

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

XENCOR, INC.,

Petitioner

v.

MERUS N.V.,

Patent Owner

IPR2025-00605
Patent No. 11,926,859

PATENT OWNER'S RESPONSE

TABLE OF CONTENTS

I. INTRODUCTION1

II. STATE OF THE PRIOR ART4

III. LEVEL OF ORDINARY SKILL IN THE ART6

IV. THE '859 PATENT7

V. SUMMARY OF XENCOR'S GROUNDS AND REFERENCES8

VI. CLAIM CONSTRUCTION9

VII. XENCOR HAS NOT MET ITS BURDEN OF PROVING THAT THE
CHALLENGED CLAIMS ARE UNPATENTABLE.....9

VIII. THERE IS WRITTEN DESCRIPTION AND ENABLEMENT SUPPORT
FOR THE CHALLENGED CLAIMS IN THE '935 APPLICATION10

 A. The '935 Application Provides Adequate Written Description
 Support For Independent Claim 112

 B. The '935 Application Provides Adequate Written Description
 Support For Dependent Claims 2-7.....31

 C. The '935 Application Is Enabling.....33

 D. The Challenged Claims Are Not Anticipated Because Xencor's
'427 Patent (Desjarlais) And Moore Are Not Prior Art To The '859 Patent.....37

IX. THE CHALLENGED CLAIMS WOULD NOT HAVE BEEN OBVIOUS
OVER LAZAR ALONE OR IN VIEW OF KANNAN.....37

 A. The *Graham* Factors39

 i. Scope And Content Of The Prior Art39

 1. Lazar39

 2. Kannan.....42

ii. Differences Between The Prior Art And The Claimed Subject	
Matter Of The '859 Patent	45
1. Lazar	45
2. Kannan.....	45
iii. Level Of Ordinary Skill In The Art.....	45
iv. Secondary Considerations Of Nonobviousness	46
1. Teaching Away / Skepticism.....	46
2. Unexpected Results	47
B. A POSA Would Not Have Been Motivated To Modify Lazar To Reach The Invention Of Independent Claim 1.....	48
C. A POSA Would Not Have Been Motivated To Combine Lazar And Kannan To Reach The Invention Of Independent Claim 1.....	53
D. 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	56
E. Even If Combined, Lazar and Kannan Together Fail To Disclose All Of The Elements Of The Challenged Claims	58
F. Dependent Claims 2-7 Would Not Have Been Obvious Over Lazar Alone Or In View Of Kannan	59
i. Dependent Claims 2 and 3.....	59
ii. Dependent Claim 4	60
iii. Dependent Claims 5 and 6.....	61
iv. Dependent Claim 7	62

X. LAZAR DOES NOT ANTICIPATE ANY OF THE CHALLENGED CLAIMS.....62

XI. DR. PRESTA’S OPINIONS ARE UNRELIABLE AND SHOULD CARRY NO WEIGHT63

 A. Dr. Presta Was Not Informed Of The Legal Standard For Assessing Written Description63

 B. Dr. Presta’s Obviousness Analysis Is Deficient63

 C. Dr. Presta’s Arguments Are Inconsistent64

XII. CONCLUSION.....64

TABLE OF AUTHORITIES

	Page(s)
Cases	
<i>Aqua Prods. v. Matal</i> , 872 F.3d 1290 (Fed. Cir. 2017)	9
<i>Ariad Pharms., Inc. v. Eli Lilly & Co.</i> , 598 F.3d 1336 (Fed. Cir. 2010) (en banc)	<i>passim</i>
<i>In re Fritch</i> , 972 F.2d 1260 (Fed. Cir. 1992)	59, 61
<i>Fujikawa v. Wattanasin</i> , 93 F.3d 1559 (Fed. Cir. 1996)	11, 21
<i>Genentech, Inc. v. Novo Nordisk A/S</i> , 108 F.3d 1361 (Fed. Cir. 1997)	11, 33
<i>Graham v. John Deere Co.</i> , 383 U.S. 1 (1966).....	3, 39, 63
<i>Hulu, LLC v. Sound View Innovations, LLC</i> , Case IPR2018-00582, Paper 34 (August 5, 2019).....	39
<i>Intelligent Bio-Systems, Inc. v. Illumina Cambridge, Ltd.</i> , 821 F.3d 1359 (Fed. Cir. 2016)	39
<i>Knauf Insulation, Inc. v. Rockwool Int’l A/S</i> , 788 F. App’x 728 (Fed. Cir. 2019)	53, 54, 55, 56
<i>KSR Int’l Co. v. Teleflex Inc.</i> , 550 U.S. 398 (2007).....	<i>passim</i>
<i>Leo Pharm. Prods. v. Rea</i> , 726 F.3d 1346 (Fed. Cir. 2013)	38, 47

<i>Microsoft Corp. v. Biscotti, Inc.</i> , 878 F.3d 1052 (Fed. Cir. 2017)	62
<i>Nidec Motor Corp. v. Zhongshan Broad Ocean Motor Co.</i> , 868 F.3d 1013 (Fed. Cir. 2017)	9
<i>Regents of Univ. of California v. Broad Inst., Inc.</i> , 903 F.3d 1286 (Fed. Cir. 2018)	<i>passim</i>
<i>Regents of the Univ. of Minn. v. Gilead Scis., Inc.</i> , 61 F.4th 1350 (Fed. Cir. 2023)	11
<i>In re Soni</i> , 54 F.3d 746 (Fed. Cir. 1995)	47
<i>Ex parte Thompson</i> , 2011-011620 (P.T.A.B. March 21, 2014).....	38
<i>Vas-Cath Inc. v. Sakharam D. Mahurkar</i> , 935 F.2d 1555 (Fed. Cir. 1991)	<i>passim</i>
<i>In re Wands</i> , 858 F.2d 731 (Fed. Cir. 1988)	11
<i>WBIP, LLC v. Kohler Co.</i> , 829 F.3d 1317 (Fed. Cir. 2016)	46, 47
<i>Ex Parte Whirlpool Corp.</i> , 2013-008232 (P.T.A.B. October 30, 2013)	38
Statutes	
35 U.S.C. § 102	37
35 U.S.C. § 103	37
35 U.S.C. § 112(a)	10, 11
35 U.S.C. § 119	10

35 U.S.C. § 316(e)9
Patent Act.....10

TABLE OF ABBREVIATIONS

Abbreviation	Definition
Merus	Patent Owner Merus N.V.
Xencor	Petitioner Xencor, Inc.
IPR	Inter partes review
Board	Patent Trial And Appeal Board
'859 Patent	Merus' U.S. Patent No. 11,926,859
Desjarlais	Xencor's U.S. Patent No. 10,472,427 to Desjarlais et al.
'935 Application	April 20, 2012 Provisional Application No. 61/635,935
POSA	Person of ordinary skill in the art
Gunasekaran Paper	Gunasekaran Kannan, et al., Enhancing antibody Fc heterodimer formation through electrostatic steering effects: applications to bispecific molecules and monovalent IgG. J Biol Chem. 2010 Jun 18;285(25):19637-46
Moore	Moore, et al., A robust heterodimeric Fc platform engineered for efficient development of bispecific antibodies of multiple formats. Methods. 2019 Feb 1;154:38-50
Lazar	U.S. Patent Application Publication No. US 2011/0054151
Kannan	International Patent Application Publication No. WO 2009/089004
Challenged Claims	Claims 1-7 of the '859 Patent
First Sutton Declaration	Declaration of Dr. Brian Sutton, Ph.D. In Support Of Patent Owner Merus' Preliminary Response
Second Sutton Declaration	Second Declaration of Brian J. Sutton, Ph.D.
Presta Declaration	Declaration of Leonard G. Presta, Ph.D.
Presta Deposition	Transcript from the Deposition of Dr. Leonard G. Presta, Ph.D. (December 5, 2025)

LIST OF EXHIBITS

Exhibit Number	Description
EX1001	'859 Patent
EX1002	Presta Declaration
EX1004	Lazar
EX1007	Kannan
EX1012	Gunasekaran Paper
EX1013	Kontermann Paper
EX1017	Merchant
EX1030	'935 Application
EX2010	First Sutton Declaration
EX2015	Presta Deposition Transcript
EX2016	Matthews (EX4001 to the Presta Deposition)
EX2019	Second Sutton Declaration

I. INTRODUCTION

The Board should deny Xencor's petition to invalidate the Challenged Claims in its entirety.

As Dr. Sutton explains in his declarations, a POSA would find both written description and enablement support for the claims of the '859 Patent in the '935 Application. The '859 Patent is thus entitled to its earliest claimed priority date of April 20, 2012. That priority date disposes of Xencor's arguments based on Moore and Desjarlais because both of those references post-date April 20, 2012.

Xencor's remaining arguments are unavailing. For example, Lazar does not disclose a heterodimeric antibody with human CH3 domains having "a positively charged amino acid residue at position 364" in one domain and "a negatively charged residue at position 368" in the other domain. In fact, Lazar discloses the opposite charges, *i.e.*, a negatively charged residue at position 364 and a positively charged residue at position 368. Xencor tries to contort this difference into an anticipation argument, but fails. Lazar does not disclose all of the claim elements arranged as they are in the claim.

Xencor fares no better with its obviousness arguments. A POSA had no reason to modify Lazar to arrive at the claimed inventions, much less a reasonable expectation of success in doing so. Indeed, a POSA would have understood that the neutral to charged substitutions in Lazar resulted in inferior heterodimeric purity and

were not used in any of Lazar's "alternative" bispecific moieties or full-length antibodies.

Kannan does not address any of Lazar's shortcomings. Like Lazar, Kannan does not disclose the required substitutions at positions 364 and/or 368. Kannan is directed to a "charge swapping" approach to creating bispecific antibodies that swaps charged wild-type residues for those of the opposite charge. Kannan does not disclose changing the charge of a residue that has already been changed from wild-type. Xencor cites a single line from Kannan mentioning neutral residues, but that line provided no motivation for a POSA to do anything with residues 364 and/or 368 in Lazar, which were already changed from wild-type to charged residues. It was also contradicted as of the priority date by Dr. Kannan's own paper (EX1012), which warned against modifying neutral residues in the hydrophobic core.¹

In short, a POSA had no reason to try to modify Lazar or combine Lazar and Kannan to arrive at the claimed inventions, much less with a reasonable expectation of success.

¹ EX1012 ("the Gunasekaran Paper") is authored by the first named inventor of the Kannan reference, Dr. Gunasekaran Kannan. The paper mistakenly switches the scientist's first and last names. Merus calls it the "Gunasekaran Paper" in this IPR for consistency.

In seeking to invalidate the Challenged Claims, Xencor relies on a declaration from Dr. Leonard Presta. But Dr. Presta's declaration was thoroughly undermined on cross-examination.

For example, Dr. Presta admitted on cross-examination that he was never made aware of the legal standard for analyzing whether a patent properly claims priority to an earlier-filed patent application. Indeed, Dr. Presta admitted that he did not remember discussing with anyone what to consider to determine whether an application provides an adequate written description of claimed subject matter. Despite this fatal flaw, Xencor still presented Dr. Presta's declaration as evidence on the alleged written description issue. The Board should give that evidence no weight. It is simply not possible to provide a reliable written description opinion without knowing the correct legal standard.

Dr. Presta also failed to do a proper obviousness analysis. Dr. Presta did not analyze the *Graham* factors—by name or otherwise—and ignored various secondary considerations that support the non-obviousness of the Challenged Claims. Dr. Presta further failed to provide a credible reason why a POSA would have been motivated to arrive at the claimed inventions with a reasonable expectation of success.

For all these reasons, as explained in more detail below, Xencor's petition to invalidate the Challenged Claims should be denied in its entirety.

II. STATE OF THE PRIOR ART

By April 20, 2012, researchers had investigated numerous ways to create bispecific antibodies for potential therapeutic uses. Indeed, by that date, a POSA would have been aware of at least 45 different approaches for creating bispecific antibodies. *See* EX2019 (Second Sutton Declaration) at ¶ 8; EX1013 (Kontermann) at Fig. 2. As Dr. Presta agreed during cross-examination, only *seven* of the 45 known approaches for creating bispecific antibodies involved modification of the antibody Fc region (which includes the CH3 domain), and only *one* of those seven approaches involved “charge pairs.” *See* EX2015 (Presta Tr.) at 138:3–139:8.

A POSA in 2012 would have had no reason to select for modification the one “charge pairs” approach to creating bispecific antibodies out of the 45 different approaches reported in the Kontermann paper (EX1013). *See* EX2019 (Second Sutton Declaration) at ¶ 10. Indeed, Xencor fails to cite any evidence suggesting that the “charge pairs” approach was superior to the other known approaches as of the invention date. Even if a POSA were interested in using the Fc region to create bispecific antibodies, they would have investigated other well-known methods for

creating bispecific antibodies—like knob into hole with disulfide bonds, which was reported to achieve 95 percent heterodimeric purity—or been content to use the existing “charge pairs” approach, which was reported to produce the desired heterodimer “almost exclusively.” *See id;* *see also* EX1017 (Merchant) and EX1012 (Gunasekaran Paper). Dr. Presta used hindsight to single out the “charge pairs” approach for modification. A POSA on April 20, 2012, however, did not have any reason to do so.

Even if a POSA ignored the 44 other known approaches for creating bispecific antibodies—and ignored the almost exclusive production of the desired heterodimer using the existing “charge pairs” approach—a POSA seeking to modify the “charge pairs” approach knew to avoid the neutral residues in the hydrophobic core of the CH3 domain. By April 20, 2012, this was well known to a POSA, including because the Gunasekaran Paper had explained that these neutral residues play an important role in protein folding and stability. *See* EX1012 at 4 (citing EX2016 (Matthews)). Indeed, this concept was so well-accepted that the Gunasekaran Paper (EX1012) is incorporated into Lazar in its entirety. *See* EX1004 (Lazar) at ¶ 125; EX2019 (Second Sutton Declaration) at ¶ 18. A POSA clearly understood on April 20, 2012—from at least the Gunasekaran Paper (EX1012) and the Matthews paper cited

therein (EX2016)—that charge modifications to improve heterodimerization should be made to the already charged residues at the periphery of the CH3 domain and not to neutral residues in the hydrophobic core. *See* EX2019 (Second Sutton Declaration) at ¶¶ 11-18.

Dr. Presta's cross-examination testimony confirms that a POSA would not have been motivated to substitute the neutral residues in the hydrophobic core of the CH3 domain to promote heterodimerization. The Gunasekaran Paper explicitly states that the neutral residues in the hydrophobic core play an important role in protein folding. According to Dr. Presta, a POSA at the relevant time was unlikely to "understand the intricacies of what controlled protein folding." EX2015 (Presta Tr.) at 86:14–21, 87:16–88:1. A POSA would have been unlikely to modify a residue when they did not understand its role.

Dr. Presta also testified that a POSA at the relevant time knew the antibody Fc region (which contains the CH3 domain) serves important biological functions and that a POSA would not have wanted to interfere with those functions. *See* EX2015 (Presta Tr.) at 42:1–16. It follows that a POSA would not have wanted to modify, and potentially destabilize, this critical domain.

III. LEVEL OF ORDINARY SKILL IN THE ART

A POSA at the time of the invention of April 20, 2012 would have had a Ph.D. in biochemistry, chemistry, molecular or structural biology, molecular biophysics, antibody engineering, immunology, or related discipline and at least 2 years of related experience in academia or industry or a Master's degree in any of the above fields with at least 4 years of related experience in academia or industry. *See* EX2010 (First Sutton Declaration) at ¶ 17; EX2019 (Second Sutton Declaration) at ¶ 6.

Xencor proposed a similar definition of a POSA, which was adopted by the Board for purposes of its institution decision. Patent Owner's arguments and Dr. Sutton's declaration evidence apply equally regardless of which definition of a POSA is applied.

IV. THE '859 PATENT

Independent claim 1 recites:

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.

EX1001.

Dependent claims 2–7 include all of the elements of independent claim 1 and further require additional limitations. *See* EX1001. Claim 2 further requires that the positively charged residue at position 364 comprises a lysine (K) or an arginine (R) residue, and that the negatively charged residue at position 368 comprises an aspartic acid (D) or glutamic acid (E) residue. Claim 3 further requires that the positively charged residue at position 364 comprises a lysine (K) residue, and that the negatively charged residue at position 368 comprises an aspartic acid (D) residue. Claim 4 further requires that the heterodimeric antibody be a bispecific antibody. Claim 5 and 6 further require that the heterodimeric antibody be human IgG or human IgG1, respectively. Claim 7 further requires that the heterodimeric antibody be combined with a pharmaceutically acceptable carrier in a pharmaceutical composition.

V. SUMMARY OF XENCOR'S GROUNDS AND REFERENCES

Xencor's petition alleges three grounds of invalidity: (1) anticipation based on Xencor's '427 Patent (Desjarlais); (2) anticipation based on Moore; and (3) obviousness based on Lazar alone (3a) or Lazar in view of Kannan (3b). For the reasons discussed herein, Xencor fails to meet its burden to prove by a

preponderance of the evidence that any of the Challenged Claims should be invalidated based on any of these grounds.

VI. CLAIM CONSTRUCTION

In its institution decision, the Board construed the terms “heterodimeric antibody” and “CH3 domain.” *See* Paper 13. Patent Owner does not believe that these terms—or any claim terms—require construction to resolve this controversy. *See Nidec Motor Corp. v. Zhongshan Broad Ocean Motor Co.*, 868 F.3d 1013, 1017 (Fed. Cir. 2017) (noting that “we need only construe terms that are in controversy, and only to the extent necessary to resolve the controversy”) (internal quotations omitted). But even if the Board’s constructions are applied, Patent Owner’s analysis and Dr. Sutton’s Second Declaration would not change. *See* EX2019 (Second Sutton Declaration) at ¶ 22.

VII. XENCOR HAS NOT MET ITS BURDEN OF PROVING THAT THE CHALLENGED CLAIMS ARE UNPATENTABLE

“In an inter partes review . . . the petitioner shall have the burden of proving a proposition of unpatentability by a preponderance of the evidence.” 35 U.S.C. § 316(e); *Aqua Prods. v. Matal*, 872 F.3d 1290, 1300 (Fed. Cir. 2017). Xencor fails to meet its burden. Because the Challenged Claims are entitled to their claimed priority date of April 20, 2012, neither Xencor’s ’427 Patent (Desjarlais) nor Moore

is available as prior art. Xencor's anticipation arguments based on these references thus fail. Xencor similarly fails to prove that the Challenged Claims would have been obvious to a POSA based on Lazar alone, or Lazar in combination with Kannan. Xencor's and Dr. Presta's sweeping assertions, unsupported by proper analyses, are insufficient to meet their burden of proof.

VIII. THERE IS WRITTEN DESCRIPTION AND ENABLEMENT SUPPORT FOR THE CHALLENGED CLAIMS IN THE '935 APPLICATION

The '859 Patent is entitled to its claimed priority date of April 20, 2012. As provided by the Patent Act, a patent application is entitled to claim priority to a filing date of an earlier application "for an invention disclosed in the manner provided by 112(a) (other than the requirement to disclose the best mode) in a provisional application." 35 U.S.C. § 119.

The test for written description sufficiency under 35 U.S.C. § 112(a) is whether the parent application's disclosure "reasonably conveys to those skilled in the art that the inventor had possession of the claimed subject matter as of the filing date." *Ariad Pharms., Inc. v. Eli Lilly & Co.*, 598 F.3d 1336, 1351 (Fed. Cir. 2010) (en banc); *see also Vas-Cath Inc. v. Sakharam D. Mahurkar*, 935 F.2d 1555, 1562–63 (Fed. Cir. 1991). That "test requires an objective inquiry into the four corners of

the specification from the perspective of a person of ordinary skill in the art.” *Ariad*, 598 F.3d 1351. The applicant “does not have to describe exactly the subject matter claimed” to comply with the written description requirement. *Vas-Cath*, 935 F.2d at 1563. Indeed, “the written description requirement does not demand either examples or an actual reduction to practice.” *Ariad*, 598 F.3d at 1352. Nor does it require “*ipsis verbis* disclosure.” *Fujikawa v. Wattanasin*, 93 F.3d 1559, 1570 (Fed. Cir. 1996). The written description requirement is satisfied when the disclosure provides sufficient “blaze marks” directing a POSA to the invention. *See id.*; *see also Regents of the Univ. of Minn. v. Gilead Scis., Inc.*, 61 F.4th 1350, 1356-58 (Fed. Cir. 2023).

To fulfill the enablement requirement of 35 U.S.C. § 112(a), “the specification of . . . [the parent application] must teach those skilled in the art how to make and use the full scope of the claimed invention without ‘undue experimentation.’” *Genentech, Inc. v. Novo Nordisk A/S*, 108 F.3d 1361, 1365 (Fed. Cir. 1997). To determine whether a disclosure requires undue experimentation, courts assess the *Wands* factors. *In re Wands*, 858 F.2d 731, 737 (Fed. Cir. 1988).

The '859 Patent claims priority to Merus' '935 Application, which was filed on April 20, 2012. The '935 Application provides adequate written description and enablement support for all of the Challenged Claims.

A. The '935 Application Provides Adequate Written Description Support For Independent Claim 1

This '935 Application “reasonably conveys to those skilled in the art that the inventor had possession of the claimed subject matter” as of April 20, 2012. *Ariad*, 598 F.3d at 1351; *see also Vas-Cath*, 935 F.2d at 1562–63.

The '935 Application describes the invention as follows:

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

The importance of bispecific antibodies was well-appreciated as of the April 20, 2012 filing date of the '935 Application. *See* EX2019 (Second Sutton Declaration) at ¶ 33. A key issue for creating bispecific antibodies as of that date was doing so without creating difficult to separate impurities. *See id.* at ¶ 34. As explained by Dr. Sutton, 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). *See id.* Given the similarities between the heterodimers and the homodimers, they can be difficult to separate from each other. *See id.*

In contrast, as the '935 Application explains, unpaired monomers “can be easily separated from the mixture by size exclusion chromatography.” EX1030 ('935 Application) at 24:22-26. A POSA reading the '935 Application would have understood that the inventors were focused on minimizing contaminating homodimers rather than easily removable unpaired monomers. *See* EX2019 (Second Sutton Declaration) at ¶ 35.

A POSA reading the '935 Application would have further understood that the inventors were providing a new solution to the problem of contaminating homodimers. *See id.* at ¶ 36. A POSA reading the '935 Application would have understood that the inventors first discussed the relevant context for the problem, including the “well-known” importance of CH₃-CH₃ interaction as “the primary driver for Fc dimerization.” *See* EX1030 ('935 Application) at 5:12-13. On further reading, a POSA would have understood that this interaction is driven by the

“contact” residues in each CH3 domain. *Id.* at 5:12-20; EX2019 (Second Sutton Declaration) at ¶ 36.

A POSA reading the '935 Application would have understood that the inventors were so focused on these “contact” residues that they provided a list of all such residues as Table A. Importantly, Table A did not just list “contact” residues for one CH3 domain, but listed these residues for a “chain A” and a “chain B” and showed for each “[i]nterface residue in chain A” the “[c]ontacting residues in chain

Table A: List of CH3 domain interface residues

Interface residue in chain A	Contacting residues in chain 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

B.” *See* EX2019 (Second Sutton Declaration) at ¶ 37; EX1030 ('935 Application) at Table A (reproduced below).

A POSA reading the '935 Application would have understood that the contact residues in one CH3 domain interact (*e.g.*, through hydrogen bonding, forming salt bridges, *etc.*) with their counterpart contact residues in the other CH3 domain. *See* EX2019 (Second Sutton Declaration) at ¶ 38. A POSA would have further understood that the CH3 contact residues account for the majority of contributions to domain folding and association. *See id.*

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 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.” *See* EX1030 ('935 Application) at 5:30-7:34; EX2019 (Second Sutton Declaration) at ¶¶ 39-44.

The inventors of the '935 Application discussed several such methods, including “complementary protuberance and cavity mutations, also known as ‘knob-in-hole’ approaches.” *See* EX1030 ('935 Application) at 5:32-6:2. The inventors went on to explain that the knob-in-hole approach had been improved upon with the

“introduction of an additional disulfide bond between the two CH3 domains in the CH3-CH3 interface.” *See id.* at 6:16-18. The inventors then described the strand-exchange engineered domain (“SEED”) method, another known method of engineering of the CH3-CH3 interface for heterodimerization. *See id.* at 6:28-7:3. The inventors then described the prior known method of “a charge reversal strategy.” Citing the Gunasekaran Paper (EX1012) and other references, the inventors explained that in this known method naturally occurring charged contact residues are replaced by residues of the opposite charge. *See id.* at 7:4-14.

Against this detailed background, the inventors began explaining their invention: “[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.” *See id.* at 19:8-11; 19:13-14.

The inventors then explained the “novel mutations” of their invention:

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. at 23:28–24:9 (emphasis added).

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.” *See id.* at 24:22-25. With this explanation, the inventors made it clear to a POSA that unpaired monomers were not a problem and were not their focus. *See* EX2019 (Second Sutton Declaration) at ¶ 47.

With this stated context, the inventors explained that neutral to charged substitutions that fully prevent homodimerization when expressed alone (*i.e.*, without a second chain) are “preferred”: “***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* EX1030 ('935 Application) at 48:10-13. Indeed, Dr.

Presta admitted during cross-examination that the '935 Application discloses this preference to a POSA. EX2015 (Presta Tr.) at 157:4-23.

As explained by Dr. Sutton, a POSA reading the '935 Application did not have to guess which CH3 domain variants met the inventors' stated preference for preventing homodimerization when expressed alone. *See* EX2019 (Second Sutton Declaration) at ¶ 50. Indeed, the inventors provided a clear chart of amino acid substitutions in the CH3 domains and their experimentally determined effects on homodimer formation in Table 7 of the '935 Application (reproduced below). *See id.* at ¶¶ 50-52; EX1030 ('935 Application) at Table 7, 51:1-14 (describing the creation of Table 7).

Table 7: list of amino acid substitutions in the various constructs that we 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	+

IPR2025-00605
Patent No. 11,926,859
Patent Owner's Response

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	+

Each substitution in Table 7 was graded for its experimentally determined effect on “homodimer formation,” with a score from the lowest of “-” for “no effect” to “+++” for “max. inhibition”:

Consistent with the “blaze marks” requirement for written description, a POSA reading the '935 Application would have understood which variants best embodied the inventors' stated preference for preventing homodimerization when expressed alone: the fourteen variants having a “++” or “+++” rating in Table 7. *Fujikawa*, 93 F.3d at 1570 (describing the “blaze marks” requirement); *see* EX2019 (Second Sutton Declaration) at ¶ 53.

A POSA would have further understood from reading the '935 Application that the inventors believed that variants without the F405K and/or Y407K substitutions could avoid potential problems:

[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 EX1030 ('935 Application) at 54:12-16 (emphasis added); *see* EX2019 (Second Sutton Declaration) at ¶¶ 54-55. Dr. Presta agrees, admitting on cross-examination

that the '935 Application “discusses problems” with F405K and Y407K. *See* EX2015 (Presta Tr.) at 165:18-166:13, 176:13-18.

A POSA reviewing the fourteen variants that have a “++” or “+++” rating in Table 7 and the inventors' discussion of potential problems with the F405K and Y407K would have understood that there were eight variants that have a “++” or “+++” rating in Table 7 without using a F405K and/or Y407K substitution. *See* EX2019 (Second Sutton Declaration) at ¶ 55. Of these eight variants, the T366K and S364K substitutions occur most frequently, in three variants each. *See id.* at ¶ 56. For example, a POSA reading Table 7 would have understood that—removing the potentially “problematic” F405K and Y407K substitutions—the S364K variant appears in one of the two “+++” ratings in Table 7 and appears in two of the six “++” ratings in Table 7. *See id.* at ¶ 56. A POSA would have further taken notice that S364K is the only variant in Table 7 to achieve a “++” rating as a single substitution. *See id.*

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.”

EX1030 ('935 Application) at 51:14-17 (emphasis added). A POSA reading this statement would have understood that the inventors invented, and had possession of, bispecific antibodies produced by engineering matched pairs for: (a) the fourteen variants that have a “++” or “+++” rating in Table 7; (b) the eight variants that have a “++” or “+++” rating in Table 7 without using a F405K and/or Y407K substitution; (c) the T366K and S364K variants identified in Table 7; and (d) the S364K variant identified in Table 7, the only single amino acid variant with a “++” or “+++” rating. *See* EX2019 (Second Sutton Declaration) at ¶¶ 54-58.

A POSA reading the '935 Application further understood what a “matched pair” was for each of these variants. *See id.* As explained by Dr. Sutton, for S364K, a POSA would have understood that to create a “matched pair” they must look first to Table A of the '935 Application, which discloses the contacting residue(s) in Chain B for an S364K residue in Chain A. *See id.* at ¶ 59. A POSA would have readily identified S364K in Table A and understood its contacting residues. *See* EX1030 ('935 Application) at 54:12-16, p. 17 at Table A.

Specifically, a POSA would have understood that the contacting residues listed for S364K in Table A were L368 and K370. *See* EX2019 (Second Sutton Declaration) at ¶ 60. 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). *See id.* Given the above, a POSA reading the '935 Application would have known that there were only four possibilities for creating a “matched pair” with the S364K substitution disclosed in Table 7: L368D, L368E, K370D, and K370E. *See id.* A POSA reading the '935 Application would have readily envisaged each of these matched pairs and would have reasonably believed that the inventors had possession of, and were the inventors of, each of these “matched pairs” with S364K as of the April 20, 2012 filing date of that application. *See id.*

A POSA reading the '935 Application would have further understood that the inventors had reasons to prefer L368 over K370 for modification to have a negative D or E charge to create a “matched pair” with S364K. *See id.* at ¶ 61. Based on Table A and their knowledge of the literature in 2012, a POSA would have understood that K370: (a) was already charged in wild-type; (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, in wild-type; and (d) was already part of one of the four conserved salt bridges of the CH3-CH3 interface in wild-type. *See EX1030*

('935 Application) at Table A; EX1012 (Gunasekaran Paper) at page 4; *see also* EX2019 (Second Sutton Declaration) at ¶¶ 62–63.

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 change the existing charge-charge interaction between K370 and E357. *See id.* This would deny such a “matched pair” one of the advantages disclosed by the inventors of the '935 Application: creating an “additional charge-charge interaction” with resulting improvements in stability. *See* EX1030 ('935 Application) at 24:3-9; *see also* EX2019 (Second Sutton Declaration) at ¶¶ 62 and 73–76.

To obtain this advantage, the '935 Application explained that new charge pairs can be added to the existing pairs, like those creating the existing salt bridges, stating:

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 ('935 Application)) 51:17-22 (emphasis added); *see also* EX2019 (Second Sutton Declaration) at ¶ 75.

Regardless of any preference between L368 and K370, a POSA reading the '935 Application would have understood that there are only two possible residues for creating a “matched pair” with the S364K substitution disclosed in Table 7—L368 and K370—and only four possible “matched pairs” with the S364K substitution—L368D, L368E, K370D, and K370E. *See* EX2019 (Second Sutton Declaration) at ¶ 60. A POSA reading the '935 Application would have readily envisaged each of these “matched pairs” and would have reasonably believed that the inventors had possession of, and were the inventors of, each of these “matched pairs” with S364K as of the April 20, 2012 filing date of that application. *See id.*

A POSA reading the '935 Application would have understood that to make a “matched pair” with the positively charged lysine (K) in S364K and L368, there needs to be a negatively charged residue at position 368. *See id.* at ¶ 70. A POSA would have further understood that there are two negatively charged residues, aspartic acid (D) and glutamic acid (E). *Id.* 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. *Id.* Indeed, during cross-examination, Dr. Presta admitted that based on the disclosures of Table A and Table 7 in the '935

Application, the L368 residue is the only contact residue with S364K that is not already charged in wild-type and could introduce a complementary charge. *See* EX2015 (Presta Tr.) at 163:10-164:22.

A POSA reading the '935 Application would have further understood that it provides multiple examples of L368 variants, including examples of both the L368D and L368E substitutions. *See* EX2019 (Second Sutton Declaration) at ¶ 70; *see also* EX1030 ('935 Application) at Tables B, 7, and 13–15. A POSA reading the '935 Application and seeing the L368D and L368E substituted variants would have reasonably believed that the inventors possessed them, including to form a “matched pair” with the S364K variant disclosed in Table 7. *See* EX2019 (Second Sutton Declaration) at ¶¶ 71, 76.

For all these reasons, the '935 Application reasonably conveyed to a POSA that the inventors possessed the charge substitution of S364K identified in Table 7 and its use to form a “matched pair” with L368D or L368E. *See* EX2019 (Second Sutton Declaration) at ¶ 76. This would add an additional charge-charge interaction of the kind the inventors deemed advantageous. *See id.*

Based on at least the above disclosures, the '935 Application “reasonably conveys to those skilled in the art that the inventor[s] had possession of” a

heterodimeric antibody comprising “a positively charged amino acid residue at position 364” and “a negatively charged amino acid residue at position 368” as of April 20, 2012. *See Ariad*, 598 F.3d at 1351; *see also Vas-Cath*, 935 F.2d at 1562–63; *see* EX2019 (Second Sutton Declaration) at ¶ 77. Put another way, a POSA reading the '935 Application would have understood that a heterodimeric antibody with S364K in a “matched pair” with L368D or L368E was something that the inventors invented and possessed by April 20, 2012.

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* Paper 13 at pages 35-36. The Board also stated that the “follow-up experiments” did not include the specific paired substitutions at positions 364 and 368. *Id.*

As discussed above and explained by Dr. Sutton, in making these preliminary statements the Board overlooked 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 EX1030 ('935 Application) at 51:14-17 (emphasis added); *see also* EX2019 (Second Sutton Declaration) at ¶ 79. For the reasons explained above, upon reading this and other disclosure of the '935 Application, a POSA would have understood that the inventors invented and possessed “matched pairs of CH3 residues” with the S364K variant disclosed in Table 7 and that those “matched pairs” included L368D and L368E. *See* EX2019 (Second Sutton Declaration) at ¶ 79.

As Dr. Sutton further explains, the Board's preliminary statement that Table A does not teach the claimed subject matter overlooks that Table A is intended to be read in conjunction with Table 7 and the rest of the '935 Application. *See id.* at ¶ 80. As discussed above, a POSA reading the '935 Application would have understood that they should take the substitutions identified by Table 7 as preventing homodimerization and then use Table A to determine the contacting residues for those substitutions with which to create “matched pairs.” *See id.* Table A does not, and was not intended to, disclose the claimed subject matter by itself. *See id.*

As explained above, as of April 20, 2012, Table A, Table 7, and the other disclosures of the '935 Application reasonably conveyed to a POSA that the inventors invented, and had possession of, the “matched pairs” with S364K, including the “matched pairs” of S364K with L368D or L368E. *See id.* at ¶ 81.

Dr. Presta asserts that S364K has similar potential problems as those disclosed by the inventors for F405K and Y407K. But, as explained by Dr. Sutton, there is no statement about S364K being potentially problematic in the '935 Application. *See id.* at ¶ 82. Moreover, as shown by Table A, S364K has fewer contacting residues (two) than either F405K (three) or Y407K (four). *See id.* With fewer contacting residues, a POSA would have known that there are fewer possible complications with substituting S364 than with substituting F405 or Y407. *See id.* That is especially true given that two of F405's three contacting residues in Table A are already charged. In any event, just because the inventors noted potential problems with certain residues, that does not mean they did not invent or possess them.

Indeed, the '935 Application explicitly states that for the variants identified by Table 7 as preventing homodimerization:

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

For all of the reasons discussed above and in Dr. Sutton's declaration, the '935 Application “reasonably conveys to those skilled in the art that the inventor had

possession of the claimed subject matter” as of April 20, 2012. *Ariad*, 598 F.3d at 1351; *see also Vas-Cath*, 935 F.2d at 1562–63.

B. The '935 Application Provides Adequate Written Description Support For Dependent Claims 2-7

The '935 Application further conveys to a POSA that the inventors had possession of the subject matter claimed by the dependent claims of the '859 Patent.

Dependent claims 2 and 3 add the limitation of specific positively charged residues (*i.e.*, lysine or arginine) at position 364 and negatively charged residues (*i.e.*, aspartic acid or glutamic acid) at position 368. *See* EX1001. As discussed above, the '935 Application lists the positively and negatively charged residues and further provides relevant examples throughout the specification. *See* EX1030 ('935 Application) at 17:4-14, Tables B, 7, and 13-15. As explained by Dr. Sutton, a POSA would have understood that Table 7 of the '935 Application specifically identifies S364K as preventing homodimerization; Table A identifies L368 as being a contact residue for S364; and the specification explicitly states that bispecific antibodies will be generated by engineering “matched pairs.” EX2019 (Second Sutton Declaration) at ¶ 85. A POSA reading the '935 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. *Id.*

Dependent claim 4 adds the limitation that the heterodimeric antibody is a bispecific antibody. *See* EX1001. As explained by Dr. Sutton, the '935 Application makes clear that bispecific antibodies are the focus of the application. EX2019 (Second Sutton Declaration) at ¶ 86.

Dependent claims 5 and 6 add the limitations that the heterodimeric antibody is human IgG or human IgG1, respectively. *See* EX1001. As explained by Dr. Sutton, the '935 Application discloses that the exemplified heterodimeric antibodies are human IgG1, which a POSA would have understood to be a particular form of human IgG. EX2019 (Second Sutton Declaration) at ¶ 87.

Dependent claim 7 adds the limitation that the heterodimeric antibody is combined with a pharmaceutically acceptable carrier in a pharmaceutical composition. *See* EX1001. The '935 Application discloses examples of pharmaceutical compositions, and a POSA would have understood from this that the heterodimeric antibody of independent claim 1 should be administered with a pharmaceutically acceptable carrier in a pharmaceutical composition. *See, e.g.,*

EX1030 ('935 Application) at 36:8-19; *see also* EX2019 (Second Sutton Declaration) at ¶ 88.

For all these reasons, the '935 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 IgG or IgG1, bispecific, and usable in a pharmaceutical composition with a pharmaceutically acceptable carrier. For at least these reasons, the '935 Application reasonably conveys to a POSA that the inventors had possession of all of the subject matter claimed by dependent claims 2-7 as of their earliest claimed priority date of April 20, 2012.

C. The '935 Application Is Enabling

The '935 Application provides sufficient disclosure to teach a POSA to make and use the full scope of the Challenged Claims without undue experimentation. *See Genentech*, 108 F.3d at 1365.

As explained in more detail by Dr. Sutton, the inventors disclosed sufficient information for a POSA to make charged substitutions to the residues at positions 364 and/or 368 in Examples 1, 13, 14, 16, and 17. The examples of the '935 Application further provided sufficient information to a POSA about how to make

an antibody with charged substitutions at positions 364 and/or 368. *See* EX2019 (Second Sutton Declaration) at ¶ 93.

As explained by Dr. Sutton, Examples 1 through 12 provide a POSA with a roadmap on how to make the heterodimeric antibody with the claimed CH3 residue substitutions. *Id.* Example 2 explains how to clone VH into constructs with CH3 mutations. *Id.* Example 3 explains how to transfect and express a full IgG in HEK cells. *Id.* Example 4 explains how to purify IgG, including IgG made from Example 3. *Id.* 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. *Id.* Example 9 further explains to a POSA how to process and quantify the data generated from the tests of Example 5-8. *Id.* Examples 10-12 explain how to generate mixtures of antibodies from a single cell. *Id.* Further, Examples 13-17 show how to test variants for heterodimerization and stability and to identify or confirm preferred CH3 substitutions. *Id.* at ¶ 94. Example 18 shows how to test the stability of the generated IgG. *Id.* at ¶ 95.

For all these reasons, as explained in more detail by Dr. Sutton, the '935 Application contains sufficient information to teach a POSA how to make and use the claimed invention of independent claim 1 without undue experimentation.

Dependent claims 2 and 3 include all of the elements of independent claim 1 and further require specific positively charged residues (*i.e.*, lysine (K) or arginine (R)) at position 364 and negatively charged residues (*i.e.*, aspartic acid (D) or glutamic acid (E)) at position 368. *Id.* at ¶ 97. The '935 Application teaches a POSA how to make and use positively charged residues at position 364 (*i.e.*, lysine (K) or arginine (R)) and negatively charged residues (*i.e.*, aspartic acid (D) or glutamic acid (E)) at position 368 without undue experimentation. *Id.* at ¶ 98. And Examples 2-18 of the '935 Application explain to a POSA how to make an antibody with these substitutions without undue experimentation. *Id.* at ¶ 99.

Dependent claim 4 includes all of the elements of independent claim 1 and further requires that the claimed heterodimeric antibody is a bispecific antibody. *Id.* at ¶ 100. The Examples of the '935 Application provide enable a POSA to generate and test bispecific antibodies without undue experimentation. *Id.*

Dependent claims 5-6 include all of the elements of independent claim 1 and further require that the claimed heterodimeric antibody is a human IgG (claim 5) or a human IgG1 (claim 6). *Id.* at ¶ 101. The '935 Application explicitly states that the claimed antibodies can have human sequences, and examples in the '935 Application use human IgG and IgG1 antibodies. *See* EX1030 ('935 Application) at 15:1-7;

EX2019 (Second Sutton Declaration) at ¶¶ 102-103. Accordingly, a POSA reading the '935 Application would have been able to make and use a human IgG or IgG1 antibody for heterodimerization as claimed in dependent claims 5-6 without undue experimentation. *Id.* at ¶ 104.

Dependent claim 7 is directed to a pharmaceutical composition including the heterodimeric antibody of independent claim 1 with a pharmaceutically acceptable carrier. *Id.* at ¶ 105. The '935 Application provides examples of pharmaceutical compositions, and a POSA would have understood from this that the heterodimeric antibody of independent claim 1 should be administered with a pharmaceutically acceptable carrier in a pharmaceutical composition. EX1030 ('935 Application) at 36:8-19; *see also* EX2019 (Second Sutton Declaration) at ¶¶ 106-107. Accordingly, a POSA reading the '935 Application would have been able to make and use the pharmaceutical compositions of claim 7 without undue experimentation. *Id.*

Neither Xencor nor Dr. Presta question whether the '935 Application provides enablement support for any of the Challenged Claims, so Dr. Sutton's declaration is un rebutted on this issue. Given its acquiescence that the '935 Application is enabling, it is difficult to understand Xencor's written description arguments.

D. The Challenged Claims Are Not Anticipated Because Xencor's '427 Patent (Desjarlais) And Moore Are Not Prior Art To The '859 Patent

For all the reasons discussed above, the '859 patent is entitled to its earliest claimed priority date of April 20, 2012.

Xencor states that the earliest possible priority date for the '427 Patent (Desjarlais) is March 13, 2013, and that the earliest possible publication date for Moore is October 23, 2018. *See* Petition at 15, 17. Because the earliest possible dates for both Xencor's '427 Patent (Desjarlais) and Moore references are later than the earliest priority date to which the '859 patent is entitled, Xencor's '427 Patent (Desjarlais) and Moore are not prior art to the '859 patent and cannot anticipate it. *See* 35 U.S.C. § 102.

IX. THE CHALLENGED CLAIMS WOULD NOT HAVE BEEN OBVIOUS OVER LAZAR ALONE OR IN VIEW OF KANNAN

A claim is only unpatentable under 35 U.S.C. § 103 if the differences between the claimed invention and the prior art are such that the claimed invention, as a whole, would have been obvious to a POSA before the effective filing date of the claimed invention. *See KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 406 (2007).

The framework for determining alleged obviousness under 35 U.S.C. § 103 (the "*Graham* Factors") is as follows: (1) determine the scope and content of the

prior art; (2) ascertain the differences between the prior art and the claims at issue; (3) resolve the level of ordinary skill in the art; and (4) consider objective evidence indicating obviousness or non-obviousness (“secondary considerations”). *See KSR*, 550 U.S. at 406 (citing *Graham v. John Deere Co.*, 383 U.S. 1 (1966)).

The Board must consider any objective evidence of non-obviousness because such evidence can establish that “an invention appearing to have been obvious in light of the prior art was not” and may be “the most probative and cogent evidence in the record.” *Ex Parte Whirlpool Corp.*, 2013-008232, at 12 (P.T.A.B. October 30, 2013) (informative) (quoting *Apple Inc. v. Int’l Trade Comm’n*, 725 F.3d 1356, 1366 (Fed. Cir. 2013)) (internal quotations omitted); *see also Ex parte Thompson*, 2011-011620, at 5 (P.T.A.B. March 21, 2014) (informative) (“objective evidence of secondary considerations pertaining to non-obviousness must be considered”). That is, obviousness is not established by technical comparisons in isolation, but through a holistic inquiry that must account for objective indicia that reflect how the claimed invention was actually received, adopted, and valued in the real world. *See Leo Pharm. Prods. v. Rea*, 726 F.3d 1346, 1358 (Fed. Cir. 2013).

An obviousness determination furthermore requires a finding that a POSA would have been motivated to combine the asserted references to arrive at the

claimed subject matter with a reasonable expectation of success in doing so. *See Regents of Univ. of California v. Broad Inst., Inc.*, 903 F.3d 1286, 1291 (Fed. Cir. 2018); *Intelligent Bio-Systems, Inc. v. Illumina Cambridge, Ltd.*, 821 F.3d 1359, 1367 (Fed. Cir. 2016); *Hulu, LLC v. Sound View Innovations, LLC*, Case IPR2018-00582, Paper 34 (August 5, 2019) (informative) (no claims unpatentable, insufficient reason to combine references).

Under this well-settled precedent, the Challenged Claims of the '859 Patent are not obvious based on Lazar alone or based on Lazar in view of Kannan. Dr. Presta provides no credible reason for a POSA to modify or combine these references to achieve the claimed inventions, much less with a reasonable expectation of success in doing so. The non-obviousness of the Challenged Claims is further bolstered by secondary considerations of non-obviousness, which Xencor and Dr. Presta have failed to consider.

A. The *Graham* Factors

i. Scope And Content Of The Prior Art

1. Lazar

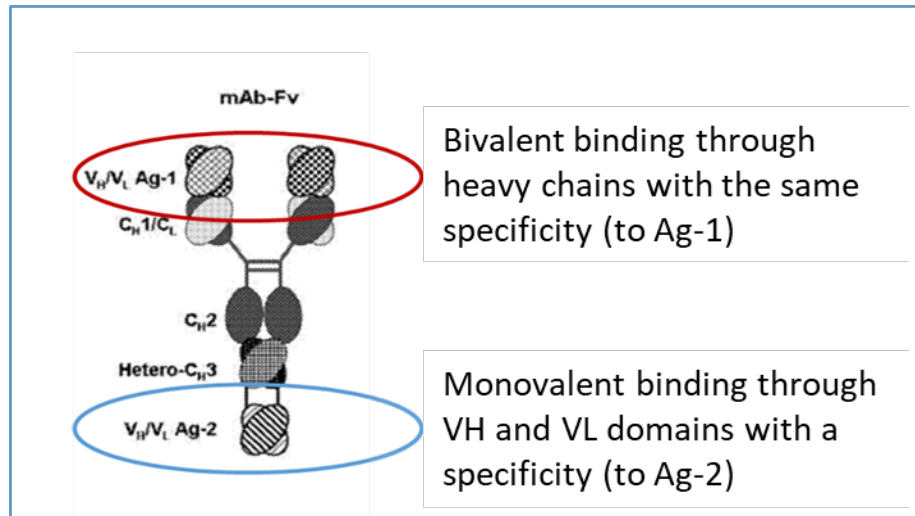
The experiments in Lazar were directed to finding alternative bispecific immunoglobulin structures that were better than “full length antibody-like

formats.” See EX1004 (Lazar) at ¶ 007; see also EX2019 (Second Sutton Declaration) at ¶ 113. 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 EX1004 (Lazar) at ¶ 007 (emphasis added).

To avoid the undesired non-specific activation and toxicity of “full length antibody-like formats,” Lazar created alternative bispecific moieties (*i.e.*, mAb-Fv, mAb-Fab, Fab-Fv, and Fab-Fab) ***that did not need CH3 heterodimerization.*** See EX1004 (Lazar) at ¶ 46; see also EX2019 (Second Sutton Declaration) at ¶ 115. These moieties did not need CH3 heterodimerization because, among other reasons, the VH and CH domains were the same and Lazar made these moieties bispecific by adding a third antigen binding site (*e.g.*, Fv or Fab) at the C termini of the Fc region (instead of by having two different VH domains attached to the two CH1 domains). See Lazar (EX1004) at ¶¶46 and 108. The below excerpt from Figure 8 of Lazar illustrates one of Lazar's alternative bispecific moieties:



Lazar explained that its scFv-Fc/empty-Fc construct, and only its scFv-Fc/empty-Fc construct, was used to test certain CH3 substitutions for their effect on Fc heterodimerization. *See* EX1004 (Lazar) at ¶¶ 238-239. Neither Lazar's alternative bispecific moieties nor "full length antibody-like formats" were used for such testing. *See* EX1004 (Lazar) at ¶ 16 and Examples 3-6. Indeed, Dr. Sutton has confirmed that all of the CH3 substitution experiments that were conducted and reported in Lazar were done using the scFv-Fc/empty-Fc construct. *See* EX2019 (Second Sutton Declaration) at ¶ 116.

Lazar does not disclose a single example or embodiment that includes a positively charged residue at position 364 in one CH3 domain and a negatively charged residue at position 368 in the other CH3 domain in one of its alternative bispecific moieties or any full length antibody format. *See id.* Notably, after

conducting its Fc heterodimerization experiments, Lazar used only one substitution (*i.e.*, Y349T/T394F and S364H/F405A) for its alternative bispecific moieties in the follow-up experiments. *See id.* at ¶ 117. Lazar does not suggest any paired substitutions on positions 364 and 368 for the alternative bispecific moieties. *See id.*

Moreover, Lazar did not use any charged substitutions, much less the charge substitutions required by the Challenged Claims, in any IgG, IgG1, or other full length antibodies. *See id.* at ¶ 118. In fact, Lazar specifically taught away from using IgG, IgG1, and other full length antibodies and proposed his bispecific antibody moieties as an alternative. *See id.*

2. Kannan

Kannan is directed to electrostatic steering through charged to charged residue substitution techniques, *i.e.*, “charge swapping.” *See* EX2019 (Second Sutton Declaration) at ¶ 119. Kannan does not disclose *any* examples or embodiments of substitutions to the neutral residues of the CH3 region. *Id.* This is not surprising given that Dr. Gunasekaran Kannan authored the 2010 Gunasekaran Paper (EX1012) and warned against making any changes to the neutral residues in the hydrophobic region of the CH3 interface. *Id.* As Dr. Presta admitted on cross-

examination, the Gunasekaran Paper says that it is long established that the hydrophobic core is important to protein stability and folding. *See* EX2015 (Presta Tr.) at 183:8-184:3.

As explained by Dr. Sutton, a POSA would have understood that the focus of Kannan is on swapping charged residues *without modifying neutral residues in hydrophobic core regions*. *See* EX2019 (Second Sutton Declaration) at ¶ 119; EX1012 (Gunasekaran Paper) at p. 1 (explaining that the publication “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.”).

Kannan includes one sentence (with no data, example, or citation) that “this strategy can also be extended to modifying uncharged residues to charged residues at the CH3 domain interface.” *See* EX1007 (Kannan) at 10:16-18; EX2019 (Second Sutton Declaration) at ¶ 120. All of the working examples and suggested substitutions in Kannan, however, are directed to substitutions of charged residues with oppositely charged residues, *i.e.*, charge swapping. *See id.*

Furthermore, all of the working examples and suggested substitutions in Kannan involve the substitution of wild-type residues, not of residues that have

already been substituted. *See* EX2019 (Second Sutton Declaration) at ¶ 121. As Dr. Sutton explains, a POSA would have had to take into consideration the structural consequences of substitution or switching of wild-type residues and then the further structural consequences of substitution or switching residues that had already been substituted and were no longer wild-type. *See id.* As Dr. Sutton explains, the latter is even more complicated. *See id.* There is nothing in Kannan that gives a POSA a reason to undertake such a complicated analysis of the possible effect of changes upon changes. *See id.* Kannan never suggests making changes to anything other than wild-type residues.

In any event, Dr. Kannan taught away from modifying neutral residues in the hydrophobic core of the CH3 domain interface for fear of negatively impacting protein folding and stability. *See* EX1012 (Gunasekaran Paper); EX2019 (Second Sutton Declaration) at ¶ 123. Instead, Dr. Kannan taught 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 id.*

ii. Differences Between The Prior Art And The Claimed Subject Matter Of The '859 Patent

1. Lazar

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.” *See* EX2019 (Second Sutton Declaration) at ¶ 124. Lazar discloses the opposite charges, *i.e.*, a negatively charged amino acid residue at position 364 and a positively charged amino acid residue at position 368, in an scFv-Fc/empty-Fc construct. *See id.*

2. Kannan

Kannan does not disclose any charged substitutions at positions at 364 and/or 368. Moreover, Kannan does not disclose making any charged substitutions to residues that have already been substituted from wild-type. Kannan is directed to charge swapping techniques that swap the charges of charged wild-type residues with those of the opposite charge. *See* EX2019 (Second Sutton Declaration) at ¶ 125. Xencor distorts Kannan when it asserts that the reference discloses a charge swapping strategy for previous neutral to charged residue substitutions. It does not.

iii. Level Of Ordinary Skill In The Art

The applicable definition of a POSA is set out in, *supra*, Section III.

iv. Secondary Considerations Of Nonobviousness

The non-obviousness of the Challenged Claims of the '859 Patent is further bolstered by secondary considerations of non-obviousness, including industry skepticism, teaching away, and unexpected results, all of which Xencor and Dr. Presta have failed to address.

1. Teaching Away / Skepticism

“Evidence of industry skepticism weighs in favor of non-obviousness.... Doubt or disbelief by skilled artisans regarding the likely success of a combination or solution weighs against the notion that one would combine elements in references to achieve the claimed invention.” *WBIP, LLC v. Kohler Co.*, 829 F.3d 1317, 1335 (Fed. Cir. 2016). Xencor's own asserted prior art teaches away from the claimed subject matter of the '859 Patent. For example, as discussed above, Dr. Gunasekaran Kannan's paper (which was incorporated in its entirety in Lazar) specifically warns against substituting the neutral residues of the hydrophobic core. *See* EX2019 (Second Sutton Declaration) at ¶ 153. This would have taught POSAs away from the claimed invention of the '859 Patent. *Id.*

Further, Lazar—Xencor's own asserted reference—taught a POSA that charged substitutions at positions 364 and 368 produce low heterodimer yields as compared with other substitutions. *See* EX1012 (Gunasekaran Paper); EX2019

(Second Sutton Declaration) at ¶ 153. This teaching would also have taught a POSA away from the claimed inventions of the '859 Patent. *Id.*

2. Unexpected Results

In considering unexpected results, courts ask whether “the claimed invention exhibits some superior property or advantage that a person of ordinary skill in the relevant art would have found surprising or unexpected.” *In re Soni*, 54 F.3d 746, 750 (Fed. Cir. 1995).

The claimed inventions of the '859 Patent produce unexpected results. As explained in the specification, the claimed inventions produce heterodimeric antibodies with increased stability. EX1001 at 18:45–56. This was unexpected given the Gunasekaran Paper as well as the data from Lazar and Kannan. EX2019 (Second Sutton Declaration) at ¶¶ 155-156.

These secondary consideration further support the non-obviousness of the Challenged Claims. Dr. Presta and Xencor ignored these secondary considerations of non-obviousness. Indeed, Petitioner's obviousness theory was presented as if secondary considerations could not exist or, if they did, could not affect the outcome of this proceeding. *See Leo Pharm.*, 726 F.3d at 1358 (“Objective indicia ‘can be the most probative evidence of nonobviousness in the record, and enable the court

to avert the trap of hindsight.”)(citing *Crocs, Inc. v. Int'l Trade Comm'n*, 598 F.3d 1294, 1310 (Fed. Cir. 2010)).

Given Drs. Presta's silence on the issue, Dr. Sutton's opinions regarding secondary considerations are unrebutted.

B. A POSA Would Not Have Been Motivated To Modify Lazar To Reach The Invention Of Independent Claim 1

“An obviousness determination requires finding that a person of ordinary skill in the art would have been motivated to combine or modify the teachings in the prior art and would have had a reasonable expectation of success in doing so.” *Regents of the Univ. of Cal.*, 903 F.3d at 1291(citing *In re Stepan Co.*, 868 F.3d 1342, 1345-46 (Fed. Cir. 2017)). A POSA would not have been motivated to modify the teachings of Lazar to arrive at the invention of independent claim 1. *Id.*

As explained by Dr. Sutton, 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. *See* EX2019 (Second Sutton Declaration) at ¶ 127. Although Lazar tested numerous substitutions at positions 364 and 368 in the ScFv-Fc/empty-Fc construct, not a single variant includes “a positively charged amino acid residue at position 364” and “a negatively charged amino acid residue at position 368.” *Id.* As the Board correctly

acknowledged in its institution decision, Lazar does not disclose “a positively charged amino acid residue at position 364” and “a negatively charged amino acid residue at position 368.” *See* Paper 13 at 45. 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, in the ScFv-Fc/empty-Fc construct. *See* EX2019 (Second Sutton Declaration) at ¶ 128.

These substitutions—S364E and L368K—are shown in Table 1, which is titled “Preferred CH3 domain variants that favor Fc heterodimerization.” *See* EX1004 (Lazar) at ¶ 241 and Table 1; *see also* EX2019 (Second Sutton Declaration) at ¶ 128. Lazar does not teach or suggest modifying the variants disclosed in Table 1 for improvement. *See id.* Rather, Lazar states that the variants were selected after testing a number of variants using quantitative electrophoretic methods. *See* EX1004 (Lazar) at ¶ 241; *see also* EX2019 (Second Sutton Declaration) at ¶ 129.

Moreover, the S364E and L368K variant listed in Table 1 provides the highest heterodimeric yield (*i.e.*, 64%) among the variants with charged substitutions at positions 364 and 368. *See* EX1004 (Lazar), Figures 5-7; *see also* EX2019 (Second Sutton Declaration) at ¶ 129. A POSA reading Lazar would not expect further improvement. Furthermore, there are many other examples of substitutions at other

positions listed in Figures 5–7 that produce much higher heterodimeric yields. *See* EX1004 (Lazar) at Figures 6 and 7 (K370D/K392D/K409D and E356K/E357K/D399K); *see also* EX2019 (Second Sutton Declaration) at ¶ 129.

A POSA reading Lazar would have looked to the variants with the highest heterodimerization yield, such as K370D/K392D/K409D and E356K/E357K/D399K, which resulted in 100% heterodimerization. *See* EX2019 (Second Sutton Declaration) at ¶ 130. A POSA would have seen S364E and L368K and noted that its heterodimerization yield was significantly lower at 64%. *See id.* Thus, a POSA would not have been motivated to pick the 364/368 pair for further modification; a POSA would have focused on the variants in Lazar with higher heterodimerization yields, which in Lazar reached 100%. *See id.* Certainly, a POSA would have had no reason or motivation to reverse the charge of S364E and L368K and expect that this reversal would increase the heterodimerization yield. *See id.*

Instead of following the data in Lazar, Dr. Presta improperly used hindsight to cherry-pick the claimed residues in Lazar and provides no scientific support or explanation as to why Lazar would have guided a POSA to select residues S364E and L368K *and* then reverse the substitutions. *See KSR*, 550 U.S. at 421 (cautioning the trier of fact against “the distortion caused by hindsight bias” and “arguments reliant

upon ex post reasoning” in determining obviousness); *see* EX2019 (Second Sutton Declaration) at ¶ 131. As explained by Dr. Sutton, there is no data to support Dr. Presta's assertion that a POSA would have been guided by Lazar to select positions 364 and 368 for substitution and further modify those substitutions to arrive at the claimed inventions of the '859 Patent. *See* EX2019 (Second Sutton Declaration) at ¶ 131.

A POSA would not have been motivated to select any of the claimed substitutions from a long list of potential amino acid substitutions at a number of residue positions. *Id.* at ¶ 132. Indeed, highlighting Dr. Presta's hindsight-driven approach, paragraphs 52 and 123 of Lazar disclose over 62 substitutions that can be introduced in one chain. *See id.* at ¶ 133; EX1004 (Lazar) at ¶¶ 52 and 123. There is no data or other reason for a POSA to have selected either residue 364 or 368 from this list. *See* EX2019 (Second Sutton Declaration) at ¶ 133. In fact, Lazar explains that heterodimeric Fc variants with paired substitutions are “not a necessity” for its preferred bispecific antibody moieties. *See* EX1004 (Lazar) at ¶ 108. But even if a POSA overlooked that explicit teaching, there is no data or other reason to select residues 364 or 368 for further modification out of a long list of possibilities. Rather, a POSA would have been guided by Lazar's heterodimerization data. *See* EX2019

(Second Sutton Declaration) at ¶ 133. Thus, as explained by Dr. Sutton, a POSA would not have been motivated by Lazar to select 364/368 for possible modification. *See id.* at ¶ 134.

In its institution decision, the Board stated 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 368 (*e.g.*, 368E).” *See* Paper 13 at 47. Respectfully, this statement overreads Lazar, including because Lazar never shows a positive charge at 364 paired with a negative charge at 368 in Table 1 or Table 2. EX1004 at Tables 1 and 2. Indeed, the only example of a pairing of residues 364 and 368 in Tables 1 and 2 of Lazar is S364E and L368K, which residues have the opposite of the charges in the Challenged Claims. *Id.* As confirmed by Dr. Sutton, Tables 1 and 2 of Lazar, which list Lazar “Preferred” and “Most preferred” variants for Fc heterodimerization, do not include any example of 364R or 368E. *See* EX2019 (Second Sutton Declaration) at ¶ 135. These Tables similarly do not include any other combinations of a positive charge at 364 and a negative charge at 368. *See id.* Furthermore, none of the many variants reported in Lazar Figures 5–7 have a positive charge at 364 and a negative charge at 368. *See id.*

Lazar does not teach or suggest modifying variants that include only either a positive charge at 364 (*e.g.*, 364H or 364R) or a negative charge at 368 (*e.g.*, 368E). *See id.* Rather, Lazar states that a number of variants were tested by quantitative electrophoretic methods, and preferred variants are listed in Tables 1 and 2. *See id.* The variant listed in Table 1 (*i.e.*, S364E and L368K, with the opposite orientation of charges) provides the highest heterodimeric yield (*i.e.*, 64%) among variants with substitutions at positions 364 and 368, but there are many other residue substitutions with much higher heterodimer yields. *See id.*

Thus, a POSA would not have been motivated to modify Lazar to arrive at claim 1.

C. A POSA Would Not Have Been Motivated To Combine Lazar And Kannan To Reach The Invention Of Independent Claim 1

Kannan does not remedy the deficiencies in Lazar, including because a POSA would not have been motivated to combine Lazar and Kannan. *Knauf Insulation, Inc. v. Rockwool Int'l A/S*, 788 F. App'x 728, 732 (Fed. Cir. 2019) (“using the claims ‘as a frame,’ and taking the ‘naked parts of separate prior art references [] as a mosaic to recreate a facsimile of the claimed invention’ without a finding of why ordinary artisans would have found that mosaic obvious, improperly employs hindsight bias”

(quoting *W.L. Gore & Assocs., Inc. v. Garlock, Inc.*, 721 F.2d 1540, 1552-53 (Fed. Cir. 1983)).

For the reasons stated above, a POSA would not have been motivated to modify Lazar to arrive at the claimed invention. A POSA would similarly have had no reason to combine Lazar with Kannan to arrive at the claimed invention. A POSA, based on Kannan, would not have made further changes to any of the already-substituted residues in Lazar. In particular, there is no disclosure in Lazar or Kannan that would have motivated a POSA to reverse the neutral to charged substitutions of the residues at positions 364 and 368 in Lazar.

As described by Dr. Sutton, it is clear from Kannan's disclosures that charge swapping does not provide the same or similar level of heterodimerization at every position. *See id.* at ¶ 139. Rather, Kannan is highly selective regarding the locations of substitutions, and none of those locations include 364 or 368. *See id.* 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 EX1007 (Kannan)* at 10:6-10. These comments are in accord with the description of the structural consequences of charge swapping discussed above, *i.e.*, that these

structural consequences are difficult enough to predict for substituting and/or swapping wild-type residues, but are even more unpredictable 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; none were substitutions of previous substitutions. *See id.* As a result, Kannan offers Xencor no help in modifying Lazar's S364E/L368K variant.

Furthermore, Lazar, like Kannan, does not suggest charge-swapping at positions 364 and 368. *See id.* at ¶ 140. As discussed above, the "Preferred CH3 domain variants" in Table 1 represent Lazar's view of the most promising residue substitutions for Fc heterodimerization. *See id.* A POSA would have had no basis to further modify these variants, including because, as discussed above, the data in Lazar showed that making such modifications to Lazar's neutral to charged substitutions would only reduce the heterodimerization yield. *See id.*

Indeed, a POSA would have understood that swapping the charges of Lazar's preferred variants may lead to a decrease in heterodimerization yield. *See id.* at ¶ 141. As discussed by Dr. Sutton, Lazar tested positions 364 and 368 with various variants. Among the various variants, the S364E/L368K variant listed in Table 1 provides the highest heterodimeric yields (*i.e.*, 64%), suggesting that the

S364E/L368K substitutions cause the most favorable heterodimerization effects. *See id.*

For all these reasons, a POSA would not have been motivated to combine Lazar with Kannan to reach the invention of claim 1.

D. 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

A POSA would have had no reasonable expectation of success in modifying the already-modified variants in Lazar or in combining the already-modified variants of Lazar with Kannan to arrive at the claimed inventions. *See Regents of the Univ. of Cal.*, 903 F.3d at 1291 (“An obviousness determination requires finding that a person of ordinary skill in the art would have been motivated to combine or modify the teachings in the prior art and would have had a reasonable expectation of success in doing so.” (citing *In re Stepan*, 868 F.3d at 1345-46)).

As a preliminary matter, a POSA reading Lazar would not have had a reasonable expectation of increasing heterodimerization yields by modifying the already-modified variants listed in Table 1. *See* EX2019 (Second Sutton Declaration) at ¶ 143. Lazar asserts that the variants in Table 1 represent the most promising amino acid residue substitutions for heterodimerization at the positions

considered by Lazar. *See* EX1004 (Lazar) at ¶¶ 240-241. Lazar states that it first used “computational structure-based methods” to “evaluate possible amino acid substitutions in the CH3 region for their ability to stabilize Fc heterodimers and destabilize Fc homodimers.” *See id.* at ¶ 236. Lazar states that selected variants were then screened using the scFv-Fc and empty-Fc construct. *See id.* 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* EX1004 (Lazar) at ¶¶ 240-241.

As of April 20, 2012, a POSA would have understood from the Gunasekaran Paper (EX 1012) that substituting wild-type neutral CH3 domain residues affects protein folding and stability. Introducing additional substitutions to wild-type neutral residues that had already been modified by Lazar's substitution processes would create a high risk of failure and, at a minimum, of decreasing the degree of heterodimerization. *See* EX2019 (Second Sutton Declaration) at ¶ 144.

Indeed, Dr. Presta admitted that Kannan says that charge swapping only reduces homodimer formation when applied to native occurring chains. *See* EX2015 (Presta Tr.) at 186:21-187:12. 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). As a result, a POSA would not have reasonably expected that reengineering these already modified structures/environments, especially at the exact same residue positions that are neutral in wild-type, would have been successful, much less beneficial. *See* EX2019 (Second Sutton Declaration) at ¶¶ 145–146. *See id.*

For at least these reasons, a POSA would not have had a reasonable expectation of success in arriving at claim 1 based on modifying Lazar or combining it with Kannan.

E. Even If Combined, Lazar and Kannan Together Fail To Disclose All Of The Elements Of The Challenged Claims

In addition to the other failings of Xencor's obviousness arguments discussed above, the combination of Lazar and Kannan does not disclose all of the elements of the Challenged Claims. As explained by Dr. Sutton, even in combination, Lazar and Kannan fail to disclose a heterodimeric antibody with a positively charged residue at position 364 in one CH3 domain and a negatively charged residue at position 368 in another CH3 domain. *See* EX2019 (Second Sutton Declaration) at ¶ 149.

Lazar discloses the *opposite charges* of the invention of claim 1, as Lazar discloses a negatively charged amino acid residue at position 364 and a positively charged amino acid residue at position 368 in its scFv-Fc and empty-Fc construct.

See id. at ¶ 150. Kannan does not provide any disclosure regarding the residues at positions 364 and 368. *See id.* at ¶ 151. Kannan does not disclose, teach, or suggest anything about reversing the charges on already neutral to charged substituted residues, much less the already neutral to charged substituted residues at positions 364 and 368 in the Lazar scFv-Fc and empty-Fc construct. *See id.*

F. Dependent Claims 2-7 Would Not Have Been Obvious Over Lazar Alone Or In View Of Kannan

Dependent Claims 2-7 include all of the elements of independent claim 1. For the same reasons that independent claim 1 is not obvious, none of dependent claims 2–7 is obvious. *See In re Fritch*, 972 F.2d 1260, 1266 (Fed. Cir. 1992) (“[D]ependent claims are nonobvious if the independent claims from which they depend are nonobvious.”). Moreover, each of dependent claims 2–7 requires an additional limitation that further renders it non-obvious.

i. Dependent Claims 2 and 3

Dependent claims 2 and 3 include all of the elements of independent claim 1 and further require 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. *See* EX1001. As discussed above, Lazar and Kannan fail to disclose a single example or embodiment with a positively charged residue at position 364

and a negatively charged residue at position 368. Moreover, Lazar and Kannan do not provide any motivation for a POSA to arrive at this claimed subject matter with any reasonable expectation of success. *See* EX2019 (Second Sutton Declaration) at ¶ 158. Therefore, dependent claims 2 and 3 are not obvious over Lazar alone or in combination with Kannan.

ii. Dependent Claim 4

Dependent claim 4 includes all of the elements of independent claim 1 and further requires that the claimed heterodimeric antibody is a bispecific antibody. *See* EX1001. As explained by Dr. Sutton, 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 Challenged Claims. *See* EX2019 (Second Sutton Declaration) at ¶ 160. Because Lazar, with or without Kannan, fails to disclose, teach, or suggest the claimed features of independent claim 1 that are incorporated into dependent claim 4, this claim cannot be obvious in view of these references. EX2019 (Second Sutton Declaration) at ¶¶ 159-161.

iii. Dependent Claims 5 and 6

Dependent Claims 5-6 include all of the elements of independent claim 1 and further require that the claimed heterodimeric antibody be a human IgG (Claim 5) or a human IgG1 (Claim 6). *See* EX1001.

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. EX2019 (Second Sutton Declaration) at ¶ 163. Lazar does not disclose, teach, or suggest any substitutions at positions 364 and 368 of a human IgG or a human IgG1. *See id.*

As discussed above, the substitutions disclosed by Lazar closest to those recited in the Challenged Claims 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, in Lazar's scFv-Fc/empty-Fc format, which is not a human IgG or a human IgG1. *See id.* For the reasons discussed above, a POSA would not have combined Lazar with Kannan to arrive at claim 1, much less have further modified the combination to be an IgG or IgG1 antibody. *See id.* at ¶ 164.

For all these reasons, Lazar alone or in combination with Kannan fails to disclose the claimed inventions of dependent claims 5 and 6.

iv. Dependent Claim 7

Dependent claim 7 is directed to a pharmaceutical composition including the heterodimeric antibody of claim 1 and a pharmaceutically acceptable carrier. *See* EX1001. Because Lazar, with or without Kannan, fails to disclose, teach, or suggest the claimed features of independent claim 1 that are incorporated into dependent claim 7, this claim cannot be obvious in view of these references. EX2019 (Second Sutton Declaration) at ¶ 166.

X. LAZAR DOES NOT ANTICIPATE ANY OF THE CHALLENGED CLAIMS

Despite not being an instituted ground in this proceeding, Xencor and Dr. Presta make a half-hearted attempt to argue that Lazar anticipates the Challenged Claims.² For all the reasons discussed above, 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.” *See also* EX2019 (Second Sutton Declaration) at ¶ 169. And Lazar certainly does not disclose all of the elements of independent claim 1 “as arranged in the claim.” *See Microsoft Corp. v. Biscotti, Inc.*, 878 F.3d 1052, 1068 (Fed. Cir. 2017).

² Xencor does not list anticipation by Lazar as one of its invalidity grounds. Patent Owner sets forth this argument only out of an abundance of caution.

Therefore, even if it were procedurally possible for Xencor or Dr. Presta to make this argument, Lazar does anticipate any of the Challenged Claims.

XI. DR. PRESTA'S OPINIONS ARE UNRELIABLE AND SHOULD CARRY NO WEIGHT

A. Dr. Presta Was Not Informed Of The Legal Standard For Assessing Written Description

Dr. Presta's cross-examination revealed that he was never informed of the legal standard for assessing whether the '935 Application contains an adequate written description. *See* EX2015 (Presta Tr.) at 148:11–151:8. It is simply not possible for an expert to provide reliable written description opinions without knowing the legal standard to apply in their analyses. Dr. Presta's written description opinions should thus be afforded no weight.

B. Dr. Presta's Obviousness Analysis Is Deficient

Dr. Presta fails to articulate an understanding of the legal standard for assessing obviousness in his declaration and does not undertake a proper obviousness analysis. For example, Dr. Presta makes no mention of the *Graham* factors—by name or otherwise—which the Federal Circuit deems essential to an obviousness analysis. *See KSR*, 550 U.S. at 406 (citing *Graham*, 383 U.S. 1). Moreover, as discussed above, Dr. Presta's analysis is hindsight-driven and fails to articulate any credible reason or motivation to modify Lazar or combine Lazar with

Kannan to arrive at the Challenged Claims, much less with a reasonable expectation of success. Dr. Presta's obviousness opinions should thus be afforded no weight.

C. Dr. Presta's Arguments Are Inconsistent

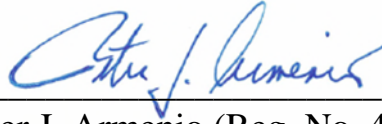
While Dr. Presta attempts to characterize the Challenged Claims as being allegedly simple and well understood, Dr. Presta represented in his own patent applications that heterodimerization was difficult at the relevant time frame. For example, Dr. Presta stated in his own patent application filed in September 2013—well after the '859 Patent's April 20, 2012 priority date—that prior heterodimerization efforts “have been fraught with difficulty.” *See* EX2015 (Presta Tr.) at 130:5–21. This inconsistency undermines Dr. Presta's obviousness opinions.

XII. CONCLUSION

For at least the foregoing reasons, Xencor's petition to invalidate the Challenged Claims should be denied in its entirety.

Dated: January 9, 2026

Respectfully submitted,



Peter J. Armenio (Reg. No. 41,588)
Colleen Tracy James (Reg. No 52,295)
CAHILL GORDON & REINDEL LLP
32 Old Slip
New York, NY 10005

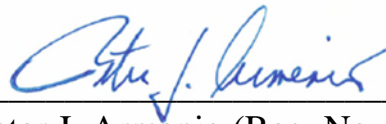
Counsel for Patent Owner Merus N.V.

CERTIFICATE OF COMPLIANCE

Pursuant to 37 C.F.R. § 42.24(d), the undersigned certifies that the foregoing **PATENT OWNER MERUS' RESPONSE** contains, as measured by the word-processing system used to prepare this paper, 13,237 words. This word count does not include the items excluded by 37 C.F.R. § 42.24 as not counting towards the word limit.

Dated: January 9, 2026

Respectfully submitted,



Peter J. Armenio (Reg. No. 41,588)
Colleen Tracy James (Reg. No 52,295)
CAHILL GORDON & REINDEL LLP
32 Old Slip
New York, NY 10005

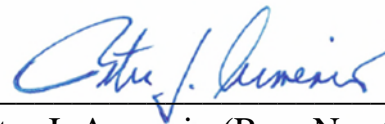
Counsel for Patent Owner Merus N.V.

CERTIFICATE OF SERVICE

I hereby certify that I caused to be served a true and correct copy of the foregoing: **PATENT OWNER MERUS' RESPONSE** and **EXHIBITS** were served by filing this document through the Patent Trial and Appeal Case Tracking System (P-TACTS) as well as via electronic mail at the email address below on January 9, 2026, in its entirety on the following:

Naveen Modi
Eric W. Dittmann
Isaac S. Ashkenazi
Ashley N. Mays-Williams
Daniel Zeilberger
Michael A. Wolfe
Ryan Meuth
Amanda K. Taylor

PAUL HASTINGS LLP
2050 M Street N.W.
WASHINGTON, DC 20036
PH-Xencor-Merus-IPR@paulhastings.com



Peter J. Armenio (Reg. No. 41,588)
Colleen Tracy James (Reg. No 52,295)
CAHILL GORDON & REINDEL LLP
32 Old Slip
New York, NY 10005

Counsel for Patent Owner Merus N.V.