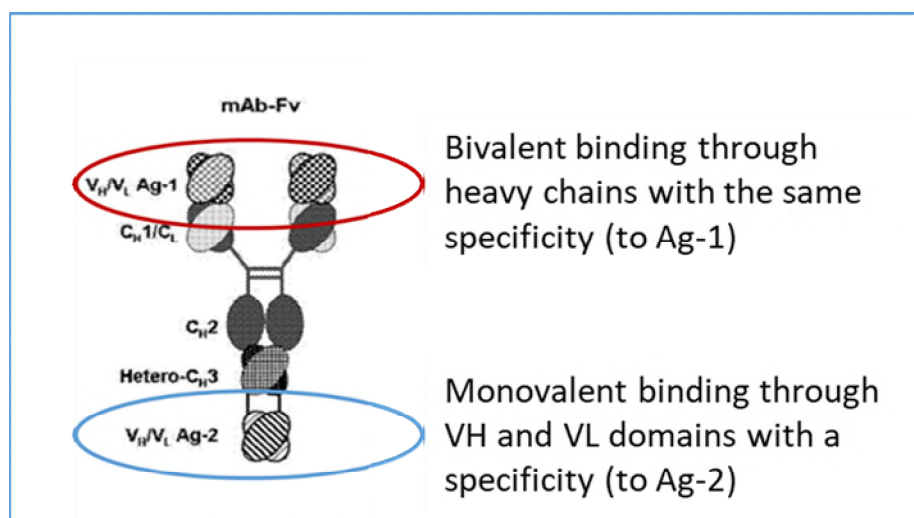
heterodimerization, but instead discloses to a POSA an alternative bispecific

construct, which includes chains with the same specificity. Lazar states:

Thus while bispecifics generated from antibody fragments suffer biophysical and pharmacokinetic hurdles, a drawback of those built with full length antibody-like formats is that they engage co-target antigens multivalently in the absence of the primary target antigen, leading to nonspecific activation and potentially toxicity. **The present invention solves this problem by introducing a novel set of bispecific formats that enable the simultaneous bivalent and monovalent co-engagement of distinct target antigens.**

See Lazar (EX1004) at ¶ 007 (emphasis added).

66. Lazar's alternative bispecific format has two binding sites for Antigen 1 (Ag-1) and one binding site for Antigen 2 (Ag-2) as shown below:



Lazar Alternative Bispecific Construct

67. The alternative bispecific format includes two chains that consist of five domains (as depicted above for the mAb-Fv construct) or six (for the mAb-Fab construct) with the *same* antigen specificity. Therefore, a POSA would not be motivated to produce the heterodimeric antibody claimed in the '286 Patent based on Lazar's monospecific alternative format.

68. Therefore, a POSA would not substitute neutral residues in CH3 domains with charged residues based on Lazar's disclosures. Rather, a POSA would look to the heterodimerization yield data presented in Figures 5 – 7 and be directed away from making neutral to positive substitutions based on the data.

69. The 230 variants (including some repeats and wild-type controls) reported in Lazar Figures 5-7 include examples of neutral to neutral, charged to charged, neutral to charged, and charged to neutral substitutions, with some as single modifications, others as double, and yet others as triple modifications. These were all screened only using Lazar's scFv-Fc/empty-Fc format. Lazar neither highlights, nor does the data support, any particular advantage of neutral to charged substitutions. Dr. Presta notes that there are neutral to charged changes in Tables 1 and 2, but a POSA would not have any cause to choose those over others, and in fact the data would suggest that other modifications, not involving neutral to charged substitutions, would be chosen. Dr. Presta also identifies two modifications in Table 2 that involve

neutral to charged substitutions at known contact residues in the native CH3 interface (indicated by Dr. Presta by red boxes). Lazar does not discuss contacting residues, only the overall interfaces, and thus again, a POSA would have no reason to select these particular changes. I note that one of the boxed modifications in Table 2 (L351K, L351E) has no supporting experimental data, and thus there would be no reason for a POSA to select this change.

70. Lazar reports in Figures 5-7 the heterodimerization yields for each of the variants. The variant with the best heterodimerization yield, indeed the only variant with 100% yield of heterodimer, involves three simultaneous charged to charged substitutions in each chain (*i.e.*, K370D/K392D/K409D in one chain and E356K/E357K/D399K in the other chain). Importantly, this was in keeping with the dogma of the time, which was to only modify hydrophilic or charged residues leaving the hydrophobic core intact to promote stability. Furthermore, the only modification that was taken into the alternative bispecific construct (with the next highest heterodimer yield of up to 85%) involved only neutral to neutral modifications (*i.e.*, S364H/F405A in one chain and Y349T/T394F in the other chain). Again, this was consistent with the understanding of the POSA at the time of the invention—only change hydrophobic to hydrophobic, or hydrophilic to hydrophilic. The neutral to charged variants that Dr. Presta highlighted from the “Most Preferred CH3 Domain

Variants” in Table 2 provide lower heterodimer yield. See Lazar (EX1004) at Table 2 and Figures 5-7. A POSA would not substitute neutral residues with charged residues based on Lazar’s disclosures that suggest other modifications with higher heterodimerization yields.

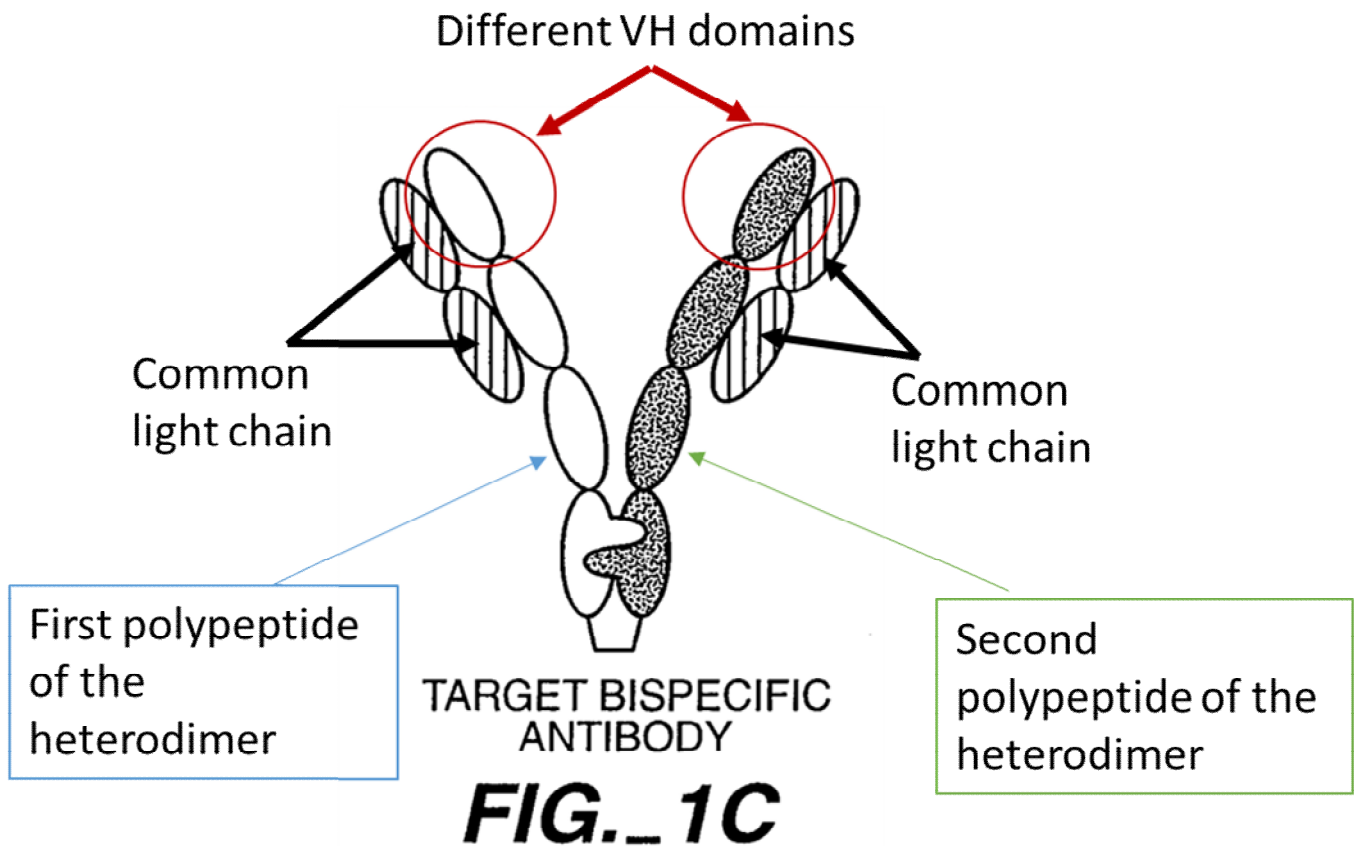
71. Lazar further states that CH3 domain modifications to yield “[h]eterodimeric Fc variants are not a necessity” for generation of the alternative bispecific moieties, since the VH and VL domains attached to the heavy chains to provide specificity for Ag-2 might themselves preferentially associate with each other or at least provide a means to purify the heterodimer utilizing its affinity for Ag-2. See Lazar (EX1004) at ¶ 108.

72. Accordingly, it is my opinion that a POSA looking at the data presented by Lazar would not conclude that making neutral to positive and neutral to negative modifications would be advantageous for the formation of heterodimers; other types of modifications, or indeed other approaches, would be more attractive to a POSA.

73. Like Lazar, Arathoon also does not disclose a heterodimeric antibody with substitutions of neutral to positive and neutral to negative residues on heavy chains as defined in the Specification of the ’286 Patent that interact with each other to promote heterodimerization and as required by Independent Claims 1, 26 and 30. Dr. Presta relies on Arathoon for its disclosure of a common light chain to challenge

Dependent Claim 2. In my opinion, a POSA would not combine the disclosure of Lazar and Arathoon because of the structural differences in their respectively disclosed moieties.

74. Arathoon concerns the production of multi-specific antibodies with “a common light chain associated with each heterodimeric polypeptide having an antibody binding domain.” See Arathoon (EX1006) at Abstract. Arathoon’s common light chain is “provided to pair with each of the variable heavy chains of the multi-specific antibody” to produce “a desired heteromultimeric antibody.” See Arathoon (EX1006) at p. 6, lines 24-26. Arathoon’s antibody with a common light chain is shown below in reproduced Figure 1C of Lazar.



75. In Lazar's scFv-Fc/empty-Fc format moiety, as shown in Figure 1 of Lazar (below), the empty-Fc does not have any variable regions to which a common light chain can attach, and thus Arathoon's common light chain cannot be "provided to pair with each of the variable heavy chains." See Arathoon (EX1006) at p. 6, lines 24-26.

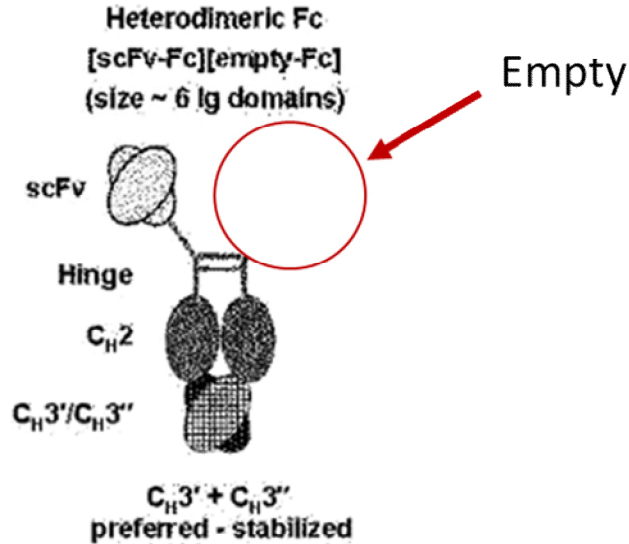


Figure 1

76. Lazar's alternative bispecific constructs (See Figure 8 of Lazar below) do not include two different heavy chains as defined by the '286 Patent with which Arathoon's common light chain can be associated to enhance the production of the "desired heteromultimeric antibody" in Arathoon. See Arathoon (EX1006) at p. 6, lines 24-26. A POSA could not combine these references as they set out incompatible formats. Furthermore, a POSA would understand that Lazar's alternative bispecific constructs with identical chains do not need Arathoon's common light chain to enhance the production of bispecific antibodies with two different heavy chains.

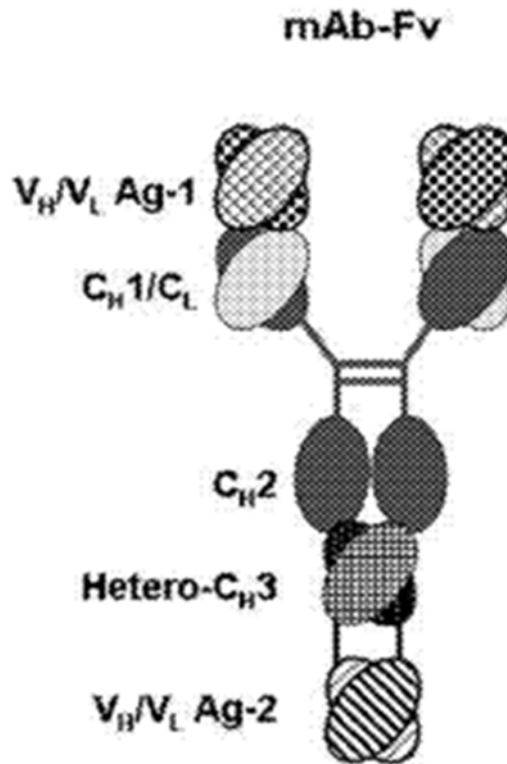


Figure 8

77. Accordingly, a POSA would not combine the disclosures of Arathoon and Lazar. In fact, Arathoon discloses information that would tell a POSA not to use substitutions of neutral to charged residues because the variants in Arathoon only have neutral to neutral or charged to neutral substitutions. See Arathoon (EX1006) at Tables 3-4 and p. 43. Table 4 of Arathoon (below) shows that variants with neutral to neutral mutations and/or charged to neutral mutations (*e.g.*, v11 and v16) result in 95% or more of heterodimer yield.

Table 4
Yields of Heterodimers from C_H3 Variants

Variant	Mutations		Yield of heterodimer (%)
	Subunit A	Subunit B	
wildtype	-	-	51 ± 1
v1	Y349C	S354C	54 ± 4
v2	Y349C	E356C	55 ± 6
v3	Y349C	E357C	57 ± 4
v4	L351C	E354C	56 ± 3
v5	T394C	E397C	57 ± 2
v6	D399C	K392C	73 ± 3
v7	D399S	L392S	55 ± 1
v8	T366W	T366S:L368A:Y407V	86.7 ± 2.3
v9	T366W:D399C	T366S:L368A:K392C:Y407V	86.5 ± 0.5
v11	S354C:T366W	Y349C:T366S:L368A:Y407V	95 ± 2
v12	E356C:T366W	Y349C:T366S:L368A:Y407V	94 ± 2
v13	E357C:T366W	Y349C:T366S:L368A:Y407V	93 ± 2
v14	T366W:K392C	T366S:D399C:L368A:Y407V	92 ± 1
v15	Y349C:T366W	S354C:T366S:L368A:Y407V	90 ± 1
v16	Y349C:T366W	E356C:T366S:L368A:Y407V	95.5 ± 0.5
v17	Y349C:T366W	E357C:T366S:L368A:Y407V	91.0 ± 1.0

78. Accordingly, a POSA reading Lazar and Arathoon would not arrive at the inventions of Independent Claims 1, 26, and 30 of the '286 Patent, namely neutral to positive and neutral to negatively charged substitutions that interact to promote heterodimerization. Further, it is my opinion, that Lazar and Arathoon also do not disclose to a POSA the elements of Dependent Claims 2, 7-24, 27-28, and 31-32 because, in part, these claims depend from and include all of the elements of the Independent Claims.

VIII. CABRERA DOES NOT DISCLOSE INTERACTING NEUTRAL TO CHARGED SUBSTITUTIONS TO PRODUCE A HETERODIMERIC ANTIBODY

79. Cabrera does not disclose a heterodimeric antibody with substitutions of neutral to positive and neutral to negative residues in heavy chains that interact with each other to promote heterodimerization.

80. Cabrera discloses “a novel method for designing Fc heterodimers” [p. 22 of Cabrera] that involves an iterative procedure [Fig. 24 of Cabrera] with rounds of computational modelling, molecular dynamics (MD) simulation, cavity and packing analysis *etc.* and provides over 2900 variants that were created through this iterative multistep-modification process. See Cabrera (EX1005) at Tables 1 and 6-7.

81. However, Cabrera does not contain a single example that shows an interaction between residues substituted from neutral to positive and neutral to negative charged amino acids that interact with each other to promote Fc heterodimerization. In figures 1-4, 6-7, 9, 11, 13, 16, and 29-34 of Cabrera, the results of modelling and MD analyses are provided, but there are *no data* supporting or illustrating any residues substituted from neutral to positive and neutral to negatively charged amino acids that are interacting with each other, much less doing so to promote heterodimerization as required by the claims of the '286 Patent.

82. Dr. Presta appears to make the assumption that known native CH3 interface contact residues will necessarily remain contact residues following their substitution. Indeed, Dr. Presta selects one variant, namely AZ34, one of the more than 2900 variants reported in Cabrera, and highlights one particular pair of substitutions (*i.e.*, S400E and N390R) out of the 6 total substitutions in AZ34, and assumes that these substituted, oppositely charged residues (400E and 390R) would interact because “S400 and N390 are among those identified as interacting residues” at the native CH3-CH3 interface. See Presta Declaration at ¶ 128. As I explain in further detail below, the melting temperature (T_m) data for the variant AZ34 that Dr. Presta selected contradicts Dr. Presta’s opinion that the substituted residues (400E and 390R) interact with each other.

83. AZ34 comprises the substitutions L351Y, S400E, F405A, and Y407V in the first CH3 domain and T366I, N390R, K392M, and T394W in the second CH3 domain. The effects of substitutions at S400 and N390 in the AZ34 variant can be identified by direct comparison with the AZ33 variant. AZ33 and AZ34 variants share the same residue substitutions except that AZ34 also has the S400E/N390R substitutions. See Cabrera (EX1005) at Table 1.

TABLE 1-continued

CH3 domain amino acid modifications for the generation of Fc variant heterodimers.								
Variant	Chains	Fc Mutations						
AZ33	A	L351Y	F405A	Y407V	-	-	-	-
	B	T366I	K392M	T394W	-	-	-	-
AZ34	A	L351Y	S400E	F405A	Y407V	-	-	-
	B	T366I	N390R	K392M	T394W	-	-	-

84. The interaction between two heavy chains of a heterodimeric antibody can be assessed by measuring the melting temperature (T_m). The purpose of CH3 domain engineering in the production of heterodimeric antibodies is to create a stronger and more stable interaction between the CH3 domains, and a stronger, more stable interaction will require a higher temperature to break the non-covalent bonds between the two different heavy chains. Cabrera also acknowledges that “[s]tability is measured as the melting temperature (T_m) of the CH3 domain.” See Cabrera (EX1005) at p. 17 of 239, lines 4-6. Accordingly, a POSA would understand that energetically favorable interactions introduced by substitutions at the interface would increase the melting temperature of the antibody because they would stabilize the binding of the two chains to each other and require a higher temperature to break them apart.

85. Cabrera’s T_m data directly oppose Dr. Presta’s assumption that the substituted residues in S400E and N390R (*i.e.* E400 and R390) would interact to promote heterodimerization because S400 and N390 are among those identified as

interacting residues in the wild-type interaction. Tables 3 and 4 explicitly show that the melting temperature for AZ33 (*i.e.*, 74 °C) is higher than in AZ34, which is identical except for the introduction of the S400E and N390R modifications (*i.e.*, 73.5 °C), meaning that the interaction between the two different heavy chains in Cabrera's antibody is actually weakened.

Table 3: Melting temperature measurements of variant CH3 domains in an IgG1 antibody having 90% or more heterodimer formation compared to homodimer formation

Variant	T _m °C	Variant	T _m °C	Variant	T _m °C	Variant	T _m °C
Wild-Type	81	AZ29	70	AZ63	71.5	AZ87	71
Control 1	69	AZ30	71	AZ64	74	AZ88	72
Control 2	69	AZ31	68	AZ65	73	AZ89	72.5
AZ3	65	AZ32	71.5	AZ66	72.5	AZ91	71.5
AZ6	68	AZ33	74	AZ67	72	AZ92	71.5
AZ8	68	AZ34	73.5	AZ68	72	AZ93	71.5
AZ12	77	AZ38	69	AZ69	71	AZ94	73.5
AZ14	77	AZ42	70	AZ70	75.5	AZ95	72
AZ15	71.5	AZ43	67	AZ71	71	AZ98	70
AZ16	68.5	AZ44	71.5	AZ72	70.5	AZ99	69
AZ17	71	AZ46	70.5	AZ73	71	AZ100	71.5
AZ18	69.5	AZ47	70.5	AZ74	71	AZ101	74

Table 4: Melting temperature measurements of select variant CH3 domains in an IgG1 antibody

Variant	T _m °C	Variant	T _m °C	Variant	T _m °C	Variant	T _m °C
Wild-Type	81.5	AZ42	70	AZ73	71	AZ91	71.5
Control 1	69	AZ44	71.5	AZ74	71	AZ92	71.5
Control 2	69	AZ46	70.5	AZ75	70	AZ93	71.5
AZ12	>77	AZ47	70.5	AZ76	71.5	AZ94	73.5
AZ14	>77	AZ48	70.5	AZ77	71	AZ95	72
AZ15	71.5	AZ49	71	AZ78	70	AZ98	70
AZ17	71	AZ63	71.5	AZ79	70	AZ100	71.5
AZ19	70.5	AZ64	74	AZ81	70.5	AZ101	74
AZ20	70	AZ65	73	AZ82	71	AZ106	74
AZ21	70	AZ66	72.5	AZ83	71	AZ114	71
AZ25	70.5	AZ67	72	AZ84	71.5	AZ115	70
AZ29	70	AZ68	72	AZ85	71.5	AZ122	71
AZ30	71	AZ69	71	AZ86	72.5	AZ123	70
AZ32	71.5	AZ70	75.5	AZ87	71	AZ124	70
AZ33	74	AZ71	71	AZ88	72	AZ129	70.5
AZ34	73.5	AZ72	70.5	AZ89	72.5	AZ130	71

86. If E400 and R390 in the AZ34 variant interact to promote heterodimerization, then the melting temperature of AZ34 would be higher—requiring more energy to destabilize the interface, than AZ33, which is identical but for the absence of the S400E and N390R substitutions. However, the opposite is true. AZ33 has the higher melting temperature, indicating that it is more stable and that the substituted residues in S400E and N390R of AZ34 (*i.e.* E400 and R390) do not interact, and in fact destabilize the CH3 domain.

87. In fact, the wild-type residues S400 and N390 interact with each other by forming a hydrogen bond of ideal length (2.8Å) between the O_γ atom of the S400

side chain and the N82 atom of the N390 side-chain. Substitution to E400 and R390 removes this stabilizing hydrogen bond between the two CH3 domains, and due to the location of the two amino acid residues at the extremity of the interface, the side chains of the two new substituted residues, E400 and R390, will be fully exposed to the surrounding water. This would explain the decrease in T_m upon introduction of the substitutions S400E and N390R, and illustrates how the structural context of a proposed mutation is important.

88. Accordingly, Cabrera does not disclose the claimed neutral to charged residue substitutions that interact to produce a heterodimeric antibody required by the Independent Claims.

89. Cabrera also does not disclose all of the limitations of Dependent Claims.

IX. CABRERA, ARATHOON AND LAZAR DO NOT DISCLOSE ALL THE CLAIM ELEMENTS OF THE '286 PATENT

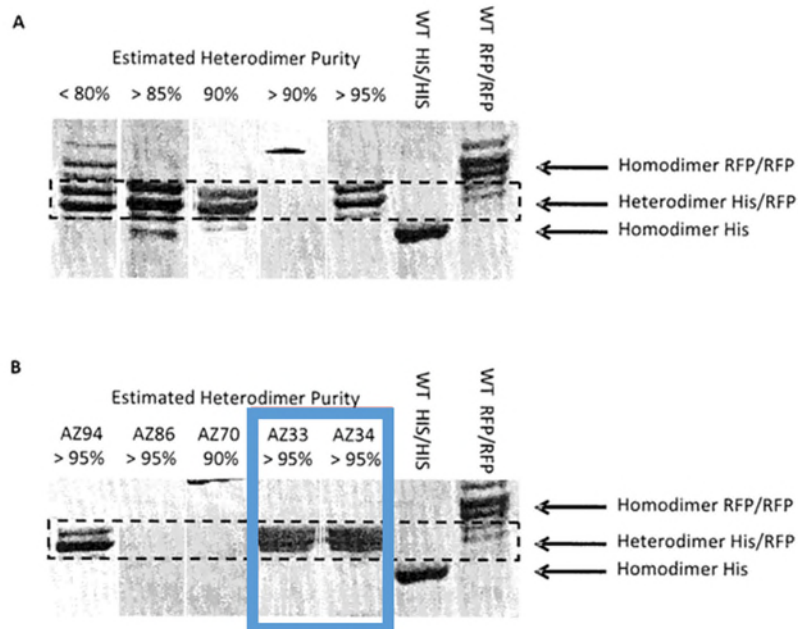
A. Cabrera Does Not Disclose The Claimed Substitutions

90. A POSA would not substitute neutral residues with charged residues based on Cabrera. Cabrera does not disclose a heterodimeric antibody with substitutions of neutral to positive and neutral to negative residues on heavy chains as defined in the Specification of the '286 Patent that interact with each other to promote heterodimerization. A POSA would look at the melting temperature data (as discussed above) and purity data disclosed in Cabrera and select different

substitutions, and avoid changes from neutral to positive and neutral to negative based on the lower melting temperature.

91. Dr. Presta's opinion that a POSA would substitute neutral to charged residues that interact with each other based on Cabrera's AZ34 variant is scientifically incorrect. The AZ34 variant in fact discloses to a POSA not to select neutral to charged mutations. Furthermore, according to Figure 26 of Cabrera, there is no improvement in heterodimer purity after introducing the S400E/N390R substitution. Both AZ33 and AZ34 variants provide over 95% heterodimer purity, which given the lower melting temperature of AZ34, would be understood by a POSA to be driven by the other residue changes in both AZ33 and AZ34, namely L351Y, F405A, and Y407V in the first CH3 domain and T366I, K392M, and T394W in the second CH3 domain, which are with one exception neutral to neutral substitutions.

Figure 26:
Heterodimer Purity Determination after Protein A purification using non-reducing SDS-PAGE



92. There is no meaningful difference in heterodimer purity level between AZ33 and AZ34, but Tables 3-4 of Cabrera show decreased stability after introducing the S400E/N390R substitution. Therefore, based on the purity and T_m data disclosed in Cabrera, a POSA would understand that neutral to charged substitutions were not appropriate to promote heterodimerization.

93. Cabrera also discloses another example (*i.e.*, AZ28 and AZ29 variants), which shows that a variant with neutral to neutral substitutions has a higher melting temperature than a variant with neutral to charged substitutions. AZ28, which includes a neutral to negatively charged substitution (*i.e.*, S354E) in one chain and a neutral to positively charged substitution (*i.e.*, Q347R) in the other chain, shares the

same substitutions with AZ29, except that the S354E substitution (neutral to negatively charged) in AZ28 is replaced with S354N (neutral to neutral) substitution in AZ29. See Cabrera (EX1005) at Table 1, p. 41 of 239.

TABLE 1-continued

CH3 domain amino acid modifications for the generation of Fc variant heterodimers.						
Variant	Chains	Fc Mutations				
AZ28	A	Q347R	L351Y	V397T	F405M	Y407V
	B	S354E	K360E	T366I	T394W	-
AZ29	A	Q347R	L351Y	V397T	F405M	Y407V
	B	S354N	K360E	T366I	T394W	-

94. Table 3 shows that the melting temperature of AZ28 (*i.e.*, 69.5 °C) increases to 70 °C for AZ29 after replacing S354E with S354N, undermining any suggestion that making neutral to charged substitutions will improve heterodimerization and stability. See Cabrera (EX1005) at Table 3.

Table 3: Melting temperature measurements of variant CH3 domains in an IgG1 antibody having 90% or more heterodimer formation compared to homodimer formation

Variant	Tm °C	Variant	Tm °C	Variant	Tm °C	Variant	Tm °C
Wild-Type	81	AZ29	70	AZ63	71.5	AZ87	71
Control 1	69	AZ30	71	AZ64	74	AZ88	72
Control 2	69	AZ31	68	AZ65	73	AZ89	72.5
AZ3	65	AZ32	71.5	AZ66	72.5	AZ91	71.5
AZ6	68	AZ33	74	AZ67	72	AZ92	71.5
AZ8	68	AZ34	73.5	AZ68	72	AZ93	71.5
AZ12	77	AZ38	69	AZ69	71	AZ94	73.5
AZ14	77	AZ42	70	AZ70	75.5	AZ95	72
AZ15	71.5	AZ43	67	AZ71	71	AZ98	70
AZ16	68.5	AZ44	71.5	AZ72	70.5	AZ99	69
AZ17	71	AZ46	70.5	AZ73	71	AZ100	71.5
AZ18	69.5	AZ47	70.5	AZ74	71	AZ101	74
AZ19	70.5	AZ48	70.5	AZ75	70	AZ106	74
AZ20	70	AZ49	71	AZ76	71.5	AZ114	71
AZ21	70	AZ50	69	AZ77	71	AZ115	70
AZ22	69	AZ52	68	AZ78	70	AZ117	69.5
AZ23	69	AZ53	68	AZ79	70	AZ122	71
AZ24	69.5	AZ54	67	AZ81	70.5	AZ123	70
AZ25	70.5	AZ58	69	AZ82	71	AZ124	70
AZ26	69	AZ59	69	AZ83	71	AZ125	69
AZ27	68	AZ60	67	AZ84	71.5	AZ126	69
AZ28	69.5	AZ61	69	AZ85	71.5	AZ129	70.5
		AZ62	68	AZ86	72.5	AZ130	71

95. I note that 108 of the 132 variants listed in Table 1 (*i.e.* 82%) include mutations that lead to loss of one or more of the four naturally occurring salt bridges that surround the principally hydrophobic CH3-CH3 wild-type interface. These losses of salt bridges are generally compensated by the introduction of more hydrophobic side chain interactions, and thus again, Cabrera discloses information that would tell a POSA not to introduce neutral to charged substitutions.

96. Therefore, a POSA, based on the disclosures of Cabrera, would not make neutral to charged substitutions to produce the heterodimeric antibody of the claims of the '286 patent.

B. A POSA Would Not Combine The Disclosures of Lazar, Arathoon, and Cabrera

97. It is my opinion that a POSA would not arrive at the inventions of the Independent Claims, based on the disclosures of Cabrera alone or in combination with Lazar and Arathoon.

98. There is simply no basis to combine the references of Cabrera and Lazar, which set out incompatible formats. Moreover, Lazar's alternative bispecific format has no need for the introduction of any heterodimerization technology. As shown in Figure 8 of Lazar, the alternative bispecific moieties are created by adding a Fab or a Fv to the C termini of the chains in a wild type IgG antibody. Lazar's alternative moieties include two identical chains that do not need to be stabilized through CH3

domain mutations for heterodimerization. Lazar states that “[h]eterodimeric Fc variants are not a necessity” for generation of the alternative bispecific antibodies. See Lazar (EX1004) at ¶ 108. Cabrera’s disclosures are directed to techniques for restoring decreased stability of an antibody after Fc heterodimerization engineering, this being significantly less stable than wild-type.

99. Cabrera’s disclosures cannot be applied to Lazar. The methodology employed by Cabrera to improve stability at the CH3-CH3 interface in heterodimeric antibodies is not required for the already stable interface between identical chains in this region. Cabrera discloses numerous variants with restored stability but the wild-type antibodies still show the highest stability and melting temperature, compared to Cabrera’s heterodimeric antibodies in Tables 3-4. A POSA would not therefore apply Cabrera’s iterative multistep-modification process to Lazar’s alternative bispecific moieties, which include a wild-type IgG with additional domains at the C-termini.

100. Arathoon would not add any helpful information to the disclosures of Cabrera and/or Lazar regarding CH3 domain engineering to promote heterodimerization, because Arathoon only suggests known methodologies (*e.g.*, knobs-into-holes mutations, disulphide bonds) and use of a common light chain, which is incompatible with the format used by Lazar.

101. Accordingly, it is my opinion that Lazar, Arathoon, and Cabrera do not disclose or suggest, at least, features of substitutions of neutral residues in the claimed heavy chains with charged residues that interact with each other to produce a heterodimeric antibody of the claims of the '286 Patent.

C. Cabrera Fails to Suggest Claim Limitations That Are Not Disclosed by Lazar And Arathoon

102. For the reasons stated herein, it is my opinion that a POSA would not arrive at the inventions of the Independent Claims, based on the disclosures of Cabrera alone or in combination with Lazar and Arathoon.

X. CONCLUSION

103. I declare that all statements made herein to my knowledge are true, that all statements made on information and belief are believed to be true, and that these statements were made with 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.

Date: 28th June 2025



Brian J. Sutton, Ph.D.