

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 PRELIMINARY RESPONSE
UNDER 37 C.F.R. § 42.107**

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TABLE OF ABBREVIATIONS

Abbreviation	Definition
Merus	Patent Owner Merus N.V.
Xencor	Petitioner Xencor, Inc.
IPR	<i>Inter partes</i> review
Office	United States Patent And Trademark Office
Board	Patent Trial And Appeal Board
'859 Patent	Merus' U.S. Patent No. 11,926,859
'427 Patent	Xencor's U.S. Patent No. 10,472,427
'935 Provisional Application	April 20, 2012 Provisional Application No. 61/635,935
'805 Patent	Dr. Presta's U.S. Patent No. 8,216,805
POSA	Person of ordinary skill in the art
Gunasekaran	Gunasekaran, <i>et al.</i> , Enhancing antibody Fc heterodimer formation through electrostatic steering effects: applications to bispecific molecules and monovalent IgG. <i>J Biol Chem.</i> 2010 Jun 18;285(25):19637-46
Moore	Moore, <i>et al.</i> , A robust heterodimeric Fc platform engineered for efficient development of bispecific antibodies of multiple formats. <i>Methods.</i> 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

LIST OF EXHIBITS

Exhibit Number	Description
EX1001	U.S. Patent No. 11,926,859
EX1002	Declaration of Leonard G. Presta, Ph.D.
EX1004	Lazar
EX1007	Kannan
EX1012	Gunasekaran
EX1030	'935 Provisional
EX2010	Declaration of Dr. Brian Sutton, Ph.D. In Support Of Patent Owner Merus' Preliminary Response
EX2011	Curriculum Vitae of Dr. Brian Sutton, Ph.D.
EX2012	'805 Patent
EX2013	August 25, 2011 Amendment Under 37 C.F.R. § 1.116 (U.S. Application No. 12/700,618)

I. INTRODUCTION

Xencor's IPR for the '859 Patent should not be instituted. *First*, Xencor manufactures a meritless priority attack on Merus' '935 Provisional Application in an attempt to improperly insert two references that are clearly *not prior art*. *Second*, Xencor's only two actual prior art references were already before the Office during prosecution of the '859 Patent and not only undisputedly fail to disclose each element of the challenged claims, but in fact actually teach away from the claimed invention. *Third*, Xencor withheld from the Board that its petition flies in the face of its own arguments before the Office—having itself obtained a patent to the *same* invention, overcoming the *same* prior art it now raises as allegedly invalidating, and doing so with a later priority date.

First, Merus is entitled to the April 20, 2012 filing date of its '935 Provisional Application. As further explained by Merus' expert, Dr. Brian J. Sutton, Ph.D. in his Declaration (EX2010), the '935 Provisional Application discloses in sufficient detail all elements of the claimed heterodimeric antibody demonstrating that the inventors of the '859 Patent had possession of the invention and disclosed all the necessary and sufficient elements of a heterodimeric antibody with CH3-CH3 substitutions of "a positively charged amino acid residue at position 364" and "a negatively charged amino acid residue at position 368" on April 20, 2012. The

disclosure of the '935 Provisional Application (which is the same disclosure as that in the application that matured into the '859 Patent) reasonably conveys to a POSA that the inventors had possession of the claimed invention. Therefore, two of the references Xencor asserts—Xencor's '427 Patent (Desjarlais) and Moore—are not prior art, because they post-date the '859 Patent's earliest effective filing date.

Second, Xencor's remaining asserted prior art references, Lazar and Kannan, which were already before the Office during prosecution of the '859 Patent, individually or in combination, undisputedly fail to disclose each element of the challenged claims. Rather, Lazar discloses the opposite: a negatively charged amino acid residue at position 364 and a positively charged amino acid residue at position 368. Kannan also does not disclose a positively charged amino acid residue at position 364 in one CH3 domain and a negatively charged amino acid residue at position 368 in the other CH3 domain. A combination of the teachings of Lazar and Kannan therefore does not result in the claimed subject-matter. Xencor attempts to argue that a POSA would swap the substitutions made in one of Lazar's preferred constructs based on Kannan. However, in doing so, Xencor's expert, Dr. Leonard G. Presta, ignores the actual data in both Lazar and Kannan that shows that a POSA would not have any rational, scientific reason to choose the S364E and L368K modifications and swap these to arrive at the substitutions of the '859 Patent. In

fact, the data in Lazar and Kannan suggests that other modifications, not involving substitutions at positions claimed in the '859 Patent, would be preferred. Dr. Presta, in contradiction of statements made in the specifications of his own patents, ignores the scientific reality that modifying amino acids has significant consequences on their ability to fold and in turn affect antibody functionality.

Third, Xencor's petition fails to inform the Board that Xencor *patented the same invention* it now attacks, *over the same prior art* it now asserts, *using a later priority date* than Merus' '859 Patent. As Merus explained in its request for discretionary denial under the March 26, 2025 Process Memorandum, Xencor's lack of candor and contradiction in seeking to invalidate the same invention that it patented with a later priority date should not be rewarded with institution. Xencor's contradictory, untenable assertion of "patentable to me who filed later, but not to them who filed earlier" in its Petition would waste the Board's precious resources.

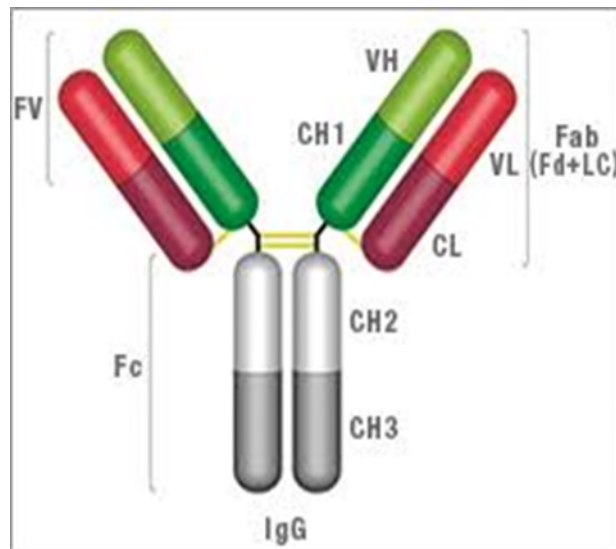
For all these reasons, as explained in more detail below, Merus respectfully requests that the Board deny institution.

II. TECHNOLOGY OVERVIEW

Antibodies or Igs naturally occur in the body and are key for an immune response and eliminating cancer cells. *See* EX1010 at ¶ 19.

Natural or wild type Igs have a particular structure made of two identical light

(L) chains and two identical heavy (H) chains. *See* EX1010 at ¶ 23. Each Ig heavy chain consists of three constant domains (CH1, CH2, and CH3) and one variable domain (VH). *See* EX1010 at ¶ 24.



The heavy chains are held together (dimerized) through covalent disulfide bridges in the “hinge” region between the Fab and Fc regions (see figure above), and by strong non-covalent interactions such as hydrophobic interactions, salt bridges, van der Waals forces and hydrogen bonds between interacting surfaces of the two CH3 domains. *See* EX1010 at ¶ 25.

Fc dimerization is a complex process in which the proper folding of each CH3 domain must first occur, after which the CH3 domain of one heavy chain can interact with the CH3 domain of the other heavy chain to form a non-covalent dimer and maintain the dimeric structure of the antibody. *See* EX1010 at ¶ 26. The

accompanying Sutton Declaration explains in more detail the complexities of the makeup of the amino acids of an Ig (*see* EX1010 at ¶¶ 20 – 22) and the folding of the CH3 domain. *See* EX1010 at ¶¶ 27 – 29.

Making modifications to the amino acids that make up the hydrophobic core of the CH3 domains may negatively affect their ability to fold, and this may also be the case for amino acids at the hydrophobic interface, which are likely to affect folding and/or dimerization. *See* EX1010 at ¶ 30. In fact, it was known at the relevant time of April 20, 2012 *not* to modify the neutral residues in the “hydrophobic core” of the CH3 region, since “[i]t has long been established that the hydrophobic core of protein domains plays an important role in protein folding and stability.” *See* EX1012 at 4; EX1010 at ¶ 31. It was further known that “exploiting charged residues as opposed to hydrophobic residues at the CH3 domain interface may have benefits in terms of retaining the generally favorable biophysical properties of the Fc.” *Id.*

A POSA knew that engineering a bispecific Ig with two different heavy chains would be challenging because, for example, it is difficult to promote the interaction of the CH3 domains from two different heavy chains while maintaining antibody stability and functionality. *See* EX1010 at ¶ 33. As of April 20, 2012, POSAs were aware of techniques such as “knobs-into-holes” and “charge reversal” or

“electrostatic steering” to try to create bispecific antibodies; these approaches enhance heterodimerization of different heavy chains and reduce the homodimerization that occurs in the formation of the wild type antibodies. *See* EX1010 at ¶ 34. However, POSAs also understood that these techniques had shortcomings because they often resulted in insufficient yield of the desired heterodimer compared with that of the two homodimers, as well as reduced protein stability and consequent functionality of the heterodimeric antibody. *Id.*

Merus pursued a different approach that went against conventional wisdom by modifying a neutral residue in the hydrophobic interface of the CH3 dimer, one on each heavy chain, from an amino acid having a neutral side chain to an amino acid having a charged side chain, to create a new salt bridge to enhance the stability of the CH3-CH3 dimer interface. *See* EX1010 at ¶ 35.

Surprisingly, Merus' heterodimerization technique achieves heterodimeric antibodies with higher yield and increased stability. *See* EX1010 at ¶ 36. Merus was granted the '859 patent for its novel invention. *Id.*

III. OVERVIEW OF THE '859 Patent

The '859 Patent claims certain aspects of Merus' heterodimerization technology.

Independent Claim 1 is directed to a heterodimeric antibody. Independent

Claim 1 of the '859 Patent 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 at Claim 1.

Dependent Claims 2 – 7 depend from Independent Claim 1. *See id.* at Claims 2 – 7. Dependent Claims 2 – 7 include all of the elements of Independent Claim 1 and further require additional limitations, including that the said positively charged amino acid 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 2), and that the said positively charged amino acid 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 3), and a bispecific antibody (Claim 4), a human IgG (Claim 5), a human IgG 1 (Claim 6), and a pharmaceutically acceptable carrier (Claim 7). EX1010 at ¶ 39.

IV. CLAIM CONSTRUCTION

The Board need not construe any claim term to deny institution.

V. PERSON OF ORDINARY SKILL IN THE ART

Petitioner purposes the following definition of a POSA: A POSA at the time of the invention of April 20, 2012 would have a Ph.D. in biochemistry, chemistry, molecular or structural biology, molecular biophysics, antibody engineering, immunology, or related discipline and at least 2 years of related experience in academia or industry or a Master's degree in any of the above fields with at least 4 years of related experience in academia or industry. *See* EX1010 at ¶ 17. For purposes of the Preliminary Response, Patent Owner applies Petitioner's proposed definition of a POSA. Under either definition of POSA, however, Xencor still fails to meet its burden for IPR institution.

VI. SUMMARY OF PETITIONER'S GROUNDS AND REFERENCES

Xencor alleges three grounds based on Lazar, Kannan, Moore, and Xencor's '427 Patent (Desjarlais). Xencor's alleged grounds are: Ground 1: The '427 Patent Anticipates Claims 1 – 7; Ground 2: Moore Anticipates Claims 1 – 7; and Ground 3: Lazar Alone or in view of Kannan Renders Obvious Claims 1 – 6.

All grounds fail because Xencor's '427 Patent and Moore are not prior art to the '859 Patent, and Lazar and Kannan do not contain all of the elements of the claims under either anticipation or obviousness theories. Lazar and Kannan do not disclose a heterodimeric antibody comprising a first human CH3 domain comprising

a positively charged amino acid residue at position 364 and a second human CH3 domain comprising a negatively charged amino acid residue at position 368 as required by Claim 1 of the '859 Patent.

VII. PETITIONER HAS NOT ESTABLISHED A REASONABLE LIKELIHOOD ANY CLAIM IS UNPATENTABLE

Xencor has the burden to show alleged unpatentability for institution. *See In re Magnum Oil Tools Int'l, Ltd.*, 829 F.3d 1364, 1375 (Fed. Cir. 2016); 35 U.S.C. § 314(a) (“The Director may not authorize an inter partes review to be instituted unless the Director determines that the information presented in the petition . . . and any response . . . shows that there is a reasonable likelihood that the petitioner would prevail with respect to at least 1 of the claims challenged in the petition.”). Xencor has not met its burden.

Xencor's three grounds of alleged unpatentability cannot invalidate any claim of the '859 Patent. Grounds 1 and 2 rely on references that are not prior art to the '859 Patent. As discussed in Merus' request for discretionary denial, Xencor's '427 Patent claims the *same* invention as the '859 Patent, but with a *later* priority date. Therefore, Grounds 1 and 2 cannot possibly invalidate any claim of the '859 Patent. Likewise, Ground 3 does not withstand scientific scrutiny. Lazar and Kannan do not disclose all of the elements of the Claims of the '859 Patent. Xencor's expert Dr. Presta's declaration is unsupported by data, conclusory, and unreliable. *See Xerox*

Corp. v. Bytemark, Inc., IPR2022-00624, Paper 9, at 15–17 (P.T.A.B. Aug. 24, 2022) (precedential) (denying institution because “declaration testimony is conclusory and unsupported, adds little to the conclusory assertion for which it is offered to support, and is entitled to little weight”). Accordingly, the Board should not institute Xencor's IPR petition.

A. The Board Should Not Institute On Grounds 1 and 2 Because Merus Is Entitled to Its Earliest Priority Date and Xencor's '472 Patent And Moore Are Not Prior Art To The '859 Patent

Merus is entitled to the April 20, 2012 priority date for the '859 Patent. Indeed, this was the priority date afforded by the Examiner, and Examiners must receive deference as they are presumed to perform their duties and responsibilities as Examiners, understand the cited references, and issue only valid patents. *PowerOasis, Inc. v. T-Mobile USA, Inc.*, 522 F.3d 1299, 1304 (Fed. Cir. 2008). Xencor's '427 Patent's earliest possible filing date is January 14, 2013, and Moore's earliest publicly available date is October 23, 2018. Therefore, The '427 Patent and Moore are not prior art to the '859 Patent.

Whether claims are entitled to the benefit of an earlier effective filing date is based on disclosure of the claimed invention “in the manner provided by section 112(a)” (*i.e.*, the written description requirement) in a related and earlier-filed application. *See* 35 U.S.C. §§ 119(e), 120. To comply with the written description

requirement under Federal Circuit precedent, the applicant “does not have to describe exactly the subject matter claimed,” though “the description must clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed.” *Vas-Cath Inc. v. Sakharam D. Mahurkar*, 935 F.2d 1555, 1562–1563 (Fed. Cir. 1991) (quoting *In re Gosteli*, 872 F.2d 1008, 1012 (Fed. Cir. 1989)) (citations omitted). That is, “[t]he test for sufficiency of support in a parent application is whether the disclosure of the application relied upon ‘reasonably conveys to the artisan that the inventor had possession at that time of the later claimed subject matter.’” *Id.* at 1653 (quoting *Ralston Purina Co. v. Far-Mar-Co, Inc.*, 772 F.2d 1570, 1575 (Fed. Cir. 1985)); *see also Ariad Pharms., Inc. v. Eli Lilly & Co.*, 598 F.3d 1336, 1351 (Fed. Cir. 2010).

The Specification of Merus’ ’935 Provisional Application provides written description support for all claims of the ’859 Patent. As Dr. Sutton explains in his Declaration, the ’935 Provisional Application allows a POSA to recognize that Merus invented what is claimed in the ’859 Patent. That is, the inventors of the ’859 Patent had possession of all the elements of the claimed heterodimeric antibodies, including CH3-CH3 substitutions of “a positively charged amino acid residue at position 364” and “a negatively charged amino acid residue at position 368,” on April 20, 2012. *See* EX1010 at ¶ 41.

Independent Claim 1 of the '859 Patent is fully supported by the '935 Provisional Application. Based on the disclosure of the '935 Provisional Application, the inventors of the '859 Patent possessed the claimed heterodimeric antibody (EX1010 at ¶ 42), including the claimed CH3 domain (EX1010 at ¶ 43) with a positively charged amino acid residue at position 364 and a negatively charged amino acid residue at position 368 (EX1010 at ¶ 44). According to Dr. Sutton, based on this disclosure in the '935 Provisional Application, a POSA would understand that substituting neutral residues in the CH3 domain with charged residues would result in the production of the claimed heterodimeric antibody. EX1010 at ¶ 45.

The '935 Provisional Application's disclosure *specifies* the *exact* substitutions for a POSA to make (*i.e.*, neutral to charged) and the exact CH3 residues on each heavy chain that a POSA could substitute to achieve heterodimerization through neutral to charged substitutions. EX1010 at ¶¶ 45 – 46. As Dr. Sutton points out in his Declaration, in Table A and Table 7 of the '935 Provisional Application, the inventors list CH3 residues that a POSA may modify with the exact substitutions, including CH3 residues 364 and 368. *See* EX1010 at ¶ 46.

In particular, Table A of the '935 Provisional Application discloses the specific residues of 364 and 368 as “interface residues,” and the '859 Patent

specification specifically recites the positive substitution at 364 and negative substitution at 386. *See* EX1030 at 16:16–18. Table A lists neutral residues located in the CH3 domain, including 364 and 368 specifically, as “involved in interdomain contacts.” *Id.*; EX1010 at ¶ 47. Table 7 of the '935 Provisional Application discloses specific positions for “identification of novel charge pair mutants.” *See* EX1030 at 51–54, Example 13; EX1010 at ¶ 48. Page 17 of the '935 Provisional Application and Table 7 furthermore specify that the positively charged residue at position 364 is a lysine (K) or an arginine (R) residue, and that the negatively charged residue at position 368 is an aspartic acid (D) or glutamic acid (E) residue. EX1010 at ¶ 48.

Based on this information from the Specification of the '935 Provisional Application, Dr. Sutton opines that a POSA would reasonably understand that substituting known contacting pairs 364 and 368 with a lysine (K) or an arginine (R) residue at position 364 and an aspartic acid (D) or glutamic acid (E) residue at position 368 would produce the claimed heterodimeric antibody in Claims 1 – 3 of the '859 Patent, and that the inventors were in possession of such an invention. EX1010 at ¶ 49. The heterodimeric antibody of Claims 1 – 3 of the '859 Patent is thus sufficiently disclosed in the '935 Provisional Application. *Id.*

The Specification of the '935 Provisional Application also provides written description support for the dependent claims. *See* EX1010 at ¶¶ 50 – 52. As Dr.

Sutton explains, dependent Claim 4 of the '859 Patent adds the limitation that the heterodimeric antibody is a bispecific antibody, and the Specification of the '935 Provisional Application discloses that the claimed antibodies are bispecific. *See, e.g.*, EX1030 at 19:8–14; EX1010 at ¶ 50. Likewise, dependent Claims 5 and 6 of the '859 Patent add the limitations that the heterodimeric antibody is human IgG (Claim 5), and further human IgG 1 (Claim 6), and the Specification of the '935 Provisional Application discloses that the heterodimeric antibody is human IgG1. EX1010 at ¶ 51. Finally, dependent Claim 7 of the '859 Patent adds the limitation that the heterodimeric antibody is in a pharmaceutically acceptable carrier, and the Specification of the '935 Provisional Application discloses a pharmaceutical composition of the heterodimeric antibody and a pharmaceutically acceptable carrier. EX1010 at ¶ 52.

Therefore, every claim of the '859 Patent has sufficient written description support and is entitled to the April 20, 2012 priority date. The '935 Provisional Application reasonably conveys to a POSA that Merus had possession of the invention claimed by the '859 Patent as of the April 20, 2012 priority date. The disclosure of the '935 Provisional Application is clear enough to inform a POSA that Merus invented what is claimed: the claimed heterodimeric antibody with positive and negative substitutions at certain neutral contact residues of the CH3 domain,

including at positions 364 and 368.

In his declaration supporting Xencor's petition, Dr. Presta argues (parroting attorney argument in Xencor's brief) that Merus did not provide a prophetic example of a heterodimeric antibody with the claimed substitutions, *i.e.*, that Merus did not list out every possible iteration of its invention. *See, e.g.*, EX1002 at ¶ 108. However, "the written description requirement does not demand either examples or an actual reduction to practice." *Ariad Pharms.*, 598 F.3d at 1352. Furthermore, "[a] specification may . . . contain a written description of a broadly claimed invention without describing all species that [the] claim encompasses." *Cordis Corp. v. Medtronic Ave*, 339 F.3d 1352, 1365 (Fed. Cir. 2003) (quoting *Utter v. Hiraga*, 845 F.2d 993, 998 (Fed. Cir. 1988)). Given its other specification disclosures, Merus need not describe an example of the type Dr. Presta demands. Indeed, Merus set out the exact residues to be substituted, noting they are interfacing residues on opposing chains, and set out the exact substitutions to be made (neutral to positive at position 364, and neutral to negative at 368), providing clear disclosure of the claimed invention. Merus thus satisfies the well-settled "possession" requirement for written description—a POSA would understand that Merus possessed the claimed antibody.

It is worth noting, Dr. Presta has obtained patents on similar subject matter

while arguing that he was in possession of his invention based on *the same type of* disclosure he seeks to criticize here.

Like Merus, Dr. Presta also pursued a patent for engineered antibodies with changes to certain pairs of amino acids in the CH3 region to promote heterodimerization; for example, the '805 Patent (EX2012). In that patent, Dr. Presta claims a method of preparing a heteromultimer by engineering a CH3-CH3 domain in which “the contact residue to be replaced on the first polypeptide corresponds to an IgG residue selected from the group consisting of amino acid residues 347, 349, 350, 351, 366, 368, 370, 392, 394, 395, 397, 398, 399, 405, 407 and 409.” However, the Specification of the '805 Patent *discloses the specific corresponding contact residues for only four of these residues* (366, 394, 405, 407); corresponding contact residues are not explicitly disclosed in the specification for the other twelve contact amino acid residues (347, 349 – 351, 368, 370, 392, 395 – 399 and 409). *See* EX2013 at 10. That is, Dr. Presta explicitly disclosed only 4 amino acid pairs and left it up to the POSA to determine the remaining 12 pairs based on the disclosure in the Specification.

In response to a § 112 rejection, Dr. Presta argued in his patent application that the specification discloses that IgG amino acid positions 347, 349 – 351, 368, 370, 392, 395 – 399 and 409 *are suitable for modification*, that these positions are

a working example. The Specification of the '859 Patent discloses that positions 364 and 368 *are suitable for modification*, that these positions are “*interface residues*,” and provides the *positions* of these residues with respect to one another, and discloses the precise substitutions of neutral to positive, and neutral to negative to be made. *See* EX1010 at ¶ 47 (emphasis added). This is more than enough for a POSA to recognize that Merus possessed the invention and satisfied the written description requirement. Dr. Presta's own dealings with the Office confirm this conclusion.

For the reasons discussed above, the '859 Patent is entitled to its earliest claimed priority date, the April 20, 2012 filing date of '935 Provisional Application. As a result, the '427 Patent and Moore are not available as prior art to the '859 Patent, and Xencor cannot invalidate any claim of the '859 Patent on Grounds 1 and 2.

B. The Board Should Not Institute On Ground 3 Because Lazar Alone Or In Combination With Kannan Does Not Disclose Or Suggest Every Element Of Claims 1 – 7 Of The '859 Patent

Lazar alone or in combination with Kannan does not render the claims of the '859 Patent obvious because a POSA would not “*have been motivated to make* the combinations or modifications” of Lazar (alone or with Kannan) “to arrive at the claimed invention.” *See Curio Bioscience, Inc., v. Prognosys Biosciences Inc., et al.*, IPR2025-00192, Paper 8, at 21 (P.T.A.B. May 21, 2025) (quoting *Belden Inc. v. Berk-*

Tek LLC, 805 F.3d 1064, 1073 (Fed. Cir. 2015)) (emphasis in original) (denying institution because petitioner fails to teach or suggest the elements required by the challenged claims and fails to adequately articulate why a POSA would have modified the prior art to make the claimed invention).

As Dr. Sutton explains, a POSA would not arrive at the invention of Independent Claim 1 based on the teachings of Lazar alone or in combination with Kannan. *See* EX1010 at ¶ 53. Independent Claim 1 of the '859 Patent requires a heterodimeric antibody with a positively charged amino acid residue at position 364 in one CH3 domain and a negatively charged amino acid residue at position 368 in the other CH3 domain, but 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. *Id.* Kannan also does not disclose a positively charged amino acid residue at position 364 in one CH3 domain and a negatively charged amino acid residue at position 368 in the other CH3 domain. *Id.* Therefore, a POSA would not be able to arrive at the heterodimeric antibody of Independent Claim 1 by combining the disclosures of Lazar and/or Kannan.

1. Lazar Does Not Disclose Or Suggest The Claimed CH3 Domain And Heterodimeric Antibody

As Dr. Sutton explains in his Declaration, Lazar does not disclose or suggest the claimed CH3 domain and heterodimeric antibody. Based on the Specification of

the '859 Patent, a POSA would understand that the '859 Patent is directed to a heterodimeric antibody with two heavy chains with four domains, VH, CH1, CH2, and CH3, and two Fab arms each with a different binding site specificity. *See* EX1010 at ¶¶ 54 – 56. Lazar, however, discloses formats that *do not* have two different heavy chains consisting of four domains, and which have different binding site specificities than those defined in the Specification of the '859 Patent: the (1) scFv-Fc/empty-Fc format, and (2) alternative bispecific formats.

(a) Lazar's scFv-Fc/empty-Fc Format Do Not Meet The Limitations of the Claims

Lazar discloses a format for screening purposes, called the scFv-Fc/empty-Fc format, which does not have two different heavy chains consisting of four domains and which have different binding site specificities than those defined in the Specification of the '859 Patent. EX1010 at ¶ 57. The scFv-Fc/empty-Fc format of Lazar is not the claimed heterodimeric antibody with two different binding specificities as defined in the Specification of the '859 Patent. EX1010 at ¶ 58.

As Dr. Sutton explains in his Declaration, the empty-Fc does not have any antigen-binding site, and the scFv-Fc has only one binding site (*i.e.*, a single-chain variable fragment (scFv)). *Id.* Thus, the scFv-Fc/empty-Fc format is monospecific. *Id.*

Furthermore, the CH3 domains of the scFv-Fc/empty-Fc format are not CH3 domains in heavy chains with four domains as defined in the Specification of the '859 Patent—the scFv-Fc lacks a CH1 domain, and the empty-Fc lacks VH and CH1 domains. EX2010 at ¶ 59. Therefore, Lazar's scFv-Fc/empty-Fc formats have only one antigen-binding specificity from one chain, not “two different paired heavy chains with different specificity” as required by the Specification of the '859 Patent. EX1010 at ¶ 60.

Dr. Presta relies on variants disclosed in Table 1 and Figures 5 – 7 of Lazar to argue that Lazar discloses or suggests every limitation of Claim 1. EX1010 at ¶ 60. Dr. Presta states “Table 1 identifies a heterodimer incorporating CH3 domains with amino acid substitutions at those very positions—*i.e.*, position 364 and position 368” and “[e]qually, Figures 5 – 7 of *Lazar* depict various heterodimers with corresponding negative/positive and positive/negative amino acid substitutions at contact residues to measure impact on heterodimer formation.” See EX1002 at ¶¶ 197 – 198; EX1010 at ¶ 61. Nowhere is there disclosure of position 364 with a positive substitution and 368 with a negative substitution.

Moreover, as Dr. Sutton explains, all of the variants in Table 1 and Figures 5 – 7 were tested in the scFv-Fc/empty-Fc format. EX1010 at ¶¶ 62 – 63. Lazar's scFv-Fc/empty-Fc format is not the claimed heterodimeric antibody with different

specificity as defined in the '859 Patent. EX1010 at ¶ 64. Therefore, the variants in Table 1 and Figures 5 – 7, which were used only for scFv-Fc/empty-Fc format, do not disclose or suggest the subject matter claimed in Independent Claim 1. EX1010 at ¶ 64.

(b) Lazar's Alternative Bispecific Formats Do Not Disclose The Limitations of the Claims

Lazar also discloses an alternative type of bispecific format in which the interaction with the first antigen [Ag 1] is bivalent and the interaction with the second antigen [Ag 2] is monovalent, meaning the two chains are identical with respect to their antigen specificity [Ag 1]. EX1010 at ¶ 57. In these constructs, referred to as mAb-Fv and mAb-Fab, the second specificity [Ag 2] is generated by fusion of Fv or Fab domains to the C termini of the two chains, separated by a linker region. EX1010 at ¶ 57. In two other alternative bispecific constructs, Fab-Fv and Fab-Fab, an Fv or Fab is fused to the C terminus of a Fab-Fc construct. The first specificity [Ag 1] is provided by the Fab of the Fab-Fc and the second specificity [Ag 2] by the C-terminal Fv or Fab. As shown in Fig 8, Fab-Fv and Fab-Fab are “analogues of the mAb-Fv and mAb-Fab that bind both antigen-1 and antigen-2 monovalently.” See EX1004 at ¶ 48. Lazar's alternative bispecific formats (*i.e.*, mAb-Fv, mAb-Fab, Fab-Fv, and

Fab-Fab) are not the claimed heterodimeric antibody with different specificity as defined in the '859 Patent. EX1010 at ¶ 65.

According to Lazar, the alternative format is created by adding a Fv or Fab at the C termini of wild type IgG. *See* EX1004 at ¶¶ 46, 48; EX1010 at ¶ 66. However, the addition of a Fv or a Fab does not change the fact that the two chains have the same antigen specificity (for Ag1) in the Fab regions. EX1010 at ¶¶ 66 – 67. Further, the Fab-Fc of the Fab-Fv and Fab-Fab constructs comprise a single chain with specificity to Ag 1. Therefore, the alternative bispecific formats are not the antibodies of the '859 Patent that have heavy chains with different binding specificities. EX1010 at ¶ 67.

Furthermore, Lazar incorporated only one combination of substitutions (*i.e.*, Y349T/T394F and S364H/F405A) into the alternative bispecific format. EX1010 at ¶ 68.

Therefore, Lazar does not disclose or suggest the claimed heterodimeric antibody with chains having different specificities as defined in the Specification of the '859 Patent and required by Independent Claim 1. EX1010 at ¶ 69.

2. Lazar Does Not Disclose Or Suggest The Claimed Amino Acid Residues

As Dr. Sutton explains, Lazar does not disclose or suggest the features of “a positively charged amino acid residue at position 364” and “a negatively charged

amino acid residue at position 368” as required by Independent Claim 1 of the '859 Patent. EX1010 at ¶ 70.

Rather, Lazar suggests the opposite: a negatively charged amino acid residue at position 364 and a positively charged amino acid residue at position 368. The modification S364E and L368K are shown in Table 1, “Preferred CH3 domain variants that favor Fc heterodimerization.” See EX1004 at ¶ 241 and Table 1; EX1010 at ¶ 71. Dr. Presta admits that “Table 1 of Lazar identifies a heterodimer incorporating CH3 domains substituting in 364E (negatively charged) on a first CH3 domain and 368K (positively charged) on a second CH3,” whereas the '859 Patent claims are for the opposite charges. See EX1002 at ¶ 198; EX1010 at ¶ 71.

Dr. Presta is of the opinion that a POSA would change Lazar's preferred substitutions to arrive at the claimed residue pair. See EX1002 at ¶ 198; EX1010 at ¶ 72. But Dr. Presta fails to explain *why*, if at all, a POSA would swap the substitutions disclosed by Lazar. See EX1010 at ¶¶ 72 – 73; EX1002 ¶ 189. And in fact, a POSA would *not* swap the substitutions disclosed by Lazar because there is no teaching, suggestion or motivation to do so. Moreover, Lazar and the state of the art at the time of the invention taught against making neutral to charged substitutions, as the result is capable of destabilizing the Fc region. See EX1010 at ¶¶ 31, 91. Therefore, Lazar does not disclose the claimed heterodimeric antibody.

In support of his position, Dr. Presta engages in conjecture asserting that Lazar must have tested “both S364D/K370R (negative/positive substitution) and S364R/K370D (positive/negative substitution).” *See* EX1002 at ¶ 198; EX1010 at ¶ 73. However, Dr. Presta’s scientific analysis is flawed and there is no such disclosure in Lazar.

As explained by Dr. Sutton, positions 364 and 370 are self-evidently not the same as positions 364 and 368, so the example variants at positions 364 and 370 that Dr. Presta selected cannot be directly compared to variants at positions 364 and 368. EX1010 at ¶75. Specifically, positions 364 and 370 have different residue locations and surrounding environments that are critical for heterodimerization. *Id.* The data in Lazar also reveals that swapping the modifications causes a substantial effect upon the degree of heterodimerization—for example, S364R and K370D lead to a high fraction of heterodimer (*i.e.*, 59%, lane 17) whereas the swapped pair of mutations with opposite charges leads to a low fraction of heterodimer (*i.e.*, 38%, lane 14). *Id.*; *see also* EX1004 at Figure 5, lanes 20 and 22 (demonstrate that swapping of the charged mutations causes a substantial effect upon the fraction of heterodimerization). Therefore, from the data presented in Lazar, a POSA would understand that charge swap could have a significant, likely negative, effect upon heterodimerization. EX1010 at ¶ 75.

Dr. Sutton also points out that a POSA would see that neutral to neutral modifications of these same residues highlighted by Dr. Presta, namely S364F and K370G (EX1004 at Figure 5, lane 15), yields an even higher fraction of heterodimer (*i.e.*, 65%), suggesting to the POSA that the substitution of neutral residues to neutral residues is preferred to neutral to charged substitutions. EX1010 at ¶ 75.

Therefore, Dr. Presta's allegation that a POSA would swap the disclosed charges at positions 364 and 368 (*i.e.*, changing S364E into S364K or S364H and L368K into L368D or L368E) is pure conjecture, contrary to the disclosure of Lazar, and contrary to the art at the time of the invention.

3. Lazar Teaches Away From The Claimed Residue Pair

Lazar teaches away from the claimed heterodimeric antibody because it “leads [a POSA] in a direction divergent from the path taken by the applicant.” *See Voltage, LLC, v. Shoals Technologies Group, LLC*, IPR2024-00877, Paper 9, at 19 (P.T.A.B. Nov. 22, 2024) (citing *In re Gurley*, 27 F.3d 551, 553 (Fed. Cir. 1994)). Contrary to Dr. Presta's assertion, a POSA would *not* change Lazar's preferred substitutions to arrive at the claimed residue pair, but rather, would use certain of Lazar's preferred substitutions, *unmodified*.

According to the disclosure in Lazar, the “Preferred CH3 domain variants” in Table 1 represent the most promising amino acid residue substitutions for

heterodimerization at the positions considered by Lazar. *See* EX1010 at ¶¶ 76 – 77. A POSA would not swap these charges. This is because, as Dr. Sutton describes in his declaration, the data in Lazar suggests that swapping the charges of the “Preferred CH3 domain variants” will only *decrease* the degree of heterodimerization. EX1010 at ¶ 77.

Dr. Presta attempts to support his opinion with variants S364D & K370R and S364R & K370D, which happen to have a neutral to charged mutation of one of the residues, but charged to charged for the other. *See* EX1010 at ¶ 78. So, again, this is not the invention claimed by the '859 Patent—it is not the right residues, and not the right approach. Moreover, the disclosed heterodimer yield for these variants would discourage a POSA from using them—the S364D & K370R variant yields 38%, and the S364R & K370D variant yields 59%. *Id.* Tellingly, neither of these pairs is listed among the “Preferred CH3 domain variants.” *Id.*; EX1004 at Table 1. In fact, a variant with substitutions from *charged to neutral* residues (*i.e.*, S364F and K370G) is listed as a preferred variant because it provides a higher degree of heterodimerization (65%) than the two variants that Dr. Presta highlighted. EX1010 at ¶ 78. Therefore, a POSA would not select variants S364D & K370R and S364R & K370D for further development, but would instead select S364F & K370G, which has *charged to neutral* substitutions. *Id.*

Furthermore, the list of “Preferred CH3 domain variants” includes the variant S364E & L368K. The charge-swapped version of this (*i.e.*, a positively charged amino acid residue at position 364 and a negatively charged amino acid residue at position 368) is not even listed in Figure 5 – 7. Therefore, a POSA would not swap the substitutions of the “Preferred” (Table 1) and “Most preferred” (Table 2) variants based on the data of Lazar. EX1010 at ¶¶ 79 – 80.

In particular, a POSA looking at the data presented by Lazar would not conclude that substituting residues at positions 364 and 368 with positively or negatively charged residues would be advantageous for the formation of heterodimers; indeed, other types of modifications at different locations, or even other approaches, would be those that were appropriate to a POSA. EX1010 at ¶ 81.

The 230 variants (including some repeats and wild type controls) reported in Lazar Figures 5 – 7 were screened only using Lazar's scFv-Fc/empty-Fc format, which does not meet the claimed antibodies of the '859 Patent, and none of the variants include the claimed residues with the claimed substitutions. EX1010 at ¶ 82. Moreover, Lazar neither highlights, nor do the data support, any particular advantage of neutral to charged substitutions. *Id.* Dr. Presta notes that the variant S364E & L368K is disclosed in Table 1 (which is the opposite of the substitutions of the '859 Patent claims), and a POSA would not have any cause to choose those modifications

over others. In fact, the data suggest that other modifications, not involving substitutions at positions 364 and 368, would be appropriate for use in heterodimerization. *Id.*

Based on the disclosure of Lazar, a POSA would likely choose the variant K370D/K392D/K409D & E356K/E357K/D399K, which reports 100% heterodimer yield. *See* EX1010 at ¶ 83. A POSA may also select the variant S364H/F405A & Y349T/T394F, which Lazar used for the alternative bispecific construct and which has the next highest heterodimer yield of up to 85%. *Id.* Therefore, a POSA would firstly not select the 364/368 residue pair for modification and secondly not substitute residues with a positive charge at position 364 and a negative charge at 368 based on Lazar's disclosures, which suggest other modifications at different locations with higher yield fractions of heterodimer.

Lazar further states that CH3 domain modifications to yield “[h]eterodimeric Fc variants are not a necessity” for generation of the alternative bispecific formats, since the VH and VL domains attached to the chains to provide specificity for Ag-2 might themselves preferentially associate with each other or at least provide a means to purify the heterodimer utilizing its affinity for Ag-2. *See* EX1004 at ¶ 108; EX1010 at ¶ 84.

A POSA looking at the data presented by Lazar would conclude that other types of modifications at different locations, or indeed other approaches, would be more advantageous for the formation of heterodimers and not select the claimed residues at positions 364 and 368 for modification. EX1010 at ¶ 85.

4. Lazar In Combination With Kannan Does Not Disclose Or Suggest The Claimed Amino Acid Residues

As explained by Dr. Sutton, a POSA would furthermore not arrive at the invention of Independent Claim 1 based on the disclosures of Lazar in combination with Kannan. EX1010 at ¶ 86. Like Lazar, Kannan also does not disclose or suggest “a positively charged amino acid residue at position 364” and “a negatively charged amino acid residue at position 368” as required by Independent Claim 1 of the '859 Patent. *Id.* Dr. Presta relies on Kannan for its disclosure of the charge reversal technique to argue that a POSA would reverse the charges of Lazar's preferred CH3 domain variants. *Id.* However, applying Kannan's charge reversal technique to the preferred CH3 domain variants in Lazar is without scientific basis. *Id.*

As Dr. Sutton explained, there is no disclosure in Lazar that would direct a POSA to substitute the neutral amino acid with a positively charged amino acid residue at position 364 (364(+)) and the neutral amino acid with a negatively charged amino acid residue at position 368 (368(-)). EX1010 at ¶ 87. In fact, Dr. Presta admits that Lazar actually discloses the opposite, *i.e.*, substituting to a negatively charged

amino acid residue at position 364 and a positively charged amino acid residue at position 368. EX1010 at ¶ 87. However, Dr. Presta has to argue a POSA would reverse the charges disclosed in Lazar at positions 364 and 368 based on Kannan because Kannan generally discloses reversing negative and positive charges at the CH3 domain interface. *See* EX1002 at ¶¶ 191 – 192; EX1010 at ¶ 88.

Dr. Presta's argument does not make sense. Dr. Presta is essentially arguing that a POSA would *re-engineer* variants that had already been exhaustively engineered through Lazar's modification selection processes and thorough screening. EX1010 at ¶ 89. A POSA would not do this. As explained by Dr. Sutton, in the absence of any additional data, a POSA would not consider generating further substitutions, such as reversing negatively and positively charged residues, because this already had been thoroughly explored by Lazar. *Id.* Unlike Kannan's variants that were modified from wild type, the engineered variants of Lazar *already have modified structures* and surrounding environments. *Id.* Kannan is also highly selective regarding the locations of modifications. *Id.* Therefore, a POSA would not consider reversing charges according to Kannan's disclosure for any of Lazar's preferred variants with any expectation of success. *Id.*

For the same reasons discussed above, a POSA would also not be motivated to modify the "Preferred CH3 domain variants" disclosed by Lazar, including by

applying charge reversal as suggested by Kannan. EX1010 at ¶ 90. No examples or data are offered for modifying the “Preferred CH3 domain variants,” and, in fact, the data in Lazar suggests that doing so would only reduce the heterodimerization yield.

Id.

Dr. Sutton also points out that Kannan and Gunasekaran are both attributable to the same person: Dr. Gunasekaran Kannan. The Gunasekaran and Kannan references are directed to the same heterodimerization technique (*i.e.*, electrostatic steering through charge reversing). EX1010 at ¶ 91. Importantly, these references warn against modifying the hydrophobic residues, as doing so may destabilize the antibody and Fc region. *See* EX1012; EX1010 at ¶ 91. According to Gunasekaran, “[i]t has long been established that the hydrophobic core of protein domains plays an important role in protein folding and stability,” and therefore one may attempt “exploiting charged residues *as opposed to hydrophobic residues at the CH3 domain interface*” and that doing so, “may have benefits in terms of retaining the generally favorable biophysical properties of the Fc.” *See* EX1012 at 4 (emphasis added). Considering the teachings by Dr. Gunasekaran Kannan in both Gunasekaran and Kannan, a POSA would not be motivated to modify the hydrophobic core residues of the CH3 region, which comprises primarily neutral, nonpolar amino acids, using the charge reversing technique disclosed in Kannan. EX1010 at ¶ 91.

Given the above, Lazar alone or in combination with Kannan does not disclose or suggest “a positively charged amino acid residue at position 364” and “a negatively charged amino acid residue at position 368” as required by Independent Claim 1 of the '859 Patent. EX1010 at ¶ 92. Lazar alone or in combination with Kannan also does not disclose the limitations in Dependent Claims 2 – 7 of the '859 Patent because Dependent Claims 2 – 7 of the '859 Patent depend from Independent Claim 1. *Id.*

For the reasons discussed above, Lazar (alone or in view of Kannan) does not render the claims of the '859 Patent obvious. *Id.* A POSA would not have been *motivated to make* the combinations or modifications of Lazar and Kannan to arrive at the claimed invention. And even if combined, Lazar and Kannan do not disclose, as defined by the '859 Patent Specification, a heterodimeric antibody with a positively charged amino acid residue at position 364 and a negatively charged amino acid residue at position 368 in the CH3 region.

VIII. CONCLUSION

For at least the foregoing reasons, the Petition should be denied as to each of the requested grounds. For brevity, Patent Owner may not have addressed all of the defects in the Petition, including in the characterizations of the applied references and the challenged claims, and reserves the right to do so should institution be

granted. The absence of a response by Patent Owner to any of the positions presented in the Petition or the associated expert declaration does not constitute a concession to those positions. The fact that Patent Owner's Preliminary Response has focused on particular arguments is not a concession that there are no other arguments for patentability of the challenged claims.

Dated: June 30, 2025



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CERTIFICATE OF COMPLIANCE

Pursuant to 37 C.F.R. § 42.24(d), the undersigned certifies that the foregoing **PATENT OWNER MERUS' PRELIMINARY RESPONSE** contains, as measured by the word-processing system used to prepare this paper, 7,501 words. This word count does not include the items excluded by 37 C.F.R. § 42.24 as not counting towards the word limit.

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I hereby certify that I caused to be served a true and correct copy of the foregoing: **PATENT OWNER MERUS' PRELIMINARY 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 on June 30, 2025, in its entirety on the following:

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