

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

XENCOR, INC.,
Petitioner

v.

MERUS N.V.,
Patent Owner

Case IPR2025-00604
Patent No. 9,358,286

PETITIONER'S REPLY TO PATENT OWNER'S RESPONSE

TABLE OF CONTENTS

	Page
I. Introduction.....	1
II. Merus’s Proposed Claim Constructions Should Be Rejected	2
A. Heavy Chains	2
1. Merus’s Construction Is Inconsistent with the Intrinsic Evidence	2
2. Merus’s Extrinsic Evidence Does Not Compel a Construction Inconsistent with the Intrinsic Record	6
B. Interacts	6
1. “Interacts” Is a Mere Intended Result and Thus Should Be Given No Patentable Weight	6
2. Merus’s “Interacts” Construction Is Wrong	7
III. <i>Lazar</i> and <i>Cabrera</i> Anticipate the Challenged Claims	10
A. <i>Lazar</i> Anticipates Claims 1, 7, 21, 22, 24, 26, 28, 30, and 32 of the ’286 Patent.....	10
1. <i>Lazar</i> ’s Test Constructs Anticipate Claim 1	10
2. <i>Lazar</i> ’s Full-length and Alternative Antibody Structures Anticipate Claim 1	11
3. <i>Lazar</i> Anticipates Dependent Claims 7, 21, 22, 24, 26, 28, 30, and 32	14
B. <i>Cabrera</i> Anticipates Claims 1, 2, 7, 21, 22, 24, 26-28, and 30-32 of the ’286 Patent	16
1. <i>Cabrera</i> ’s AZ34 Variant Anticipates Claim 1	16
2. <i>Cabrera</i> Anticipates Dependent Claims 2, 7, 21, 22, 24, 26-28, and 30-32	20
IV. <i>Lazar</i> in view of <i>Arathoon</i> or <i>Lazar</i> in view of <i>Arathoon</i> and <i>Cabrera</i> Renders the Challenged Claims Obvious	21
A. Merus’s Arguments Regarding <i>Lazar</i> Do Not Undermine Obviousness.....	21
1. Claim 1	21

2.	Dependent Claims	24
B.	Claims 1, 2, 7-24, 26-28, and 30-32 Would Have Been Obvious over <i>Lazar</i> in View of <i>Arathoon</i>	26
1.	Claim 1	26
2.	Claim 2	28
3.	Claim 7	28
C.	Claims 1, 2, 7-24, 26-28, and 30-32 Would Have Been Obvious over <i>Lazar</i> in View of <i>Arathoon</i> and <i>Cabrera</i>	29
V.	Conclusion	30

TABLE OF AUTHORITIES

	Page(s)
Cases	
<i>Bristol-Myers Squibb Co. v. Ben Venue Lab ’ys., Inc.</i> , 246 F.3d 1368 (Fed. Cir. 2001)	7
<i>Broadcom Corp. v. Emulex Corp.</i> , 732 F.3d 1325 (Fed. Cir. 2013)	6
<i>Cytiva BioProcess R&D AB v. JSR Corp.</i> , 122 F.4th 876 (Fed. Cir. 2024)	21, 27, 29
<i>In re Dembiczak</i> , 175 F.3d 994 (Fed. Cir. 1999)	29
<i>Guardant Health, Inc. v. Univ. of Wash.</i> , No. 2024-1129, 2026 WL 184334 (Fed. Cir. 2026)	21, 29
<i>Kennametal, Inc. v. Ingersoll Cutting Tool Co.</i> , 780 F.3d 1376 (Fed. Cir. 2015)	14
<i>Merck & Co. v. Biocraft Lab ’ys., Inc.</i> , 874 F.2d 804 (Fed. Cir. 1989)	21, 29
<i>Minton v. NASD, Inc.</i> , 336 F.3d 1373 (Fed. Cir. 2003)	6
<i>N. Telecom Ltd. v. Samsung Elecs. Co.</i> , 215 F.3d 1281 (Fed. Cir. 2000)	6
<i>Omega Eng’g, Inc. v. Raytek Corp.</i> , 334 F.3d 1314 (Fed. Cir. 2003)	5
<i>Otsuka Pharm. Co. v. Sandoz, Inc.</i> , 678 F.3d 1280 (Fed. Cir. 2012)	27
<i>Purdue Pharma L.P. v. Epic Pharma, LLC</i> , 811 F.3d 1345 (Fed. Cir. 2016)	12
<i>Wasica Fin. GmbH v. Cont’l Auto. Sys., Inc.</i> , 853 F.3d 1272 (Fed. Cir. 2017)	2

Other Authorities

37 C.F.R. § 42.65(a).....19, 30

LIST OF EXHIBITS

Exhibit	Document	Previously Submitted
EX1001	U.S. Patent No. 9,358,286 to De Kruif, <i>et al.</i> (“the ’286 patent”)	X
EX1002	Declaration of Leonard G. Presta, Ph.D.	X
EX1003	Curriculum Vitae of Leonard G. Presta, Ph.D.	X
EX1004	U.S. Patent Application Publication No. US 2011/0054151 A1 to Lazar <i>et al.</i> (“Lazar”)	X
EX1005	International Patent Application Publication No. WO 2012/058768 A1 to Cabrera <i>et al.</i> (“Cabrera”)	X
EX1006	International Patent Application Publication No. WO 1998/050431 A2 to Arathoon <i>et al.</i> (“Arathoon”)	X
EX1007	International Patent Application Publication No. WO 2009/089004 A1 to Kannan <i>et al.</i> (“Kannan”)	X
EX1008	File History for U.S. Patent No. 9,358,286	X
EX1009	U.S. Provisional Patent Application 61/475,614	X
EX1010	Georges Köhler & César Milstein, <i>Continuous culture of fused cells secreting antibody of predefined specificity</i> , NATURE, Aug. 7, 1975, 256(5517), at 495-497	X
EX1011	<i>Excerpts from</i> Kenneth Murphy <i>et al.</i> , <i>Janeway’s Immunobiology</i> (7th ed. 2008)	X
EX1012	Gunasekaran Kannan <i>et al.</i> , <i>Enhancing Antibody Fc Heterodimer Formation through Electrostatic Steering Effects</i> , J. BIOLOGICAL CHEM., 285(25), 19637-19646 (2010) (“Gunasekaran”)	X

Exhibit	Document	Previously Submitted
EX1013	Roland Kontermann, <i>Dual targeting strategies with bispecific antibodies</i> , MABS, 4(2), 182-197 (2012)	X
EX1014	<i>Reserved</i>	
EX1015	John Ridgway <i>et al.</i> , “Knobs-into-holes” engineering of antibody CH3 domains for heavy chain heterodimerization, PROTEIN ENGINEERING, 9(7), 617-621 (1996)	X
EX1016	Ameurfina Santos & Eduardo Padlan, <i>Development of More Efficacious Antibodies for Medical Therapy and Diagnosis</i> , PROGRESS IN NUCLEIC ACID RESEARCH AND MOLECULAR BIOLOGY, 1998:60, 169-194 (1998)	X
EX1017	A. Margaret Merchant <i>et al.</i> , <i>An efficient route to human bispecific IgG</i> , NATURE BIOTECH., 16(7), 677-81 (1998)	X
EX1018	Maria A. Angela <i>et al.</i> , <i>Effects of engineering charged amino acids in the CH3 domains on antibody heavy chain dimerization</i> , PHILIPPINE SCI. LETTERS, 4(1), 48-55 (2011) (“Diaz”)	X
EX1019	U.S. Provisional Patent Application No. 61/019,569	X
EX1020	U.S. Provisional Patent Application No. 61/120,305	X
EX1021	U.S. Patent No. 5,731,168 to Carter <i>et al.</i>	X
EX1022	<i>Reserved</i>	
EX1023	Tae Kyung Kim & James Eberwine, <i>Mammalian cell transfection: the present and the future</i> , ANALYTICAL AND BIOANALYTICAL CHEM., 397(8), 3173-3178 (2010)	X

Exhibit	Document	Previously Submitted
EX1024	Hui F. Liu <i>et al.</i> , <i>Recovery and purification process development for monoclonal antibody production</i> , MABS, 2(5), 480-499 (2010)	X
EX1025	<i>Reserved</i>	X
EX1026	<i>Excerpts from</i> Jan-Christer Janson & Lars Rydén, <i>Protein Purification</i> (2nd ed. 1998)	X
EX1027	Jonathan Marvin & Zhenping Zhu, <i>Recombinant approaches to IgG-like bispecific antibodies</i> , ACTA PHARMACOLOGICA SINICA, 26(6), 649-658 (2005)	X
EX1028	<i>Reserved</i>	
EX1029	<i>Reserved</i>	
EX1030	<i>Reserved</i>	
EX1031	<i>Reserved</i>	
EX1032	<i>Reserved</i>	
EX1033	<i>Reserved</i>	
EX1034	<i>Reserved</i>	
EX1035	<i>Reserved</i>	
EX1036	<i>Reserved</i>	
EX1037	<i>Reserved</i>	
EX1038	<i>Reserved</i>	
EX1039	Patrick Dufner <i>et al.</i> , <i>Harnessing phage and ribosome display for antibody optimization</i> , TRENDS IN BIOTECH., 24(11), 523-529 (2006)	X

Exhibit	Document	Previously Submitted
EX1040	John R. Birch & Andrew J. Racher, <i>Antibody production</i> , ADVANCED DRUG DELIVERY REVIEWS, 58(5-6), 671-685 (2006)	X
EX1041	Florian M. Wurm, <i>Production of recombinant protein therapeutics in cultivated mammalian cells</i> , NATURE BIOTECH., 22(11), 1393-1398 (2004)	X
EX1042	<i>Excerpts from</i> Bruce Alberts <i>et al.</i> , <i>Molecular Biology of the Cell</i> (5th ed 2008)	X
EX1043	<i>Monoclonal Antibody</i> , National Cancer Institute, https://www.cancer.gov/sites/g/files/xnrzdm211/files/styles/cgov_enlarged/public/cgov_image/media_image/2019-12/Monoclonal-antibodies-illustration.gif (last visited Feb. 7, 2025)	X
EX1044	Bibliographic Data, U.S. Patent Application No. 14/081,848, Patent Center, USPTO	X
EX1045	Prosecution History for U.S. Patent Application No. 13/866,747 – Application Data Sheet Dated Apr. 19, 2013	X
EX1046	<i>United States District Courts – National Judicial Caseload File</i> , https://www.uscourts.gov/sites/default/files/2024-12/fcms_na_distprofile0930.2024.pdf (last visited Feb. 7, 2025)	X
EX1047	<i>Interim Procedure for Discretionary Denials in AIA Post-Grant Proceedings With Parallel District Court Litigation</i> , https://www.uspto.gov/sites/default/files/documents/interim_proc_discretionary_denials_aia_parallel_district_court_litigation_memo_20220621_.pdf (last visited Feb. 7, 2025)	X

Exhibit	Document	Previously Submitted
EX1048	Docket Sheet, <i>Merus N.V. v. Xencor, Inc.</i> , Civil Action No. 24-913-CFC (D. Del.)	X
EX1049	Hongcheng Liu & Kimberly May, <i>Disulfide bond structures of IgG molecules</i> , MABS, 4(1), 17-23 (2012)	X
EX1050	<i>Reserved</i>	
EX1051	<i>Reserved</i>	
EX1052	<i>Merus N.V. v. Xencor, Inc.</i> , D.I. 1 (D. Del. Aug. 5, 2024) (“Complaint”)	X
EX1053	Docket Sheet, <i>Merus N.V. v. Xencor, Inc.</i> , Civil Action No. 24-913-JCB (D. Del.) (updated June 27, 2025)	X
EX1054	<i>Merus N.V. v. Xencor, Inc.</i> , Civil Action No. 24-913-JCB, D.I. 13 (D. Del. Oct. 10, 2024) (Defendant Xencor, Inc.’s Opening Brief in Support of Its Motion to Dismiss Pursuant To Federal Rule of Civil Procedure 12(b)(6)) (“Motion to Dismiss”)	X
EX1055	<i>Docket Navigator – Motion Success Statistics – Motions to Stay Pending IPR in the District of Delaware</i> , retrieved June 27, 2025	X
EX1056	<i>United States District Courts – National Judicial Caseload File</i> , https://www.uscourts.gov/sites/default/files/document/fcms_na_distprofile0331.2025.pdf (last visited June 25, 2025)	X
EX1057	Case scheduling orders from Case Nos. 6:24-cv-00263 (D.I. 40), 6:19-cv-00133 (D.I. 28), 1:24-cv-00620 (D.I. 21), 1:24-cv-00507 (D.I. 31), and 1:23-cv-00772 (D.I. 55)	X

Exhibit	Document	Previously Submitted
EX1058	Email correspondence dated April 30, 2025 (<i>Sotera Stipulation</i>)	X
EX1059	Merus N.V. 10-K for Fiscal Year Ended Dec. 31, 2024	X
EX1060	Merus N.V. 10-K for Fiscal Year Ended Dec. 31, 2019	X
EX1061	<i>Reserved</i>	
EX1062	Deposition Transcript of Brian J. Sutton, Ph.D. (March 19, 2026)	

I. INTRODUCTION

Merus secured the '286 patent by incorrectly convincing the Examiner that the prior art lacked neutral-to-charged substitutions in the CH3 domain. Now faced with the reality that *Lazar* and *Cabrera* indisputably teach those substitutions, Merus advances a series of incorrect claim constructions, misstated legal standards, and distortions of the prior art. Merus's arguments fail for several reasons.

Merus fashions an artificially narrow construction of the term "heavy chains" to exclude *Lazar*'s "proof-of-concept" test constructs and avoid anticipation. Merus's construction contradicts the intrinsic record. And even under Merus's construction *Lazar* anticipates, as its own expert, Dr. Sutton, conceded. Moreover, Merus does not even contend that this construction impacts Xencor's unpatentability arguments based on *Cabrera*, *Arathoon*, or *Kannan*.

Merus also attempts to transform the term "interacts" from an intended functional result—owed no patentable weight—into a rigid structural requirement absent from the claims. This transparent attempt to avoid *Cabrera* lacks any grounding in the intrinsic record. And similar to Merus's prior construction, Merus does not argue that its construction impacts Xencor's unpatentability arguments based on *Lazar*, *Arathoon*, or *Kannan*.

For obviousness, Merus makes scattershot and unsupported arguments that ignore Xencor's arguments: the references are highly analogous—each teaching CH3 modifications for heterodimerization to produce bispecific antibodies—and expressly contemplate combination by cross-referencing each other.

All of Merus's arguments should be rejected and the claims held unpatentable.

II. MERUS'S PROPOSED CLAIM CONSTRUCTIONS SHOULD BE REJECTED

A. Heavy Chains

Merus now argues the term “heavy chain” should be construed as: “a polypeptide chain starting at the N-terminal residue in the variable region (VH) and ending at the C-terminal residue in the final constant region (CH), including all intervening constant regions (CH) and the hinge region.” (POR, 16.) But just like Merus's pre-institution construction (POPR, 9) that was criticized at institution (Paper 13, 14-17), Merus's new construction is not supported by the intrinsic record and improperly excludes embodiments of the alleged invention.

1. Merus's Construction Is Inconsistent with the Intrinsic Evidence

a) Claims

Merus's construction should be rejected because it would render claim language superfluous. *See Wasica Fin. GmbH v. Cont'l Auto. Sys., Inc.*, 853 F.3d 1272, 1288 (Fed. Cir. 2017). Claim 1 recites that the “antibody comprises two

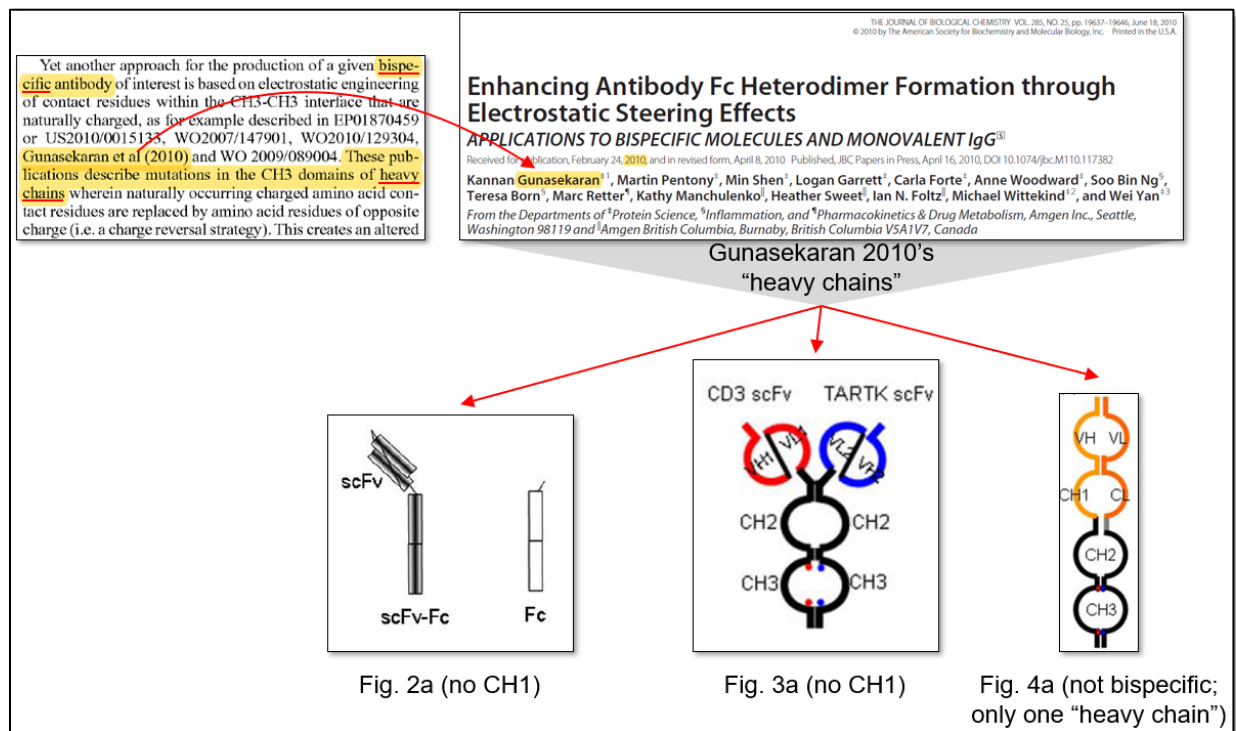
heavy chains with CH3 domains.” (EX1001, Claim 1 (emphasis added).) If Merus’s construction were adopted, the term “heavy chain” would already definitionally include the CH3 domain, making the “with CH3 domains” language redundant and superfluous.

In an attempt to support its construction, Merus improperly reads a limitation from dependent claim 8 into the independent claim. (POR, 16-17.) The limitation in claim 8 on which Merus relies—“each variable region of the 1st and 2nd antibody heavy chains recognizes a different target epitope”—is a narrowing limitation of dependent claim 8, not claim 1. By referencing “each variable region,” the claim simply limits the scope of such variable regions *when they are present*.

b) Specification

Merus’s construction must also be rejected because, under such a claim construction, structures that are expressly called “heavy chains” by the ’286 patent would be excluded. According to the ’286 patent, *Gunasekaran* (EX1012) describes “the production of a given bispecific antibody of interest” with “mutations in the CH3 domains of *heavy chains* wherein naturally occurring charged amino acid contact residues are replaced by amino acid residues of opposite charge.” (EX1001, 5:17-32 (emphasis added).) *Gunasekaran* describes

CH3 domain mutations in three constructs, shown in Figures 2a, 3a, and 4a, each of which are excluded from Merus's construction of "heavy chains":



(See EX1012, Figs. 2a, 3a, 4a.) Indeed, Dr. Sutton admitted during deposition that none of these constructs has modifications in two "heavy chains" under Merus's construction. (See, e.g., EX1062, 140:8-11, 142:6-10, 142:19-143:6, 149:2-150:6, 150:7-11.)

Merus's specification-based arguments purport to address the Board's concern that the patent's definition of "antibody" includes more than just IgG. (POR, 17; see also EX2016, ¶37.) Merus conveniently omits, however, that this same definition also references "fragments"—which the Board expressly identified at institution. (Paper 13, 15 n.11, 16-17, 31-32.) Dr. Sutton acknowledged at

deposition that his opinion on the meaning of “heavy chain” was in the context of an “intact antibody” having “the complete structure conforming to one of the known human subclasses,” confirming that Merus’s construction improperly omits antibody fragments. (EX1062, 118:2-119:2, 126:5-17, 129:13-22.)

c) Prosecution History

Merus’s characterization of the prosecution history (POR, 18) is equally unpersuasive. While Merus did amend claim 1 to replace “CH3-domain comprising polypeptide chain” with “antibody heavy chain,” Merus’s arguments focused on *Carter* and *Kannan* purportedly not disclosing neutral-to-charged substitutions, (EX1008, 244-246)—an incorrect representation, as even Merus’s expert admits that *Kannan* teaches such substitutions (EX1007, 10:16-18; EX1062, 229:17-230:1 (agreeing that *Kannan* discloses making “neutral or uncharged residues to charge residues at the CH3 domain interface residues”)); *see also id.*, 185:15-186:3, 186:11-15). Merus made no argument that replacing “CH3-domain comprising polypeptide chain” with “antibody heavy chain” created any patentable distinction over the prior art. *Cf. Omega Eng’g, Inc. v. Raytek Corp.*, 334 F.3d 1314, 1324 (Fed. Cir. 2003) (requiring patentee to “unequivocally disavow[] a certain meaning” to “narrow[] the ordinary meaning of the claim” through prosecution history disclaimer).

2. Merus’s Extrinsic Evidence Does Not Compel a Construction Inconsistent with the Intrinsic Record

Merus alleges that prior art papers and textbooks support its new construction. (*See* POR, 18-20; *see also* POR, 59 (faulting Dr. Presta for focusing on claims instead of “papers, textbooks, or other evidence”).) But the construction that Merus urges from this extrinsic evidence improperly reads embodiments (*e.g.*, antibody fragments) out of the claims and is inconsistent with the intrinsic evidence. *See, e.g., Broadcom Corp. v. Emulex Corp.*, 732 F.3d 1325, 1333 (Fed. Cir. 2013); *N. Telecom Ltd. v. Samsung Elecs. Co.*, 215 F.3d 1281, 1295 (Fed. Cir. 2000).

B. Interacts

Merus’s arguments regarding the “interacts” limitation fail for two independent reasons: the limitation is not entitled to patentable weight, and Merus’s proposed construction is incorrect.

1. “Interacts” Is a Mere Intended Result and Thus Should Be Given No Patentable Weight

The “interacts” wherein clause merely expresses an intended result—interaction between the charged amino acids in the 1st and 2nd antibody heavy chains—within the “culturing . . . to produce a heterodimeric antibody” step. Where, as here, “a where[in] clause . . . simply expresses the intended result of a process step positively recited,” it “is not given weight.” *Minton v. NASD, Inc.*, 336 F.3d 1373, 1381 (Fed. Cir. 2003). The intended result of the “interacts”

language does not result in a manipulative difference in the steps of the claim, either: the steps may all be completed independent of whether the intended result (“interacts”) is realized. Claim language that “does not result in a manipulative difference in the steps of [a] claim”—like the wherein clause here—is generally not limiting. *See Bristol-Myers Squibb Co. v. Ben Venue Lab ’ys., Inc.*, 246 F.3d 1368, 1376 (Fed. Cir. 2001).

Merus’s argument that “interacts” is owed patentable weight because it was “added during prosecution to overcome a prior art rejection,” is unpersuasive. (POR, 24.) Merus never argued that the addition of “interacts” distinguished the claim from *Carter* or *Kannan* (the cited art). Instead, as explained above (Section II.A.1.c), Merus argued that neither *Carter* nor *Kannan* disclosed neutral-to-charged substitutions. And, contrary to Merus’s suggestion (POR, 24), the Examiner did not even mention “interacts” in the reasons for allowance. (EX1008, 274.)

2. Merus’s “Interacts” Construction Is Wrong

Even if “interacts” is given patentable weight, Merus’s construction should be rejected as it narrows the claims to only a subset of the broad, non-limiting description of “interaction” in the specification, and also renders the claims indefinite and unsupported by the written description of the ’286 patent.

The '286 patent does not expressly define the claim term “interacts.” And the specification describes “interacting amino acid residues” broadly when discussing the CH3-CH3 domain interface, including several non-limiting examples. (EX1001, 13:18-29.) Merus points to this same passage in arguing the '286 patent describes “interaction” in terms of individual atoms of the substituted residues being “in contact distance” with each other. (POR, 21-22; EX2016, ¶50.) But this passage does not even mention the claimed substituted residues—let alone “contact distance.” (EX1001, 13:18-29.) In fact, the passage actually discusses the CH3 interface *in general*, explaining that “association” between two CH3 domains is a result of interactions between amino acids of two CH3 domains generally—not “substituted” amino acids exclusively. (*Id.*)

Merus is attempting to read into the “interacts” term a requirement that the interaction be of a certain quality such that the interaction, by itself, causes heterodimerization. (POR, 22, 23; *see also* EX2016, ¶¶45-47, 49, 52.) As Dr. Sutton admitted during deposition, however, claim 1 merely “states that there is an interaction between the two substituted residues, but . . . it doesn’t describe in any greater details the nature of that interaction.” (EX1062, 153:1-9.)

Merus also argues that the prosecution history supports its construction, but characterized the amendment adding “interacts” as merely requiring that “the two substituted amino acids interact within the CH3 interface (*e.g., form an*

electrostatically favorable interaction)." (EX1008, 245 (emphasis added).) As Dr. Sutton confirmed during deposition, Merus made no arguments during prosecution that this amendment introduced any "structural" interactions or "but-for" cause of heterodimerization to the claims. (EX1062, 188:2-20, 189:12-190:2.)

Finally, Merus characterizes deposition testimony from Dr. Presta as an admission consistent with its construction. (See POR, 5 (citing EX2012, 52:10-53:5).) But the testimony to which Merus points—that "just because the two interact, that might not necessarily give you the heterodimeric antibody" (EX2012, 52:10-19)—merely establishes that the claimed interaction, on its own, may or may not give rise to a heterodimeric antibody. In fact, Dr. Presta's explanation lays bare that Merus's construction—requiring a single residue-residue interaction be responsible for "produc[ing]" a heterodimeric antibody—cannot be correct because it would render the claim indefinite and is unsupported by the written description, which has no data, definition, or test for "interaction." To the extent Merus relies on Dr. Presta's answer regarding whether a hypothetical interaction would "satisfy claim 1," (EX2012, 52:24-53:5), Merus misunderstands his testimony: Dr. Presta is a technical expert, not a legal one, and his testimony was simply an attempt to disentangle the "interacts" and "produce" claim limitations.

III. ***LAZAR AND CABRERA*** **ANTICIPATE THE CHALLENGED CLAIMS**

Lazar and *Cabrera* each anticipate the challenged claims. Merus's principal bases for distinguishing both references are its claim constructions. Because those constructions should be rejected, Merus's anticipation defenses fail. Regardless, as discussed below, *Lazar* and *Cabrera* anticipate even under Merus's erroneous constructions.

A. ***Lazar* Anticipates Claims 1, 7, 21, 22, 24, 26, 28, 30, and 32 of the '286 Patent**

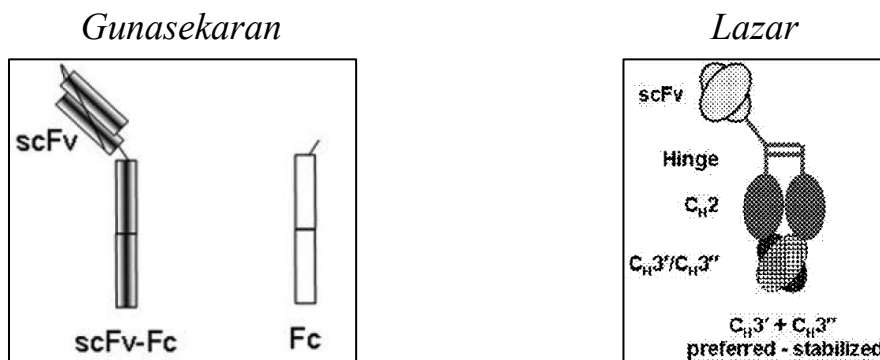
1. ***Lazar's* Test Constructs Anticipate Claim 1**

Merus's only argument regarding *Lazar's* scFv-Fc/empty-Fc construct is that it does not contain "heavy chains" under Merus's construction. (POR, 27.) Merus does not contest that *Lazar* discloses the claimed neutral-to-charged substitutions. (EX1062, 195:12-17.) Merus also does not contest that these neutral-to-charged substitutions are in both CH3 domains (EX1004, ¶¶65, 115, 119-122) and would "interact" to promote heterodimerization even under Merus's incorrect "salt bridge" construction (*see* EX1062, 160:11-161:11, 161:21-162:4, 169:22-170:7). Dr. Sutton even confirmed that *Lazar's* neutral-to-negative/neutral-to-positive test constructs that showed greater than fifty percent heterodimer formation—such as the S364E-L368K construct in lane 11 of Fig. 5—demonstrate improved heterodimerization. (EX1062, 219:21-220:6, 213:16-21; EX1004, Fig. 5.) The test constructs thus anticipate.

Indeed, under any reasonable interpretation, *Lazar* anticipates because the '286 patent itself describes *Gunasekaran* as disclosing “mutations in the CH3 domains of heavy chains,” where *Gunasekaran* uses the same construct as *Lazar*.

'286 Patent

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



(EX1001, 5:17-26; EX1012, Fig. 2a; EX1004, Fig. 1.)

2. *Lazar's* Full-length and Alternative Antibody Structures Anticipate Claim 1

Even assuming Merus's incorrect construction, *Lazar* still anticipates. As the Board correctly found, a POSA would have understood from *Lazar's* teachings that the purpose of the modifications in *Lazar's* test system was to include those modifications in “traditional” antibody structures (or “entire antibodies”), which contain a “heavy chain” even under Merus's construction. (Paper 13, 32-33;

EX1062, 138:3-7 (Dr. Sutton agreeing that “the mAb-Fv and the mAb-Fab structures shown in figure 8 of Lazar contain heavy chains on both sides of the antibody”); *see also id.*, 134:14-135:2, 135:14-21, 136:8-16.)

Merus’s principal retort is that Xencor is supposedly “picking and choosing” the modifications in *Lazar*’s test constructs and “combining them with a separate, general reference to IgG antibodies.” (POR, 28.) But *Lazar* itself expressly links these teachings. Just as the Federal Circuit found in *Purdue Pharma L.P. v. Epic Pharma, LLC*, where the teachings in a single reference are directly related, the fact that they are “in a distinct section of the reference” is irrelevant. 811 F.3d 1345, 1358-59 (Fed. Cir. 2016).

Here, *Lazar* repeatedly teaches that its “invention provides antibody analogs” that “include full length antibodies.” (EX1004, ¶¶85, 99-100.) And *Lazar* expressly teaches that “Fc variants that favor heterodimerization of the Fc region” are of “particular benefit to the immunoglobulins of the invention,” further describing those “Fc variants” as those shown in Table 2 below. (*Id.*, ¶¶119-125; *see also id.*, ¶107.)

TABLE 2	
Most preferred CH3 domain variants that favor Fc heterodimerization.	
Variant 1	Variant 2
F405A	T394F
S364D	Y349K
S364E	Y349K
S364H	Y349T
L351K	L351E
D401K	T411E
S364D/T394F	Y349K/F405A
S364E/F405A	Y349K/T394F
S364H/D401K	Y349T/T411E
S364H/F405A	Y349T/T394F
S364H/T394F	Y349T/F405A
L351K/S364H/D401K	Y349T/L351E/T411E
S364H/D401K/F405A	Y349T/T394F/T411E
S364H/F405A/T411E	Y349T/T394F/D401K

(EX1004, ¶241; EX1002, ¶¶115-117.)

Thus, *Lazar* itself expressly links its teachings of the heterodimerization variants tested in its test constructs (which include numerous neutral-to-charged substitutions) to full-length antibodies and constructs that meet Merus’s construction of “heavy chains.” (EX1062, 138:3-7, 191:4-15 (Dr. Sutton agreeing that prior art teachings of modifications in Fc domain test constructs would “apply . . . broadly to antibody heterodimerization”).)

Merus argues that no neutral-to-charged substitutions were made in *Lazar*’s alternative bispecific antibodies (e.g., mAb-Fv and mAb-Fab) because the examples in *Lazar*’s Tables 3-5 use only the S364H/F405A and Y349T/T394F

(“Hetero TF-HA”) neutral-to-neutral modifications. (POR, 36.) But there is no requirement that the prior art provide experimental data for its disclosures of using Fc variants in full-length antibodies. Moreover, *Lazar* must be considered for all of its teachings, which include that “the mAb-Fv and mAB-Fab formats are particularly suited for the use of variants that favor Fc heterodimerization and disfavor Fc homodimerization.” (EX1004, ¶107.) These variants include neutral-to-charged substitutions. (See EX1004, Tables 1-2; Pet. 26-27; EX1002, ¶81.) And the Hetero TF-HA variant used in *Lazar*’s Examples 4-6 (reflected in Tables 3-5) is one of fourteen “Most preferred CH3 domain variants that favor Fc heterodimerization” listed in Table 2 of *Lazar*. Contrary to Merus’s cursory assertion, a POSA reading *Lazar* would indeed “at once envisage” the use of each of the thirteen other variants listed in Table 2 in *Lazar*’s alternative antibody formats. See *Kennametal, Inc. v. Ingersoll Cutting Tool Co.*, 780 F.3d 1376, 1383 (Fed. Cir. 2015) (affirming Board’s anticipation finding where “[the reference] effectively teaches 15 combinations, of which one anticipates . . . claim 1”).

3. *Lazar* Anticipates Dependent Claims 7, 21, 22, 24, 26, 28, 30, and 32

Claim 7: In addressing claim 7 (POR, 29), Merus ignores the teachings of *Lazar* as a whole, including *Lazar*’s express teaching that its “hetero-Fc variants” (which include neutral-to-charged substitutions) “may reduce the homodimer populations to 2.5% and 2.5% while increasing the heterodimer population to

95%.” (EX1004, ¶¶122-23.) And Merus ignores that a POSA would have understood from *Lazar*’s express teachings that its “hetero-Fc variants” could be combined with other heterodimerization techniques—*e.g.*, knobs-in-holes or charge swap—to boost heterodimer purity to meet the expressly taught “95%” in *Lazar*. (EX1004, ¶125; *see also* EX1062, 212:22-213:9.)

Claims 21, 24, 28, and 32: Merus (POR, 29) fails to address that *Lazar* explicitly discloses that, “[i]n one embodiment, the antibody is a fully human antibody with at least one modification as outlined herein” (EX1004, ¶97) and that, “[i]n certain embodiments, the Fc variants disclosed herein are based on human IgG sequences” (EX1004, ¶118). Moreover, *Lazar*’s test construct itself is based on IgG1, and *Lazar*’s Example 2 expressly describes applying preferred and most preferred neutral-to-charged substitutions in the test construct. (*See* EX1004, ¶¶238-241.) As explained above, a POSA would also “at once envisage” incorporating *Lazar*’s neutral-to-charged substitutions into alternative antibody formats such as mAb-Fv, which “comprises an IgG antibody with a C-terminal Fv fusion.” (EX1004, ¶46; *see also* EX1062, 138:3-7, 191:9-15.)

Claims 22, 26, and 30: Merus does not provide separate arguments for these claims, and they are anticipated for the reasons previously provided. (Pet., 30-33.)

B. *Cabrera* Anticipates Claims 1, 2, 7, 21, 22, 24, 26-28, and 30-32 of the '286 Patent

1. *Cabrera*'s AZ34 Variant Anticipates Claim 1

Merus does not dispute that *Cabrera*'s AZ34 variant includes a neutral-to-negative and a neutral-to-positive mutation at known contact residues in the CH3 domain (S400E/N390R). (*See* Pet., 61-62; *see also* POR, 30-31; EX1001, 19:5-12.) According to the '286 patent, that two CH3 domain positions are “a pair of contact residues in the CH3-CH3 interface” is sufficient to show they are “capable of interacting” (*i.e.*, if charges are introduced at those locations) such that “the first CH3 domain will preferentially pair with the second CH3 domain.” (EX1001, 19:5-12; *see also* EX1062, 190:3-18 (Dr. Sutton admitting same).) Thus, *Cabrera*'s creation of a charged pair at S400 and N390, which were known interface contact residues, would be sufficient for interaction to cause preferential pairing.

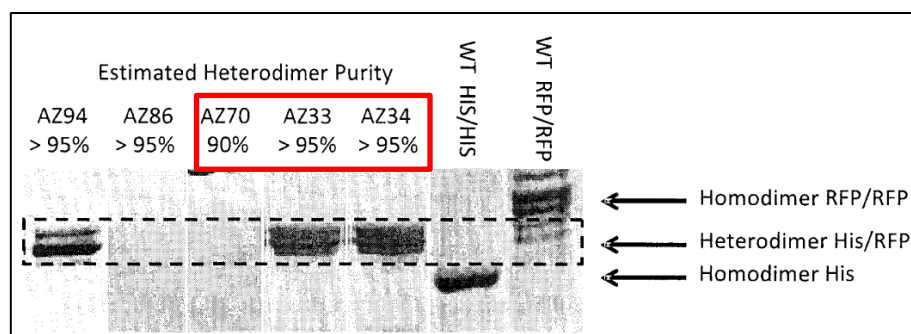
Merus attempts to obscure these disclosures in arguing that *Cabrera*'s AZ34 variant does not disclose the “interacts . . . to produce a heterodimeric antibody” language of claim 1. (POR, 20-24, 30-33.) None of Merus's arguments have merit.

As an initial matter, the “interacts” language is merely an intended result. (*See supra*, Section II.B.1.) In any event, Merus's purity argument—that *Cabrera*'s AZ34 variant does not anticipate because it does not expressly state that

AZ34's purity is even higher than AZ33's >95% purity—is an improper attempt to import into the independent claim an *even higher* purity limitation than recited in dependent claim 7. (See EX2016, ¶77.)

Merus's melting temperature argument fails, too, because it conflates stability with promoting heterodimerization. Neither Merus nor Dr. Sutton provides any support for using melting temperature as a proxy for heterodimerization promotion (to the extent that is even required for “interacts”). And Merus's argument is contradicted by *Cabrera* and the '286 patent itself. *Cabrera*'s AZ70, for example, had a higher melting temperature of (75.5 °C), but a lower heterodimer purity (90%), than either AZ33 (74 °C and >95%) or AZ34 (73.5 °C and >95%):

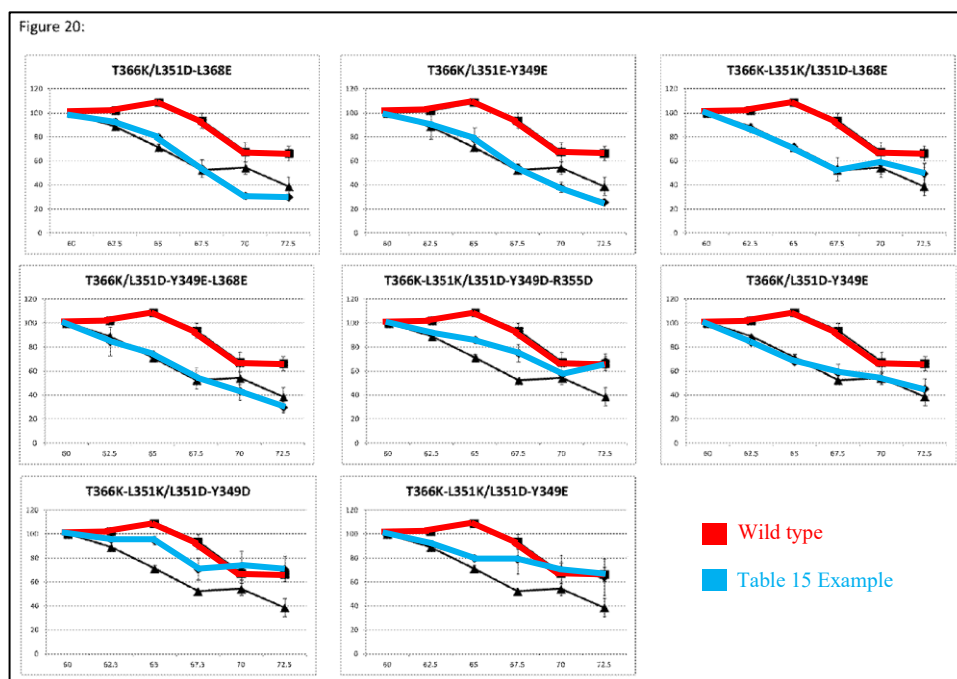
AZ30	71	AZ69	71
AZ32	71.5	AZ70	75.5
AZ33	74	AZ71	71
AZ34	73.5	AZ72	70.5



(EX1005, Tables 3-4, Fig. 26 (annotations added).)

Similarly, the '286 patent explains that “[t]he bispecific molecules from combinations 3-6 and 9-12 [of Table 15] . . . demonstrated a *reduced thermal stability* as compared to wildtype [bispecifics]” (those “without CH3 mutations”), yet an increased heterodimerization rate:

Combination of 2 different chain A*/mutations heavy chains (construct #)	chain B*/mutations (construct #)	% AA found	% AB found	% BB found	% half A found	% half B found
1 T366E (78)	L351R (77)	3	81	2	13	0
2 T366K (43)	L351D (63)	0	88	3	9	0
3 T366K (43)	L351D, L368E (69)	0	87	0	12	0
4 T366K (43)	L351E, Y349E (70)	2	85	0	11	0
5 T366K (43)	L351D, Y349E (71)	2	92	1	5	0
6 T366K (43)	L351D, Y349E, L368E (73)	0	96	1	4	0
7 T366K, L351K (68)	L351D (63)	0	77	12	10	1
8 T366K, L351K (68)	L351D, R355D (72)	0	79	8	10	1
9 T366K, L351K (68)	L351D, Y349D, R355D (75)	1	93	2	4	1
10 T366K, L351K (68)	L351D, Y349D (74)	1	95	1	3	0
11 T366K, L351K (68)	L351D, Y349E (71)	1	95	0	3	1
12 T366K, L351K (68)	L351D, L368E (69)	0	92	0	8	0
13 T366K (43)	L351E (80)	0	70	10	18	2
14 T366R (79)	L351E (80)	4	38	36	21	1
15 T366D (64)	L351K, L368K (76)	3	92	2.5	2.5	0
16 T366D (64)	L351R (77)	30	69	1	0	0



(EX1001, 50:56-66, 51:34-39, Table 15, Fig. 20 (annotations added).)

Finally, Merus and Dr. Sutton further argue that the S400E and N390R substitutions cannot interact due to solvation and water interactions (EX2016, ¶78), but offer no analysis to support this position. Dr. Sutton cites the Krapp 2003 paper, but Krapp 2003 does not even mention the S400 or N390 residues. To the extent Dr. Sutton relies on the wildtype IgG-Fc crystal structure from Krapp 2003 (PDB code 1h3v), his assertions are devoid of meaningful analysis because Dr. Sutton (1) does not analyze the crystal structure in his report, (2) did not make the S400E and N390R substitutions, and (3) provides no citations or data to support his assertions. Dr. Sutton's "analysis" amounts to pure conjecture and should be given no weight. *See* 37 C.F.R. § 42.65(a).

Merus's arguments also contradict the '286 patent's description that being a "pair of contact residues in the CH3-CH3 interface, mean[s] that they are located sufficiently close to each other" such that that they are "capable of interacting." (EX1001, 19:5-12.) Here, AZ34 includes the claimed neutral-to-positive and neutral-to-negative modifications at known CH3 interface contact residues, and the AZ34 example results in a heterodimeric antibody. That is all that is required for claim 1. Dr. Sutton even confirmed on cross-examination that known contact residues were expected to interact (*see* EX1007, Table 1; EX1062, 157:9-158:8, 218:14-18; *see also id.*, 34:2-9, 34:22-35:4, 36:10-14), and that making an

oppositely charged pair at known contact residues would be expected to form a salt bridge (EX1062, 44:8-17, 158:22-159:9, 159:18-160:6). Dr. Sutton likewise agreed that, when substitutions create “a positive on one side of the interface and a negative on the other side of the interface for amino acids that are known to correspond to one another at the interface,” “there will be an interaction, which will be electrostatic and favorable.” (EX1062, 190:3-18.) That is all Merus said that “interacts” required during prosecution, and that is all that it requires now. (*See supra*, Section II.B.2.)

**2. *Cabrera* Anticipates Dependent
Claims 2, 7, 21, 22, 24, 26-28, and 30-32**

Claim 28: Merus’s demands of the prior art (POR, 33) stretch far beyond the limitations of claim 28, which recites only a “pharmaceutical composition comprising” the heterodimeric antibody “and a pharmaceutically acceptable carrier.” (EX1001, claim 28.) The claim mentions nothing about half-life, cell-mediated toxicity, or therapeutic value. Because Cabrera discloses the heterodimeric antibody and a pharmaceutically acceptable carrier, the claim is anticipated. (Pet., 31.)

Claims 2, 7, 21, 22, 24, 26, 27, and 30-32: Merus does not provide separate arguments for these claims, and they are anticipated for the reasons previously provided. (Pet., 63-69.)

**IV. LAZAR IN VIEW OF ARATHOON
OR LAZAR IN VIEW OF ARATHOON AND
CABRERA RENDERS THE CHALLENGED CLAIMS OBVIOUS**

**A. Merus’s Arguments Regarding
Lazar Do Not Undermine Obviousness**

1. Claim 1

First, Merus argues a lack of motivation to combine due to *Lazar*’s disclosure of an alternative 100% purity charge-swap variant. (POR, 42-43.) But a POSA does not need motivation to select what is expressly disclosed in *Lazar*—the neutral-to-charged variants in the “preferred” and “most preferred” tables. (EX1002, ¶116); *see Guardant Health, Inc. v. Univ. of Wash.*, No. 2024-1129, 2026 WL 184334, at *4 (Fed. Cir. 2026); *see also Cytiva BioProcess R&D AB v. JSR Corp.*, 122 F.4th 876, 884 (Fed. Cir. 2024). And even if *Lazar*’s disclosures had not been expressly labeled “preferred” (providing motivation by itself), the prior art is good for all it teaches, not just preferred embodiments. *Merck & Co. v. Biocraft Lab ’ys., Inc.*, 874 F.2d 804, 807 (Fed. Cir. 1989).

Second, Merus speculates there is a “potential disconnect” between *Lazar*’s test constructs and full antibodies. (POR, 43.) Merus relies on Dr. Sutton for this supposition, but his speculative opinion cites nothing in support. (EX2016, ¶119.) Merus also emphasizes *Lazar*’s use of the term “variants that favor *Fc heterodimerization*” (POR, 43 (emphasis Merus’s)), but completely avoids *Lazar*’s disclosure that those Fc variants would be used in full-length antibodies. (*See*

supra, Section III.A.2.) And Dr. Sutton agreed that prior art modifications in Fc domain test constructs, such as those in *Lazar*, were evaluated for the purpose of applying them “broadly to antibody heterodimerization.” (EX1062, 191:4-15.)

Third, Merus argues that *Lazar* does not use neutral-to-charged variants in its later examples testing alternative constructs. (POR, 43-44.) But Merus’s demand for test data is unfounded and should be rejected in light of *Lazar*’s express disclosures that those alternative constructs “are particularly suited for the use of variants that favor Fc heterodimerization.” (EX1004, ¶107; *see also* EX1062, 191:4-15.)

Fourth, Merus argues that *Gunasekaran* teaches away from the modifications expressly taught in *Lazar* (and *Cabrera*) involving neutral-to-charged substitutions in the “hydrophobic core” of the CH3 domain. (POR, 44; *see also id.*, 40; EX1062, 224:3-8.) Merus emphasizes that *Gunasekaran* is incorporated by reference into *Lazar*, arguing this shows an “incorporated warning.” (POR, 44.) But this incorporation actually cuts against teaching away. The *Lazar* inventors were clearly aware of *Gunasekaran*’s teachings, but still made numerous neutral-to-charged substitutions in the hydrophobic core of the CH3 domain. (EX1004, Tables 1-2; EX1002, ¶115 (annotating those tables); *see also* EX1062, 236:8-12, 240:20-241:4.)

This makes sense because the actual wording of *Gunasekaran* does not teach away. (See EX1012, 19640.) The statement Merus cites in no way discourages modification of neutral-to-charged substitutions; it notes only the potential “benefits” of using a charged-residue strategy. (*Id.*) In fact, other portions of *Gunasekaran* recognize that modifications to the hydrophobic core may be necessary to facilitate increased heterodimerization. For example, *Gunasekaran* praises the “pioneering . . . knobs-into-holes strategy” that “increased the production of heterodimer significantly” using “mutations involv[ing] structurally conserved buried residues at the core of the interface.” (EX1012, 19645; EX1062, 224:16-20.) In fact, the same author, around the same time, expressly disclosed using “electrostatic steering effects” by “modifying uncharged residues to charged residues at the CH3 domain interface.” (EX1007, 10:16-18, 2:35-37; EX1062, 229:17-230:1.) As Dr. Sutton admitted, this teaching is inconsistent with the reading of *Gunasekaran* urged by Dr. Sutton and Merus. (EX1062, 228:11-19.)

Fifth, Merus argues “unexpected results.” (POR, 41-42.) Merus argues that the claimed antibodies are “more stable than their wild-type counterparts.” (POR, 41.) But Merus ignores that the ’286 patent’s “stability analyses” regarding “Thermo Stability” actually showed “reduced thermal stability as compared to wildtype.” (See *supra*, Section III.B.1; (EX1001, 51:34-36, Fig. 20).) Merus also argues that the claimed antibodies “have very low levels of contaminating

homodimers” such that they are “essentially absent.” (POR, 41.) But this argument crashes headfirst into Merus’s other arguments that the prior art charge swap and KIH techniques were sufficiently pure such that a POSA would have had no motivation to modify them. (*E.g.*, POR, 42-43, 48.) And the data reported for Merus’s tested constructs contradicts this argument. (EX1001, Table 15 (showing between 38-96% heterodimer).) Furthermore, only challenged claim 7 contains any purity limitations, and even that claim does not require homodimers to be “essentially absent,” rendering Merus’s unexpected results argument untethered to the scope of the challenged claims.

Finally, Merus makes a passing accusation that Dr. Presta’s acknowledgement of prior heterodimerization efforts as “fraught with difficulty” somehow undermines his obviousness analysis. (POR 60.) It does not. Dr. Presta’s statement about the state of the art does not detract from his factually supported opinions that the ’286 patent claims would have been obvious.

2. Dependent Claims

Claim 2: Merus argues there was no motivation to use a common light chain with *Lazar*’s test construct. (POR, 45.) This argument incorrectly assumes *Lazar*’s neutral-to-charged substitutions were limited to those test constructs, while in fact *Lazar* teaches the neutral-to-charged modifications in full-length antibodies and *Lazar*’s alternative constructs. (*See supra*, Section III.A.2.)

Claim 7: Merus argues that because *Lazar* reports 12% to 93% contaminating homodimer from neutral-to-charged substitutions in its test constructs, a POSA would have lacked motivation to modify the neutral-to-charged substitutions to achieve the claimed less than 5% contaminating homodimers. (POR, 45.) But *Lazar* already expressly discloses heterodimer purity of 95% (EX1004, ¶122), and describes the use of its heterodimerization variants with “other Fc variants that favor heterodimerization”—such as the knobs-in-holes approach—for “creation of the antibody analogs of the invention” (EX1004, ¶¶125-29). Even though *Lazar* anticipates claim 7 (*see supra*, Section III.A), a POSA would also have been motivated to combine, and had a reasonable expectation of success in combining, *Lazar*’s variants with other heterodimerization strategies (such as knobs-in-holes) to achieve less than 5% contaminating homodimers. (Pet., 42-43; *see also* EX1062, 212:22-213:9.)

Claims 8-20: Merus’s argument against these claims (POR, 46) improperly attempts to limit *Lazar* to its test construct even though, as Xencor’s Petition explained, those variants would have been applied to other antibody structures like full-length antibodies or *Lazar*’s alternative constructs. (Pet., 43-56; EX1062, 191:9-15.) For example, *Lazar* teaches engineering antibodies (including antibody analogues) through: (1) Fc region modifications for promoting heterodimerization; and (2) incorporating two different antigen binding domains to coengage two

distinct target antigens. (Pet., 43-44.) Merus’s argument also fails to rebut Xencor’s argument that a POSA would have been motivated to apply *Lazar*’s CH3 domain modifications to *Arathoon*’s bispecific, heterodimeric antibody to increase heterodimerization. (Pet., 46-47.)

Claims 21, 24, 28, and 32: Merus’s argument relies on the same mistaken assumption above that *Lazar*’s disclosures are limited to its test constructs. (POR, 46-47.) That argument fails for the reasons above. (*See supra*, Sections III.A.2-3.)

B. Claims 1, 2, 7-24, 26-28, and 30-32 Would Have Been Obvious over *Lazar* in View of *Arathoon*

Merus includes separate arguments only for claims 1, 2, and 7. Those arguments are addressed below, and the remainder of the claims would have been obvious for the reasons explained in Xencor’s Petition and those discussed above. (Pet., 34-59; *see also supra*, Sections III.A, IV.A.)

1. Claim 1

Merus provides only unsupported attorney argument that “a POSA would have understood in 2012 that *Lazar*’s scFv-Fc/empty-Fc construct and ‘alternative’ bispecific moieties have structural incompatibilities with *Arathoon*’s knob-into-hole with disulfide bonds moieties.” (POR 43-44.) Merus cites paragraphs 123-126 of Dr. Sutton’s second declaration as support for argument, but none of those paragraphs mention, let alone explain, the so-called “structural incompatibilities” between *Lazar* and *Arathoon*. (EX2016, ¶¶123-126.) Moreover, *Lazar* expressly

teaches the opposite—that its heterodimerization strategies can be combined with the knobs-in-holes approach (among others). (See EX1004, ¶125 (citing knobs-into-holes references including Ridgway 1996 (EX1015) and Carter ’168 patent (EX1021)); EX1062, 212:22-213:9; *see also id.*, 89:19-22, 90:6-16.)

Merus also argues that the high purity of the “charge-reversal constructs” from *Lazar* and the KIH plus disulfide bond embodiment from *Arathoon* would have undermined motivation to combine. (POR 48.) Merus’s argument implicitly (and improperly) relies on a lead-compound analysis that assumes a POSA would have had to select between individual chemical compounds as starting points and choose only the best embodiments to iterate from. *Cf. Otsuka Pharm. Co. v. Sandoz, Inc.*, 678 F.3d 1280, 1291 (Fed. Cir. 2012). A “lead-compound analysis,” however, “is not required where the prior-art references expressly suggest the proposed modification.” *Cytiva* 122 F.4th at 884. Here, *Lazar* expressly teaches that its Fc variants can be combined with other heterodimerization strategies, including *Arathoon*’s KIH approach (*see* EX1004, ¶125; *see also* EX1062, 90:6-16, 89:19-22, 212:22-213:9), making a strict lead-compound framework a poor fit for these facts. A POSA would not have had to choose one lead, either charge swap or KIH. *Lazar* expressly taught combining techniques. Thus, Merus’s suggestion that other embodiments might have been more promising is irrelevant.

2. Claim 2

Merus argues that, because *Lazar*'s scFv-Fc/empty Fc construct has only one variable region, a POSA would have lacked motivation and a reasonable expectation of success in modifying *Lazar* to utilize a common light chain. (POR, 45.) But as explained above, *Lazar*'s teachings are not limited to the test constructs. Additionally, Merus fails to consider that POSA would have also been motivated to modify *Arathoon*'s heterodimeric antibody construct (including a common light chain) to promote heterodimerization by incorporating *Lazar*'s modifications in the Fc domain. (Pet., 37-41.) *Arathoon* teaches using complimentary techniques to facilitate heterodimerization (*e.g.*, knob-in-hole and interchain disulfide bonds (*see* EX1006, 53:22-28)), so a POSA would have been motivated to use *Lazar*'s complimentary neutral-to-charged substitutions with a reasonable expectation of successfully increasing heterodimerization. (*See* Pet., 37; EX1062, 90:6-16; *see also id.*, 89:19-22, 212:22-213:9.)

3. Claim 7

Merus confronts none of the rationales Xencor presented in its Petition explaining the similarity between *Lazar* and *Arathoon*'s teachings regarding the desirability of high heterodimer purity with both references expressly disclosing yields above 95%. (Pet., 42-43; EX1004, ¶¶122, 125-29.) Instead, Merus fixates on certain embodiments that Merus concludes would be better. But obviousness

does not look only to preferred embodiments. *Merck*, 874 F.2d at 807 (Fed. Cir. 1989). As discussed above, *Lazar* anticipates claim 7. (*See supra*, Section III.A.) *Lazar* certainly renders claim 7 obvious in further combination with *Arathoon*, which provides additional heterodimerization strategies for improving purity. (*See* EX1062, 89:19-22, 90:6-16, 212:22-213:9.)

C. Claims 1, 2, 7-24, 26-28, and 30-32 Would Have Been Obvious over *Lazar* in View of *Arathoon* and *Cabrera*

Merus includes separate arguments only for claim 1. Those arguments are addressed below. Otherwise, Merus recycles arguments “as discussed above” (POR, 56-57), which fail for the reasons described above (*see supra*, Sections II.A-B, III.A-B, IV.A-B).

Merus argues there is no motivation to combine *Lazar* and *Cabrera* because (1) *Lazar*’s charge-swap variants already achieved 100% heterodimeric purity and (2) heterodimerization strategies were not “necessary” for *Lazar*’s alternative bispecific moieties. (POR 53-54.)

Merus’s argument regarding *Lazar*’s charge-swap variants once again improperly assumes that a POSA would have needed to select a particular “starting point” under a lead compound-style analysis. *See Cytiva*, 122 F.4th at 884. *Lazar* and *Cabrera* both explicitly disclose neutral-to-charged substitutions, and a POSA would not have needed a “motivation” to select these variants. *See Guardant*, 2026 WL 184334, at *4; *see also In re Dembiczak*, 175 F.3d 994, 999 (Fed. Cir.

1999) (“motivation to combine may flow from the prior art references themselves”); (EX1062, 229:17-230:1 (Merus’s expert admitting *Kannan* also teaches neutral-to-charged substitutions)).

Merus’s argument that heterodimerization strategies were not “necessary” for *Lazar*’s alternative formats (*see* POR, 54; EX2016, ¶¶115-16) is also unpersuasive. For starters, *Lazar* expressly discloses that mAb-Fv and mAb-Fab are “particularly suited for the use of variants that favor Fc heterodimerization and disfavor Fc homodimerization.” (EX1004, ¶107.) Moreover, *Lazar*’s Figure 8 shows CH3 modifications that promote heterodimerization in the heavy chains of each of *Lazar*’s alternative antibody formats. (*Id.*, Fig. 8.; EX1062, 138:3-7.) These disclosures would have taught a POSA that heterodimerization strategies would be used with *Lazar*’s alternative constructs. (EX1062, 191:9-15.) Dr. Sutton’s contrary argument, based on a theory that *Lazar*’s alternative antibodies can be heterodimerized through their additional VH and VL domains (*see* EX2016, ¶115), is supported by nothing but speculation and thus entitled to no weight. *See* 37 C.F.R. § 42.65(a).

V. CONCLUSION

For at least the above reasons, Xencor respectfully requests that the Board find the challenged claims unpatentable.

Respectfully submitted,

Dated: April 3, 2026

By: /Naveen Modi/
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Counsel for Petitioner

CERTIFICATE OF COMPLIANCE

Pursuant to 37 C.F.R. § 42.24(d), the undersigned certifies that the foregoing Petitioner's Reply contains, as measured by the word-processing system used to prepare this paper, 5,556 words. This word count does not include the items excluded by 37 C.F.R. § 42.24.

Respectfully submitted,

Dated: April 3, 2026

By: /Naveen Modi/
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CERTIFICATE OF SERVICE

I hereby certify that on April 3, 2026, I caused a true and correct copy of the foregoing Petitioner's Reply to be served via email on Patent Owner at the following addresses:

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