

UNITED STATES PATENT AND TRADEMARK OFFICE

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BEFORE THE PATENT TRIAL AND APPEAL BOARD

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XENCOR, INC.,

Petitioner

v.

MERUS N.V.,

Patent Owner

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IPR2025-00604  
Patent No. 9,358,286

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

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**I. INTRODUCTION**

1. I, Brian J. Sutton, Ph.D., declare as follows:
2. I submit this declaration to supplement the opinions and explanations expressed in my June 28, 2025 Declaration (EX2008) and respectfully to address the questions and other issues raised by the Board in its Decision Granting Institution of *Inter Partes* Review of U.S. Patent No. 9,358,286 (“the ’286 Patent”)(EX1001).

**II. EXPERIENCE AND QUALIFICATIONS**

3. My full experience and qualifications are in my CV, which I submitted along with my June 28, 2025 Declaration as Exhibit 2009. I believe that I am uniquely qualified to opine on the complexities of the structures of antibodies, and in particular the CH3 domains in the Fc region, and how any modifications to it may affect antibody folding, stability, and functionality.

4. For over 45 years, since receiving my Ph.D. from Oxford in 1980, I have devoted my entire professional life to the pursuit of studying and understanding the structure and function of antibodies. I believe that this experience places me in a unique position, and that I can thus consider myself one of the world’s preeminent experts on the structure of the Fc regions, including the CH3 domains, of antibodies. My training and extensive experience in X-ray crystallography have aided me in my investigation and understanding of the three-dimensional structure of antibodies,

including the structure and function of the CH3 domains of these immunoglobulin molecules.

5. I have authored more than 140 peer-reviewed publications on the structure and function of antibodies, and I am currently involved in studying: (a) the structure of the Fc region of the least well-known class of human antibody, IgD; (b) allosteric effects in the Fc region of IgE and the development of IgE inhibitors for the treatment of allergic disease; and (c) the effect of changing antibody class and CH domains of IgG, IgA, IgE, IgM and IgD on the antigen-binding activity of the VH and VL domains. I have always had a broader interest in the evolutionary biology of antibody structure and function, and this has involved studying the structure of the Fc region of avian IgY, an evolutionary successor to the primordial IgM, and evolutionary precursor to mammalian IgG and IgE.

### **III. DEFINITION OF A PERSON OF ORDINARY SKILL IN THE ART**

6. As I stated in my previous declaration, 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 a 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. None of my opinions in

7. Prior to April 2012, researchers investigated a wide variety of ways to create bispecific antibodies for potential therapeutic uses.

**bispecific antibody conjugates**

sp<sub>0</sub>, rFv<sub>2</sub>, Covalent body

**bispecific IgG and IgG-like molecules**

IgG, scFv-Ig, IgG-scFv, scFv-IgG, DVS-Ig, IgG-sIg, sIg-IgG, 2 in 1-IgG, mAbI, tandemly connected LC, HH

**asymmetric bispecific IgG and IgG-like molecules**

kln-IgG, kln-IgG common LC, CrossMa, kln-IgG-scFab, scAb-Iv, charge pairs, SEED-body

**small bispecific antibody molecules**

Dimeric scD<sub>2</sub>, DART, scD<sub>2</sub>, tandem, tandem scFv, single body, triple heads, Fab-scFv, F(ab')<sub>2</sub>-scFv, random dAb-VHH

**bispecific Fc and C<sub>3</sub>/3 fusion proteins**

scFv-Fc, scD<sub>2</sub>-Fc, scD<sub>2</sub>-C<sub>3</sub>, scFv-Fc-IGT, ICAB-HH, scFv-kDa-Fc, scFv-C<sub>3</sub>

**bispecific fusion proteins**

scFv-albumin, scFv-albumin, scFv-bovin, DHL-Fab, DHL-Fab-IgG, DHL-Fab-IgG-cytokine

**Figure 2.** Bispecific antibody formats. Variable heavy chain domains (V<sub>H</sub>) are shown in dark blue and dark red, variable light chain domains (V<sub>L</sub>) are shown in light blue and light red, red and blue indicating different specificities. Antibody constant domains are shown in white boxes and fusion proteins in white circles.

See Kontermann's 2012 Landes Bioscience Paper (EX1013), at 186, Figure 2.

9. As Dr. Presta agreed during his cross-examination (Presta Tr. at 138:3-23), only seven of the 45 known approaches for creating bispecific antibodies in 2012 involved modification of the antibody Fc region. As Dr. Presta further agreed (Presta Tr. at 138:24–139:8), only one of those seven approaches for creating bispecific antibodies in 2012 involved “charges”. Accordingly, Dr. Presta and I agree that only one of the 45 approaches for creating bispecific antibodies known to a POSA in 2012 involved “charge pairs”.

10. Dr. Presta is silent on whether and for what reason a POSA in 2012 would focus—as he did in his declaration—on modifying the one “charge pairs” approach to creating bispecific antibodies out of the 45 different approaches reported in the Kontermann Paper (EX1013). This is a noticeable omission given that Dr. Presta and his colleagues had already reported achieving 95% heterodimeric purity without any charge modifications in the 1998 Merchant Paper (EX1017). Even if a POSA were interested in using the Fc region to create bispecific antibodies, they would have investigated other well-known methods for creating bispecific antibodies—like knob into hole with disulfide bonds, which reported 95% heterodimeric purity—or been content to use the existing “charge pairs” approach, which reported production of the desired heterodimer “almost exclusively.”

11. If a POSA chose to ignore the other 44 known approaches to creating bispecific antibodies in 2012 and sought to modify the “charge pairs” approach, they knew to avoid the hydrophobic core of the CH3 domain. For example, Dr. Gunasekaran Kannan clearly instructed POSAs *not* to modify the neutral residues in the hydrophobic core of the CH3 region or in the hydrophobic region of the CH3-CH3 interface. See Gunasekaran Paper (EX1012) at 19640. This paper switches Dr. Gunasekaran Kannan’s first and last names. For consistency of citation, I call it the Gunasekaran Paper in my Declarations, as Dr. Presta does in his Declarations.

12. According to Dr. Kannan, “[i]t has long been established that the hydrophobic core of protein domains plays an important role in protein folding and stability.” A POSA clearly understood from Dr. Kannan that any modifications of the CH3 domain to improve heterodimerization should be made to the already charged residues at the periphery of the CH3 domain, ***and not the neutral residues in the hydrophobic core.*** *Id.* In providing this statement, Dr. Kannan cited the 1995 Matthews Paper (EX2013), which similarly teaches that the hydrophobic core of protein domains plays an important role in protein folding and stability.

13. I understand from Dr. Presta’s cross-examination that Xencor questions the authenticity of the Matthews Paper marked as EX2013. I read this review paper several years ago as part of my academic work, and incorporated material from it into

undergraduate lectures that were part of a course entitled *Protein Structure & Design*.

I have recently reviewed the Matthews Paper for this proceeding and can confirm its authenticity.

14. Dr. Kannan's warning would have made sense to a POSA. As a preliminary matter, a POSA would have understood that before any Fc dimerization, each CH3 domain must first fold. Only after it is properly folded can the CH3 domain of one heavy chain interact with the CH3 domain of another heavy chain to form a non-covalent dimer and maintain the dimeric structure of an antibody. *Id.* at ¶ 26. A POSA would have further understood that the folding of the CH3 domain is largely controlled by the hydrophobic amino acid residues clustering together in the core of the protein domain to avoid contact with water. *Id.* at ¶ 27. Given this understanding, even though POSAs may not have grasped all of the intricacies of protein folding, they knew to avoid substitutions that were published in the literature as being potentially detrimental to protein folding. A POSA would be unlikely to modify a residue when they did not understand its role.

15. In addition to protein folding, a POSA certainly would have understood that the Fc region contributed to antibody stability. As Dr. Presta testified:

Q. From general knowledge from a person of ordinary skill in the art and/or from their review of Exhibit Xencor 1012 and Merus 4001, a person of ordinary skill in the art would know that the hydrophobic core of the

CH3 region in a heavy chain is very important to protein folding and stability, right?

- A. A POSA, in 2012, would know that the hydrophobic core was one of the factors contributing to stability. I'm not sure a POSA would understand the intricacies of what controlled protein folding.

See Presta Tr. at 87:16–88:1.

16. A POSA would not want to harm protein folding or stability in the Fc region because, among other reasons, the Fc portion of the molecule has biological functions. For example, the Fc region affects the half-life of an antibody and controls cell-mediated cytotoxicity. As Dr. Presta testified during his cross-examination, the Fc region has three primary functions: (1) it is “involved in homeostasis of antibodies”; (2) it “binds to the complement system”; and (3) it binds to a “set of receptors called Fc gamma receptors”. See Presta Tr. at 42:1-8. Dr. Presta went on to testify that the potential for making changes to and disrupting the Fc region “is actually a very big research area in antibodies.” See Presta Tr. at 42:10–16.

17. Dr. Presta agreed during his cross-examination that both the 2012 Gunasekaran Paper and the 1995 Paper by Dr. Matthews state that the hydrophobic core is important to protein folding and stability, which was also already known from other sources. See Presta Tr. at 86:14–21 (“These statements were known even before these.”); see also Brian Matthews, *Studies on Protein Stability With T4 Lysozyme*, at pp. 268-271 (EX2013).

18. POSAs at the time, including Lazar and Cabrera, were well aware of Dr. Gunasekaran Kannan's warning. In fact, it was such an important teaching at the time that both Lazar and Cabrera incorporated Dr. Gunasekaran's Paper in its entirety into their own publications. See Lazar (EX1004) at ¶ 12; Cabrera (EX1005) at page 129.

19. Merus' novel approach to heterodimerization deviated from, and improved upon, previous methods such as "knob into hole" and "electrostatic steering." Merus went against Dr. Kannan's warning and unexpectedly and surprisingly achieved heterodimerization by modifying neutral residues in the hydrophobic core of the CH3 domain to create stable, functional bispecific antibodies at an acceptable yield for manufacturability and human administration.

20. Confirming Merus' pioneering work, Merus was the first company to win FDA approval for a bispecific antibody using a charge engineering approach to heterodimerization. (EX2001).

## **V. SUMMARY OF OPINIONS**

21. For the reasons stated herein and in my June 28, 2025 Declaration, it is my opinion that: (1) Lazar (Ex. 1004) does not anticipate claims 1, 7, 21, 22, 24, 26, 28, 30, and 32 of the '286 Patent; (2) Cabrera (Ex. 1005) does not anticipate claims 1-2, 7, 21, 22, 24, 26-28, and 30-32 of the '286 Patent; (3) claims 1-2, 7-24, 26-28, and 30-32 of the '286 Patent are not obvious based on the combination of Lazar (Ex. 1004)

and Arathoon (Ex. 1006); and (4) claims 1-2, 7-24, 26-28, and 30-32 of the '286 Patent are not obvious based on the combination of Lazar (Ex. 1004), Cabrera (Ex. 1005), and Arathoon (Ex. 1006).

## **VI. CLAIM CONSTRUCTION**

22. I understand from counsel that claim construction is the process that is used to determine the meaning of patent claim terms. I further understand that claim terms should be defined in accordance with their ordinary and customary meaning in the absence of a clear definition or disclaimer by the inventors. I understand from counsel that the ordinary and customary meaning of a claim term is the meaning that the term would have had to a POSA as of the effective filing date, which here is April 2012, upon reviewing the entire patent, including all of the claims and the Specification, and its prosecution history.

23. In his analysis and declaration, Dr. Presta uses an incorrect claim construction for two claim terms in the '286 Patent, namely “heavy chain”/“heavy chains” and “wherein the at least one positively charged amino acid residue substituted in the CH3 domain of said 1<sup>st</sup> antibody heavy chain interacts with the at least one negatively charged amino acid residue substituted in the CH3 domain of said 2<sup>nd</sup> antibody heavy chain in the interface between said 1<sup>st</sup> and 2<sup>nd</sup> antibody heavy chains to produce a heterodimeric antibody.” Properly construing these terms is essential to

understanding the claims of the '286 Patent and properly analyzing their validity. I provide my opinions regarding the proper construction of each of these claim terms below.

**A. “Heavy Chain”/“Heavy Chains”**

24. The terms “heavy chain” and “heavy chains” are used throughout the independent and dependent claims of the '286 Patent. My analysis of “heavy chains” applies equally to whether it is used in the singular or plural.

**i. Ordinary And Customary Meaning**

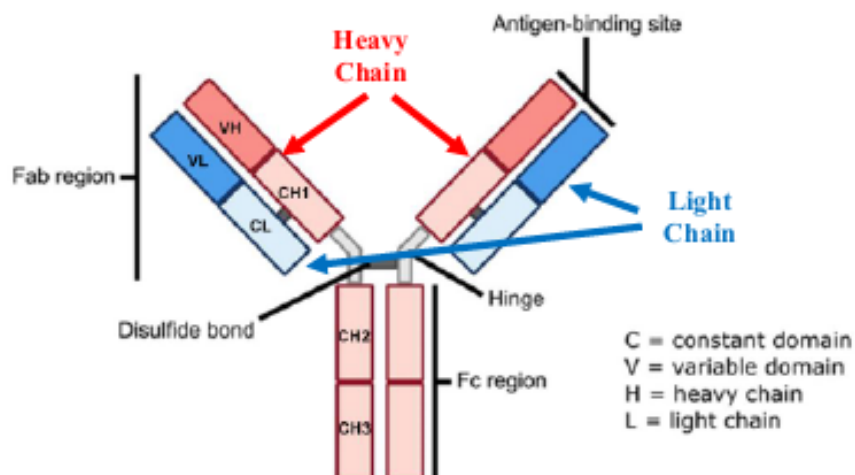
25. A POSA would have understood the term “heavy chain” of an antibody to mean a polypeptide chain starting at the N-terminal residue in the variable region (VH) and ending at the C-terminal residue in the final constant region (CH), including all intervening constant regions (CH) and the hinge region.

26. The term “heavy chain” was a well-defined term in the art of immunology and would have been well understood by a POSA in 2012. The term “heavy chain” was first introduced by Porter in 1962, and immunology textbooks define and use the term “heavy chain” consistent with my definition above. Porter’s Nobel Lecture (*Structural Studies of Immunoglobulins*, Nobel Lecture, R.R. Porter, December 1972) (EX2017) clearly indicates in Figure 5 that the heavy chain starts at the N-terminal residue of the VH domain and ends at the C-terminal residue of the

CH3 domain, thus comprising four domains and the hinge region of IgG. A further illustration that the heavy chain is defined as the entire chain from N- to C-terminus encompassing the four domains and hinge region of IgG is provided in an article by Porter (Scientific American, October 1967, pages 31-38 (EX2018); the Figure is on pages 32 and 33). An immunology textbook example is *Immunology*, Roitt, Brostoff and Male, 3<sup>rd</sup> Edition, 1994; Chapter 4 Figures 4.1, 4.3, 4.5 4.7 and 4.9 (EX2019). Roitt *et al.* state “the larger (heavy) chain has a molecular weight of 50,000-77,000 and is structurally distinct for each class or subclass.” This range of molecular weight indicates that the heavy chain is the *entire* polypeptide chain from the N- terminus to the C-terminus, including the variable VH domain and the three CH domains of IgG and IgA antibodies and their hinge regions, or the four CH domains of IgE and IgM antibodies and their hinge regions. Two further immunology textbook definitions are provided by Kuby, *Immunology* (6<sup>th</sup> Edition, 2007) page 80 (EX2020): “heavy chains contain one variable domain (VH), and either three or four constant domains (CH1, CH2, CH3, and CH4), depending on the antibody class”; Abbas, *Cellular and Molecular Immunology* (5<sup>th</sup> Edition, 2001) page 489 (EX2021): “Each heavy chain is composed of a variable (V) Ig domain and three or four constant (C) Ig domains”. A protein structure textbook example is *Introduction to Protein Structure*, Branden and Tooze, Garland Publishing, 1991; Chapter 12 Figures 12.2a and 12.2b (EX2022). The

legend to Figure 12.2a, which depicts an IgG molecule, states that “The heavy chain folds into four domains...”, and Figure 12.2b shows the other classes of antibody, with five domains in the heavy chains of IgM and IgE. A POSA would understand that a fragment lacking a VH region would not fit with the plain and ordinary definition of “heavy chain(s).” Similarly, a POSA would understand that a fragment lacking a CH1 domain would not fit with the plain and ordinary definition of “heavy chains(s).” Indeed, sub-fragments of antibody molecules that include only sub-fragments of the heavy chain are defined by names such as **Fv** (only VH region of heavy chain, with VL of light chain), **Fab** (only VH and CH1 regions of heavy chain, with VL and CL of light chain), **Fc** (only hinge, CH2 and CH3 regions of heavy chain, as a covalent dimer), **Fab’** (only VH, CH1 and hinge regions of heavy chain, with VL and CL of light chain), **F(ab’)<sub>2</sub>** (only VH, CH1 and hinge regions of heavy chain, with VL and CL of light chain as a covalent dimer), **Fc’** (only CH2 and CH3 regions of heavy chain as a non-covalent dimer), **pFc’** (only CH3 with little or no CH2 region, as a non-covalent dimer), **Fd** (only VH and CH1 regions of heavy chain).

27. Notably, Dr. Presta’s illustration of a “naturally occurring antibody” in his declaration includes a “heavy chain” with VH region and a CH1 domain, plus the hinge region and CH2 and CH3 domains. See Presta Declaration (EX1002), p. 10, 22, and 26.

**Demonstrative 2 – Monoclonal Antibody Structure**

28. Moreover, Lazar understood the ordinary and customary meaning of the term “heavy chain” and, thus, used the different term “immunoglobulin polypeptides” to describe their scFv-Fc/empty-Fc format. See Lazar (EX1004) at ¶ 238 (“DNA constructs were designed encoding two different immunoglobulin polypeptides: (i) scFv-Fc (VH-linker-V $\kappa$ -Hinge-CH2-CH3’) and (ii) empty-Fc (Hinge-CH2-CH3”)”).

29. Lazar’s use of the term “immunoglobulin polypeptides” is notable especially given Lazar’s use of the term “heavy chains” elsewhere in the reference. Lazar states “[e]ach of the light and heavy chains are made up of two distinct regions, referred to as the variable and constant regions.” See Lazar (EX1004) at ¶ 80. Lazar further provides:

Antibodies are immunoglobulins that bind a specific antigen. In most mammals, including humans and mice, antibodies are

constructed from paired heavy and light polypeptide chains. The light and heavy chain variable regions show significant sequence diversity between antibodies, and are responsible for binding the target antigen. Each chain is made up of individual immunoglobulin (Ig) domains, and thus the generic term immunoglobulin can be used for such proteins.

See Lazar (EX1004) at ¶ 78

30. This understanding—which is consistent with the ordinary and customary meaning of “heavy chain”—explains why Lazar did not once refer to its scFv-Fc/empty-Fc construct as having a heavy chain.

31. Given the above, it is clear that POSAs would have understood that the ordinary and customary meaning of the term “heavy chain” is distinguishable from the term “polypeptides” or “immunoglobulin peptides.”

## ii. Other Claims

32. Other claims in the '286 Patent further confirm the ordinary and customary meaning of “heavy chains.”

33. For example, dependent claim 8 reads:

The method of claim 1, wherein ***each variable region of the 1st and 2nd antibody heavy chains recognizes a different target epitope.***

34. Claim 8 specifies that “each variable region” of the first and second antibody heavy chains is different (*i.e.*, recognizes a different target epitope). A POSA reading claim 8 would understand that each heavy chain in claim 1 must have a variable

region and that in claim 8 each of those variable regions must be different (*i.e.*, recognize a different target epitope). Dependent claim 8 thus confirms the ordinary and customary meaning of “heavy chain” as including a variable region.

### **iii. Specification**

35. I agree with the Board’s observation that the Specification of the ’286 Patent does not apply any special meaning to the term “heavy chains” or use the term “heavy chains” in any way deviating from its ordinary and customary meaning in the art.

36. Reviewing the Specification of the ’286 Patent as a whole, a POSA would understand that the use of the term “heavy chains” is consistent with how a POSA would understand “heavy chains” to comprise one VH domain and at least three CH domains.

37. In its decision, the Board correctly noted that the Specification of the ’286 Patent references IgG, IgA, IgE, and IgM. Each of these classes of antibodies has two heavy chains as that term is understood by a POSA (*i.e.*, from the N-terminal residue in the variable region (VH) to the C-terminal residue in the final constant (CH) region, including all intervening constant (CH) regions and the hinge region).

38. When I stated in my June 28, 2025 Declaration that heavy chains consist of one variable domain (VH) and three constant domains (CH1, CH2, and CH3), I was

using that example to describe an IgG antibody for instructive purposes, and to refer to an illustrative Figure depicting an IgG antibody. However, I did not mean to imply that only three constant domains could be present, or to exclude other antibodies such as IgE or IgM that have four constant domains. To be clear, it is my opinion that the ordinary and customary meaning of heavy chain includes one VH domain and **at least** three CH domains in each heavy chain. This definition of “heavy chain” works for all of the claims of the ‘286 patent, including dependent claims 21, 24, and 32, which are limited to IgG antibodies (claims 21 and 24) or IgG1 antibodies (claim 32), .

39. For dependent claims 21, 24, and 32, which are limited to human IgG or human IgG1 antibodies, the requirement that each “heavy chain” have a variable region and at least three CH3 regions is further confirmed by the Specification, which states that:

The term CH3 domain is well known in the art. 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 (EX1001), Col. 11:58-63

Whether or not this statement constitutes a clear definition for claim construction purposes, a POSA reading it in 2012 would understand that—consistent with ordinary

and customary meaning—each “heavy chain” in an IgG or IgG1 claim in the ‘286 patent must have a variable region and at least three constant regions.

#### **iv. Prosecution History**

40. I understand that, in an April 10, 2015 non-final Office Action, the USPTO rejected certain claims of the patent application that became the ‘286 Patent based on, among other references, Carter *et al.* (US 7,642,228), which purportedly discloses “methods of preparing a heteromultimeric Ig molecule comprising ‘a first polypeptide and a second polypeptide which meet at the CH3-CH3 interface, wherein the first polypeptide has a protuberance at the interface thereof which is positionable in a cavity at the interface of the second polypeptide.’” See ‘286 Patent File History (EX1008) at p. 217. In citing Carter, the Examiner referred specifically to Figure 4, which shows a method of preparing a heteromultimer including “a first CH3-domain-containing polypeptide and a second CH3-domain-containing polypeptide which meet at the CH3-CH3 interface See ‘286 Patent File History (EX1008) at p. 217. In response to the office action, in an October 13, 2015 Amendment, Patent Owner traversed the rejection, but amended the language of pending claim 1 to replace the term “CH3-domain-containing polypeptide chain” with the narrower term “antibody heavy chain.” See ‘286 Patent File History (EX1008) at pp. 239 and 244.

41. “Polypeptides” are defined in the Specification as “a chain of amino acids that are covalently joined together through peptide bonds.” See ’286 Patent (EX1001), Col. 14, lines 19-22.

42. Patent Owner expressly amended the claimed subject matter from “polypeptide chain” to specifically recite “heavy chain,” which requires a VH region and at least three CH regions, rather than any chain of amino acids.

43. In making this amendment, the prosecution history of the ’286 Patent uses the term “heavy chains” in accordance with its ordinary and customary meaning (*i.e.*, a heavy chain is more than just a string of amino acids) and requires a VH region and at least three CH regions.

**B. “Interacts...To Produce A Heterodimeric Antibody”**

44. Claim 1 of the ’286 patent reads as follows:

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.

See '286 Patent (Ex. 1001), Claim 1, emphasis added.

#### **i. Ordinary And Customary Meaning**

45. A POSA would have understood that the claims of the '286 Patent require that there be an “interaction” between the at least one positively charged amino acid of the first CH3 region and at least one negatively charged amino acid of the second CH3 region of the heavy chains “to produce a heterodimeric antibody.” This is a two-part requirement, interaction and production, that would result in a structural feature (a salt bridge linking the two different heavy chains in a heterodimer). A POSA would have understood that if there is no “interaction” between the substituted residues in the CH3 regions of the heavy chains, or if any such “interaction” does not “produce a heterodimeric antibody,” then the claim requirements are not satisfied. In such a situation, heterodimerization may still occur, but it would be the result of other

interactions at the CH3-CH3 interface, and the heterodimeric antibody would be produced by those interactions, not the claimed interactions.

46. A POSA would have understood that the claim term “wherein the at least one positively charged amino acid residue substituted in the CH3 domain of said first antibody heavy chain ***interacts*** with the at least one negatively charged amino acid residue substituted in the CH3 domain of said second antibody heavy chain in the interface between said first and second antibody heavy chains ***‘to produce a heterodimeric antibody’***” to mean that specific charge interactions connect different heavy chains (*i.e.*, the heterodimers in a heterodimeric antibody). A POSA would have understood that the connection-forming interactions are, and have to be, structural, such as the formation of salt bridges or hydrogen bonds. In the absence of a structure formed by the required charge interactions, there is nothing in the claims to connect the heavy chains to produce a heterodimeric antibody. Consistent with a POSA’s understanding, Dr. Presta admitted during his cross-examination that interactions between residues can create structural changes through the formation of salt bridges and/or hydrogen bonds. *See* Presta Tr. at 49:16-50:8. Dr. Presta also admitted why this is a two-part claim limitation: “just because the two interact, that might not necessarily give you the heterodimeric antibody.” *See* Presta Tr. at 52:16-19.

47. Dr. Presta has thus admitted, as I have explained above, that this claim language requires both interaction and production of a heterodimeric antibody. Meeting one of those requirements is not enough to satisfy the claims. When both are met, the interaction that produces the heterodimeric antibody is structural, *i.e.* it is literally a connection that holds the heterodimeric antibody together.

**ii. Specification**

48. A POSA reading the Specification would have understood that the “interacts...to produce a heterodimeric antibody” limitation of the claims of the '286 Patent is a required element to produce Fc heterodimerization, and that such interactions may take the form of, for example, hydrogen bonds or salt bridges between substituted amino acid residues in each of the two CH3 domains.

49. Importantly, claim 1 refers to the interaction at the interface to produce a heterodimer, again showing this refers to a structural feature created by specific electrostatic forces from each CH3 domain that exist as a result of the recited substitutions. In the Specification, “interaction” of the substituted residues at the “interface” is described as one or more atoms of the first substituted residue being in contact distance with one or more atoms of the second substituted residue, such as to form either a van der Waals interaction, hydrogen bond (directly or mediated by a water molecule) or salt bridge. See '286 Patent (Ex. 1001), Col. 13, lines 18-29.

50. The Specification of the '286 Patent states:

The term 'CH3-CH3 domain interface', or 'CH3 interface', 'CH3-CH3 pairing', 'domain interface' or simply 'interface', as used herein, refers to the association between two CH3 domains of separate CH3-domain comprising polypeptides that is a result of ***interacting amino acid residues***, i.e. at least one interaction between an amino acid of a first CH3 domain and an amino acid of a second CH3 domain. ***Such interaction is for instance via Van der Waals forces, hydrogen bonds, water-mediated hydrogen bonds, salt bridges or other electrostatic forces, attractive interactions between aromatic side chains, the formation of disulfide bonds, or other forces known to one skilled in the art.***

See '286 Patent (Ex. 1001), Col. 13, lines 18-29, emphasis added.

51. In addition, the Specification of the '286 Patent provides examples of substituted residues interacting at the CH3/CH3 interface. For example, Figure 15 (reproduced below) shows the modeled, docked structures (using the program HADDOCK) of the double substitutions T366K-L351K/L351'D-Y349'D (left panel) and T366K-L351K/L351'E-L368'E (right panel). In the former (left panel), two salt

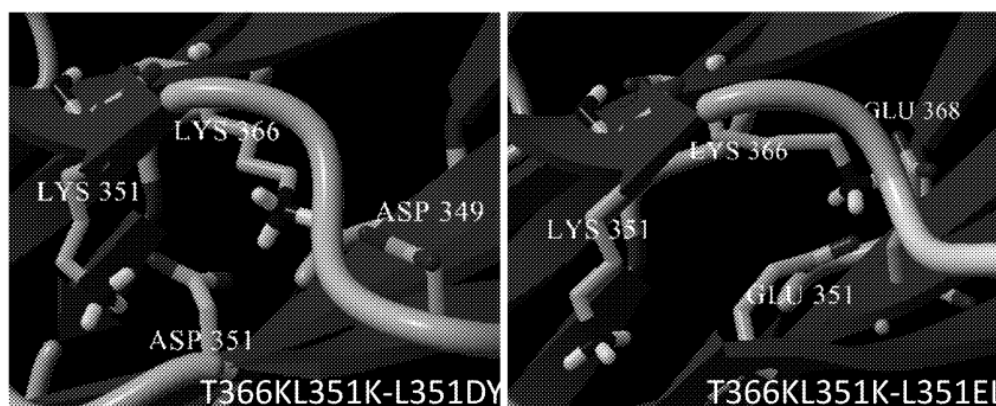


Fig. 15

bridges are formed: one between the interacting, substituted residues K351 and D351' and one between the interacting, substituted residues K366 and D349'. In the latter (right panel) two salt bridges are formed: both between residue K366 of one chain and residues E368' and E351' of the other chain. The K351 residue of the first chain is not in contact with, and does not interact with, the other residues of the other chain. This illustrates the difference between "interacting" residues (*e.g.*, the two salt bridges in the left panel), and a non-interacting residue (K351 in the right panel); it also illustrates the structural nature of the interactions that produce a heterodimeric antibody.

52. A POSA would have understood that for two different heavy chains to form a heterodimeric antibody by means of specified charge interaction at the CH3/CH3 interface in the Fc region, there must be a strong non-covalent interaction such as a salt bridge or hydrogen bonding between the substituted amino acids. *See* June 28, 2025 Declaration (EX2008) at ¶ 25. These bonds are difficult to break once formed and would require, for example, high temperatures to dissociate the heterodimer. This is the teaching of the '286 Patent—and the requirement of its claims—that such neutral to charged substitutions form a new interaction at the CH3/CH3 interface, which interaction produces a heterodimeric antibody by creating a structural link such as a new salt bridge and/or hydrogen bonding.

53. The claims refer specifically to the interaction created by the substituted amino acids, rather than an interaction created by other amino acids or a general interaction of the interface of the two CH3 domains as a whole: for example, claim 1 recites that “wherein the at least one positively charged amino acid residue substituted in the CH3 domain of said 1<sup>st</sup> antibody heavy chain ***interacts*** with the at least one negatively charged amino acid residue substituted in the CH3 domain of said 2<sup>nd</sup> antibody heavy chain in the interface between said 1<sup>st</sup> and 2<sup>nd</sup> antibody heavy chains ***to produce a heterodimeric antibody.***”

54. A POSA would also have understood that this claim term does not include substitutions to charged residues that either do not interact at all or interact to disrupt heterodimerization. For example, a change of a neutral to positive residue in one CH3 domain and a neutral to negative residue in another could be distal to each other in the CH3-CH3 interface and not interact at all. In another example, a change of a neutral to positive residue in one CH3 domain and neutral to negative residue in the other could disrupt the hydrophobic core of the interface and cause secondary, consequential conformational changes such that the CH3 domains would repel each other. This repulsion might not be enough to prevent heterodimerization caused by other residues in the CH3-CH3 interface, but any repulsion is clearly outside the claim requirements that the residues “interact . . . to produce a heterodimeric antibody.”

**iii. Prosecution History**

55. I understand that, in an April 10, 2015 non-final Office Action, the USPTO rejected certain claims of the patent application that became the '286 Patent based on, among other references, Kannan *et al.* (US 2010/0286374). The USPTO stated that Kannan disclosed “one or more residues that make up the CH3-CH3 interface can be replaced with a charged amino acid such that the interaction between homodimers becomes electrostatically unfavorable.” See '286 Patent File History (EX1008) pp. 218-220. In response to the office action, in an October 13, 2015 Amendment, Patent Owner requested reconsideration and withdrawal of the rejection, but amended the language of pending claim 1 to add the “interacts...to produce a heterodimeric antibody” language. See '286 Patent File History (EX1008) at pp. 240 and 245-246.

56. Patent Owner expressly required that “said 1<sup>st</sup> antibody heavy chain and said 2<sup>nd</sup> antibody heavy chain, wherein the at least one positively charged amino acid residue substituted in the CH3 domain of said 1<sup>st</sup> antibody heavy chain ***interacts*** with the at least one negatively charged amino acid residue substituted in the CH3 domain of said 2<sup>nd</sup> antibody heavy chain in the interface between said 1<sup>st</sup> and 2<sup>nd</sup> antibody heavy chains ***to produce a heterodimeric antibody.***”

57. In adding this language, the Patent Owner required that the interactions between the substituted amino acid residues be of a particular type – the type that produces a heterodimeric antibody. The required type of interaction is structural—it creates the salt bridge and/or hydrogen bonding that connects different heavy chains to produce a heterodimeric antibody.

58. The prosecution history of the '286 Patent thus uses the term “wherein the at least one positively charged amino acid residue substituted in the CH3 domain of said 1<sup>st</sup> antibody heavy chain interacts with the at least one negatively charged amino acid residue substituted in the CH3 domain of said 2<sup>nd</sup> antibody heavy chain in the interface between said 1<sup>st</sup> and 2<sup>nd</sup> antibody heavy chains to produce a heterodimeric antibody” in accordance with its ordinary and customary meaning.

## **VII. ANTICIPATION ANALYSIS**

59. I understand from counsel that for an invention to be “anticipated” a prior art reference must disclose the elements of the claim within the four corners of the document, and it must disclose those elements arranged as they are arranged in the Challenged Claims. I also understand that it is not permissible, as Dr. Presta did, to pick and choose different pieces of information from a prior art reference and rearrange them in an anticipation analysis.

60. In my opinion, neither Lazar nor Cabrera discloses the elements of any of the Challenged Claims arranged as they are arranged in the claims.

**A. Lazar Does Not Anticipate The Challenged Claims**

61. Independent claim 1 of the '286 Patent is directed to the production of a heterodimeric antibody with a first antibody *heavy chain* with 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 a second antibody *heavy chain to produce a heterodimeric antibody*.

62. Lazar does not disclose **any** example or embodiment of a heterodimeric antibody with two heavy chains, as that term is understood by a POSA, with neutral to charged substitutions. The only disclosure of neutral to charged substitutions in Lazar is in Example 2. But Example 2 is limited to discussing a construct that does not have even one heavy chain, much less two. In his analysis, Dr. Presta resorts to picking and choosing different disclosures of substitutions in an “empty format” construct with no heavy chains, and he only makes a separate general reference to IgG antibodies. Such picking and choosing is not permitted, and it is also contradicted by the Lazar reference itself.

63. Dr. Presta points to the variants reported in Tables 1-2 of Example 2 of Lazar. See Presta Declaration (EX1002), at ¶ 115. But, as I discussed in my June 28, 2025 Declaration, Tables 1-2 of Lazar only show substitutions tested in a construct that Lazar refers to as the “scFv-Fc/empty-Fc format.” See June 28, 2025 Declaration (EX2008) at ¶ 51-53. The scFv-Fc/empty-Fc format **does not include any heavy chain** as that term is understood by a POSA (*i.e.*, a polypeptide chain from the N-terminal residue in the variable region (VH) to the C-terminal residue in the final constant region (CH), including at least three constant regions (CH) and the hinge region).

64. I understand that Dr. Presta did not perform any claim construction analysis and relied instead on his personal view of what “heavy chain” means. I further understand that Dr. Presta opined that “heavy chain” is context dependent. See Presta Tr. at 30:14-38:25. I disagree. There is no context in which a POSA would ever view the Lazar empty-Fc construct as a “heavy chain,” including because it lacks a variable region. Similarly, there is no context in which a POSA would ever view the Lazar scFv-Fc construct as a “heavy chain,” including because it lacks the CH1 domain.

65. As Fig. 1 from Lazar below shows, the scFv-Fc polypeptide chain of Lazar’s empty format has a sequence of VH-linker-V<sub>K</sub>-Hinge-CH2-CH3’. The attached scFv was derived from a murine anti-CD3 antibody OKT3. See Lazar

(EX1004) at ¶ 239; *see also* Dr. Presta Tr. at 92:20-23. The other polypeptide chain of Lazar's format, the empty-Fc chain, has a sequence of Hinge-CH2-CH3''.

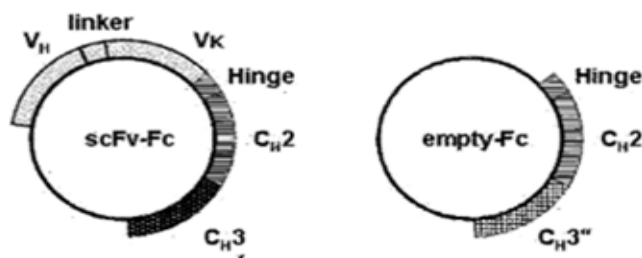


Figure 1

66. The scFv-Fc polypeptide chain of Lazar lacks a CH1 domain and, therefore, is not a “heavy chain” as understood by a POSA and as required by the claims. *See* Lazar (EX1004) at ¶ 238 and Figure 1. The empty-Fc polypeptide chain of Lazar lacks a VH domain and a CH1 domain and, therefore, is not a “heavy chain” as understood by a POSA and as required by the claims. Given these deficiencies, neither half of the Lazar construct is a “heavy chain” as understood by a POSA and required by the claims.

67. The inventors of Lazar understood this construct not to contain a heavy chain, eschewing use of that term to describe either half of the construct and instead using the term “immunoglobulin polypeptides” to describe the scFv-Fc/empty-Fc format. *See* Lazar (EX1004) at ¶ 238 (“DNA constructs were designed encoding two

different immunoglobulin polypeptides: (i) scFv-Fc (VH-linker-V $\kappa$ -Hinge-CH2-CH3') and (ii) empty-Fc (Hinge-CH2-CH3'')). As noted above, the inventors of the '286 Patent amended the claims during prosecution away from the more general term "polypeptide" to specifically recite "heavy chains." Dr. Presta ignores the proper construction of "heavy chain," including the ordinary and customary meaning, and also ignores the other claims of the '286 Patent and prosecution history when he mistakenly calls the "immunoglobulin polypeptides" of Lazar "heavy chains." They are not.

68. As discussed above, Lazar's use of the term "immunoglobulin polypeptides" is notable especially in light of Lazar's use of the term "heavy chains" elsewhere in the reference. Lazar states "[e]ach of the light and heavy chains are made up of two distinct regions, referred to as the variable and constant regions." See Lazar (EX1004) at ¶ 80.

69. Given the above, it is clear that Lazar's scFv-Fc/empty-Fc format does not meet the "heavy chains" limitation of the claims of the '286 Patent as properly construed. Indeed, this understanding explains why Lazar did not once refer to such an scFv-Fc/empty-Fc format construct as having a heavy chain.

70. Dr. Presta admitted during his cross-examination that only the Figure 1 constructs were used to screen Fc binding in Lazar, that these variants were not a combining of a human IgG heavy chain with another human IgG heavy chain, and that

“the system they [Lazar] used was designed to make analysis of their variant as easy as possible.” See Presta Tr. at 92:2-93:14. All of these admissions support my opinion that Lazar does not anticipate any of the Challenged Claims.

71. In its Institution Decision, the Board stated that Lazar “discloses modifying human IgG1 antibodies to favor heterodimerization.” See Institution Decision, at page 32. I respectfully disagree. Lazar merely discloses a wild-type IgG antibody without any substitutions as a reference illustration in his Figure 8. See Lazar (EX1004) at ¶ 16 (“A native IgG1 antibody is included for reference.”). No substitutions were tested in such a molecule. Furthermore, no neutral to charged substitutions were made in Lazar’s alternative bispecific moieties (*i.e.*, mAb-Fv, mAb-Fab, Fab-Fv, and Fab-Fab). As discussed in my June 28, 2025 Declaration, the only modifications that were made in the alternative bispecific moieties were neutral to neutral modifications (*i.e.*, S364H/F405A in one chain and Y349T/T394F in the other chain, as shown in Lazar, Tables 3 – 5). See June 28, 2025 Declaration (EX2008) at ¶70. Accordingly, Lazar does not disclose any “traditional antibodies,” or even alternative antibody-like bispecific moieties, with neutral to charged substitutions. Such substitutions are only used in Lazar in its Figure 1 constructs, which constructs lack the required heavy chains.

72. For the reasons discussed above, and in my June 28, 2025 declaration, it is my opinion that Lazar fails to disclose at least the required “heavy chain” elements of the independent claims of the ’286 Patent. Therefore, Lazar also fails to disclose the required elements of the dependent claims. As a result, Lazar does not anticipate any of the Challenged Claims.

**B. Cabrera Does Not Anticipate The Challenged Claims**

73. Cabrera does not anticipate because it does not disclose the elements of the claims. For example, Cabrera does not disclose *any* example or embodiment of a heterodimeric antibody with a first antibody heavy chain with 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 a second antibody heavy chain *to produce a heterodimeric antibody*.

74. Cabrera includes over 2900 variants that were created through an iterative computational modelling process. See Cabrera (EX1005) at Tables 1 and 6-7. Cabrera reports results of modelling and molecular dynamics (MD) simulation analyses in Figures 1-4, 6-7, 9, 11, 13, 16, and 29-34 on the 2900 variants. However, Cabrera does not disclose neutral to positive and neutral to negative substituted amino acids that interact with each other to produce Fc heterodimerization or that interact

with each other to produce a heterodimeric antibody. Instead, the data in Cabrera demonstrate to a POSA that substituting neutral to charged residues at the CH3 domain interface in the context of a full antibody (IgG1) format achieves the opposite result.

75. For example, AZ33 and AZ34 in Cabrera have the same residue substitutions (*i.e.*, L351Y/F405A/Y407V and T366I/K392M/T394W) except that AZ34 also has a pair of neutral to charged substitutions (*i.e.*, S400E/N390R).

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 | - | - | - |

76. Figure 26 of Cabrera shows that AZ33 and AZ34 both have the same heterodimer purity of greater than 95%. Indeed, Dr. Presta agreed during his cross-examination that heterodimer purity for both AZ34 with the additional claimed substitutions, and AZ33 without the additional claimed substitutions, were both greater than 95%. See Presta Tr. at 125:23-126:12. This is a first indication that the pair of neutral to charged substitutions does not promote Fc dimerization or produce a heterodimeric antibody.

77. Moreover, Tables 3 and 4 of Cabrera explicitly show that the melting temperature for AZ33 (*i.e.*, 74 °C) is higher than for AZ34 (*i.e.*, 73.5 °C), which, as noted above, is identical except for the introduction of a pair of neutral to charged substitutions (*i.e.*, S400E and N390R) in AZ34. This means that the interaction between the two different heavy chains in Cabrera's IgG1 antibody is actually weakened after substituting a pair of neutral residues (S400 and N390) with charged residues (E400 and R390). See Cabrera (EX1005) at Tables 1 and 3 - 4. The explanation for why this happens would be clear to a POSA from the published literature. Several crystal structures of human IgG-Fc have been determined, and many were known in April 2012, such as that reported by Krapp *et al.*, J. Mol. Biol., 325:979, 2003 (PDB code 1h3v) (EX2023). These structures all show that in the wild-type CH3 domain interactions, S400 and N390 interact with each other at the edge of the CH3 domain interface and form a strong hydrogen bond (with ideal stereochemistry) between the sidechains of these two residues (O $\gamma$  atom of S400 sidechain to the N $\delta$ 2 atom of the N390 sidechain). This hydrogen bond *cannot* form between the sidechains of the substituted E400 and R390 residues because the requisite atoms are no longer present. But even if a POSA did not immediately perceive the reason why, a POSA would know that an added pair of substitutions that does not increase heterodimeric

purity and decreases thermal stability is not a pair that “interacts . . . to produce a heterodimeric antibody” as required by the claims.

**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 |
|------------------|-------|---------|-------|---------|-------|---------|-------|
| <b>Wild-Type</b> | 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    |

78. In addition to not promoting Fc dimerization or producing a heterodimeric antibody, the added charged residues in AZ34 do not even interact. As a POSA would know from the published literature, E400 and R390 are fully exposed to water. In the IgG-Fc crystal structures, such as that reported by Krapp *et al.* (EX2023) the alpha-carbon atoms of the main-chain to which the side-chains of residues 400 and 390 are attached, are close to each other and at the very edge of the CH3 domains. The large glutamic acid (E400) and arginine (R390) sidechains will

necessarily be fully exposed to water and their respective negative and positive charges solvated and neutralised by the surrounding water molecules. Entropic considerations will thus dictate that these two residues will not interact with each other to form a stable salt bridge but will independently adopt flexible conformations in solution each fully solvated by water molecules. In contrast, the smaller, and neutral, wild-type serine (S400) and asparagine (N390) sidechains are not fully exposed to water and satisfy their hydrogen bonding potential by forming the inter-residue (and inter-domain) hydrogen bond detailed above.

79. In its Institution Decision, the Board discounted comparison of the  $T_m$  values for AZ33 (*i.e.*, 74 °C) and AZ34 (*i.e.*, 73.5 °C) because they are both higher than the arbitrary threshold  $T_m$  of 70 °C set by Cabrera. As a preliminary matter, there is no significance to this threshold value, and in any event the melting temperature for wild type IgG is 81 °C. I respectfully submit that the comparison of  $T_m$  values for AZ33 and AZ34 is directly relevant to understanding whether or not the S400E and N390R substitutions interact to produce a heterodimeric antibody as required by the claims. Here, the clear evidence of Cabrera demonstrates that these substitutions are destabilizing as a result of the loss of the hydrogen bond between the residues at the interface, which loss is inevitable because the substituted side chains do not contain the requisite atoms, and which loss is not compensated by any salt bridge formation or

other interaction between E400 and R390 as explained above. This is reflected in the decreased T<sub>m</sub> of AZ34.

80. Respectfully, I submit that this is where the Board's institution decision appears to misapprehend the issue. To meet the "interacts . . . to produce a heterodimeric antibody" claim requirement, it is not enough to say that there is a minimum level of interaction at the CH3-CH3 interface as a whole. The question is whether Cabrera discloses that the specific substitutions of neutral to positive and neutral to negative residues interact at the CH3 interface to produce the heterodimeric antibody (by creating a salt bridge or hydrogen bonds or otherwise). Here, the T<sub>m</sub> data in Cabrera demonstrates the exact opposite.

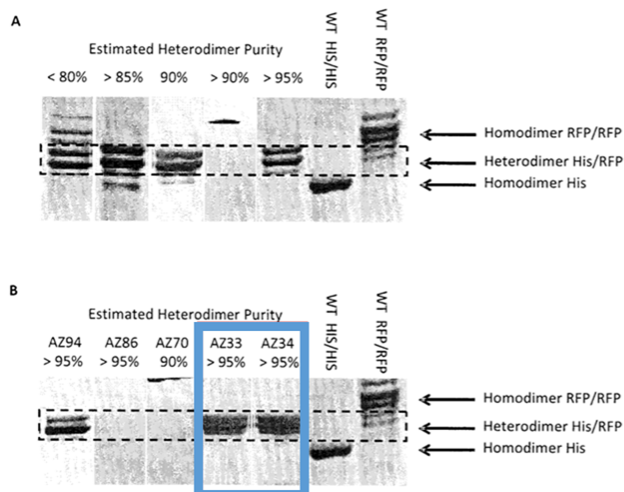
81. Stated simply, if these additional substitutions interacted at the interface to produce a heterodimeric antibody, the melting temperature and/or the yield of heterodimers would increase. Neither occurs, and a POSA would understand that these S400E and N390R substitutions are not interacting at the interface to produce a heterodimeric antibody, but instead, are thwarting the production of a heterodimeric antibody. Any interaction of these residues does not produce a heterodimeric antibody as required by the claims and, in fact, thwarts the production of such an antibody, as reflected by the lower melting temperature for AZ34 and the known loss of wild-type residue hydrogen bonding, with no compensatory gain.

82. As the Cabrera data confirm: (1) residues that interact in the wild-type antibody (S400 and N390) do not interact residues after substitution; and (2) introducing neutral to charged substitutions at the CH3/CH3 interface in an antibody decreases heterodimerization and stability.

83. With reference to the data shown in Figure 26 of Cabrera, there is no significant, observable difference in the level of heterodimer purity between AZ33 and AZ34. Dr. Presta admitted that AZ33 forms a heterodimer without the additional substitutions in AZ34 (*i.e.*, S400E/N390R) and forms that heterodimer at above 95% purity as shown in Figure 26 of Cabrera. *See* Presta Tr. at 123:11-126:12.

84. Tables 3-4 of Cabrera, however, show decreased stability after introducing the S400E/N390R substitutions, in the more sensitive melting temperature assay.

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



85. In summary, based on the heterodimer purity and  $T_m$  data disclosed in Cabrera, a POSA would understand that neutral to charged substitutions in Cabrera did not produce, and actually thwarted production of, a heterodimeric antibody.

86. For the reasons discussed above, and in my June 28, 2025 declaration, it is my opinion that Cabrera fails to disclose at least the “interacts ... to produce a heterodimeric antibody” element of the independent claims of the ’286 Patent. Therefore, Cabrera also fails to disclose the required elements of the dependent claims. As a result, Cabrera does not anticipate any of the Challenged Claims.

### VIII. OBVIOUSNESS ANALYSIS

87. I understand from counsel that a patented invention may be invalidated as “obvious” to a POSA at the time of the invention based on prior art. I also

understand that an obviousness analysis involves consideration of: (1) the scope and content of the prior art; (2) differences between the prior art and the patented invention; (3) the elements present if prior art references are combined; and (4) a POSA's motivation to combine prior art with a reasonable expectation of success. My analysis of these factors is provided below.

88. I further understand from counsel that I should consider factors that are frequently referred to as "secondary considerations of non-obviousness." I understand from counsel that these factors can include, when present: teaching away, skepticism, failure of others, and unexpected results. I also assess these factors below.

89. In my opinion, the inventions of the '286 Patent are not obvious based on (1) Lazar in view of Arathoon or (2) Lazar in view of Arathoon and Cabrera. In my opinion, Dr. Presta uses impermissible hindsight to pick and choose the elements of the invention of the '286 Patent from disparate, inapplicable prior art without scientific rigor and basis.

#### **A. Scope And Content Of The Prior Art**

##### **i. Lazar**

90. As discussed in my June 28, 2025 Declaration, the experiments in Lazar were directed to finding alternative bispecific immunoglobulin structures that were

better than the traditional “full length antibody-like formats.” See Lazar (EX1004) at

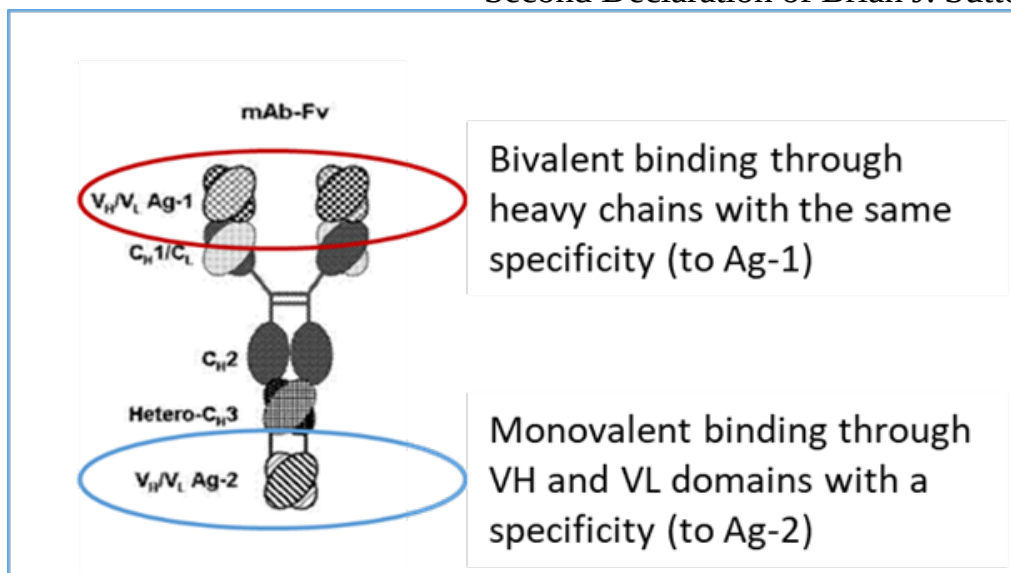
¶ 007; See also June 28, 2025 Declaration (EX2008) at ¶¶65-68.

91. Lazar specifically states that:

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.

To avoid the undesired non-specific activation and toxicity of the traditional “full length antibody-like formats,” Lazar created alternative bispecific moieties (*i.e.*, mAb-Fv, mAb-Fab, Fab-Fv, and Fab-Fab) **that did not need CH3 heterodimerization** because Lazar added an additional binding site (*e.g.*, Fv or Fab) at the C termini of wild-type IgG to provide the simultaneous bivalent and monovalent co-engagement of distinct target antigens. See Lazar (EX1004) at ¶ 46.

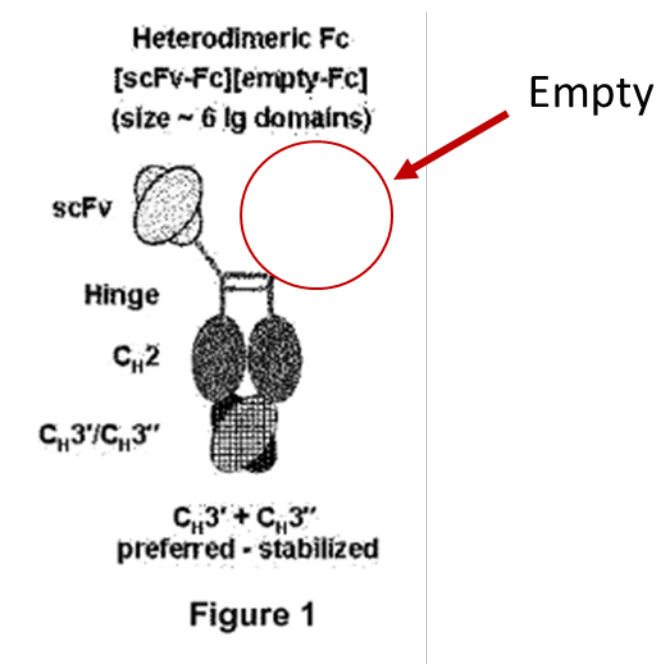


92. I wish to stress that in Lazar, the scFv-Fc/empty-Fc format was used for screening all of the reported CH3 substitutions for heterodimerization. Only one variant, which does not have the neutral to positive charge and neutral to negative charge substitutions required by the claims (*i.e.*, Y349T/T394F and S364H/F405A), was tested in the alternative bispecific constructs (*i.e.*, mAb-Fv, mAb-Fab, Fab-Fv, and Fab-Fab). **No** CH3 domain substitutions were tested in traditional “full length antibody-like formats” and certainly not in an IgG or IgG1 antibody. Furthermore, Lazar does not mention the word “charged” or say that charges are a relevant consideration.

93. 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 region or CH1 domain to which a common light chain can attach, and thus Arathoon’s common light chain

disclosure cannot be “provided to pair with each of the variable heavy chains.” See

Arathoon (EX1006) at p. 6, lines 24-26.



94. As discussed above, Lazar’s alternative bispecific constructs (*i.e.*, mAb-Fv, mAb-Fab, Fab-Fv, and Fab-Fab) also do not include two different variable regions to which a common light chain can attach to enhance the production of the “desired heteromultimeric antibody”. As Lazar’s alternative bispecific constructs were designed specifically to provide “simultaneous bivalent and monovalent co-engagement of distinct target antigens,” a POSA would understand that Lazar’s alternative bispecific constructs with identical VH and CH1 do not need a common light chain to enhance the production of bispecific antibodies with two different heavy chains.

95. Notably, after the screening experiments, Lazar used only one variant (*i.e.*, Y349T/T394F and S364H/F405A) for the alternative bispecific moieties in the follow-up experiments. These substitutions are different from the neutral to charge substitutions required by the claims.

96. Moreover, according to Lazar's experiments, there was 100% heterodimerization for a charge swap variant (K370D/K392D/K409D and E356K/E357K/D399K), and much lower heterodimerization for variants with neutral to charge substitutions. *See* Lazar (EX1004), Figures 5-7. This heterodimerization purity was not subject to improvement.

## **ii. Cabrera**

97. 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.* Over 2900 variants were created through this iterative multistep-modification process. *See* Cabrera (EX1005) at Tables 1 and 6-7. Notably, among 2900 variants, Cabrera provides a list of variants with a purity over 90-95% (*e.g.*, AZ33 and AZ34; Cabrera Table 3 and Figure 26). A POSA would not combine disclosures of Cabrera with other references that provide similar or lower heterodimeric yields.

98. Furthermore, Cabrera discloses numerous variants with some 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.

### **iii. Arathoon**

99. Arathoon only discloses production of multi-specific antibodies using the known prior art techniques of knob-into-hole and disulphide bonds, plus the use of a common light chain. *See* Arathoon (EX1006) at Abstract. These known techniques are disclosed and discussed in the '286 Patent. 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 heterodimeric antibody." *See* Arathoon (EX1006) at p. 6, lines 24-26. As Dr. Presta admitted during his cross-examination, using a common light chain does not affect heterodimerization; it merely reduces the number of possible dimers. *See* Presta Tr. at 59:6-13). As Dr. Presta admitted, Arathoon does not discuss charge engineering. *See* Presta Tr. at 102:7-17. Dr. Presta stated: "We did not consider charges, reversal or otherwise, in this particular study." *See* Presta Tr. at 96:6-

7. There is no reason to combine Arathoon and their approach to creating bispecific antibodies with any charge engineering in Lazar or Cabrera.

**B. Differences Between The Prior Art And The Claimed Subject Matter**

**i. Lazar**

100. Lazar does not disclose a heterodimeric antibody with substitutions of neutral to positive and neutral to negative residues in the “heavy chains,” as that term is understood by a POSA. Lazar also points away from neutral to charged substitutions in heavy chains given that 100% heterodimeric purity is reached with a charge reversal strategy in the Lazar construct (*i.e.*, K370D/K392D/K409D and E356K/E357K/D399K). *See* Lazar (EX1004) Figures 6 & 7. Lazar further points away from the claims because it focuses on a different approach to creating a bispecific antibody that does not need, much less rely upon, changes to the CH3 domain of any heavy chains. *See* Lazar (EX1004) at ¶¶ 007 and 108.

**ii. Cabrera**

101. Cabrera does not disclose a heterodimeric antibody with substitutions of neutral to positive and neutral to negative residues in the heavy chains that “interacts . . . to produce a heterodimeric antibody.” Cabrera does not contain a single example that shows an interaction between residues substituted from neutral to positive and neutral to negative to produce a heterodimeric antibody. The heterodimer purity and

Tm data in Cabrera confirm that, contrary to Dr. Presta's assertions, the substitutions in AZ34 do not meet the "interacts . . . to produce a heterodimeric antibody" limitation found in every Challenged Claim.

### **iii. Arathoon**

102. Arathoon does not disclose a heterodimeric antibody with heavy chain substitutions of neutral to positive and neutral to negative residues that interact with each other to produce a heterodimeric antibody. The only substitutions in the variants disclosed in Arathoon are neutral to neutral or charge to neutral substitutions and Arathoon only suggests known methodologies such as knob-into-hole substitutions, disulphide bonds, and use of a common light chain. During his cross-examination, Dr. Presta, as a co-inventor of Arathoon, admitted that Arathoon does not disclose anything about charge engineering. *See Presta Tr. at 102:1-17.*

## **C. The Claimed Subject Matter Of The '286 Patent Would Not Have Been Obvious Over Lazar Alone Or In View Of Arathoon**

103. A POSA would not arrive at the inventions of the independent claims of the '286 Patent based on the disclosures of Lazar alone or in combination with Arathoon.

### **i. No Motivation To Combine Lazar And Arathoon To Reach The Claimed Subject Matter**

104. At the relevant time in 2012, it was well known to a POSA that substituting the neutral residues of the hydrophobic core of the CH3 region was not a sensible or promising approach because of the important role that these residues play in protein folding and stability.

105. In his 2012 publication, Dr. Gunasekaran Kannan stated that “[i]t has long been established that the hydrophobic core of protein domains plays an important role in protein folding and stability.” See Gunasekaran Paper (EX1012) at page 19740. Therefore, a POSA in 2012 knew of the important role in protein folding and stability of the neutral residues in the hydrophobic core and would avoid substituting the neutral residues of the hydrophobic region to improve heterodimerization. Instead, a POSA would be motivated to modify charged residues, not neutral hydrophobic residues, to improve heterodimerization. For example, the Gunasekaran Paper suggests electrostatic techniques that can retain the hydrophobic core integrity and stated that “exploiting charged residues as opposed to hydrophobic residues at the CH3 domain interface may have benefits in terms of retaining the generally favorable biophysical properties of the Fc.” See Gunasekaran Paper (EX1012) at page 19640. In 2012, a POSA would avoid modifying neutral residues and would employ the electrostatic techniques that the Gunasekaran Paper suggested.

106. Even Lazar acknowledged the warnings in the Gunasekaran Paper not to introduce neutral to charged substitutions in heavy chains by incorporating the entire Gunasekaran Paper by reference. *See* Lazar (EX1004) at ¶ 125.

107. A POSA would not modify the neutral residues in the CH3 domain's hydrophobic core in an effort to increase heterodimerization yields. Moreover, Lazar's data would not motivate a POSA to introduce neutral to charged substitutions to increase heterodimerization yields. Consistent with the teachings of the Gunasekaran Paper, the screening data of Lazar's scFv-Fc/empty-Fc format show unstable and lower yields of heterodimer formation with neutral to charged substitutions, relative to other substitutions that produce more stable and higher yields of heterodimer, and teaches away from the claimed neutral to charged substitutions.

108. If a POSA were to look at all the substitutions in Tables 1 and 2 of Lazar, all of which are made within a truncated scFv-Fc/empty-Fc format, a POSA would not be motivated to select the neutral to charged substitutions for further experimentation because the heterodimerization data (Figures 5 – 7) for those variants are poor in relation to other reported variants. Instead, a POSA would consider further experiments with the variants in Lazar that produced the best heterodimerization data.

109. The variants in Lazar that achieved the best heterodimerization results were not neutral to charged substitutions as claimed in the '286 Patent, but charged to

charged substitutions. Figures 6 and 7 report that certain substitutions in the Lazar construct achieved 100% heterodimerization yields. For example, Figures 6 and 7 of Lazar show charged to charged substitutions (*i.e.*, K370D/K392D/K409D and E356K/E357K/D399K) that provide 100% heterodimerization yields in repeated experiments.

Figure 6 (continued)

| Empty-Fc                      | scFv-Fc           | Empty<br>-M | Empty<br>-D | Hetero | scFv<br>-D | scFv<br>-M |
|-------------------------------|-------------------|-------------|-------------|--------|------------|------------|
| S364E/F405A                   | Y349K/T394F       | 14%         | 12%         | 71%    | 2%         | 0%         |
| S364E/F405A                   | Y349K/T394F       | 21%         | 28%         | 51%    | 0%         | 0%         |
| S364E/F405S                   | Y349K/T394Y       | 11%         | 19%         | 65%    | 5%         | 0%         |
| S364E/K370C                   | Y349K/S364C       | 27%         | 37%         | 36%    | 0%         | 0%         |
| S364E/T394F                   | Y349K/F405A       | 35%         | 39%         | 26%    | 0%         | 0%         |
| S364E/T394F                   | Y349K/F405A       | 21%         | 22%         | 57%    | 0%         | 0%         |
| S364E/T411E                   | L368K/D401K       | 5%          | 55%         | 40%    | 0%         | 0%         |
| S364E/T411E                   | Y349K/D401K       | 4%          | 47%         | 49%    | 0%         | 0%         |
| S364E/T411E                   | Y349K/D401K       | 0%          | 31%         | 68%    | 1%         | 0%         |
| S364F/D401K                   | K370G/T411E       | 0%          | 6%          | 46%    | 48%        | 0%         |
| S364H/D401K                   | Y349T/T411E       | 0%          | 13%         | 77%    | 10%        | 0%         |
| S364H/D401K                   | Y349T/T411E       | 0%          | 7%          | 79%    | 14%        | 0%         |
| S364H/D401K                   | Y349T/T411E       | 5%          | 24%         | 66%    | 4%         | 0%         |
| S364H/F405A                   | Y349T/T394F       | 32%         | 45%         | 23%    | 0%         | 0%         |
| S364H/F405A                   | Y349T/T394F       | 5%          | 9%          | 81%    | 5%         | 0%         |
| S364H/F405S                   | Y349T/T394Y       | 35%         | 48%         | 17%    | 0%         | 0%         |
| S364H/K370G                   | Y349T/S364F       | 4%          | 84%         | 12%    | 0%         | 0%         |
| S364H/T394F                   | Y349T/F405A       | 4%          | 12%         | 78%    | 6%         | 0%         |
| S364Y/K370V                   | S364T/K370G       | 5%          | 35%         | 38%    | 22%        | 0%         |
| T366S/L368A/Y407V             | T366W             | 14%         | 17%         | 68%    | 1%         | 0%         |
| T366S/L368A/Y407V             | T366W             | 15%         | 18%         | 67%    | 0%         | 0%         |
| Y349C/S364E                   | Y349K/S354C       | 9%          | 22%         | 68%    | 1%         | 0%         |
| Y349I/S364F                   | Y349E/S364D       | 0%          | 29%         | 48%    | 23%        | 0%         |
| Y349W/S364H                   | Y349T/S364G       | 0%          | 12%         | 45%    | 43%        | 0%         |
| Y349W/S364H                   | Y349T/S364G       | 12%         | 39%         | 40%    | 9%         | 0%         |
| Y349W/S364H                   | Y349T/S364G       | 9%          | 36%         | 45%    | 10%        | 0%         |
| Y349W/S364H                   | Y349T/S364G       | 18%         | 50%         | 31%    | 5%         | 0%         |
| K370D/K392D/K409D             | E356K/E357K/D399K | 0%          | 0%          | 100%   | 0%         | 0%         |
| K370D/K392D/K409D             | E356K/E357K/D399K | 0%          | 0%          | 100%   | 0%         | 0%         |
| L351E/S364D/T411E             | Y349K/L351K/D401K | 5%          | 46%         | 49%    | 0%         | 0%         |
| L351E/S364H/F405A             | Y349T/L351K/T394F | 18%         | 21%         | 55%    | 6%         | 0%         |
| L351K/S364H/D401K             | Y349T/L351E/T411E | 11%         | 11%         | 76%    | 2%         | 0%         |
| L351K/S364H/F405A             | Y349T/L351E/T394F | 28%         | 25%         | 46%    | 1%         | 0%         |
| S364E/T411E/F405A             | Y349K/T394F/D401K | 29%         | 14%         | 57%    | 0%         | 0%         |
| S364H/D401K/F405A             | Y349T/T394F/T411E | 13%         | 10%         | 73%    | 4%         | 0%         |
| S364H/F405A/T411E             | Y349T/T394F/D401K | 24%         | 15%         | 60%    | 1%         | 0%         |
| S364H/T394F/D401K             | Y349T/F405A/T411E | 3%          | 21%         | 61%    | 15%        | 0%         |
| T394S/P395V/P396T/V397E/F405S | T394F             | 7%          | 20%         | 72%    | 1%         | 0%         |

110. Despite its 100% yield in the repeated experiments, the K370D/K392D/K409D and E356K/E357K/D399K substitutions in the Lazar construct are not included in Tables 1 and 2 as a “preferred variant” or the “most preferred variant”. This is consistent with the fact that Lazar was seeking to create new alternative bispecific antibody formats for which “heterodimeric” Fc variants are not a necessity.

111. The substitutions listed in Tables 1 and 2 of Lazar for variants with neutral to charged substitutions showed much lower heterodimerization yields. For example, as shown in Figure 6 of Lazar, S364E and Y349K substitutions were tested at least six times using the scFv-Fc/empty-Fc format. However, all six experiments produced relatively lower yields of heterodimer, ranging from 0% to 75%.

Figure 6

| Empty-Fc | scFv-Fc | Empty<br>-M | Empty<br>-D | Hetero | scFv<br>-D | scFv<br>-M |
|----------|---------|-------------|-------------|--------|------------|------------|
| F405A    | T394F   | 3%          | 26%         | 66%    | 5%         | 0%         |
| F405A    | T394W   | 3%          | 31%         | 64%    | 2%         | 0%         |
| F405A    | T394W   | 0%          | 5%          | 59%    | 36%        | 0%         |
| F405S    | T394Y   | 0%          | 6%          | 44%    | 50%        | 0%         |
| K370C    | S364C   | 0%          | 40%         | 0%     | 60%        | 0%         |
| K392E    | D399K   | 0%          | 10%         | 73%    | 18%        | 0%         |
| K409D    | D399K   | 0%          | 9%          | 81%    | 10%        | 0%         |
| K409D    | D399K   | 3%          | 13%         | 78%    | 7%         | 0%         |
| K409D    | D399K   | 2%          | 8%          | 77%    | 13%        | 0%         |
| K409D    | D399K   | 4%          | 24%         | 71%    | 1%         | 0%         |
| K409D    | D399K   | 0%          | 6%          | 52%    | 42%        | 0%         |
| K409D    | L368K   | 0%          | 4%          | 73%    | 23%        | 0%         |
| K409E    | D399K   | 0%          | 11%         | 81%    | 9%         | 0%         |
| K409E    | L368K   | 4%          | 24%         | 70%    | 1%         | 0%         |
| K439D    | E356K   | 0%          | 17%         | 69%    | 14%        | 0%         |
| S364D    | K370R   | 0%          | 24%         | 38%    | 38%        | 0%         |
| S364D    | L368K   | 6%          | 32%         | 51%    | 12%        | 0%         |
| S364D    | Y349K   | 0%          | 6%          | 73%    | 21%        | 0%         |
| S364E    | L368K   | 3%          | 19%         | 64%    | 14%        | 0%         |
| S364F    | L368S   | 4%          | 37%         | 54%    | 5%         | 0%         |
| S364E    | Y349K   | 0%          | 7%          | 75%    | 18%        | 0%         |
| S364E    | Y349K   | 0%          | 0%          | 0%     | 91%        | 9%         |
| S364E    | Y349K   | 0%          | 0%          | 63%    | 30%        | 7%         |
| S364E    | Y349K   | 5%          | 27%         | 68%    | 1%         | 0%         |
| S364E    | Y349K   | 7%          | 75%         | 18%    | 0%         | 0%         |
| S364E    | Y349K   | 7%          | 93%         | 0%     | 0%         | 0%         |
| S364E    | Y349T   | 4%          | 27%         | 56%    | 13%        | 0%         |
| S364E    | Y349T   | 6%          | 41%         | 47%    | 6%         | 0%         |
| S364E    | Y349T   | 7%          | 57%         | 35%    | 1%         | 0%         |
| S364F    | K370G   | 0%          | 22%         | 65%    | 13%        | 0%         |
| S364F    | Y349A   | 0%          | 13%         | 59%    | 29%        | 0%         |
| S364G    | Y349W   | 0%          | 26%         | 52%    | 23%        | 0%         |
| S364H    | K370S   | 0%          | 0%          | 35%    | 65%        | 0%         |
| S364H    | K370S   | 4%          | 30%         | 58%    | 8%         | 0%         |
| S364H    | K370S   | 5%          | 44%         | 49%    | 3%         | 0%         |
| S364H    | K370S   | 5%          | 42%         | 50%    | 4%         | 0%         |
| S364H    | L368S   | 3%          | 19%         | 61%    | 17%        | 0%         |
| S364H    | L368S   | 4%          | 35%         | 55%    | 6%         | 0%         |
| S364H    | L368S   | 4%          | 28%         | 59%    | 9%         | 0%         |
| S364H    | Y349K   | 2%          | 9%          | 61%    | 29%        | 0%         |
| S364H    | Y349K   | 3%          | 16%         | 72%    | 9%         | 0%         |
| S364H    | Y349K   | 4%          | 25%         | 68%    | 3%         | 0%         |
| S364H    | Y349T   | 0%          | 0%          | 64%    | 36%        | 0%         |
| S364H    | Y349T   | 0%          | 0%          | 0%     | 94%        | 6%         |
| S364H    | Y349T   | 0%          | 0%          | 77%    | 9%         | 14%        |
| S364H    | Y349T   | 3%          | 19%         | 60%    | 19%        | 0%         |
| S364H    | Y349T   | 7%          | 60%         | 32%    | 1%         | 0%         |
| S364H    | Y349T   | 8%          | 92%         | 0%     | 0%         | 0%         |

112. Dr. Presta and the Board give much weight to Lazar including neutral to charged substitutions in Table 2 “Most preferred CH3 domain variants that favor Fc

heterodimerization” (*e.g.*, S364D and Y349K; and L351K and L351E). See Presta Declaration (EX1002), at ¶81. The name of Table 2, however, shows the limitation of its disclosure. It is discussing **Fc** heterodimerization, not heavy chain heterodimerization or antibody heterodimerization. Moreover, none of the cited substitutions provides a heterodimerization yield that compares favorably with that of the K370D/K392D/K409D and E356K/E357K/D399K substitutions, which are not themselves listed as a preferred or most preferred variant in Tables 1 and 2. S364D and Y349K substitutions, for example, yield only 73% heterodimer, and strangely, Lazar does not provide any data related to L351K and L351E substitutions (in Figures 5 – 7), even though this variant is listed as a “most preferred” variant in Table 2.

113. Accordingly, in my opinion, this designation of “most preferred CH3 domain variants that favor Fc heterodimerization” is not what a POSA would rely upon, and instead would be guided by the heterodimerization data in order to select substitutions. Moreover, what may have been “most preferred” for the Fc fragments for Lazar is not what a POSA would rely on for heavy chain dimerization. In any event, a POSA would view the data for the neutral to charged substitutions as sub-optimal, and would not be motivated to select neutral to charged substitutions for further experiments.

114. Lazar does not explain or provide any indication why neutral to charged substitutions would be “most preferred CH3 domain variants that favor Fc heterodimerization” of the finally selected substitutions, or why the substitutions with the highest heterodimerization yield and stability were not selected (*i.e.*, K370D/K392D/K409D and E356K/E357K/D399K) or otherwise called “most preferred.” Lazar’s Tables 1-2 and Figures 5-7 do not show or provide any results or trends favorable to neutral to charged substitutions. Petitioner, using impermissible hindsight, cherry-picked a few data points from the screening data of over 150 variants based on the disclosures of the ’286 Patent. Without such impermissible hindsight, a POSA would not select the neutral to charged substitutions, which showed lower heterodimerization yields, and lower stability.

115. Furthermore, Lazar clearly states that “[h]eterodimeric Fc variants are not a necessity” for the generation of Lazar’s alternative bispecific moieties (*i.e.*, mAb-Fv, mAb-Fab, Fab-Fv, and Fab-Fab). *See* Lazar (EX1004) at ¶ 108. A POSA would understand that Lazar’s alternative bispecific moieties (Figure 8) can be heterodimerized by virtue of the fact that one heavy chain has an extra VH domain (with or without a CH domain) attached to its C-terminus, while the other heavy chain has an extra VL domain (with or without a CL domain) attached to its C-terminus; the preferential association of these extra VH and VL domains (and not VH/VH or VL/VL)

not only ensures heterodimerization, but generates the second specificity of these alternative bispecific constructs for Ag2.

116. CH3 domain modifications, although indicated in Figure 8, are “not a necessity” (as noted above), and in any case were not tested in these alternative bispecific constructs. A POSA would not unnecessarily substitute the neutral residues in the hydrophobic core and interface region of the CH3 domains, which can affect protein folding, safety, immunogenicity, and functionality.

117. What is even more telling is that Lazar did not introduce any neutral to charged substitutions in any of the follow-up experiments with these alternative bispecific constructs (Lazar, Tables 3 – 5). Lazar used only one substitution (*i.e.*, Y349T/T394F and S364H/F405A) for the alternative bispecific moieties (*i.e.*, mAb-Fv, mAb-Fab, Fab-Fv, and Fab-Fab) in the follow-up experiments. A POSA would reasonably assume that Lazar selected the best variant for the follow-up experiments. A POSA would not be motivated to select the substitutions that were not used for the follow-up experiments without a clear reason, which Lazar fails to provide, especially when the data regarding such substitutions showed low heterodimeric purity relative to other variants.

118. Therefore, in my opinion, a POSA would not be motivated to introduce neutral to charged substitutions into the paired heavy chains of a heterodimeric

antibody based on the disclosures of Lazar. It is important to appreciate that Lazar never reported doing this experiment, and therefore offers no encouragement for others to do so. In addition, a POSA would have been aware of the data in Cabrera (discussed in detail above) showing that all neutral to charged residue substitutions for which data were presented (*i.e.*, the experimental  $T_m$  and SDS-PAGE data), did not “interact” and therefore did not promote Fc heterodimerization or produce a heterodimeric antibody.

**ii. No Reasonable Expectation Of Success**

119. A POSA would not have a reasonable expectation of success that substitutions in the scFv-Fc/empty-Fc format would have the same heterodimerization effects on antibodies or antibody-like alternative constructs. Substitutions tested in the scFv-Fc/empty-Fc format, which heterodimerize the two chains of an Fc fragment, each of which consists of only two CH domains, are likely to be less effective in bringing together the heavy chains of an antibody or antibody-like construct, which are at least twice as long (*i.e.*, twice the molecular weight), consisting of a VH domain and at least three CH domains. In addition, the heterodimerization of the Fc region may be structurally constrained in the presence of the full hinge region and the VH and CH1 domains of the heavy chains, and thus substitutions that are effective in bringing together the two chains of an Fc fragment will not necessarily be effective in the context of a whole antibody or antibody-like construct.

120. Moreover, dependent claim 7 of the '286 Patent requires that the method of claim 1 for producing less than 5% of contaminating homodimers. Claim 7 reads:

The method according to claim 1, wherein the presence of contaminating homodimers is less than 5%, preferably less than 2%, more preferably less than 1%, and most preferably contaminating homodimers are essentially absent.

121. A POSA would have no reasonable expectation of success to reach such a high yield of heterodimerization by making neutral to charged substitutions in the CH3 region based on the teachings of Lazar. Lazar's data generated from tests in the empty format show that Lazar's variants with neutral to charged substitutions could not achieve anywhere near less than 5% of contaminating homodimer yield. As shown in Figure 5-7 of Lazar, the highest heterodimer yield achieved by Lazar's variants with neutral to charged substitutions is only 84% (*i.e.*, L351K/S364H/D401K in one chain and Y349T/L351E/T411E in the other chain). Furthermore, as this variant includes six substitutions, including neutral to neutral substitution and charged to charged substitution, a POSA would not know whether neutral to charged substitutions indeed interact together to achieve the 84% heterodimerization. Accordingly, Lazar fails to provide a POSA with a reasonable expectation of achieving less than 5% of contaminating homodimer yield required by claim 7, because Lazar's data show that such a high heterodimeric yield was not achievable with any of Lazar's neutral to charged variants.

122. For all the reasons stated above, together with those in my June 28, 2025

Declaration, it is my opinion that a POSA in 2012 would not be motivated to make neutral to charged substitutions in the CH3 region with any reasonable expectation of success to produce a sufficient level of heterodimerization based on the teachings of Lazar.

123. Arathoon does not compensate the deficiencies in Lazar. Arathoon discloses information that would tell a POSA not to use substitutions of neutral to charged residues because the variants in Arathoon have only neutral to neutral or charged to neutral substitutions. See Arathoon (EX1006) at Tables 3-4 and p. 43. Table 4 of Arathoon (below) does however show that variants with neutral to neutral substitutions and/or charged to neutral substitutions (*e.g.*, v11 and v16) can result in 95% or higher heterodimer yield.

Table 4

Yields of Heterodimers from C<sub>H3</sub> 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               |

124. A POSA would not look to combine the teachings of Lazar with the teachings of Arathoon because Arathoon would not provide a POSA with any further information to achieve sufficient heterodimerization through substitutions in the CH3 region. Arathoon would not add any helpful information to the disclosures of Lazar regarding CH3 domain engineering to produce heterodimerization, because, as I explained in my June 28, 2025 Declaration, Arathoon only suggests known methodologies (*e.g.*, knob-into-hole substitutions and disulphide bonds) and use of a common light chain.

125. A POSA reading Lazar and Arathoon together would not see any reason to combine the disclosures of these two references. In fact, as discussed in my June 28, 2025 Declaration, 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.

126. Therefore, a POSA would not have any motivation to combine the disclosures of Lazar with the disclosures of Arathoon. And even using hindsight to combine the disclosures of these references, a combination of Lazar with Arathoon does not lead to the claimed invention. The teachings of Arathoon do not make up for the deficiencies in Lazar.

### **iii. Not All Elements Present**

127. A combination of all of the elements of Lazar and Arathoon does not lead to all of the elements of the claims of the '286 Patent. Lazar does not disclose antibodies with heavy chains as defined in the Specification of the '286 Patent and as required by the independent claims. Dr. Presta only cites Arathoon for use of a common light chain, which approach is incompatible with the formats used by Lazar.

128. For the reasons stated above, and in my June 28, 2025 Declaration, it is my opinion that the independent claims of the '286 Patent are not obvious based on the

teachings of Lazar alone or in combination with the teachings of Arathoon. For the same reasons, and additional reasons as set forth below, the dependent claims of the '286 Patent are not obvious based on the teachings of Lazar alone or in combination with the teachings of Arathoon.

**D. The Claimed Subject Matter Would Not Have Been Obvious Over Lazar Alone Or In View Of Arathoon And Cabrera**

129. A POSA would not arrive at the invention of the independent claims of the '286 Patent based on the disclosures of Lazar alone or in combination with Arathoon and Cabrera; furthermore, a POSA would not have been motivated to combine these references with any reasonable expectation of success. The teachings of Lazar would not have guided a POSA to the claimed inventions of the '286 Patent, and neither Arathoon nor Cabrera make up for the deficiencies of Lazar in this respect. Accordingly, the independent claims of the '286 Patent are not obvious.

130. A POSA would not arrive at the inventions of the independent claims of the '286 Patent based on the disclosures of Cabrera, alone or in combination with Lazar and Arathoon. Accordingly, a POSA would thus not arrive at the inventions of the dependent claims of the '286 Patent.

**i. No Motivation To Combine Lazar, Arathoon, And Cabrera To Reach The Claimed Subject Matter**

131. A POSA would not arrive at the claimed subject matter of the '286 Patent with a reasonable expectation of success based on Lazar alone. Additionally, a POSA would have no motivation to combine the teachings of Lazar with the teachings of Arathoon, and would not have arrived at the claimed subject matter of the '286 Patent. This deficiency is not compensated by the addition of Cabrera.

132. As of April 20, 2012, a POSA would not be motivated to arrive at the claimed subject matter based on Cabrera's disclosures because Cabrera's data (*e.g.*, melting temperature and MD simulation data) do not suggest the claimed neutral to charged substitutions in the CH3 domain of heavy chains. Dr. Presta again cherry-picked a few variants from the list of over 2900 variants using impermissible hindsight. As I explained above however, those cherry-picked variants (*e.g.*, AZ34) actually teach a POSA *not* to introduce the neutral to charged residues into an antibody to promote heterodimerization.

133. Also as discussed above, Cabrera fails to disclose any significant difference in heterodimer purity level between variants with the claimed substitution (*e.g.*, AZ34) and without the claimed substitution (*e.g.*, AZ33). Dr. Presta agreed during his cross-examination that the level of heterodimer purity, better than 95%, achieved for both, is something a POSA would have been happy with in 2012 and still happy with today. *See* Presta Tr. at 125:23-126:12. *See* Presta Tr. at 126:19-127:2.

134. Furthermore, Cabrera discloses another example (*i.e.*, AZ28 and AZ29 variants), which shows that a variant with a neutral to neutral substitution (S354N) has a higher melting temperature, and therefore greater stability, than a variant with a neutral to charged substitution (S354E).

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 | -     |

135. 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    |

136. Furthermore, 108 of the 132 variants listed in Table 1 (*i.e.* 82%) include substitutions 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, which will certainly have a destabilizing effect.

137. Furthermore, like Lazar, Cabrera also teaches away from the claimed subject matter by entirely incorporating the Gunasekaran Paper by reference, which expressly discourages disrupting the hydrophobic core and interface of the CH3 domain, which is exactly what would happen with the neutral to charged substitutions claimed in the '286 Patent. *See* Cabrera (EX1005) at page 129.

138. As of 2012, a POSA would consider the experimental data of Cabrera consistent with the teachings of the Gunasekaran Paper, given that the melting point data show that the stability decreased after incorporation of neutral to charged substitutions.

139. Based on the above, a POSA would have no reason to combine any of Dr. Presta's asserted references. The data provided in Cabrera, like that of the Gunasekaran Paper, teaches a POSA *not* to introduce neutral to charged substitutions into an antibody to promote Fc heterodimerization or produce a heterodimeric antibody.

140. Moreover, as discussed above, dependent claim 7 of the '286 Patent requires that the method of claim 1 for produces a heterodimeric antibody with a yield of at least 95%. Nothing in Lazar, Arathoon, or Cabrera gave a POSA any reason to combine these references to even try to reach that level of purity using neutral to charged residue substitutions.

## **ii. No Reasonable Expectation Of Success**

141. A POSA would have no reasonable expectation of success to reach such a high yield of heterodimerization by making neutral to charged residue substitutions in the CH3 region based on the teachings of Cabrera. Even if Cabrera states that certain variants, such as AZ33 and AZ34, can provide over 95% heterodimer purity, a POSA would know that this yield was not achieved by making the neutral to charged residue substitutions. As described in detail above, AZ33 and AZ34 together show that the additional neutral to charged residue substitutions *decrease* the stability of the heterodimers, and this is also the case for all the other examples of neutral to charged residue substitutions for which data are provided. Accordingly, Cabrera fails to provide a POSA with a reasonable expectation of achieving over 95% of heterodimerization yield by making substitutions from neutral to charged residues.

142. Further, a POSA would have no motivation to combine Cabrera and Lazar. As discussed in my June 28, 2025 Declaration, Cabrera and Lazar disclose incompatible formats, and there is nothing that would indicate to a POSA that Lazar's alternative bispecific formats would benefit from the introduction of heterodimerization technology.

143. A POSA would not look to combine the teachings of Cabrera or Lazar with the teachings of Arathoon because Arathoon would not provide a POSA with any further information to achieve sufficient heterodimerization through substitutions in

the CH3 region. For example, Arathoon would not add any helpful information to the disclosures Cabrera or Lazar regarding charged residue substitutions to produce heterodimerization, because, as I explained in my June 28, 2025 Declaration, Arathoon only suggests other methodologies (*e.g.*, knob-into-hole substitutions and disulphide bonds) and use of a common light chain.

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

### **iii. Not All Elements Present**

145. As discussed above, Lazar, Arathoon, and Cabrera fail to provide a motivation to combine them with a reasonable expectation of success. Furthermore, Lazar, Arathoon, and Cabrera do not disclose the key improvement claimed in the '286 Patent that the interaction and corresponding structural changes created by the neutral to charged substitutions produce a heterodimeric antibody.

146. A combination of all of the elements of Lazar, Arathoon, and Cabrera does not lead to all of the elements of the '286 Patent. A POSA would not arrive at the invention claimed in the '286 Patent because the combination fails to disclose, at

least, the feature of interaction between substituted residues to produce a heterodimeric antibody” recited in independent claim 1.

147. Discussion regarding interactions to produce 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.

148. Indeed, Dr. Presta does not identify any information in Lazar to support his opinions concerning any residue-to residue-interactions. Critically, it is the interaction of the substituted positive and negative residues that is required by 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.

149. As discussed above, Cabrera also fails to disclose or suggest that the substituted residues interact to produce a heterodimeric antibody as required by independent claim 1.

150. Arathoon does not provide any further information related to interaction between neutral to charged substitutions to produce a heterodimeric antibody because Arathoon does not disclose pairing any neutral to charged residue substitutions. Indeed, Arathoon was cited only for the disclosure of a common light chain, which is incompatible with the format used by Lazar.

151. For the reasons stated above, and in my June 28, 2025 Declaration, it is my opinion that the independent claims of the '286 Patent are not obvious based on the teachings of Lazar alone or in combination with the teachings of Arathoon and Cabrera. For the same reasons, and additional reasons discussed below, the dependent claims of the '286 Patent are not obvious based on the teachings of Lazar alone or in combination with the teachings of Arathoon and Cabrera.

#### **E. Secondary Considerations Of Non-Obviousness**

152. I have been instructed by counsel to consider some additional specific factors in providing my opinion on whether or not the inventions of the '286 Patent would have been obvious to a POSA. I understand these factors are usually called

“secondary considerations of non-obviousness.” These factors include, when present:

teaching away, skepticism, failure of others, and unexpected results, for example.

153. Teaching Away / Skepticism: The warning in the Gunasekaran Paper against substituting the neutral residues of the hydrophobic core clearly would teach POSAs away from the claimed invention of the ‘286 Patent. Moreover, as explained above, the data in Lazar showing a lower heterodimerization yield for neutral to charged residue substitutions compared with other substitutions would also have taught a POSA away from the claimed invention of the ‘286 Patent. The lower melting temperature data in Cabrera would have also taught a POSA not to consider neutral to charge substitutions because they did not necessarily interact and, where their effect could be identified, they were destabilizing. Moreover, Arathoon taught 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.

154. Unexpected results: Merus went against the Gunasekaran Paper’s warning and unexpectedly and surprisingly achieved heterodimerization by modifying neutral residues in the hydrophobic interface region of the CH3 domain to create stable, functional bispecific antibodies at an acceptable yield for manufacturability and human administration.

155. For example, the Specification of the ‘286 Patent states:

The approach of the present invention provides not only a method for efficiently steering the dimerization of CH3 domains ***but also has the advantage that at least one additional charge-charge interaction in the CH3 interface is created, in view of this additional charge-charge interaction on top of the existing charge-pairs in the CH3-CH3 interface, the dimers according to the invention are generally more stable*** as compared to the wild type dimers (the wild type dimer is defined as a bispecific IgG (AB) without CH3 engineering in contrast to its parental homodimers (AA or BB)).

See '286 Patent (EX1001), Col. 18, lines 10-20, emphasis added.

156. The Specification of the '286 Patent further discloses unexpected improvements of the interaction created by the claimed neutral to charged substitutions on heterodimeric yields by comparing heterodimeric yields of other technologies. For example, the '286 Patent states:

Moreover, it has surprisingly become possible to increase the proportion of one or more Ig-like molecules of interest in a mixture even further. As described herein before, methods known in the art for preferential production of a bispecific antibody typically involves the production of some undesired dimeric side products. For instance, the proportion of a bispecific antibody of interest using ***the knob-into-hole technology is at best 87%, whereas the electrostatic engineering approach wherein charged contact amino acids are substituted by amino acids of opposite charge, also results in proportions of up to 96%*** (see for instance Example 11). Quite surprisingly, the present inventors have succeeded in introducing mutations that further enhance the proportion of an Ig-like molecule of interest in a mixture. For instance, ***Example 17 discloses a method using mutations according to the present invention, wherein the proportion of a bispecific antibody of interest was raised to such extent that no dimeric by-product was detectable in the resulting mixture at***

*all.... Hence, with such mutations according, to the present invention, a bispecific Ig-like molecule can be produced in a single cell with a high proportion **with essentially no contaminating dimeric by-products being present, which is particularly suitable for the production of a pharmaceutical composition.***

See '286 Patent (EX1001), Col. 18, lines 20-48, emphasis added.

157. Lazar, Cabrera and Arathoon are all silent regarding any interaction created by neutral to charged substitutions. During his cross-examination Dr. Presta, a co-inventor of Arathoon, admitted that the prior art that he cited in his Declaration does not disclose creating a new charge-charge interaction. See Presta Tr. at 115:22-116:1.

158. In my opinion, each of these “secondary considerations” further supports my above opinion that the claimed inventions of the '286 Patent would not have been obvious to a POSA at the time of the invention.

#### **IX. THE DEPENDENT CLAIMS ARE NOT ANTICIPATED OR OBVIOUS OVER ASSERTED PRIOR ART**

159. Dependent claims 2, 7-24, 27-28, and 31-32 depend from independent claims, and therefore must include all of the elements of the independent claims and further claim additional elements. Dependent claims 2, 7-24, 27-28, and 31-32 are not anticipated by Lazar or Cabrera because neither of these references disclose all elements in the independent and dependent claims as arranged in the claims. The

dependent claims are not obvious over Lazar and Cabrera in combination with Arathoon because a POSA would not have been motivated to arrive at the additional elements claimed in the dependent claims and the elements of the independent claims from which these claims depend, based on Lazar, Carera and/or Arathoon.

**A. Dependent Claims 2, 27, and 31**

160. Dependent claims 2, 27, and 31 include all of the elements of the independent claims and further claim the additional limitation of a common light chain. Lazar alone or in combination with Cabrera and/or Arathoon does not disclose all of the elements of dependent claims 2, 27 and 31 as arranged in the claims. Moreover, a POSA would not have been motivated to combine Lazar, Cabrera, and/or Arathoon with any reasonable expectation of success.

161. Lazar's scFv-Fc/empty-Fc format is not compatible with the addition of a common light chain because Lazar's scFv-Fc/empty-Fc format does not have any variable region or CH1 domain to which a common light chain can attach. *See* Lazar (EX1004), Figure 1.

162. Lazar's alternative bispecific constructs (*i.e.*, mAb-Fv, mAb-Fab, Fab-Fv, and Fab-Fab) also do not include two different variable regions to which a common light chain can attach to enhance the production of the desired heteromultimeric antibody. Lazar created the alternative bispecific moieties (*i.e.*, mAb-Fv, mAb-Fab,

Fab-Fv, and Fab-Fab) by adding an additional binding site (*e.g.*, Fv or Fab) at the C termini of wild-type IgG heavy chains. See Lazar (EX1004) at ¶ 46. Accordingly, Lazar's alternative bispecific constructs already include the same light chains, and thus do not need to further introduce common light chains. Indeed, Lazar does not discuss a common light chain at all.

163. Cabrera does not disclose heterodimeric antibodies with Fc variants that can benefit from the use of common light chains. All of the antibodies with heterodimeric Fc variants that are disclosed in Cabrera are “bivalent ***monospecific***” antibodies, which have two identical variable regions (VH and VL). See Cabrera (EX1005), Examples 1-3. Such bivalent monospecific antibodies have two heavy chains that are identical in their VH and CH1 domains (and also CH2 domains). The only mention of “common light chain” in Cabrera appears in connection with Figure 18 and would be confusing to a POSA. Indeed, I personally do not see a common light chain in Figure 18 or understand what Cabrera intends to depict with the figure. Thus, a POSA reading Cabrera would have no motivation to attach a common light chain to enhance the production of the “desired heteromultimeric antibody” of Cabrera's variants that had over 95% heterodimerization yields. Dr. Presta admitted during his deposition that using a common light chain does not affect heterodimerization; it merely reduces the number of possible dimers. See Presta Tr. at 59:6-13).

164. A POSA would not have been motivated to combine Arathoon with Lazar and/or Cabrera because, as Dr. Presta admitted, Arathoon does not discuss charge engineering and/or combination with charge engineering techniques. *See* Presta Tr. at 96:6-7 and 102:7-17 (“We did not consider charges, reversal or otherwise, in this particular study”). None of the asserted prior art references disclose or suggest combining the disclosures of each reference that would result in the subject matter claimed in dependent claims 2, 27 and 33.

165. Furthermore, a POSA would not have a reasonable expectation of success to enhance the production of the desired heteromultimeric antibody by attaching common light chains of Arathoon to constructs disclosed in Lazar and/or Cabrera. As discussed above, constructs disclosed in Lazar and Cabrera are incompatible with common light chains or already have the same light chains attached to identical VH and CH1 regions, which provide the same functions as Arathoon’s common light chains.

**B. Dependent Claim 7**

166. Dependent claim 7 includes all of the elements of independent claim 1 and further requires additional limitations, including that “the presence of contaminating homodimers is less than 5%, preferably less than 2%, more preferably less than 1%, and most preferably contaminating homodimers are essentially absent.”

167. Lazar alone or in combination with Cabrera and/or Arathoon does not disclose all of the elements of dependent claim 7 as arranged in the claim because they do not disclose acceptable heterodimerization yields in human IgG antibodies with neutral to charged mutations in the CH3 domain. Moreover, a POSA would not have been motivated to combine Lazar, Cabrera, and/or Arathoon with any reasonable expectation of success.

168. Indeed, as shown in Figures 5-7 of Lazar, the highest heterodimer yield achieved by Lazar's variants with neutral to charged substitutions is only 84% (*i.e.*, L351K/S364H/D401K in one chain and Y349T/L351E/T411E in the other chain). Furthermore, as this variant includes six substitutions, including a neutral to neutral substitution and charged to charged substitutions, a POSA would not know whether neutral to charged substitutions interact at all, much less contribute to the 84% heterodimerization yield.

169. Cabrera also fails to make up for the deficiencies of Lazar. Although it discloses certain variants that provide over 95% purity, Cabrera fails to disclose any interactions between neutral to charged residues for producing heterodimers with over 95% purity. Rather, as discussed above, several example variants (*e.g.*, AZ28, 29, 33, and 34) show that neutral to charged residue substitutions decrease heterodimerization.

170. Arathoon also fails to make up for the deficiencies of Lazar and Cabrera, as it does not disclose or suggest any neutral to charged residue substitutions.

171. As Dr. Presta admitted during his cross-examination, none of the papers in his '286 Patent Declaration discloses creating a new charge-charge interaction. See Presta Tr. at 115:22-116:1. Accordingly, a POSA cannot achieve such unexpected improvements (*e.g.*, purity) from disclosures of Lazar, Cabrera, and Arathoon alone or in combination.

172. Accordingly, a POSA would not be motivated to combine Lazar, Cabrera, and Arathoon with a reasonable expectation of success to achieve over 95% purity level, as all of the asserted prior art references fail to disclose or suggest over 95% purity levels through interactions between neutral to charged residue substitutions. None of the asserted prior art references disclose or suggest combining the disclosures of each reference that would result in the subject matter claimed in dependent claim 7.

### **C. Dependent Claim 8**

173. Dependent claim 8 includes all of the elements of independent claim 1 and further requires additional limitations, including that “each variable region of the 1<sup>st</sup> and 2<sup>nd</sup> antibody heavy chains recognizes a different target epitope.”

174. Lazar alone or in combination with Cabrera and/or Arathoon does not disclose all of the elements of dependent claim 8 as arranged in the claim because they

do not disclose human IgG antibodies in which “each variable region of the 1<sup>st</sup> and 2<sup>nd</sup> antibody heavy chains recognizes a different target epitope” as claimed in dependent claim 8. Moreover, a POSA would not have been motivated to combine Lazar, Cabrera, and/or Arathoon with any reasonable expectation of success.

175. Lazar’s scFv-Fc/empty-Fc format includes only one binding site attached to one chain and thus cannot recognize different target epitopes. Lazar’s alternative bispecific constructs (*i.e.*, mAb-Fv, mAb-Fab, Fab-Fv, and Fab-Fab) also do not have heavy chains that recognize different target epitopes because Lazar’s alternative bispecific constructs include two chains with identical specificity.

176. Cabrera also fails to disclose heterodimeric antibodies that include heavy chains that recognize different target epitopes. As discussed above, all of Cabrera’s antibodies with heterodimeric Fc variants in the Examples are “bivalent ***monospecific***” antibodies that do not have two different variable regions. *See* Cabrera (EX1005), Examples 1-3.

177. Furthermore, a POSA would not be motivated to combine the disclosure of Arathoon with the monospecific antibodies of Lazar and Cabrera because Arathoon does not disclose charge engineering. *See* Presta Tr. at 96:6-7 and 102:7-17 (“We did not consider charges, reversal or otherwise, in this particular study.”)

178. Accordingly, a POSA would not combine the constructs of Lazar or Cabrera—constructs that are designed to be bivalent monospecific (*i.e.*, recognize the same target epitope) with potentially a third antigen binding site at the C termini—to meet the requirements of claim 8. Furthermore, a POSA would not have a reasonable expectation of success in doing so.

**D. Dependent Claim 9-20 and 23**

179. Dependent claims 9-20 and 23 include all of the elements of independent claim 1 and further require additional limitations, including the location of target epitopes (claims 9 and 23), types of target molecules (claims 10-18 and 20), and an effector cell (claim 19).

180. Lazar alone or in combination with Cabrera and/or Arathoon does not disclose the limitations in dependent claims 9-20 and 23 as arranged in the claims because Lazar, Cabrera, and/or Arathoon fail to disclose or suggest the claimed features of independent claim 1 that are incorporated into dependent claims 9-20 and 23. Moreover, a POSA would not have been motivated to combine Lazar, Cabrera, and/or Arathoon with any reasonable expectation of success.

**E. Dependent Claims 21, 24, and 32**

181. Dependent claims 21, 24, and 32 include all of the elements of independent claim 1 and further require additional limitations, including that the

claimed heterodimeric antibody is a human IgG (claims 21 and 24) or a human IgG 1 (claim 32). Lazar alone or in combination with Cabrera and/or Arathoon fail to disclose the features of a human IgG or a human IgG1 with a neutral to negatively charged substitution and a neutral to positively charged substitution that interact with each other to produce a heterodimeric antibody as arranged in the claims. Moreover, a POSA would not have been motivated to combine Lazar, Cabrera, and/or Arathoon with any reasonable expectation of success.

182. The only substitutions in an IgG-like molecule in Lazar is the Y349T/T394F and S364H/F405A pair. Lazar does not disclose or suggest any substitutions that include a neutral to negatively charged residue substitution in one heavy chain and a neutral to positively charged residue substitution in another heavy chain. All substitutions other than the Y349T/T394F and S364H/F405A pair were introduced into the scFv-Fc/empty-Fc format, which is not an IgG or IgG1. Furthermore, as discussed above, Lazar is silent regarding interactions between neutral to charged residue substitutions for producing heterodimers.

183. Cabrera fails to make up for the deficiencies of Lazar, as it does not disclose any neutral to charged residue substitutions that interact with each other to produce IgG or IgG1 heterodimers. Arathoon does not provide any further information related to interaction between neutral to charged residue substitutions to produce a

heterodimeric antibody because Arathoon does not disclose any neutral to charged residue substitutions. Indeed, Arathoon was cited only for the disclosure of a common light chain, which in any case is incompatible with the format used by Lazar.

Accordingly, a POSA would not be motivated to combine the disclosures of Lazar, Cabrera, and Arathoon with a reasonable expectation of success because all of the asserted prior art references fail to disclose or suggest human IgG or IgG1 heterodimers with the claimed neutral to charged residue substitutions that interact with each other to produce heterodimeric antibodies. None of the asserted prior art references disclose or suggest combining the disclosures of each reference that would result in the subject matter claimed in dependent claims 21, 24, and 32.

#### **F. Dependent Claims 22 and 28**

184. Dependent claims 22 and 28 include all of the elements of independent claim 1 and further require additional limitations, including that a heterodimeric antibody (claim 22) obtained by independent claim 1 be combined with a pharmaceutically acceptable carrier (claim 28).

185. Lazar alone or in combination with Cabrera and/or Arathoon do not disclose the limitations in dependent claims 22 and 28 of the '286 Patent because Lazar, Cabrera, and/or Arathoon fail to disclose or suggest the claimed features of independent claim 1 that are incorporated into dependent claims 22 and 28. Moreover,

a POSA would not have been motivated to combine Lazar, Cabrera, and/or Arathoon with any reasonable expectation of success.

186. Neither the Lazar part mouse construct in Figure 1 nor the alternative bispecific constructs had any indication of safety for delivery to a human. These deficiencies are not corrected by Cabrera or Arathoon.

## **X. CONCLUSION**

187. 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 penalty of perjury under the laws of the United States of America.

Date: 9<sup>th</sup> January, 2026

A handwritten signature in blue ink, appearing to read "BJS Sutton", is written over a horizontal line.

Brian J. Sutton, Ph.D.