

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

XENCOR, INC.,

Petitioner

v.

MERUS N.V.,

Patent Owner

IPR2025-00604

Patent No. 9,358,286

**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
Board	Patent Trial And Appeal Board
'286 Patent	Patent No. 9,358,286
POSA	Person of ordinary skill in the art
Lazar	U.S. Patent Application Publication No. US 2011/0054151
Arathoon	International Patent Application Publication No. WO 1998/050431
Cabrera	International Patent Application Publication No. WO 2012/058768
FDA	U.S. Food & Drug Administration
SEC	U.S. Securities And Exchange Commission
BTD	Breakthrough Therapy designation

LIST OF EXHIBITS

Exhibit Number	Description
EX1001	The '286 Patent
EX1002	Declaration of Leonard G. Presta, Ph.D.
EX1004	Lazar
EX1005	Cabrera
EX1006	Arathoon
EX1012	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
EX2007	Xencor Form 10-K for the fiscal year ended December 31, 2017
EX2008	Declaration of Dr. Brian Sutton, Ph.D. In Support Of Patent Owner Merus' Preliminary Response
EX2009	Curriculum Vitae of Dr. Brian Sutton, Ph.D.
EX2010	U.S. Patent No. 9,493,579

I. INTRODUCTION

It would be a waste of the Board's limited resources to institute an IPR of Merus' '286 Patent—a patent known to Xencor since at least 2017—because Xencor's petition is entirely meritless. The '286 Patent claims certain aspects of Merus' pioneering heterodimerization technology—a technology that has led to one FDA-approved cancer therapy and another BTD therapy in the pipeline. In an attempt to undermine Merus' innovation, Xencor and its expert advance frivolous invalidity grounds, including by: (a) ignoring the express definition of “heavy chains” in the specification of the '286 Patent; and (b) relying on references that do not, individually or in combination, disclose all of the claimed elements, but in fact teach away from the claimed invention.

For Grounds 1 and 2, Xencor asserts Lazar and Arathoon, which were considered by the Examiner during the prosecution of the '286 Patent and clearly do not apply when the term “heavy chains” is properly construed. Xencor's expert, Dr. Presta, completely ignores the explicit definition of “heavy chains” in the Specification of the '286 Patent as having **“four domains, the variable heavy chain (VH) and three constant heavy chain domains (CH1, CH2, CH3).”** The constructs disclosed in primary reference Lazar indisputably do not disclose antibodies that meet the patent's definition of heavy chain. Dr. Presta's mistake is

fatal to Grounds 1 and 2 and calls into question the reliability of his entire declaration. A key element of the claims—indeed the invention of the '286 Patent—is that the neutral to positive and neutral to negative **residue** substitutions in the CH3 domains of the heavy chains **interact with each other to promote heterodimerization**. Yet, Dr. Presta completely ignores that Lazar does not disclose **any information or data** with respect to any interactions between individual residues. Instead, Dr. Presta makes assumptions about contact residues with no data while ignoring key factors such as residue location and its surrounding environment. Dr. Presta also impermissibly uses hindsight to pick and choose the disclosure of Lazar while ignoring the data that actually teaches a POSA away from the claimed invention. Moreover, Dr. Presta advances combinations—Lazar and Arathoon—that a POSA could not combine in the first instance and, even if they did, would not arrive at the claimed invention.

For Grounds 3 and 4, Xencor adds Cabrera, which like Lazar, does not disclose any data showing substitutions of neutral to positive and neutral to negative residues in heavy chains that interact with each other to promote heterodimerization. In fact, the melting point and purity data for the only example that Dr. Presta points to in Cabrera shows the **exact opposite, teaching away from Merus' pioneering invention**.

The combination of Cabrera, Lazar and Arathoon also fails. Cabrera's disclosures are directed to techniques for **restoring stability** of an antibody after it has destabilized during Fc heterodimerization engineering. On the other hand, Lazar discloses an **already stable** interface between identical chains. And, Arathoon adds no information to the disclosures of Cabrera and/or Lazar regarding CH3 domain engineering to promote heterodimerization.

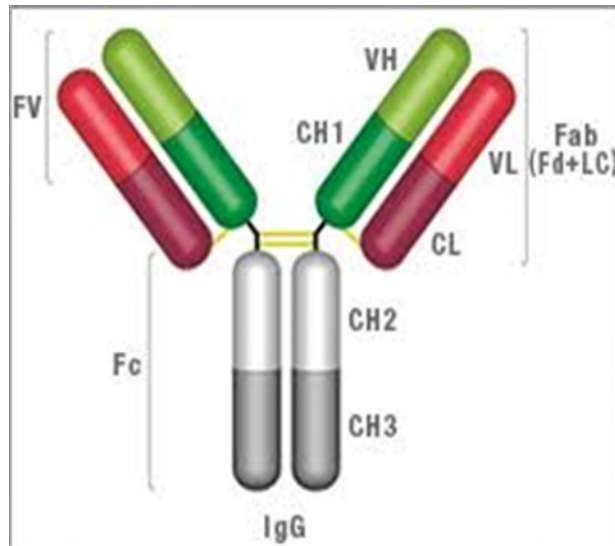
Xencor has not established a reasonable likelihood that any claim of the '286 Patent is unpatentable on the grounds that it advances in its Petition and has waited over 8 years to challenge it. Indeed, the '286 Patent has been in force for nearly 9 years, has not previously been challenged, and Xencor has known about it since its 2017 Form 10-K SEC filing. *See* EX2007 at 46. For all these reasons, as explained in more detail below, institution should be denied under 35 U.S.C. §314(a).

II. TECHNOLOGY OVERVIEW

Antibodies or immunoglobulins (Igs) naturally occur in the body and are key for eliciting an immune response and eliminating cancer cells. *See* EX2008 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* EX2008 at ¶ 23. Each Ig heavy chain consists of three constant domains (CH1, CH2, and CH3) and one variable

domain (VH), which is also consistent with the definition of heavy chain in the '286 Patent. See EX2008 at ¶ 24; EX1001 at 11:58–66.



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 EX2008 at ¶ 25.

Fc dimerization is a complex process that depends on the proper folding of each CH3 domain, which must first fold before the CH3 domain of one heavy chain can then interact with the CH3 domain of the other heavy chain to form a non-covalent dimer and maintain the dimeric structure of the antibody. See EX2008 at ¶ 26. The accompanying Sutton Declaration explains in more detail the complexities

of the makeup of the amino acids of an Ig (*see* EX2008 at ¶¶ 20 – 22) and the folding of the CH3 domain. *See* EX2008 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 may affect folding and/or dimerization. *See* EX2008 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; EX2008 at ¶ 31. Accordingly, it was understood to modify charged residues, not hydrophobic residues to improve heterodimerization, as the prior art notes “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.*

It was known 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* EX2008 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 homodimerization. *See* EX2008 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 heterodimerization approach that went against conventional wisdom by substituting a neutral residue in the hydrophobic interface of the CH3 dimer, one on each heavy chain, with a charged residue, to enhance the stability of the CH3-CH3 dimer interface. *See* EX2008 at ¶ 35.

Surprisingly, Merus' heterodimerization technique is capable of achieving heterodimeric antibodies with higher yield and increased stability, thereby going against the teaching in the art and meeting a long felt need. Merus was granted the '286 patent for its novel and non-obvious invention.

III. OVERVIEW OF THE '286 PATENT

The '286 Patent claims certain aspects of Merus' pioneering heterodimerization technology. The pioneering invention of the '286 Patent is the

neutral to positive and neutral to negative substitutions of residues in the hydrophobic core of heavy chains as defined in the Specification of the '286 Patent that interact to promote heterodimerization.

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

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

- a. providing a host cell comprising
 - (i) a first nucleic acid molecule encoding a 1st antibody heavy chain comprising at least one substitution of a neutral amino acid residue in the CH3 domain by a positively charged amino acid residue, and
 - (ii) a second nucleic acid molecule encoding a 2nd antibody heavy chain comprising at least one substitution of a neutral amino acid residue in the CH3 domain by a negatively charged amino acid residue;
- b. culturing said host cell and allowing for expression of said two nucleic acid molecules to produce said 1st antibody heavy chain and said 2nd antibody heavy chain, **wherein the at least one positively charged amino acid residue substituted in the CH3 domain of said 1st antibody heavy chain interacts with the at least one negatively charged amino acid residue substituted in the CH3 domain of said 2nd antibody heavy chain in the interface between said 1st and 2nd antibody heavy chains to produce a heterodimeric antibody**; and
- c. harvesting said heterodimeric antibody from the culture.

(emphasis added).

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

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

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

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

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

Independent Claim 30 of the '286 Patent recites:

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

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

IV. CLAIM CONSTRUCTION

Petitioner does not propose any claim constructions and ignores the explicit definition of “heavy chains” in the Specification of the '286 Patent. A POSA would understand that the '286 Patent is directed to producing bispecific antibodies with two “heavy chains” with VH, CH1, CH2, and CH3 domains and two Fab arms each with a different binding site specificity. Petitioner and its expert's failure to apply

the correct construction for “heavy chains” is fatal to its Petition. The Board need not construe any other claim term for the purpose of deciding to deny institution.

V. PERSON OF ORDINARY SKILL IN THE ART

Petitioner proposes the following definition of a POSA: a POSA would have a PhD 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 Masters degree in any of the above fields with at least 4 years of related experience in academia or industry. *See* EX2008 at ¶ 17. For purposes of the Preliminary Response, Patent Owner applies Petitioner's proposed definition of a POSA. Under either definition of a POSA, however, Xencor still fails to meet its burden for IPR institution.

VI. SUMMARY OF PETITIONER'S GROUNDS AND REFERENCES

Xencor asserts four grounds based on Lazar, Cabrera, and Arathoon. Xencor's alleged grounds for petition are: Ground 1: Lazar Anticipates Claims 1, 7, 21, 22, 24, 26, 28, 30, and 32; Ground 2: Lazar in view of Arathoon Renders Obvious Claims 1 – 2, 7 – 24, 26 – 28, and 30 – 32; Ground 3: Cabrera Anticipates Claims 1 – 2, 7, 21, 22, 24, 26 – 28, and 30 – 32; and Ground 4: Lazar in View of Arathoon and Cabrera Renders Obvious Claims 1 – 2, 7 – 24, 26 – 28, and 30 – 32.

All grounds fail because these references do not contain all of the elements of the claims under either anticipation or obviousness theories. Lazar, Arathoon, and Cabrera do not disclose a heterodimeric antibody with substitutions of neutral to positive and neutral to negative residues in heavy chains as defined in the Specification of the '286 Patent, including that interact with each other to promote heterodimerization as required by Claim 1 of the '286 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). “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.” 35 U.S.C. § 314(a). Xencor cannot meet its burden.

Xencor's four grounds of alleged unpatentability cannot invalidate any claim of the '286 Patent. Xencor's grounds do not adhere to the legal standards for showing unpatentability, nor do they withstand scientific scrutiny. In fact, Lazar, Cabrera, and Arathoon do not even disclose all of the elements of the Claims of the '286 Patent. Moreover, Xencor's expert Dr. Presta's declaration is unsupported by

data, conclusory, and unreliable. Accordingly, the Board should not institute Xencor's IPR petition. *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”).

Notably, and as discussed in Merus' request for discretionary denial, many of Dr. Presta's “opinions” are verbatim parroting of Petitioner's arguments. *See, e.g.*, Paper 1 at 61–62, *c.f.*, EX1002 at 127–129. Dr. Presta's conclusory and incorrect arguments cannot support Xencor's position. *See* 37 C.F.R. § 42.65(a) (“Expert testimony that does not disclose the underlying facts or data on which the opinion is based is entitled to little or no weight”); *see also TQ Delta, LLC v. CISCO Sys., Inc.*, 942 F.3d 1352, 1359 (Fed. Cir. 2019) (holding that conclusory expert testimony is insufficient). The Board should deny institution of Xencor's IPR petition.

A. The Board Should Not Institute On Ground 1 Because Lazar Does Not Disclose All Of The Elements Of The Claims Of The '286 Patent

Lazar does not anticipate the Claims of the '286 Patent because it does not “disclose all elements of the claim within the four corners of the document,” or “disclose those elements ‘arranged as in the claim,’” as required by settled Federal Circuit precedent. *See Microsoft Corp. v. Biscotti, Inc.*, 878 F.3d 1052, 1068 (Fed.

Cir. 2017) (quoting *Net MoneyIN, Inc. v. VeriSign, Inc.*, 545 F.3d 1359, 1369 (Fed. Cir. 2008)) (affirming that IPR challenger failed to show the challenged claims were anticipated); *see also Precision Cancer Technologies Inc., v. Oncoustics Inc.*, IPR2025-00242, Paper 7, at 5 (P.T.A.B. June 3, 2025) (denying IPR institution because petitioner failed to establish that asserted reference disclosed claim element).

Lazar does not disclose at least two elements required by Independent Claim 1: (1) Lazar does not disclose antibodies with “heavy chains” as defined in the Specification of the '286 Patent; and (2) Lazar does not disclose neutral to positive and neutral to negative substitutions of residues on heavy chains as defined in the Specification of the '286 Patent that interact to promote heterodimerization. *See* EX2008 at ¶ 44.

i. Lazar Does Not Disclose Antibodies With Heavy Chains As Defined In The Specification Of The '286 Patent

Xencor's anticipation argument fails because it ignores the Specification's definition of “heavy chains” and, when applied, it is clear that Lazar is inapplicable. The Specification of the '286 Patent defines heavy chains as follows:

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

EX1001 at 11:58–63 (emphasis added). The Specification of the '286 Patent also requires that the heavy chains have different specificity. The Specification of the '286 Patent states that the: “bispecific dimers (also called heterodimers) contain two different paired heavy chains with different specificity.” EX1001 at 3:27–31.

A POSA would understand that the claim term “heavy chain” in light of its definition in the Specification of the '286 Patent requires heavy chains with four domains (*i.e.*, VH, CH1, CH2, and CH3) with each heavy chain having different specificity. *See AT&T Services Inc., et al, v. Innovative Sonic Limited*, IPR2024-01145, Paper 12, at 11–12 (P.T.A.B. Jan. 24 2025) (quoting *Phillips v. AWH Corp.*, 415 F.3d 1303 (Fed. Cir. 2005) (en banc)) (claims are construed using their “ordinary and customary meaning . . . at the time of the invention ***and in the context of the entire patent disclosure.***”) (emphasis added). This definition is consistent with the ordinary and customary meaning of “heavy chains.” But even if it were not, as the Federal Circuit has explained, “our cases recognize that the specification may reveal a special definition given to a claim term by the patentee that differs from the meaning it would otherwise possess. In such cases, the inventor’s lexicography governs.” *Phillips*, 415 F.3d at 1316. When the '286 Patent’s clear definition of “heavy chains” is applied, Xencor’s anticipation analysis completely fails. The moieties disclosed in Lazar do not have heavy chains as defined by the specification

because they do not have the requisite four domains (*i.e.*, VH, CH1, CH2, and CH3). Further, the chains do not have different specificity as required by the claims.

Dr. Presta does not correct Xencor's fatal claim construction error. Instead, Dr. Presta parrots Xencor's erroneous assertions. Therefore, Dr. Presta's analysis suffers from the same flaw as Xencor's, and the Board should deny institution on Ground 1. *See Roku, Inc. v. Anonymous Media Research Holdings, LLC*, IPR2024-01056, Paper 10, at 25 (P.T.A.B. Feb. 5, 2025) (declining to institute review after finding petitioner's expert's construction to be incorrect, merely parroting petitioner's own assertions).

As Dr. Sutton explains in his declaration, Lazar discloses scFv-Fc/empty-Fc formats, which do not have heavy chains with the requisite four domains (*i.e.*, VH, CH1, CH2, and CH3) as defined in the Specification of the '286 Patent. *See* EX2008 at ¶ 48. Instead, the scFv-Fc chain has a VH-linker-V_K-Hinge-CH2-CH3', and the empty-Fc chain has a sequence of Hinge-CH2-CH3". *See* EX1004 at ¶ 238, Figure 1; EX2008 at ¶ 48. Such sequences clearly show that the scFv-Fc chain lacks a CH1 domain, and the empty-Fc chain lacks VH and CH1 domains. *See id.*

Further, as Dr. Sutton explains, the scFv-Fc/empty-Fc format does not have chains with different specificities as required by the '286 Patent claims. *See* EX2008 at ¶ 49. According to the disclosed sequences and Figure 1 in Lazar, the empty-Fc

chain does not have any antigen-binding site and the scFv-Fc chain has only one binding site (*i.e.*, a single-chain variable fragment (scFv)). *See id*; EX1004 at Figure 1. Thus, the scFv-Fc/empty-Fc format is a monospecific moiety and not a heterodimeric antibody having two heavy chains with different specificities as required by the claims of the '286 Patent. *See id*.

Dr. Presta's mistakes are compounded when he relies on variants disclosed in Tables 1 – 2 of Lazar to argue that Lazar discloses substituting a neutral amino acid residue in the CH3 domain of one chain with a positive amino acid residue and substituting a neutral amino acid residue in the CH3 domain of a second chain with a negative amino acid residue, as Claim 1 requires. *See* EX1002 at ¶ 115; EX2008 at ¶ 51. Dr. Presta completely misses the fact that all of the variants in Tables 1 – 2 were tested in the scFv-Fc/empty-Fc format that clearly does not meet the Specification's definition of heavy chains. *See* EX1004 at ¶¶ 240–241; EX2008 at ¶ 52.

Lazar's alternative bispecific format, (*i.e.*, mAb-Fv, mAb-Fab, Fab-Fv, and Fab-Fab) does not fare any better. This format, like the scFv-Fc/empty-Fc format construct, also does not have two different paired heavy chains with different specificity. *See* EX2008 at ¶¶ 55 – 57. Dr. Sutton clearly explains that Lazar's mAb-Fv format is created by adding a Fv at the C termini of wild type IgG. *See* EX1004 at ¶ 46; EX2008 at ¶ 56. Likewise, as explained by Dr. Sutton, the mAb-Fab format is

created by adding a Fab at the C-termini of wild type IgG. *Id.* As shown in Figure 8 of Lazar, the addition of a Fv or a Fab does not change the fact that the two chains have the same antigen specificity (for Ag1) in the Fab regions. *See* EX1004 at Figure 8; EX2008 at ¶ 56. 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; EX2008 at ¶ 57.

Therefore, the alternative bispecific moieties are not the antibodies of the '286 Patent that have heavy chains as required by the Patent (“each heavy chain has four domains, the variable heavy chain (VH) and three constant heavy chain domains (CH1, CH2, CH3)”) with different binding specificities. *See id.* Furthermore, Lazar does not disclose the claimed substitutions of neutral to charged residues, nor the elements of heavy chains, and different specificities, with the alternative bispecific format. *See* EX2008 at ¶ 58.

ii. Lazar Does Not Show Interaction Of Residues

Independent Claim 1 requires a heterodimeric antibody with substitutions of neutral to positive and neutral to negative residues in heavy chains as defined in the Specification of the '286 Patent that interact with each other to promote heterodimerization. Lazar fails to disclose the “interacting” element required by Claim 1. *See* EX2008 at ¶ 60.

Discussion regarding interactions to promote heterodimerization in Lazar only relate to the overall CH3-CH3 interaction, not to interactions between individual residues. See EX2008 at ¶ 61. For example, Lazar states:

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

See EX1004 at ¶ 121. Indeed, Dr. Presta does not identify any information in Lazar to support his opinions concerning residue to residue interactions.

Instead, Dr. Presta incorrectly assumes that the introduction of positive and negative charges would necessarily result in favorable electrostatic interactions within the CH3 interface. See EX1002 at ¶ 112; EX2008 at ¶ 61. As Dr. Sutton explains, the residue location and its surrounding environment are critical, and it cannot be assumed that an electrostatic interaction that promotes heterodimerization occurs even after the introduction of positive and negative charges. See EX2008 at ¶ 61. Indeed, based on the teaching in the art at the time of Merus' invention, a POSA would

understand that such changes would be disruptive and destabilizing rather than promoting heterodimerization.

In fact, Dr. Presta's assumption contradicts disclosures in his own patents. Specifically, Dr. Presta highlights the importance of confirming that mutations made at known contact residues still interact after substitutions because "while the site for introducing an amino acid sequence variation is predetermined, the nature of the mutation per se need not be predetermined." *See, e.g.*, EX2010 at 51:22–41. Dr. Presta's contradictory positions here—that one can simply assume an interaction promoting heterodimerization, in contrast to the teachings and disclosure of his own patents—further underscores his lack of credibility.

For the reasons discussed above, Dr. Presta's analysis is inherently faulty. Dr. Presta relies on an incorrect claim construction for "heavy chains." Ignoring the definition in the '286 Patent, Dr. Presta also assumes that the substituted residues in Lazar "interact" to promote heterodimerization even though there is no supporting data, and the teaching in the art (and in his own patent application) regarding the unpredictability and potential disruptive impact of such substitutions. These assumptions fly in the face of Dr. Presta's own patent disclosures.

On the other hand, Dr. Sutton affirmatively demonstrates that Lazar does not disclose the heterodimeric antibody of the '286 Patent, particularly because Lazar

does not disclose antibodies with heavy chains as defined in the Specification of the '286 Patent. Lazar also does not disclose neutral to positive and neutral to negative substitutions of residues on heavy chains as defined in the Specification of the '286 Patent that interact to promote heterodimerization. *See* EX2008 at ¶ 62.

For at least these reasons, Lazar therefore also fails to disclose the claimed limitations in Dependent Claims 7, 21, 22, 24, 26, 28, 30, and 32 of the '286 Patent. *See* EX2008 at ¶ 63. Dependent Claims 7, 21, 22, 24, 26, 28, 30, and 32 of the '286 Patent depend from Independent Claims 1, 26, or 30. *See* EX1001. For the reasons discussed above, Lazar does not disclose a heterodimeric antibody with substitutions of neutral to positive and neutral to negative residues in heavy chains as defined in the Specification of the '286 Patent that interact with each other to promote heterodimerization. *See* EX2008 at ¶ 63. Therefore, Lazar also does not disclose the elements of the Dependent Claims. *Id.*

B. The Board Should Not Institute On Ground 2 Because Lazar And Arathoon Do Not Suggest All The Elements Of Claims 1, 26, And 30 Of The '286 Patent

The combination of Lazar and Arathoon does not render the claims of the '286 Patent obvious because a POSA would not “*have been motivated to make* the combinations or modifications” of Lazar and Arathoon “to arrive at the claimed invention.” *See Curio Bioscience, Inc., v. Prognosis 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). In fact, a POSA as of April 20, 2012 would not have sought to combine Lazar and Arathoon at all given their wholly incompatible formats. See *InTouch Techs., Inc. v. VGO Commc'ns, Inc.*, 751 F.3d 1327, 1352 (Fed. Cir. 2014) (obviousness requires a showing as to “why one of ordinary skill in the art at the time of the invention would have sought to combine or modify the references.”).

As Dr. Sutton explains, a POSA would not arrive at the inventions of Independent Claims 1, 26, and 30 based on the teachings of Lazar alone or in combination with Arathoon. See EX2008 at ¶¶ 64 – 78. Specifically, (1) Lazar teaches away from the claimed heterodimeric antibody, (2) a POSA would not be motivated to combine Lazar and Arathoon, and (3) a combination of Lazar and Arathoon does not lead to the heterodimeric antibody of the '286 Patent.

i. Lazar Teaches Away From The Claimed Heterodimeric Antibody

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)). Lazar teaches a POSA to make an alternative bispecific construct, which includes chains with the same specificity, rather than a bispecific antibody with heavy chains with different specificity as defined in the Specification of the 1'286 Patent. See EX1004 at Figure 8; EX2008 at ¶¶ 65 – 66.

(1) Lazar's Chains Have The Same Specificity

As Dr. Sutton explains, the alternative bispecific formats taught by Lazar include two chains that consist of five or six domains with the **same** antigen specificity. See EX2008 at ¶ 67. Therefore, a POSA would not be motivated by Lazar to produce a heterodimeric antibody with two chains with **different** antigen specificity, as claimed in the '286 Patent. *Id.*

(2) Lazar Teaches Away From Making Neutral to Charge Fc Heterodimers

As Dr. Sutton also explains, a POSA would not substitute neutral residues in CH3 domains with charged residues based on Lazar's teachings. See EX2008 at ¶ 68. Rather, a POSA would look to the heterodimerization yield data presented in Figures 5 – 7 and be taught away from making neutral to positive substitutions based on the data. *Id.*

The 230 variants (including some repeats and wild type controls) reported in Lazar Figures 5 – 7 include examples of neutral to neutral, charged to charged, neutral to charged, and charged to neutral substitutions, with some as a single modification, others as double, and yet others as triple modifications. *See* EX2008 at ¶ 69. These were all screened only using Lazar's scFv-Fc/empty-Fc format. *Id.* Lazar neither highlights, nor does the data support, any particular advantage of neutral to charged modifications. *Id.*

Dr. Presta notes that there are neutral to charged modifications in Tables 1 and 2, but a POSA would not have any cause to choose those modifications over others. *Id.* In fact the data would suggest that other modifications, not involving neutral to charged substitutions, would be selected. *Id.* Dr. Presta also identifies two modifications in Table 2 that he asserts involve neutral to charged substitutions at known contact residues in the native CH3 interface (indicated by Dr. Presta by red boxes). *Id.* But Lazar does not discuss contacting residues, only the overall interfaces, and thus again, a POSA would have no reason to select these particular modifications, as there is no indication of any use for promoting heterodimerization. *Id.* Furthermore, as Dr. Sutton explains, one of the boxed modifications in Table 2 (L351K, L351E) has no supporting experimental data, and thus there would be no reason for a POSA to select this modification. *Id.*

Lazar reports in Figures 5 – 7 the heterodimerization yields for each of the variants. *See* EX2008 at ¶ 70. The variant with the best heterodimerization yield, indeed the only variant with 100% yield of heterodimer, involves three charged to charged modifications in each chain (*i.e.*, K370D/K392D/K409D in one chain and E356K/E357K/D399K in the other chain). *Id.* This is entirely keeping with the dogma of the time—to stay away from the hydrophobic core—and teaches away from the '286 Patent. *Id.* Furthermore, the only modification that was taken into the alternative bispecific construct (with the next highest heterodimer yield of up to 85%) involved only neutral to neutral modifications (*i.e.*, S364H/F405A in one chain and Y349T/T394F in the other chain). *Id.* Again, this is entirely keeping with the dogma of the time and teaches away from the '286 Patent. The dogma at the time was to change only charged to charged or neutral to neutral so as not to disrupt the hydrophobic core. The neutral to charged variants that Dr. Presta highlighted from the “Most preferred CH3 domain variants” in Table 2 in fact provide lower heterodimeric yields, which again teaches away from the '286 Patent claims. *See* EX1004 at Table 2, Figures 5 – 7. *Id.* A POSA would not substitute neutral residues with charged residues based on Lazar's teachings and indeed would pursue charged-to-charged or neutral-to-neutral modifications for higher yields. *Id.*

In addition to teaching away from neutral to charged Fc heterodimer variants, Lazar further states that CH3 domain modifications to yield “[h]eterodimeric Fc variants are not a necessity” for generation of the alternative bispecific antibodies, citing other, more favorable techniques. *See* EX1004 at ¶ 108; EX2008 at ¶ 71. Therefore, as Dr. Sutton concluded, a POSA looking at the data presented by Lazar would not conclude that making neutral to positive and neutral to negative substitutions in the CH3 domain would be advantageous for the formation of heterodimers; other types of variations, or indeed other approaches, would be more attractive to a POSA. *See* EX2008 at ¶ 72. Therefore, Lazar teaches away from the heterodimeric antibody of the '286 Patent.

ii. A POSA Would Not Be Motivated To Combine Lazar And Arathoon

Arathoon does not teach a heterodimeric antibody with substitutions of neutral to positive and neutral to negative residues in heavy chains as defined in the Specification of the '286 Patent or that such substitutions interact with each other to promote heterodimerization, as required by Independent Claim 1. *See* EX2008 at ¶ 73. Dr. Presta relies on Arathoon for its disclosure of a common light chain to challenge Dependent Claim 2. *Id.* However, a POSA would not combine the disclosures of Lazar and Arathoon because of the structural differences in their respectively disclosed antibodies. *See* EX2008 at ¶ 74. Stated simply, these are

incompatible formats. It would be like trying to combine a LEGO with a Lincoln Log.

A POSA would not combine Lazar and Arathoon because a POSA reading these references “would be led in a direction divergent from the path that was taken by the applicant,” *i.e.*, away from the claimed heterodimeric antibody. *See In re Gurley*, 27 F.3d at 553. Lazar and Arathoon are structurally incompatible and cannot be combined to make a functional heterodimeric antibody. This is akin to *McGinley v. Franklin Sports, Inc.*, where the Federal Circuit found that “references teach away from the combination” if the “combination would produce a ‘seemingly inoperative device.’” *McGinley*, 262 F.3d 1339, 1354 (Fed. Cir. 2001) (quoting *In re Spinnoble*, 405 F.2d 578, 587 (CCPA 1969)); *see also Deere & Company, v. David's Dozer V-Loc System, Inc.*, IPR2024-01442, Paper 10, at 10–11 (P.T.A.B. March 18, 2025) (quoting *McGinley, id.*).

As Dr. Sutton explains, Arathoon concerns the production of multispecific antibodies with “a common light chain associated with each heterodimeric polypeptide having an antibody binding domain.” *See* EX1006 at Abstract; EX2008 at ¶ 74. Arathoon's common light chain is “provided to pair with each of the variable heavy chains of the multi-specific antibody” to produce “a desired heteromultimeric antibody.” *See* EX1006 at 6:24–26.

However, the empty-Fc of Lazar's scFv-Fc/empty-Fc format does not have any variable regions to which a common light chain can be paired. *See* EX2008 at ¶ 75. Therefore, Arathoon's common light chain cannot be "provided to pair with each of the variable heavy chains." *See* EX2008 at ¶ 75.

Likewise, Lazar's alternative bispecific constructs (mAb-Fv and mAb-Fab) do not include two different heavy chains as defined by the '286 Patent with which Arathoon's common light chain can be associated to enhance the production of the "desired heteromultimeric antibody." *See* EX1006 at 6:24–26; EX2008 at ¶ 76. Furthermore, a POSA would understand that Lazar's alternative bispecific constructs with identical heavy chains do not need Arathoon's common light chain to enhance the production of bispecific antibodies with two different heavy chains. EX2008 at ¶ 76. Therefore, as Dr. Sutton concluded, a POSA would not combine the teachings of Arathoon and Lazar. *See* EX2008 at ¶ 77.

In fact, Arathoon teaches away from substitutions of neutral to charged residues because the variants in Arathoon only have neutral to neutral or charged to neutral substitutions. *See* EX1006 at 43, Tables 3–4; EX2008 at ¶ 77. As Dr. Sutton explains, the data in Table 4 of Arathoon shows that variants with neutral to neutral modifications and/or charged to neutral modifications (*e.g.*, v11 and v16) result in 95% or more of heterodimer yield. *Id.*

For the reasons discussed above, the combination of Lazar and Arathoon does not render the claims of the '286 Patent obvious. A POSA would not ***“have been motivated to make*** the combinations or modifications” of Lazar and Arathoon “to arrive at the claimed invention,” and likely would not have been able to do so given their incompatible formats. And even if combined, Lazar and Arathoon do not disclose neutral to positive and neutral to negative charged substitutions that interact to promote heterodimerization. See EX2008 at ¶ 78.

C. The Board Should Not Institute On Ground 3 Because Cabrera Does Not Disclose Interacting Neutral To Charged Substitutions To Produce A Heterodimeric Antibody

Like Lazar, Cabrera also does not anticipate the Claims of the '286 Patent because it does not “disclose all elements of the claim within the four corners of the document,” or “disclose those elements ‘arranged as in the claim,’” as required by settled Federal Circuit precedent. See *Microsoft*, 878 F.3d at 1068; see also *Precision Cancer Technologies*, IPR2025-00242, Paper 7, at 5. Specifically, as Dr. Sutton explains, Cabrera does not disclose a heterodimeric antibody with substitutions of neutral to positive and neutral to negative residues in heavy chains that ***interact with each other to promote heterodimerization***. See EX2008 at ¶ 79.

Cabrera discloses “a novel method for designing Fc heterodimers” that involves an iterative procedure with rounds of computational modelling, molecular dynamics

(MD) simulation, cavity and packing analysis, etc., and provides over 2900 variants that were created through this iterative multi-step modification process. See EX1005 at 24, 169, 185–239, Tables 6–7; EX2008 at ¶ 80.

However, Cabrera does not contain a single example that shows an interaction between residues substituted from neutral to positively and neutral to negatively charged amino acids that interact with each other to promote Fc heterodimerization. EX2008 at ¶ 81. Indeed, Cabrera teaches away from this result by indicating that such modifications in the context of other variations in the CH3 domain have the effect of destabilizing heterodimer formation. See EX2008 at ¶¶ 82–86. In Figures 1–4, 6–7, 9, 11, 13, 16, and 29–34 of Cabrera, the results of modelling and MD analyses are provided, but there are **no data** supporting or illustrating any residues substituted from neutral to positively and neutral to negatively charged amino acids that are interacting with each other. EX2008 at ¶ 81.

Applying hindsight gleaned from Merus' pioneering '286 Patent, Dr. Presta simply **assumes** that known native CH3 interface contact residues will necessarily remain contact residues following their substitution. EX2008 at ¶ 82. Indeed, Dr. Presta selects one variant, namely AZ34, out of the more than 2900 variants reported in Cabrera, and highlights one particular pair of modifications (*i.e.*, S400E and N390R) out of the 8 total modifications in AZ34, and assumes that these mutated,

oppositely charged residues (400E and 390R) would interact because “S400 and N390 are among those identified as interacting residues” at the native CH3-CH3 interface. See EX1002 at ¶ 276. However, making several variations in the CH3 domain does not necessarily maintain the antibody structure in such a way that residues that interact in the wild type CH3 domain will still interact with each other in the variant CH3 domain. Moreover, the data in Cabrera show that Dr. Presta's cited residue modifications actually destabilize the heterodimer. As Dr. Sutton explains in his declaration, the lower melting temperature (T_m) data for the variant AZ34 that Dr. Presta selected contradicts Dr. Presta's opinion that the mutated residues (400E and 390R) **interact** with each other.

AZ34 comprises the substitutions L351Y, S400E, F405A, and Y407V in the first CH3 domain and T366I, N390R, K392M, and T394W in the second CH3 domain. EX2008 at ¶ 83. The effects of modifications at S400 and N390 in the AZ34 variant can be identified by direct comparison with the AZ33 variant because the AZ33 and AZ34 variants share the same residue substitutions except that AZ34 also has the S400E/N390R modification. See EX1005 at 41 (Table 1).

The **interaction** between two chains of a heterodimeric antibody can be assessed by measuring melting temperature (T_m). EX2008 at ¶ 84. The purpose of CH3 domain engineering in the production of heterodimeric antibodies is to create

a stronger and more stable interaction between the CH3 domains, and a stronger, more stable interaction will require a higher temperature to break the bonds between the two different heavy chains. Cabrera also acknowledges that “[s]tability is measured as the melting temperature (T_m) of the CH3 domain.” See EX1005 at 17:4–6.

Accordingly, a POSA would understand that energetically favorable interactions, *i.e.*, those promoting heterodimerization, introduced by modifications at the interface, would **increase** the melting temperature of the antibody because they would stabilize the binding of the two chains to each other and require a higher temperature to break them apart. See EX2008 at ¶ 84. Tellingly, the opposite is true for AZ34—the effect of the S400E and N390R modifications is to **decrease** the melting temperature, indicating that these mutated residues are not interacting to promote heterodimerization. See EX2008 at ¶ 85.

Given the lower melting temperatures for AZ34 compared to AZ33, Dr. Presta's assertions are indisputably wrong as a matter of science. The S400 and N390 modifications (400E and 390R) introduced into the heterodimer of Cabrera at AZ34 destabilize the molecule and do not promote heterodimerization, based on the very data disclosed in that reference. As Dr. Sutton explains, Cabrera's melting temperature data directly opposes Dr. Presta's assumption: Cabrera Tables 3 and 4

explicitly show that the melting temperature for AZ33 (*i.e.*, 74 °C) **decreases** after introducing the S400E/N390R modifications in AZ34 (*i.e.*, 73.5 °C), meaning that the interaction between the two different chains in Cabrera's antibody is actually weakened. EX2008 at ¶ 85. Dr. Presta's incorrect assumption, clearly refuted by the data, undermines Dr. Presta's opinion on Cabrera and calls into question the reliability of his entire declaration. *See* EX2008 at ¶ 86; *see, also, e.g., Peaklogic, Inc., v. Wave Neuroscience, Inc.*, IPR2022-01527, Paper 13, at 13, 16–17 (P.T.A.B. May 18, 2023) (denying rehearing where the explanation provided by petitioner's expert is "not the kind of technical reasoning that lends weight to [his] ultimate opinion," and "[a]bsent such evidence and reasoning," the Board had "insufficient basis on which to evaluate the credibility of [his] statements, and accorded the statements little weight.").

As Dr. Sutton explains in his declaration, the reason that the S400E and N390R residues do not interact after modification is because, once modified, these residues are no longer in close enough proximity to form a hydrogen bond of ideal length, thus removing a stabilizing bond that would otherwise exist in the wild type CH3 region. *See* EX2008 at ¶ 87. The removal of this hydrogen bond explains the decrease in melting temperature and furthermore illustrates how the structural context of a proposed modification is important. *Id.*

Therefore, according to the actual data in Cabrera, Cabrera does not disclose the claimed neutral to charged residue substitutions that ***interact to produce a heterodimeric antibody*** required by Claim 1. EX2008 at ¶ 88. Cabrera also does not disclose all of the limitations of Dependent Claims 2, 7, 21–22, 24, 28, and 32 because they depend from Claim 1. See EX2008 at ¶ 89. Cabrera does not anticipate any claim of the '286 Patent because it is missing this critical “interact” claim element.

D. The Board Should Not Institute On Ground 4 Because Cabrera Arathoon And Lazar Do Not Disclose All The Elements Of Claims 1, 26, And 30 Of The '286 Patent

The combination of Cabrera, Arathoon, and Lazar does not render the claims of the '286 Patent obvious because a POSA would not “***have been motivated to make*** the combinations or modifications” of these references “to arrive at the claimed invention.” See *Curio Bioscience*, IPR2025-00192, Paper 8, at 21. This is because (1) Cabrera teaches away from the claimed heterodimeric antibody, (2) a POSA would not be motivated to combine Cabrera with Lazar and Arathoon, and (3) a combination of these references does not lead to the heterodimeric antibody of the '286 Patent.

i. Cabrera Teaches Away From The Claimed Heterodimeric Antibody

Like Lazar, Cabrera also 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*, IPR2024-00877, Paper 9, at 19.

Cabrera does not teach a POSA to substitute neutral residues with charged residues, nor does it disclose a heterodimeric antibody with substitutions of neutral to positive and neutral to negative residues in heavy chains as defined in the Specification of the '286 Patent that interact with each other to promote heterodimerization. *See* EX2008 at ¶ 90. In fact, based on the melting temperature data for AZ33 and AZ34 discussed above, a POSA would be **discouraged** from making a neutral to charge substitution at known contact residues, like S400 and N390, because doing so **removes** a stabilizing hydrogen bond. *See* EX2008 at ¶ 90 – 91.

Cabrera also teaches away from making neutral to charged substitutions because, as Dr. Sutton explains in his declaration, data for AZ33 and AZ34 show **no promotion** of heterodimerization, but do show **decreased stability** after introducing the S400E/N390R substitution. EX2008 at ¶¶ 91 – 92. This is a lose-lose situation for the POSA attempting to obtain the claimed invention of the '286 Patent. The data in Cabrera teach the POSA that neutral to charged substitutions were not appropriate to promote heterodimerization, and would not provide a POSA with a

reasonable expectation of success to arrive at the inventions claimed by the '286 Patent. *See id.*

As a further example of teaching away from neutral to charge substitutions, Cabrera discloses another comparative example (variants AZ28 and AZ29) that show a variant with ***neutral to neutral substitutions*** has a higher melting temperature than a variant with neutral to charge substitutions. *See* EX2008 at ¶ 93. Just as they would with variants AZ33 and AZ34, a POSA would compare AZ28 and AZ29 and see that the melting temperature of AZ28 (*i.e.*, 69.5 °C) increases to 70 °C for AZ29 after replacing S354E with S354N, undermining any suggestion that making neutral to charged substitutions would generate interactions that promote heterodimerization and stability. *See* EX2008 at ¶ 94.

Therefore, Cabrera teaches away from using neutral to charged substitutions to obtain the claimed heterodimeric antibody of the '286 Patent. *See* EX2008 at ¶ 96.

ii. A POSA Would Not Be Motivated To Combine Cabrera With Lazar And Arathoon

For the reasons discussed above, a POSA would not be motivated to combine Lazar with Arathoon. Additionally, a POSA would not be motivated to combine Cabrera with these references. *See* EX2008 at ¶¶ 97 – 101. It would be nonsensical to combine the technologies that Dr. Presta relies on from Lazar, Arathoon, and Cabrera.

According to Dr. Sutton, Cabrera's disclosures are directed to techniques for **restoring stability** of an antibody after it has destabilized during Fc heterodimerization engineering. See EX2008 at ¶ 98. On the other hand, Lazar discloses an **already stable** interface between identical chains in the CH3 region. EX2008 at ¶ 99. Therefore, a POSA would have no reason to combine these references—Cabrera's disclosure is useless to Lazar, and vice versa. See *id.*

A POSA would furthermore not combine the stabilized heterodimeric variants disclosed in Cabrera with the alternative bispecific formats disclosed in Lazar (*i.e.*, mAb-Fab and mAb-Fv). See *id.* The alternative bispecific formats disclosed in Lazar use wild type chains with additional domains. See *id.* A POSA would recognize that these stable wild type constructs have no need for Cabrera's heterodimer-stabilizing technology. See *id.* Nor would a POSA be motivated to combine the stabilized heterodimers disclosed in Cabrera with the alternative bispecific formats disclosed in Lazar—Cabrera's variants are less stable and have a lower melting temperature than Lazar's alternative bispecific formats. See *id.* A POSA would see no benefit to this combination. See *id.* A POSA would therefore not apply Cabrera's iterative multi-step modification process to Lazar's alternative bispecific formats. See *id.*

A POSA would furthermore recognize that Arathoon does not add any helpful information to the disclosures of Cabrera and/or Lazar regarding CH3 domain

engineering to promote heterodimerization, because Arathoon only suggests known methodologies (e.g., knobs-into-holes mutations, disulfide bonds). EX2008 at ¶ 100. Moreover, each of these references employ incompatible formats, rendering a combination nonsensical.

For the reasons discussed above, the combination of Lazar, Cabrera, and Arathoon does not render the claims of the '286 Patent obvious. A POSA would not ***“have been motivated to make*** the combinations or modifications” of Lazar, Cabrera, and Arathoon “to arrive at the claimed invention.” And even if combined, Lazar, Arathoon, and Cabrera do not disclose or suggest, at least, features of substitutions of neutral residues in the claimed heavy chains with charged residues that interact with each other to produce a heterodimeric antibody. EX2008 at ¶¶ 101 – 102. Nor do these references disclose all of the limitations in Dependent Claims 7 – 24, 27 – 28, and 31 – 32, because these claims depend from Independent Claims 1, 26, or 30. EX2008 at ¶ 101.

V. 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, 8,473 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: June 30, 2025

Respectfully submitted,



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CERTIFICATE OF SERVICE

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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