

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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IPR2025-00605  
Patent No. 11,926,859

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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 (EX2010) 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. 11,926,859 (“the ’859 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 this declarations would change if I used Dr. Presta’s definition of a POSA instead of the one set forth above.

**IV. BACKGROUND**

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

8. As reported in Dr. Kontermann’s 2012 Landes Bioscience Paper (EX1013)—a paper relied on by Dr. Presta—as of 2012 there were at least 45 different approaches for creating bispecific antibodies known to a POSA. Figure 2 of Dr. Kontermann’s Paper illustrates these many approaches:

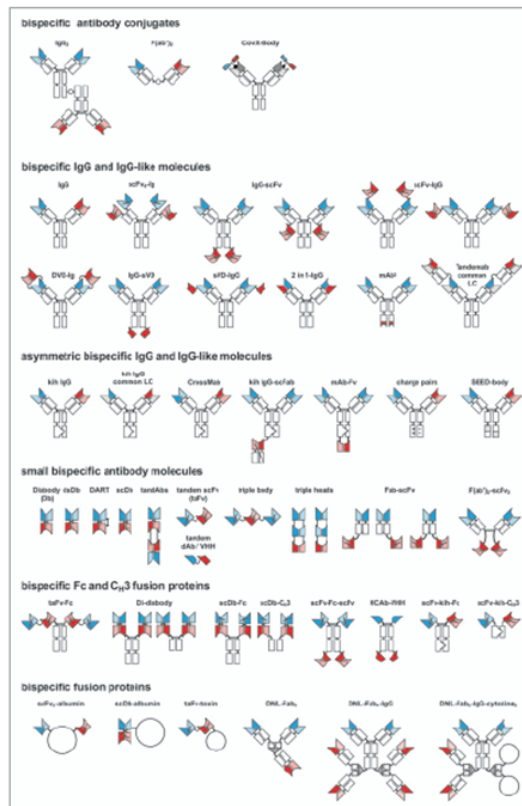


Figure 2. Bispecific antibody formats. Variable heavy chain domains (V<sub>H</sub>) are shown in dark blue and dark red, variable light chain domains (V<sub>L</sub>) are shown in light blue and light red, red and blue indicating different specificities. Antibody constant domains are shown in white boxes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

See Kontermann Paper, EX1013, at 186, Figure 2.

9. As Dr. Presta agreed at his cross examination (Presta Tr. at 138:3-23), only seven of the 45 known approaches for creating bispecific antibodies 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 involves “charges.” Accordingly, Dr. Presta and I agree that only one of the 45 approaches for creating bispecific antibodies known to a POSA in 2012 involves “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).

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 (EX2016), 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 EX2016. Having reviewed the Matthews Paper in my academic work before reviewing it in this proceeding, I can confirm that EX2016 is a true and correct copy of that published, peer-reviewed paper.

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.

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. 87:16–87:25.*

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 at 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 the Fc region also (3) 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 at 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* (EX2016), at pp. 268-271.

18. POSAs at the time, including Lazar, were well aware of the Gunasekaran Paper and its warning. In fact, it was such an important teaching at the time that the Lazar cited by Dr. Presta incorporate the Gunasekaran Paper *in its entirety*. *See* Lazar (EX1004) at ¶ 125.

19. Merus’ novel approach to heterodimerization deviated 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) there is written description and enablement support for the claimed subject matter of the '859 Patent in the '935 Provisional Application; and (2) claims 1-7 of the '859 Patent are not obvious based on Lazar (EX1004) alone or Lazar in combination with Kannan (EX1007).

## **VI. CLAIM CONSTRUCTION**

22. I understand from counsel that claim construction is the process that is used to determine the meaning of the terms used in the claims of a patent. I further understand from counsel that claim terms are typically given their ordinary and customary meaning to a POSA reviewing the specification, claims, and prosecution history. In my declarations, I have used the ordinary and customary meaning of the

claim terms to a POSA reviewing the specification, claims, and prosecution history.

I have, however, reviewed the constructions that the Board provided for “heterodimeric antibody” and “CH3 domain.” *See* Institution Decision at 15-20.

Even if these two constructions were applied, the analysis and opinions in my declarations would not change.

**VII. THERE IS WRITTEN DESCRIPTION AND ENABLEMENT SUPPORT FOR THE CLAIMED SUBJECT MATTER OF THE '859 PATENT IN THE '935 PROVISIONAL APPLICATION**

23. I understand from counsel that the '859 Patent claims priority to an earlier filed provisional patent application—the '935 Provisional Application (EX1030), which was filed on April 20, 2012. I further understand that a later filed patent application can be considered filed on the same filing date as an earlier filed application if the later application properly “claims priority” to the earlier filed patent application. I understand that to properly “claim priority” to an earlier application, the specification of the earlier application must provide an adequate written description and enablement of the subject matter claimed by the later application.

24. I have been informed by counsel that the critical inquiry for the written description analysis is whether the earlier specification reasonably conveys to a POSA that the inventors “had possession of the invention” claimed in the later

application. In other words, would a POSA reading the earlier application reasonably believe that the inventors invented what is claimed in the later application.

25. I understand from counsel that an exact words—“*ipsis verbis*”—disclosure in the earlier filed application is not necessary to convey that a POSA had possession of the claimed invention at the time of the earlier application. In other words, the earlier application need not recite the later-claimed invention word for word. I understand that, instead, the inquiry is whether there are sufficient indicators (“blaze marks”) or signposts, in the priority application that guide a POSA to the later claimed invention to reasonably convey that the inventors had possession of that invention as of the priority date. I understand that stated preferences and data disclosed in the priority application may serve as “blaze marks” guiding POSAs to the claimed invention.

26. It is my opinion that a POSA reading the '935 Provisional Application would reasonably believe that the inventors invented the subject matter claimed by the '859 Patent as of April 20, 2012. That is to say, the '935 Provisional Application reasonably conveys to a POSA that the inventors “had possession of the invention” claimed by the '859 Patent as of April 20, 2012.

27. I understand from counsel that the critical inquiry for the enablement analysis is whether the '859 Patent, when filed, contained sufficient information to enable a POSA to make and use the claimed invention without undue experimentation. I also understand from counsel that the following factors need to be considered for the enablement analysis: (1) the breadth of the claims, (2) the nature of the invention, (3) the state of the prior art, (4) the level of one of ordinary skill, (5) the level of predictability in the art, (6) the amount of direction provided by the inventor, (7) the existence of working examples, and (8) the quantity of experimentation needed to make or use the invention based on the content of the disclosure.

28. It is my opinion that the '935 Provisional Application contained sufficient information to enable a POSA to make and use the subject matter claimed in the '859 Patent as of April 20, 2012 without undue experimentation.

29. Given my opinion that there is adequate written description and enablement support in the '935 Provisional Application, I understand from counsel that the '859 Patent should be given its earliest claimed priority date of April 20, 2012. I further understand that Xencor and Dr. Presta make anticipation arguments based on two later references: Xencor's '427 Patent (Desjarlais) and the Moore Paper. I understand from counsel that all parties agree that the earliest possible

priority date for Xencor's '427 Patent (Desjarlais) is March 13, 2013, and the earliest possible publication date for the Moore Paper is October 23, 2018. Because these references have priority or publication dates after the April 20, 2012 priority date of the '859 Patent, I understand from counsel that Xencor's '427 Patent (Desjarlais) and the Moore Paper do not qualify as prior art to the '859 Patent. Therefore, I have not conducted a validity analysis with respect to Xencor's '427 Patent (Desjarlais) or the Moore Paper because both of those references post-date the April 20, 2012 priority date of the '859 Patent.

**A. The '935 Provisional Application Reasonably Conveys To A POSA That The Inventors Had Possession Of The Subject Matter Claimed By Independent Claim 1 Of The '859 Patent**

30. Independent claim 1 of the '859 Patent is directed to a heterodimeric antibody and states:

A heterodimeric antibody comprising a first human CH3 domain comprising a positively charged amino acid residue at position 364 according to the EU numbering system, and a second human CH3 domain comprising a negatively charged amino acid residue at position 368 according to the EU numbering system.

31. It is my opinion that the '935 Provisional Application reasonably conveys to a POSA that the inventors had possession of the subject matter claimed by independent claim 1 of the '859 Patent as of the April 20, 2012 filing date of the '935 Provisional Application.

32. The '935 Provisional Application provides, in the Description Of The Invention, that:

The invention provides methods and means for improved and/or alternative technologies for producing biological therapeutics in the form of mixtures or bispecific approaches for targeting multiple disease-modifying molecules, as well as products and uses resulting from these methods and means.

*See* '935 Provisional Application (EX1030) at 5:5-8.

33. The importance of bispecific antibodies was well-appreciated as of the April 20, 2012 filing date of the '935 Provisional Application. POSAs in 2012 were aware that, unlike monoclonal antibodies, bispecific antibodies had the ability to target two distinct epitopes. POSAs in 2012 knew that this dual-targeting ability could increase treatment specificity and efficacy, making bispecific antibodies promising candidates for treatment of complex diseases such as cancers. Developing and refining methods for creating bispecific antibodies suitable for human therapeutic applications was, thus, a key focus in 2012.

34. A critical issue for creating bispecific antibodies in 2012 was how to do so without creating difficult to separate impurities. For example, when two different monomers intended to form a bispecific antibody are "mixed," some percentage of the monomers will heterodimerize (*i.e.*, pair with the different type of monomer) and some percentage of the monomers will homodimerize (*i.e.*, pair with the same type

of monomer). Given the similarities between the heterodimers and the homodimers, they can be difficult to separate from each other.

35. In contrast, as the '935 Provisional Application explains, unpaired monomers “can be easily separated from the mixture by size exclusion chromatography.” See '935 Provisional Application (EX1030) at 24:22-. A POSA reading the '935 Provisional Application would have understood that the inventors focused on minimizing contaminating homodimers rather than unpaired monomers, which are easily removable.

36. A POSA reading the '935 Provisional Application would further understand that the inventors were providing a new solution to the problem of contaminating homodimers. A POSA reading the '935 Provisional Application would have understood that the inventors first discussed the relevant context for the problem, including the “well-known” importance of the CH3-CH3 interaction as “the primary driver for Fc dimerization.” (EX1030 at 5). On further reading, a POSA would have understood that this interaction is driven by “contact” residues in each CH3 domain that “are typically within 5.5 Å (preferably with 4.5 Å) of each other in the three-dimensional structure of an antibody.” *Id.* (EX1030) at 5:12-20.

37. A POSA reading the '935 Provisional Application would have understood that the inventors were so focused on the “contact” residues in the CH3

domain interface that they provided a list of all such residues in Table A.

Importantly, Table A did not just list “contact” residues for one CH3 domain.

Instead, it did so for a “chain A” and a “chain B” and showed for each “[i]nterface

residue in chain A” the “[c]ontacting residues in chain B.” Table A of the ’935

Provisional Application is reproduced below.

**Table A: List of CH3 domain interface residues**

<b>Interface residue in chain A</b>	<b>Contacting residues in chain B</b>
Q347	K360
Y349	S354, D356, E357, K360
T350	S354, R355
L351	L351, P352, P353, S354, T366
S354	Y349, T350, L351
R355	T350
D356	Y349, K439
E357	Y349, K370
K360	Q347, Y349
S364	L368, K370
T366	L351, Y407
L368	S364, K409
K370	E357, S364
N390	S400
K392	L398, D399, S400, F405
T394	T394, V397, F405, Y407
P395	V397
V397	T394, P395
D399	K392, K409
S400	N390, K392
F405	K392, T394, K409
Y407	T366, T394, Y407, K409
K409	L368, D399, F405, Y407
K439	D356

38. A POSA reading the '935 Provisional Application would have understood that contact residues in one CH3 domain can interact through structural interaction (*e.g.*, hydrogen bonds, salt bridges, *etc.*) with their counterpart contact residues in the other CH3 domain. A POSA would have understood that the CH3 contact residues account for the majority of contributions to domain folding and association. *Id.* (EX1030) at 5:20-29.

39. Understanding the inventors' focus on the contact residues of the CH3-CH3 interaction, a POSA would have further understood that the inventors of the '935 Provisional Application then reviewed various methods that had been applied prior to April 12, 2012 to "favour heterodimerization over homodimerization" of heavy chains by "engineering of the CH3-CH3 interface." *Id.* (EX1030) at 5:30-7:34.

40. As a POSA would have understood, these known methods included "complementary protuberance and cavity mutations, also known as 'knob-into-hole' approaches as described for instance in WO/1998/050431, Ridgeway et al., 1996 and Merchant et al. 1998." *Id.* (EX1030) at 5:32-62. The inventors provided a summary of the knob-into-hole approach, including how it worked and some of the reported results with the approach:

Generally, the method involves introducing a protuberance at the interface of a first polypeptide and a corresponding cavity in the

interface of a second polypeptide, such that the protuberance can be positioned in the cavity so as to promote heteromultimer formation and hinder homomultimer formation. “Protuberances” or “knobs” are constructed by replacing small amino acid side chains from the interface of the first polypeptide with larger side chains (*e.g.* tyrosine or tryptophan). Compensatory “cavities” or “holes” of identical or similar size to the protuberances are created in the interface of the second polypeptide by replacing large amino acid side chains with smaller ones (*e.g.* alanine or threonine). The protuberance and cavity can be made by synthetic means such as altering the nucleic acid encoding the polypeptides or by peptide synthesis.

Using the knob-into-hole technology alone, the proportion of a bispecific antibody of interest is at best 87% of the mixture of the 2 parental and bispecific antibodies.

*Id.* (EX1030) at 6:3-15.

41. A POSA would have further understood that, as explained by the inventors, “Merchant et al., succeeded in raising the proportion of bispecific antibodies to 95% of the mixture by introduction of an additional disulfide bond between the two CH3 domains in the CH3-CH3 interface.” *Id.* (EX1030) at 6:16-18.

42. Another example of a known method of engineering of the CH3-CH3 interface for heterodimerization was the strand-exchange engineered domain (“SEED”) method, as described, for instance, in International Patent Application No. WO2007/110205 and Davis J H. Et al., Protein Engineering, Design & Selection 2010(23)195-202. The '935 Provisional Application describes that these SEED CH3 heterodimers are derivatives of human IgG and IgA CH3 domains that are

composed of alternating segments of human IgA and IgG CH3 sequences, which results in pairs of complementary human SEED CH3 heterodimers. The Specification of the '935 Patent Application described the SEED method as follows:

Another example of such engineering of the CH3-CH3 interface is provided by a heterodimeric Fc technology that supports the design of bispecific and asymmetric fusion proteins by devising strand-exchange engineered domain (SEED) CH3 heterodimers. These SEED CH3 heterodimers are derivatives of human IgG and IgA CH3 domains that are composed of alternating segments of human IgA and IgG CH3 sequences which results in pairs of complementary human SEED CH3 heterodimers, the so-called SEED-bodies (Davis J H. Et al., Protein Engineering, Design & Selection 2010(23)195-202; WO2007/110205).

*Id.* (EX1030) at 6:28-7:3.

43. The inventors of the '935 Provisional Application also described the prior known method of “a charge reversal strategy” for engineering of the CH3-CH3 interface. According to the Gunasekaran Paper (EX1012), the naturally occurring charged amino acid CH3 contact residues are replaced by amino acid residues of opposite charge. The '935 Provisional Application provides a summary of the charge reversal strategy, including how it works:

Yet another approach for the production of a given bispecific antibody of interest is based on *electrostatic engineering of contact residues within the CH3-CH3 interface that are naturally charged*, as for example described in EP01870459 or US2010/0015133, WO2007/147901, WO2010/129304, Gunasekaran et al (2010) and WO 2009/089004. These publications describe mutations in the CH3 domains of heavy chains *wherein naturally occurring charged amino acid contact residues are replaced by amino acid residues of opposite*

***charge (i.e. a charge reversal strategy)***. This creates an altered charge polarity across the Fc dimer interface such that co-expression of electrostatically matched Fc chains support favorable attractive interactions thereby promoting desired Fc heterodimer formation, whereas unfavorable repulsive charge interactions suppress unwanted Fc homodimer formation.

*Id.* (EX1030) at 7:4-7:14 (emphasis added).

44. The inventors further explained that “it is possible to produce a bispecific antibody in a single cell with proportions ranging between about 76% and about 96%” with these prior approaches. *Id.* (EX1030) at 7:30-31.

45. Against this detailed background, the inventors explained their objective: “It is an object of the present invention to provide methods for producing a bispecific antibody in a single cell with a further improved percentage of desired bispecific antibodies.” *Id.* (EX1030) at 7:31-33. The inventors further explained how they would achieve their objective: “[T]he present invention provides novel CH3 mutations which enable the production of certain bispecific Ig-like molecules of interest without a significant amount of undesired (dimeric) by-products. The use of at least one of these CH3 mutations according to the present invention is, therefore, preferred.” *Id.* (EX1030) at 19:8-11; 19:13-14.

46. The inventors then explained the “novel mutations” of their invention. Specifically, the '935 Provisional Application explained that:

The present invention provides novel engineered CH3 domains as well as novel combinations of CH3 mutations. Before the present invention, charged contact amino acids of CH3 domains that were known to be involved in CH3-CH3 pairing were substituted by amino acids of opposite charge, thereby influencing the CH3-CH3 pairing. ***The mutations according to the present invention are an inventive alternative to this approach, because now CH3 amino acids that are non-charged or neutral in wildtype CH3 are substituted with charged residues.*** The present invention in this embodiment does not exchange charged contact amino acids by amino acids of opposite charge but substitutes non-charged CH3 amino acids for charged ones. ***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.

*See id.* (EX1030) at 23:28 – 24:9 (emphasis added).

47. The inventors further explained that the “[u]npaired half molecules consisting of only a single heavy chain” “can be easily separated from the mixture by size exclusion chromatography.” *Id.* (EX1030) at 24:22-25. With this explanation, the inventors made clear to a POSA that unpaired monomers were not their focus. Avoiding homodimers was their focus.

48. With this stated context, the inventors explained that neutral to charged residue substitutions that fully prevent homodimerization when expressed alone are “preferred.” Specifically, the ’935 Provisional states:

***CH3 variants that fully prevent homodimerization when expressed alone are preferred***, to prevent or minimize undesired byproducts (homodimers) upon co-expression with a second CH3 variant for heterodimerization.

*See id.* (EX1030) at 48:10-13 (emphasis added).

49. Dr. Presta admitted at his cross examination that the Specification of the '935 Provisional Application discloses this preference to a POSA: CH3 variants that prevent homodimerization when expressed alone are “preferred” for heterodimerization. *See* Presta Tr. at 157:4-23.

50. A POSA reading the '935 Provisional Application would not have had to guess which CH3 domain variants met the inventors' stated preference for preventing homodimerization when expressed alone. Indeed, the inventors provided a clear chart of amino acid substitutions in the CH3 domain and their experimentally determined effects on homodimer formation in Table 7 of the '935 Provisional Application.

51. In describing the creation of Table 7, the inventors explained that:

The objective of this study was to engineer the IgG CH3 region to result in the production of only heterodimers or only homodimers upon mixed expression of different IgG heavy chains in a single cell, wherein the novel engineered CH3 domains will not homo- or heterodimerize with known engineered CH3 domains, or with wildtype CH3 domains. Therefore, as a first step in identifying novel engineered CH3 domains that would meet the criteria, many interface contact residues in the IgG CH3 domain were scanned one by one or in groups for substitutions that would result in repulsion of identical heavy chains i.e., reduced

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homodimer formation—via electrostatic interactions. The objective was to obtain a list of residues that, when substituted by a charged residue, would result in repulsion of identical chains such that these mutations may be used to drive homo- and/or heterodimer formation upon mixed expression of different IgG heavy chains, whereby the obtained full length IgGs are stable and are produced with high proportions.

See '935 Provisional Application (EX1030) at 51:1-14.

52. Each disclosed variant in Table 7 was graded for its (experimentally determined) effect on “homodimer formation,” with a score from the lowest of “-”

Table 7: list of amino acid substitutions in the various constructs that were made (EU numbering)

AA substitutions in CH3	construct #	Effect on homodimer formation (- = no effect; +++ = max. inhibition; NT= not tested on gel)
Q347K	8	-
Y349D	9	+-
Y349K	10	+-
T350K	11	-
T350K, S354K	12	+-
L351K, S354K	13	+.
L351K, T366K	14	++
L351K, P352K	15	+.
L351K, P353K	16	++
S354K, Y349K	17	++
D356K	18	-
E357K	19	-
S364K	20	++
T366K, L351K	21	++
T366K, Y407K	22	+++
L368K	23	NT
L368K, S364K	24	++
N390K, S400K	25	+.
T394K, V397K	26	+

for “no effect” to “+++” for “max. inhibition”:

AA substitutions in CH3	construct #	Effect on homodimer formation (- = no effect; +++ = max. inhibition; NT= not tested on gel)
T394K, F405K	27	+++
T394K, Y407K	28	+++
P395K, V397K	29	+-
S400K	30	.
F405K	31	+++
Y407K	32	++
Q347K, V397K, T394K	33	+
Y349D, P395K, V397K	34	+
T350K, T394K, V397K	35	NT
L351K, S354K, S400K	36	+
S354K, Y349K, Y407K	37	+-
T350K, N390K, S400K	38	+-
L368K, F405K	39	++
D356K, T366K, L351K	40	+++
Q347K, S364K	41	+++
L368D, Y407F	42	+
T366K	43	+
L351K, S354K, T366K	44	+
Y349D, Y407D	45	+
Y349D, S364K,	46	+

AA substitutions in CH3	construct #	Effect on homodimer formation (- = no effect; +++ = max. inhibition; NT= not tested on gel)
Y407D		
Y349D, S364K, S400K, T407D	47	+
D399K	48	+.
D399R	49	+.
D399H	50	+.
K392D	51	+.
K392E	52	+.
K409D	53	+

53. A POSA reviewing Table 7 and the rest of the '935 Provisional Application would have understood the data and understood which variants best embodied the inventors' stated preference for preventing homodimerization when expressed alone.

54. Specifically, fourteen variants have a “++” or “+++” rating in Table 7. A POSA would have known from reading the rest of the '935 Provisional Application not to focus on the F405K and/or Y407K variants. This is because the '935 Provisional Application explicitly discloses that doing so may be “*problematic*”:

[I]t is known that *residues F405 and Y407* have *multiple interactions* at the CH3-CH3 interface, including interactions with residues that are already charged, *which may be problematic* after introduction of multiple charge mutations among these interacting residues (*see* Table A).

*See id.* (EX1030) at 54:12-16 (emphasis added). The '935 Provisional Application thus expressly discourages a POSA from selecting variants containing the F405K and/or Y407K substitutions. Indeed, Dr. Presta admitted at his cross-examination that the '935 Provisional Application “discusses problems” with F405K and Y407K. *See* Presta Tr. at 165:18-166:13 and 176:13-18

55. A POSA reviewing the fourteen variants that have a “++” or “+++” rating in Table 7 with the inventors’ explicit warning against the F405K and Y407K variants in mind would understand that there were eight variants that have a “++” or “+++” rating in Table 7 without using a F405K and/or Y407K substitution.

56. Of these eight variants, the T366K and S364K substitutions occur most frequently, in three variants each. For example, a POSA reading Table 7 would have understood that—removing the potentially “problematic” F405K and Y407K variants—the S364K variant appears in one of the two “+++” ratings in Table 7 and appears in two of the six “++” ratings in Table 7. A POSA would have further taken notice that S364K is the only variant in Table 7 to achieve a “++” rating as a single substitution.

57. In connection with Table 7, the inventors explained that:

In a follow up, *the identified substitutions will be used to generate bispecific antibodies* or mixtures of bispecific or monospecific antibodies *by engineering matched pairs of CH3 residues* in one or more IgG heavy chains—CH3 regions.”

*See* '935 Provisional Application (EX1030) at 51:14-17 (emphasis added).

58. A POSA reading this statement would have understood that the inventors invented, and could generate, *i.e.* had possession of, bispecific antibodies produced by engineering matched pairs for the T366K and S364K variants identified in Table 7. A POSA reading the '935 Provisional Application further would have understood what a “matched pair” was for each of these variants.

59. For S364K, a POSA understood that to create a “matched pair” they must look first to Table A of the '935 Provisional Application, which discloses the contacting residue(s) in Chain B for an S364K residue in Chain A. A POSA would have readily identified S364K in Table A and understood its contacting residues. *See* '935 Provisional Application at 54:12-16, p. 17 at Table A.

60. Specifically, a POSA would have understood that the contacting residues listed for S364K in Table A were L368 and K370. A POSA would have further understood that creating a “matched pair” with S364K, which has a positive charge, would require modifying one of these residues to have a negative charge (a D or E

residue). Given the above, a POSA reading the '935 Provisional Application would have known that there were only four possibilities for creating a "matched pair" with S364K: L368D, L368E, K370D, and K370E. A POSA reading the '935 Provisional Application would have readily envisaged each of these pairs and reasonably believed that the inventors had possession of, and were the inventors of, each of these pairs as of the April 20, 2012 filing date of that application.

61. A POSA would have further understood that there were a number of reasons not to modify K370 to have a negative D or E charge to create a "matched pair" with S364K.

62. Based on Table A and their knowledge of the literature in 2012, a POSA would have understood that K370: (a) was already charged; (b) had a positive charge that would have to be reversed to create a "matched pair" with S364K; (c) was already in contact with an oppositely charged residue, E357; and (d) was already part of one of the four conserved salt bridges of the CH3-CH3 interface. Given Table A and their knowledge of the literature in 2012, a POSA would have known that changing the K370 residue to K370D or K370E to make a "matched pair" with S364K would break the existing interaction between K370 and E357. This could negatively affect the stability and function of any resulting heterodimer. It would also go against the

inventors' stated objective of creating an "additional charge-charge interaction on top of the existing charge-pairs in the CH3-CH3 interface." *See id.* (EX1030) at 24:6-7.

63. As part of a POSAs knowledge of the literature in 2012, the Gunasekaran Paper highlights and explains the makeup and importance of the four CH3 salt bridges. The Gunasekaran Paper makes clear that *Lys370 is one of the residues that creates the four* salt bridges in the CH3 interface and that "[s]tudies have suggested that [these] structurally conserved and buried residues [including K370] *contribute significantly to protein-protein association.*" *See* the Gunasekaran Paper (EX1012) at page 4.

The Gunasekaran Paper further explained:

*The analysis revealed that the CH3 domain interface includes a central hydrophobic core region surrounded by charged residues that interact to promote dimer formation through favorable electrostatic interactions around the rim of the interface* (Fig. 1b and supplemental Fig. S2). High structural conservation for the hydrophobic residues at the core of the interface as well as for a few of the charged residues was noted. Further examination of the residues involved in the CH3-CH3 domain interactions (supplemental Table S1) revealed *four pairs of oppositely charged residues along the interface* (Asp356–Lys439', *Glu357–Lys370'*, Lys392–Asp399', and Asp399–Lys409').

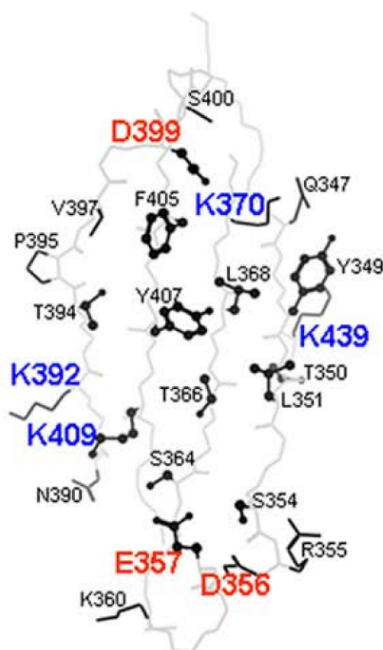
*See* the Gunasekaran Paper (EX1012) at page 19640; supplemental Table S1 is Table A, para. 38 above, emphasis added.

64. Dr. Gunasekaran's Paper further illustrates, in Figure 1b (reproduced below), that the charged residues involved in the four salt bridges listed in Table 1 are located around the edge of the hydrophobic CH3-CH3 interface region, shown

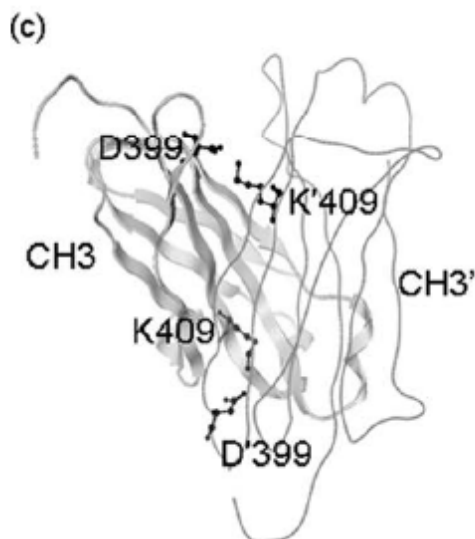
Second Declaration of Brian J. Sutton, Ph.D.

here for the interacting surface of one CH3 domain. There are seven charged residues shown because every salt bridge occurs twice in the interface due to the two-fold symmetry of the structure, and one of the residues D399 is involved in two salt bridges, to K392 and K409; hence seven residues are indicated, and not eight.

(b)



65. Figure 1C (reproduced below) shows the structure of one of the salt bridges, which occurs twice at the interface, *i.e.* D399/K'409 and D'399/K409.



66. The buried or partially buried nature of these salt bridges at the CH3-CH3 dimer interface is indicated by the low values for the accessible surface area of each, given in Table 1.

67. A POSA as of April 2012, therefore, would have understood not to make any substitutions to K370 for fear of destroying one of the four different wild-type salt bridges. A POSA would have further known that any substitution that exposed K370 to water may weaken or entirely destroy the salt bridges, which could lead to deleterious effects on antibody structural integrity and functionality. *See* First Sutton Declaration (EX2010) at paragraph 28.

68. Given any one of the reasons above, a POSA would not have substituted K370 to create a “matched pair” with S364K for fear of disrupting one of the four

conserved salt bridges and harming the stability and potentially function of the resulting antibody.

69. Having eliminated K370 from the two listed contact residues for S364 in Table A, a POSA was left with the other one—L368—for co-expression with S364K to make the “matched pair” disclosed by the inventors.

70. A POSA would have understood from the '935 Provisional Application that there are only two possible substitutions for L368 to make it a “matched pair” with S364K, namely L368D or L368E. Because neutral serine (S) is substituted with positively charged lysine (K) in S364K, there needs to be a negatively charged residue at position 368 to form a “matched pair” (*e.g.*, by forming a salt bridge). A POSA would have understood that there are two negatively charged residues, aspartic acid (D) and glutamic acid (E). As the wild-type CH3 domain includes a neutral residue, leucine (L), at position 368, a POSA would have understood that D or E should replace L at position 368 to have a complementary charge and form a “matched pair” with S364K. A POSA would also have understood that the '935 Provisional Application provides multiple examples of L368 variants, including examples of both the L368D and L368E substitutions. *See* '935 Provisional Application (EX1030), Tables B, 7, and 13–15.

71. Based on the disclosure of the L368D and L368E substituted variants, a POSA would have understood that the inventors contemplated the L368E or the L368D variant for co-expression of with S364K for heterodimerization.

72. At his cross-examination, Dr. Presta admitted that based on the disclosures of Table A and Table 7 in the '935 Provisional Application, the L368 residue is the only residue that could introduce a complementary charge for S364K. *See* Presta Tr. at 163:10-164:22.

73. The '935 Provisional Application further states that substituting a neutral residues of the CH3 region with charged substitutions creates an “*additional* charge-charge interaction in the CH3 interface” that contributes to the improved thermodynamic stability of an antibody as compared to those antibodies with wild-type CH3 domain substitutions. Specifically, the '935 Provisional Application 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)). Moreover, it has surprisingly become possible to 10 increase the proportion of one or more Ig-like molecules of interest in a mixture even further.

*See* '935 Provisional Application (EX1030) at 24:3-11 (emphasis added).

74. A POSA reading the '935 Provisional Application would have understood that an additional charge-charge interaction would be an advantage. A POSA would therefore have understood the inventors did not contemplate the K370 residue for modification to form a “matched pair” with S364K because K370 is already charged and already involved in a charge-charge interaction. Simply put, modifying K370 would not lead to the creation of an additional charge-charge interaction deemed an advantage by the inventors.

75. In the '935 Provisional Application the inventors confirmed that new charge pairs can be added to the existing pairs, like those creating the existing salt bridges. The Specification specifically states:

***Additionally, newly identified charge mutant pairs may be combined with existing pairs, such that multiple nucleic acid molecules encoding different heavy chains, all carrying different and complementing CH3 mutations, can be used*** for expression in cells such that mixtures of monospecific antibodies only, or bispecific antibodies only, or mixtures of defined monospecific and bispecific antibodies can preferentially be obtained.

*See id.* (EX1030) 51:10-22 (emphasis added).

76. For all these reasons, a POSA would have understood from the '935 Provisional Application that the newly identified charge substitution of S364K should be paired with the complementary contacting charge substitutions of L368D or L368E

to form the disclosed “matched pair.” This would add an additional charge-charge interaction of the kind deemed advantageous by the inventors.

77. Based on at least the above disclosures of the '935 Provisional Application, it is my opinion that the '935 Provisional Application reasonably conveys to a POSA that the inventors invented and possessed the claimed invention of “a positively charged amino acid residue at position 364” and “a negatively charged amino acid residue at position 368” as of April 20, 2012. Put another way, a POSA reading the '935 Provisional Application would reasonably believe that S364K in a “matched pair” with L368D or L368E was something that the inventors invented and possessed on April 20, 2012.

78. In its Institution Decision, the Board stated that Table 7 does not appear to describe heterodimer combinations because “Table 7 itself was only a ‘first step’ in the identification process” and was used only for prevention of homodimerization of identical heavy chains. *See* Institution Decision, at pp. 35-36. The Board also stated that the “follow-up experiments” did not include the specific paired substitutions at positions 364 and 368.

79. I respectfully submit that the Board should look to the inventors’ explanation of the purpose of the “first step” identification in Table 7:

In a follow up, *the identified substitutions will be used to generate bispecific antibodies* or mixtures of bispecific or

monospecific antibodies *by engineering matched pairs of CH3 residues* in one or more IgG heavy chains—CH3 regions.”

*See* '935 Provisional Application (EX1030) at 51:14-17 (emphasis added).

As explained in detail above, upon reading this and other aspects of the '935 Provisional Application, a POSA understood that the inventors invented and possessed “matched pairs” with S364K and that those “matched pairs” included L368D and L368E.

80. I also respectfully submit that the Board’s statement that Table A does not teach the claimed subject matter, is incomplete. As discussed above, a POSA reading the '935 Provisional Application would have understood that they should take the substitutions identified by Table 7 as preventing homodimerization without being potentially “problematic” and then use Table A to determine the contacting residues for those substitutions with which to create “matched pairs.” Table A does not, and was not intended to, disclose the claimed subject matter by itself.

81. As explained above, reading Table A and the other disclosures of the '935 Provisional Application would reasonably convey to a POSA that the inventors invented, and had possession of, the “matched pairs” with S364K, including the claimed matched pair of S364K and L368D.

82. I understand that Dr. Presta asserted in his cross-examination that S364K has similar problems as those disclosed by the inventors for F405K and Y407K. But there is no statement about S364K being potentially problematic in the '935 Provisional Application. Moreover, as shown by Table A, S364K has fewer contacting residues (two) than either F405K (three) or Y407K (four). With fewer contacting residues, a POSA would have known that there are fewer possible complications with substituting S364 than with substituting F405 or Y407. That is especially true given that two of F405's three contacting residues in Table A are already charged.

83. Thus, in my opinion, the '935 Provisional Application clearly suggests that the substitutions from Table 7 can be combined with a second substitution for heterodimerization, providing multiple examples that include the claimed substitutions at both positions 364 and 368. This disclosure of the '935 Provisional Application makes clear to a POSA that the inventors had possession of all of the elements of the invention of claim 1 of the '859 Patent as of April 20, 2012.

**B. The '935 Provisional Application Reasonably Conveys To A POSA That The Inventors Had Possession Of The Subject Matter Claimed By Dependent Claims 2-7 Of The '859 Patent**

84. It is my opinion that the disclosure of the '935 Provisional Application provides adequate written description that reasonably conveys to a POSA that the

inventors had possession of the subject matter claimed by dependent claims 2-7 as of April 20, 2012.

85. Dependent claims 2 and 3 of the '859 Patent add the limitation of specific positively charged residues at position 364 (*i.e.*, lysine or arginine) and negatively charged residues (*i.e.*, aspartic acid or glutamic acid) at position 368. As discussed above, the '935 Provisional Application lists positively or negatively charged residues (*Id.* 17: 4-14) and further provides relevant examples throughout the entire Specification (*e.g.*, Tables B, 7, and 13-15). The application further specifically identifies S364K as preventing homodimerization in Table 7, identifies L368 as being a contact residue for S364 in Table A, and discloses generating bispecific antibodies by engineering "matched pairs." As discussed above, a POSA reading the '935 Provisional Application would have understood that L368D and L368E form matched pairs with S364K and that the only other possible "matched pairs" with S364K (K370D or K370E) would not create the additional charge-charge interaction deemed an advantage by the inventors.

86. Dependent claim 4 of the '859 Patent adds the limitation that the heterodimeric antibody is a bispecific antibody. The '935 Provisional Application discloses that bispecific antibodies are the focus of the application. *See, e.g., id.* (EX1030) at 19:8-14. Specifically, the '935 Provisional Application states "[a]s

described herein below in more detail, the present invention provides novel CH3 mutations which enable the production of certain bispecific Ig-like molecules of interest without a significant amount of undesired (dimeric) by-products.” *See id.* (EX1030) at 19:8-11. The ’935 Provisional Application further states “[f]or 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.” *See id.* (EX1030) at 24:19-22.

87. Dependent claims 5 and 6 of the ’859 Patent add the limitations that the heterodimeric antibody is human IgG (claim 5), and further human IgG1 (claim 6). The ’935 Provisional Application discloses that the heterodimeric antibody is human IgG1. The Examples in the ’935 Provisional Application further discloses “amino acid substitutions to create various different CH3-domains” using the “construct vector MV1057,” which contains “nucleic acid sequences encoding the normal wild-type IgG 1 Fc part.” *See id.* (EX1030) at pp. 38 – 40 (Examples 1 – 6). A POSA would have further understood that the description of human IgG1 is a particular form of human IgG.

88. Dependent claim 7 of the ’859 Patent adds the limitation that the heterodimeric antibody is in a pharmaceutically acceptable carrier. The ’935

Provisional Application discloses a pharmaceutical composition of the heterodimeric antibody and a pharmaceutically acceptable carrier. For example, the '935 Provisional Application states that “[h]ence, 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 id.* (EX1030) at 24:25-29. The '935 Provisional Application further states that:

Also provided is a pharmaceutical composition comprising a mixture of at least two Ig-like molecules obtainable by a method according to the invention. Said at least two Ig-like molecules according to the invention are preferably antibodies. Said pharmaceutical composition may comprise a mixture comprising monospecific or bispecific Ig-like molecules, or a combination of monospecific and bispecific Ig-like molecules.”

*See id.* (EX1030) at 36:14-19. A POSA would understand from this disclosure that this description includes an acceptable “pharmaceutical carrier.”

89. Therefore, the '935 Provisional Application reasonably conveyed to a POSA that the inventors invented and had possession of heterodimeric antibodies with “matched pairs” of S364K and L368D or S364K and L368E including such heterodimeric antibodies that were IgG1, bispecific, and usable in a pharmaceutical composition with a pharmaceutically acceptable carrier.

90. For these reasons, it is my opinion that the '935 Provisional Application reasonably conveys to a POSA that the inventors had possession of all of the elements of the inventions of dependent claims 2-7 of the '859 Patent as of April 20, 2012.

**C. The '935 Provisional Application Provides Information Sufficient To Inform A POSA How To Make And Use The Claimed Invention**

91. It is my opinion that the '935 Provisional Application provides sufficient disclosure for a POSA to make and use the full scope of the subject matter of independent claim 1 and dependent claims 2-7 without undue experimentation.

92. As explained above in detail, the inventors disclosed sufficient information for a POSA to target substitutions with charged residues at positions 364 and/or 368 in Examples 1, 13, 14, 16, and 17.

93. In the Examples in the '935 Provisional Application, the inventors provided sufficient information to a POSA about how to make an antibody with substitutions with charged residues at positions 364 and/or 368. Examples 1 through 12 provide a POSA with sufficient details on how to make the heterodimeric antibody with the CH3 residue substitutions. Example 2 explains how to clone VH into constructs with CH3 mutations. Example 3 explains how to transfect and express a complete IgG molecule in HEK cells. Next, Example 4 explains how to

purify IgG, including IgG made from Example 3. Example 5-8 explain how to use ELISA, SDS-PAGE, enzymatic deglycosylation, and mass spectrometry assays to generate data to evaluate the IgG with the CH3 substitutions. Example 9 further explains to a POSA how to process and quantify the data generated from the tests of Example 5-8. Examples 10 to 12 explain how to generate mixtures of antibodies from a single cell.

94. Further, Examples 13-17 show how the inventors tested many variants for heterodimerization and stability and identified preferred CH3 substitutions.

95. Example 18 shows how the inventors tested the stability of the generated IgG.

96. Therefore, in my opinion, a POSA would have been able to make and use the claimed invention of independent claim 1.

97. Dependent claims 2 and 3 include all of the elements of independent claim 1 and further require additional limitations, including the specific positively charged residues at position 364 (*i.e.*, lysine (K) or arginine (R)) and negatively charged residues at position 368 (*i.e.*, aspartic acid (D) or glutamic acid (E)).

98. For the reasons stated above, the '935 Provisional Application sufficiently teaches a POSA how to make and use a positively charged residues at

position 364 (*i.e.*, lysine (K) or arginine (R)) and a negatively charged residues (*i.e.*, aspartic acid (D) or glutamic acid (E)) at position 368.

99. Further, Examples 2-18 of the '935 Provisional Application explain to a POSA how to make an antibody with these substitutions.

100. Dependent claim 4 includes all of the elements of independent claim 1 and further requires additional limitations, including that the claimed heterodimeric antibody is a bispecific antibody. The Examples of the '935 Provisional Application provide information to a POSA on the techniques to generate and test bispecific antibodies.

101. Dependent claims 5-6 include all of the elements of independent claim 1 and further require additional limitations, including that the claimed heterodimeric antibody is a human IgG (claim 5) or a human IgG1 (claim 6).

102. The '935 Provisional Application explicitly states that the claimed antibodies can have human sequences. The '935 Provisional Application states:

***Antibodies produced with methods according to the present invention can have sequences of any origin, including murine and human sequences.*** Antibodies can consist of sequences from one origin only, such as fully human antibodies, or they can have sequences of more than one origin, resulting for instance in chimeric or humanized antibodies. ***Antibodies for therapeutic use are preferably as close to natural antibodies of the subject to be treated as possible (for instance human antibodies for human subjects).***

*See id.* (EX1030) at 15:1-7 (emphasis added).

103. Further, Example 3 of the '935 Provisional Application explains that a complete human IgG was expressed in transfected HEK293T cells. In addition, Example 7 shows that IgG1 antibodies were deglycosylated, and Examples 8-14 and 17-18 show that IgG and IgG1 were tested for heterodimerization and stability.

104. Accordingly, a POSA reading the '935 Provisional Application would be able to make and use a human IgG or IgG1 antibody for heterodimerization as claimed in dependent claims 5-6.

105. Dependent claim 7 is directed to a pharmaceutical composition including the heterodimeric antibody of independent claim 1 with a pharmaceutically acceptable carrier.

106. The '935 Provisional Application provides examples of pharmaceutical compositions and acceptable carriers. The '935 Provisional Application states:

An Ig-like molecule or a mixture of at least two Ig-like molecules comprising at least one mutation as depicted in Table B is therefore also herewith provided, *as well as a pharmaceutical composition comprising at least one Ig-like molecule, or a mixture of at least two Ig-like molecules, according to the present invention.* In one embodiment said Ig-like molecule is a bispecific Ig-like molecule, such as a bispecific antibody. In another embodiment said Ig-like molecule is a monospecific Ig-like molecule, such as a monospecific antibody. Also provided is a pharmaceutical composition comprising a mixture of at least two Ig-like molecules obtainable by a method according to the invention. Said at least two Ig-like molecules according to the invention are preferably antibodies. *Said pharmaceutical composition may comprise a mixture comprising monospecific or bispecific Ig-like*

*molecules, or a combination of monospecific and bispecific Ig-like molecules.*

*See id.* (EX1030) at 36:8-19 (emphasis added).

107. Therefore, a POSA would have understood that the heterodimeric antibody of independent claim 1 should be administered with a pharmaceutically acceptable carrier.

#### **VIII. INDEPENDENT CLAIM 1 OF THE '859 PATENT WOULD NOT HAVE BEEN OBVIOUS OVER LAZAR ALONE OR IN VIEW OF KANNAN**

108. 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; (4) a POSA’s motivation to combine prior art with a reasonable expectation of success. My analysis of these factors is provided below.

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

110. In my opinion, the inventions of the '859 Patent are not obvious based on Lazar, whether alone or in view of Kannan. In my opinion, Dr. Presta uses impermissible hindsight to pick and choose the elements of the invention of the '859 Patent from disparate, inapplicable prior art without scientific rigor and basis.

111. 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 as they are arranged in the Challenged Claims. Dr. Presta asserts that Lazar alone renders the invention of the '859 Patent “anticipated.” I disagree, at least because Lazar does not disclose a single example that includes a positively charged residue at position 364 in one CH3 domain and a negatively charged residue at position 368 in another CH3 domain.

112. A POSA would not arrive at the inventions of the independent claim 1 of the '859 Patent because there is no motivation for a POSA to modify the disclosures of Lazar alone, or to combine it with Kannan with any reasonable expectation of success.

**A. Scope And Content of The Prior Art**

**i. Lazar**

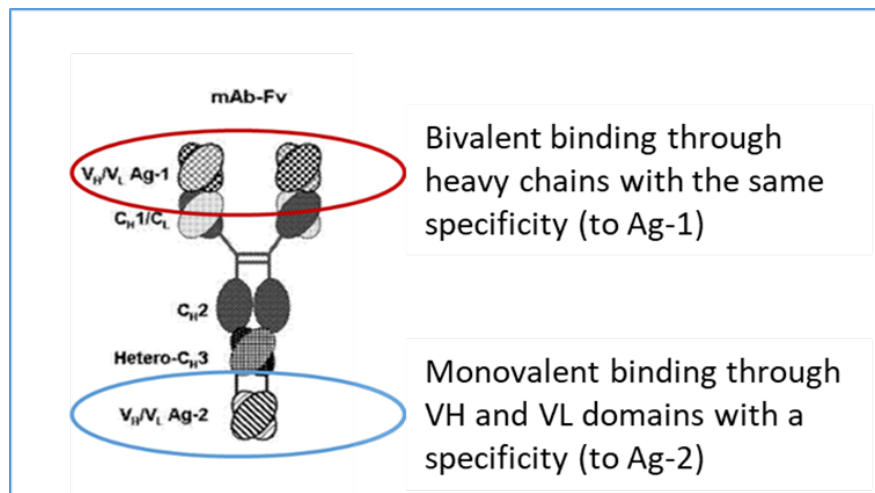
113. The experiments in Lazar were directed to finding alternative bispecific immunoglobulin structures that were better than the traditional “full length antibody-like formats.” *See* Lazar (EX1004) at ¶ 007.

114. 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 *Id.* (EX1004) at ¶ 007 (emphasis added).

115. To avoid the undesired non-specific activation and toxicity of the traditional “full length antibody-like formats,” Lazar created alternative bispecific constructs (*i.e.*, mAb-Fv, mAb-Fab, Fab-Fv, and Fab-Fab) ***that did not need CH3 heterodimerization*** because Lazar added an additional antigen binding site (*e.g.*, Fv or Fab) at the C termini of wild-type IgG heavy chains to provide the simultaneous bivalent and monovalent co-engagement of distinct target antigens. See *Id.* (EX1004) at ¶ 46. Figure 1 below illustrates Lazar’s alternative bispecific construct:



116. Lazar further explained that the scFv-Fc/empty-Fc format was used as an alternative bispecific construct for screening CH3 substitutions for heterodimerization and was not used for testing CH3 substitutions for use in traditional “full length antibody-like formats.” All of the CH3 substitution screening experiments that were conducted and reported on in Lazar were performed using only the scFv-Fc/empty-Fc format. In all of the many substitutions tested and reported in Figures 5-7, Lazar does not disclose a single example that includes a positively charged residue at position 364 in one CH3 domain and negatively charged residue at position 368 in another CH3 domain, in any of the CH3 screening experiments and certainly not in a full antibody format. In fact, Lazar does not mention the word “charged” or say that charges are a relevant consideration.

117. Furthermore, notably, after the screening experiments, Lazar used only one substitution (*i.e.*, Y349T/T394F and S364H/F405A) for the alternative bispecific moieties in the follow-up experiments. Lazar does not suggest any substitutions on the paired positions 364 or 368 for testing in the alternative bispecific moieties.

118. Moreover, Lazar did not use any charged substitutions, much less the charge substitutions required by the Challenged Claims, in any IgG or IgG1

antibodies. In fact, Lazar specifically taught away from using IgG and IgG1 antibodies and proposed the bispecific antibody format as an alternative.

**ii. Kannan**

119. Kannan is concerned with electrostatic steering through charged to charged residue substitution techniques, *i.e.*, “charge swapping.” Kannan does not disclose *any* examples of substitutions to the neutral residues of the CH3 region. This is not surprising because Dr. Gunasekaran Kannan is the same Dr. Kannan who authored the Gunasekaran Paper of 2010 (EX1012) and warned of making any changes to the neutral residues in the hydrophobic region of the CH3 interface. As Dr. Presta admitted at his cross-examination, the Gunasekaran Paper says that it is long established that the hydrophobic core is important to protein stability and folding. *See* Presta Tr. at 183:8-184:3. Instead, in both Kannan and the Gunasekaran Paper the focus is on swapping charged residues *without modifying neutral residues in hydrophobic core regions*. The Gunasekara Paper states:

A strategy was proposed earlier by Carter and co-workers (5– 8) to produce a Fc heterodimer using a set of “knob-into-hole” mutations in the CH3 domain of Fc. These mutations lead to the alteration of residue packing complementarity between the CH3 domain interface within the structurally conserved hydrophobic core so that formation of the heterodimer is favored compared with homodimers. Although the strategy led to higher heterodimer yield, the homodimers were not completely suppressed (7). *In this work, we explored the feasibility of retaining the hydrophobic core integrity whereas driving the formation of Fc heterodimer by*

*changing the charge complementarity at the CH3 domain interface.* Taking advantage of the electrostatic steering mechanism, we were able to efficiently promote Fc heterodimer formation with minimum contamination of homodimers through mutation of two pairs of peripherally located charged residues.

See Dr. Gunasekaran's Paper (EX1012), p. 19637 (emphasis added).

120. In Kannan however, there is a statement that "this strategy can also be extended to modifying uncharged residues to charged residues at the CH3 domain interface." (EX1007 10:16-18). However, it is made without further explanation or exemplification, which is surprising because a POSA would have learned from Kannan and the Gunasekaran Paper to avoid making substitutions in the hydrophobic core and interface, known to be important for folding and stability. Indeed, all of the working examples and suggested mutations in Kannan, as in the Gunasekaran Paper, are directed to substitutions of charged residues with oppositely charged residues, or switching charged residues.

121. Furthermore, all of the working examples and suggested substitutions in Kannan are of native, wild-type residues, not of residues that have already been substituted, such as those in Lazar. This is an important distinction, and will be discussed further below in relation to substitutions identified by Lazar. Consider here the substitutions proposed by Kannan and in the Gunasekaran Paper, which involve, for example, switching the positions of two oppositely charged, wild-type residues

that form a completely buried salt bridge. Such an example is the aspartic acid residue and the lysine residue in the D399-K409' salt bridge between the two CH3 domains at the edge of the interface. These residues are closely packed against surrounding residues in the hydrophobic interface, as seen in the crystal structures of IgG-Fc, and the two side-chains adopt particular rotamers as they occupy this space; this close packing of residues is the result of millions of years of evolution of the antibody structure. If these two residues are switched, each side-chain must now occupy approximately the space previously occupied by the other, and since the side-chains differ substantially in shape and range of possible rotamers, this will almost certainly involve some local reorganization of the packing, clashes with surrounding atoms or create some cavities, all of which will lead to some destabilization of the CH3/CH3 interaction. Merely switching the two residues will likely be more easily be accommodated than additionally substituting either of the residues, from aspartic acid to glutamic acid or lysine to arginine, which will require more extensive local conformational changes to form the salt bridge with the longer, bulkier sidechains. A most extensive, quantitative analysis of the structural consequences of amino-acid residue substitutions in the hydrophobic core of a protein, measuring stability and determining crystal structures, has been made by Matthews in his study of T4 lysozyme (EX2016). Here we have considered the structural considerations

accompanying substitution or switching of wild-type residues, which can be correlated with the experimentally determined effects of the substitutions on heterodimerization for example. However, the structural consequences of, for example, switching charges on residues that have already been substituted and are no longer wild-type, is even more complicated (see below).

122. Without any further information, a POSA would not have any basis to understand or apply the single, unsupported sentence in Kannan, quoted in paragraph 120 above.

123. Furthermore, modification of the CH3 domain interface uncharged residues was discouraged by the inventor of Kannan himself, Dr. Gunasekaran Kannan, the same author of the above-discussed Gunasekaran Paper (EX1012). The Gunasekaran Paper clearly teaches a POSA away from modifying neutral residues in the hydrophobic cores and warns that doing so may negatively affect the antibody folding, structure, stability and functionality. Instead, Kannan, in line with his own teachings in the Gunasekaran Paper, teaches a POSA that charged to charged residue substitutions should be made because Table 7 of Kannan shows that charged to charged residue substitutions provide the highest heterodimeric yields. *See* Kannan (EX1007), Table 7.

## **B. Differences Between The Prior Art And The Claimed Subject Matter Of The '859 Patent**

**i. Lazar**

124. Lazar does not disclose “a heterodimeric antibody comprising CH3 domains having a positively charged residue at position 364 in one domain and a negatively charged residue at position 368 in the other.” Lazar discloses the opposite, *i.e.*, a negatively charged amino acid residue at position 364 and a positively charged amino acid residue at position 368, and does in its scFv-Fc/empty-Fc construct.

**ii. Kannan**

125. Kannan does not disclose any substitutions at positions at 364 and/or 368. Kannan is directed to charge swapping techniques that swap the charges of wild-type residues with those of the opposite charge. Kannan does not have any examples of neutral to charged substitutions of the CH3 interface residues and provides no motivation for a POSA to do so, which the POSA would know to be against the warnings of the Gunasekaran Paper (EX1012).

**C. A POSA Would Not Have Been Motivated To Modify The Teachings Of Lazar To Reach The Invention Of Independent Claim 1 of the '859 Patent**

126. A POSA would not have been motivated to modify the teachings of Lazar to arrive at the invention of independent claim 1 of the '859 Patent.

127. Lazar is silent regarding the features of “a positively charged amino acid residue at position 364” and “a negatively charged amino acid residue at position 368” recited in independent claim 1 of the '859 Patent. Although Lazar tested numerous

substitutions at positions 364 and 368, not a single variant includes “a positively charged amino acid residue at position 364” and “a negatively charged amino acid residue at position 368.” As the Board correctly acknowledged, Lazar does not disclose “a positively charged amino acid residue at position 364” and “a negatively charged amino acid residue at position 368.” *See* Institution Decision, p. 45, lines 1-4.

128. In direct contrast, Lazar discloses oppositely charged substitutions, *i.e.*, a negatively charged amino acid residue at position 364 and a positively charged amino acid residue at position 368. These substitutions S364E and L368K are shown in Table 1, which is titled “Preferred CH3 domain variants that favor Fc heterodimerization.” *See* Lazar (EX1004) at ¶ 241 and Table 1. Lazar does not suggest modifying the preferred variants disclosed in Table 1 for improvements.

129. Rather, Lazar states that the preferred variants were selected after testing a number of variants using quantitative electrophoretic methods. *See* Lazar (EX1004) at ¶ 241. Indeed, the variant listed in Table 1 (*i.e.*, S364E and L368K) provides the highest heterodimeric yields (*i.e.*, 64%) among the variants with substitutions at positions 364 and 368. *See* Lazar (EX1004), Figures 5-7. Furthermore, there are many other examples of substitutions at other positions in Figures 5-7 that produce

much higher yields of heterodimer. *See* Lazar (EX1004), Figures 6 and 7 (*e.g.*, K370D/K392D/K409D and E356K/E357K/D399K).

130. Therefore, a POSA reading the disclosure of Lazar would look to the variants with the highest heterodimerization yield, such as K370D/K392D/K409D and E356K/E357K/D399K, which resulted in a yield of 100% heterodimerization. A POSA would see S364E and L368K and note that the heterodimerization yield was significantly lower at 64%. Given this data in Lazar, a POSA would not be motivated to pick the 364/368 pair for further modification; they would have focused on variants with higher heterodimerization yields, which can approach and even reach 100%. Certainly, a POSA would have no reason or motivation to reverse the charge of S364E and L368K.

131. Instead of following the data, Dr. Presta improperly used hindsight to cherry-pick the S364E/L368K substitution pair in Lazar, and provides no scientific support or explanation as to why a POSA would have then considered reversing the charges *i.e.* S364K/L368E. There are absolutely no data to support such a choice and course of action.

132. To illustrate the absurdity of Dr. Presta's position, a POSA would not have been motivated or have any reason to select the claimed substitutions from a

list of potential amino acid substitutions at a number of residue positions, which in fact offers many thousands of possible pairs.

133. Paragraphs 52 and 123 of Lazar disclose over 62 substitutions that can be introduced in one chain:

In a preferred embodiment, said variant Fc regions comprise at least one substitution selected from the group consisting of 349A, 349C, 349E, 349I, 349K, 349S, 349T, 349W, 351 E, 351 K, 354C, 356K, 357K, 364C, 364D, 364E, 364F, 364G, 364H, 364R, 364T, 364Y, 366D, 366K, 366S, 366W, 366Y, 368A, 368E, 368K, 368S, 370C, 370D, 370E, 370G, 370R, 370S, 370V, 392D, 392E, 394F, 394S, 394W, 394Y, 395T, 395V, 396T, 397E, 397S, 397T, 399K, 401 K, 405A, 405S, 407T, 407V, 409D, 409E, 411D, 411E, 411K, and 439D.

See Lazar (EX1004) at ¶¶ 52 and 123.

There are no data or other reason for a POSA to select either 364 or 368 from this list. Indeed, Lazar explains that heterodimeric Fc variants with paired substitutions are “not a necessity” (*Id.* (EX1004) at ¶108) for its preferred bispecific antibody format. But even if a POSA overlooked that teaching away, there are no data or other reason to select 364 or 368 in the face of such an enormous list of possibilities. Rather, the POSA would have been motivated to be guided by the heterodimerization data.

134. Therefore, it is my opinion that a POSA would not be motivated to select 364/368 out of Lazar for possible modification.

135. The Board and Petitioner are of the opinion that “Lazar teaches that preferred variant Fc Regions include those having a positive charge at 364 (*e.g.*, 364H and 364R) as well as those having a negative charge at (*e.g.*, 368E)” *See* Institution Decision at 47. I respectfully submit that this statement is not a correct reflection of the data and cannot be substantiated. Tables 1 and 2 of Lazar list the “Preferred” and “Most preferred” variants, and neither list includes 364R or 368E at all, let alone in combination, nor do these Tables include any other combinations with a positive charge at 364 and a negative charge at 368. Furthermore, none of the many variants reported in Lazar Figures 5-7 involves only a positive charge at 364 and a negative charge at 368. A POSA would not have been motivated to combine variants based on Lazar’s disclosures because Lazar does not suggest or teach combining variants that include only either a positive charge at 364 or a negative charge at 368. Rather, Lazar states that a number of variants were tested by quantitative electrophoretic methods, and the preferred variants are listed in Tables 1 and 2. Indeed, the variant listed in Table 1 (*i.e.*, S364E and L368K, with the opposite orientation of charges) provides the highest heterodimeric yields (*i.e.*, 64%) among variants with substitutions at positions 364 and 368, but there are many other residue substitutions with much higher heterodimer yields.

136. Thus, a POSA would not have been motivated to modify the teachings of Lazar to arrive at Claim 1 of the '859 Patent.

**D. A POSA Would Not Have Been Motivated To Combine Lazar And Kannan To Reach The Invention Of Independent Claim 1 of the '859 Patent**

137. A POSA would not have been motivated to combine the teachings of Lazar with the teachings of Kannan to arrive at the invention of independent claim 1 of the '859 Patent.

138. For the reasons stated above, a POSA would not have been motivated to modify the teachings of Lazar to arrive at the claimed invention, and certainly Kannan does not make up for the deficiencies in the disclosure of Lazar. A POSA, based on the disclosures of Kannan, would not have made substitutions to any of the variants generated by Lazar, nor is there any disclosure in Lazar or Kannan to motivate a POSA to reverse any charges of residues at positions 364 and 368.

139. It is clear from Kannan's disclosures that charge swapping does not provide the same or similar level of heterodimerization at every position. Rather, Kannan is highly selective regarding the locations of substitutions. Kannan states, "[i]t must be stated here that different combinations will have diverse effects on the quaternary (homodimer/heterodimer) structure formation depending on surrounding residues at the mutation site and role of water molecules." *See* Kannan (EX1007) at

10:6-10. These comments are in accord with the description of the structural consequences of charge swapping at paragraph 121 above, where I point out that these are difficult enough to predict for substituting and/or swapping wild-type residues, but even more difficult for residues that have already been substituted and will likely have caused some local disruption of the structure. All of Kannan's variants were substituted from wild-type.

140. Furthermore, Lazar, like Kannan, does not suggest charge-swapping at positions 364 and 368. As discussed above, the "Preferred CH3 domain variants" in Table 1 represent the most promising amino acid residue substitutions for heterodimerization amongst those residue positions tested by Lazar. A POSA would have had no basis for applying any modifications suggested in Kannan because the data in Lazar showed that making such modifications to Lazar's "Preferred CH3 domain variants" would only reduce the heterodimerization yield.

141. Rather, in direct contrast, a POSA would understand that swapping charges of Lazar's preferred variants may lead to a decrease in heterodimerization yield. As discussed above, Lazar tested positions 364 and 368 with various variants. Among the various variants, the S364E and L368K variant listed in Table 1 provides the highest heterodimeric yields (*i.e.*, 64%), suggesting that the S364E and L368K substitutions cause the most favorable, but still inferior, heterodimerization effects.

142. For the reasons discussed above, it is my opinion that a POSA would not have been motivated to modify Lazar or to combine Lazar with Kannan to reach the invention of independent claim 1 of the '859 Patent.

**E. A POSA Would Have Had No Reasonable Expectation Of Success In Modifying The Teachings Of Lazar Or Combining Lazar And Kannan To Reach The Invention Of Claim 1 of the '859 Patent**

143. A POSA reading Lazar would not have had a reasonable expectation of success of heterodimerization when they combine variants other than those of Table 1. Lazar highlights that the variants in Table 1 represent the most promising amino acid residue substitutions for heterodimerization at the positions considered by Lazar. *See* Lazar (EX1004) at ¶¶ 240-241. Lazar first used “computational structure-based methods (PDA® technology) to “evaluate possible amino acid substitutions in the CH3 region for their ability to stabilize Fc heterodimers and destabilize Fc homodimers.” *See* Lazar (EX1004) at ¶ 236. Selected variants were then screened using the scFv-Fc and empty-Fc constructs. *See* Lazar (EX1004) at ¶ 240. A quantitative summary of the variants is provided in Figures 5-7, and “Preferred” and “Most preferred” variants from this screen are listed in Tables 1 and 2, respectively. *See* Lazar (EX1004) at ¶¶ 240-241.

144. As of 2012, a POSA would have understood that substituting CH3 domain residues may affect the folding, structure, stability and functionality of an

antibody, and accordingly, introducing additional substitutions to variants that had already been exhaustively engineered through Lazar's substitution selection processes would most likely only decrease the degree of heterodimerization.

145. Moreover, as discussed above, Dr. Presta admitted that Kannan says that charge swapping only reduces homodimer formation when applied to native occurring chains – in other words that a naturally-occurring pair of charged residues, with wild-type residues, will only be less stable after charge swapping *See* Presta Tr. at 186:21-187:12. A structural explanation for this is presented at paragraph 121 above. Unlike Kannan's variants, which were substituted from wild-type, the engineered variants of Lazar already have modified structures and surrounding environments as a result of the initial substitution(s) from the wild-type residue(s), and thus a POSA cannot have reasonably expected that reengineering already modified structures, especially at the exact same position, would be beneficial, without testing.

146. Accordingly, a POSA would not have had a reasonable expectation of enhanced heterodimerization when the charges of engineered variants of Lazar are swapped. Rather, in direct contrast, a POSA would have understood that swapping charges of Lazar's preferred variants would more likely lead to a decrease in heterodimerization yield.

147. 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 have had any reasonable expectation of success in making the claimed invention based on the teachings of Lazar alone or in combination with Kannan.

**F. All Elements Present If Combined**

148. Even if a POSA had a motivation to combine Lazar and Kannan with a reasonable expectation of success, which a POSA would not have had, a combination of all of the elements of Lazar and Kannan does not lead to all of the elements of the claims of the '859 Patent.

149. A POSA would not arrive at the invention claimed in the '859 Patent because the combination of Lazar and Kannan fails to disclose at least a positively charged residue at position 364 in one CH3 domain and a negatively charged residue at position 368 in another CH3 domain.

150. Lazar discloses the exact opposite of the invention of claim 1 of the '859 Patent, as Lazar discloses a negatively charged amino acid residue at position 364 and a positively charged amino acid residue at position 368 as a preferred variant.

151. Kannan does not provide any further information related to residues at positions 364 and 368. Kannan does not disclose or suggest any substitutions at

positions 364 and 368. Kannan focuses on charge swapping technologies but only wild-type charged residues. Kannan does not disclose or suggest anything about reversing charges on substituted or modified residues.

**G. 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 '859 Patent would have been obvious to a POSA. I understand these factors are usually called "secondary considerations of non-obviousness." These factors include things like: teaching away, skepticism, and unexpected results.

153. Teaching Away / Skepticism: As discussed in more detail above, the Gunasekaran Paper warns against mutating the neutral residues of the hydrophobic core. This would teach POSAs away from the claimed invention of the '859 Patent. As I stated above, the data in Lazar showing a lower heterodimerization yield for substitutions at positions 364 and 368 compared with other substitutions would also have taught a POSA away from the claimed invention of the '859 Patent.

154. Furthermore, as residues at positions 364 and 368 of wild-type CH3 domains are neutral residues, based on such suggestions of Dr. Kannan, a POSA would not be motivated to further modify residues in the hydrophobic interface region using Dr. Gunasekaran's charge swapping technologies. Accordingly, a

POSA would have understood that Lazar's S364E and L358K variants have already modified neutral residues in a hydrophobic core region, and thus a POSA would not re-engineer or swap charges of Lazar's variant with S364E and L368K because it would not recover the functionality of the hydrophobic core or interface region.

155. Unexpected results: Merus' heterodimerization methodology surprisingly achieves heterodimeric antibodies capable of higher yield and increased stability, especially in light of the teachings of the Gunasekaran Paper and the data from Lazar and Kannan.

156. In my opinion, each of these "secondary considerations" further supports my above opinion that the inventions of the '859 Patent would not have been obvious to a POSA at the time of the invention.

**IX. DEPENDENT CLAIMS 2-7 OF THE '859 PATENT WOULD NOT HAVE BEEN OBVIOUS OVER LAZAR ALONE OR IN VIEW OF KANNAN**

157. Dependent claims 2-7 include all of the elements of independent claim 1 and further require additional limitations. Because it is my opinion that independent claim 1 would not have been obvious, it is also my opinion that each claim that depends from claim 1 is also not obvious. The dependent claims are also not obvious for additional reasons.

**A. Dependent Claims 2 and 3**

158. Dependent claims 2 and 3 include all of the elements of independent claim 1 and further require additional limitations, including the specific positively charged residues at position 364 (*i.e.*, lysine or arginine) and negatively charged residues (*i.e.*, aspartic acid or glutamic acid) at position 368. As discussed above, Lazar alone or in combination with Kannan fails to disclose the feature of a heterodimeric antibody with “a positively charged amino acid residue at position 364” and “a negatively charged amino acid residue at position 368.” Lazar and Kannan fail to disclose a single example with a positively charged residue at position 364 and a negatively charged residue at position 368. As discussed, a combination of Lazar and Kannan also would have failed to motivate a POSA to arrive at the claimed subject matter with a reasonable expectation of success for the same reason applied to independent claim 1.

**B. Dependent Claim 4**

159. Dependent claim 4 includes all of the elements of independent claim 1 and further require additional limitations, including that the claimed heterodimeric antibody is a bispecific antibody. Lazar alone or in combination with Kannan fails to disclose the feature of a bispecific antibody with “a positively charged amino acid

residue at position 364” and “a negatively charged amino acid residue at position 368.”

160. As an initial matter, Lazar’s alternative bispecific moieties (*i.e.*, mAb-Fv, mAb-Fab, Fab-Fv, and Fab-Fab) do not need Fc heterodimerization of any kind, much less Fc heterodimerization driven by the specific charge substitutions in the claims.

161. Lazar alone or in combination with Kannan also does not disclose the limitations in dependent claim 4 of the ‘859 Patent because Lazar and/or Kannan fails to disclose or suggest the claimed features of independent claim 1 that are incorporated into dependent claim 4.

### **C. Dependent Claims 5 and 6**

162. Dependent claims 5-6 include all of the elements of independent claim 1 and further require additional limitations, including that the claimed heterodimeric antibody is a human IgG (claim 5) or a human IgG1 (claim 6). Lazar alone or in combination with Kannan fails to disclose the features of a human IgG or a human IgG1 with “a positively charged amino acid residue at position 364” and “a negatively charged amino acid residue at position 368.”

163. The only substitutions tested in an IgG or IgG-like molecule in Lazar are Y349T/T394F in one chain and S364H/F405A in the other. Lazar does not

disclose or suggest any substitutions at positions 364 and 368 of a human IgG or a human IgG1. As discussed above, the closest substitutions disclosed by Lazar are the oppositely charged substitutions, *i.e.*, a negatively charged amino acid residue at position 364 and a positively charged amino acid residue at position 368, and these substitutions were introduced into the scFv-Fc/empty-Fc format, which is not a human IgG or a human IgG1. Even assuming that a POSA would apply the variants tested on the scFv-Fc/empty-Fc format to IgG-like molecules, Lazar fails to disclose the claimed substitutions.

164. Similarly, Kannan is silent regarding the claimed substitutions at positions 364 and 368. Indeed, Kannan does not disclose any substitutions at positions 364 and 368. Although Kannan suggests swapping a charged residue with an oppositely charged residue, a POSA would not have swapped the charges of Lazar's variant at positions 364 and 368 because they would know that it had already been exhaustively tested through Lazar's substitution selection processes, that only the most successful variants were reported in Table 1 of Lazar, and therefore that modification of such variant would only decrease the heterodimerization yield. Kannan is highly selective regarding the locations of charged to charged residue substitutions and the effects of charge swapping on engineered variants that are not wild-type and thus already have modified structures and altered surrounding

environments; such cases were not tested or suggested in Kannan. Accordingly, a POSA would not have had a reasonable expectation of success in promoting an increased yield of heterodimer when the charges of engineered variants of Lazar are swapped.

**D. Dependent Claim 7**

165. Dependent claim 7 is directed to a pharmaceutical composition including the heterodimeric antibody of claim 1 and a pharmaceutically acceptable carrier. Dependent claim 7 includes all of the elements of independent claim 1 and further requires a feature of a pharmaceutically acceptable carrier.

166. Lazar alone or in combination with Kannan also does not disclose the limitations in dependent claim 7 of the '859 Patent because Lazar and/or Kannan fails to disclose or suggest the claimed features of independent claim 1 that are incorporated into dependent claim 7.

**X. LAZAR DOES NOT ANTICIPATE THE CHALLENGED CLAIMS OF THE '859 PATENT**

167. 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 as they are arranged in the Challenged Claims. I also understand that it is not permissible to pick and choose

different pieces of information from a prior art reference and rearrange them in an anticipatory analysis.

168. Lazar does not disclose the elements of any of the Challenged Claims as they are arranged in the claims of the '859 Patent. To be clear, Dr. Presta does not appear to argue that Lazar anticipates the '859 Patent, but I will briefly provide my opinion out of an abundance of caution.

169. Lazar does not disclose “a heterodimeric antibody comprising CH3 domains having a positively charged residue at position 364 in one domain and a negatively charged residue at position 368 in the other.” Rather, in direct contrast to claim 1 of the '859 Patent, Lazar discloses the opposite, *i.e.*, a negatively charged amino acid residue at position 364 and a positively charged amino acid residue at position 368. Thus, Lazar cannot anticipate the Challenged Claims of the '859 Patent.

## **XI. CONCLUSION**

170. 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.

IPR2025-00605  
Patent No. 11,926,859  
Second Declaration of Brian J. Sutton, Ph.D.

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

A handwritten signature in black ink, appearing to read 'B. J. Sutton', written in a cursive style.

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Brian J. Sutton, Ph.D.