

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 RESPONSE

TABLE OF CONTENTS

I.	INTRODUCTION.....	1
II.	STATE OF THE PRIOR ART.....	8
III.	LEVEL OF ORDINARY SKILL IN THE ART	11
IV.	THE '286 PATENT	11
V.	CLAIM CONSTRUCTION	14
A.	“Heavy Chain”	16
i.	Other Claims Of The '286 Patent	16
ii.	Specification Evidence.....	17
iii.	Prosecution History Evidence.....	18
iv.	Extrinsic Evidence	18
B.	The “Interacts” Limitation.....	20
i.	Specification Evidence.....	21
ii.	Prosecution History Evidence.....	22
VI.	ANTICIPATION ANALYSIS.....	24
A.	Lazar Does Not Anticipate Any Of The Challenged Claims.....	26
i.	Claim 1	26
ii.	Claims 7, 21, 22, 24, 26, 28, 30, And 32	28
iii.	Claim 26	29
iv.	Claim 30	30
B.	Cabrera Does Not Anticipate Any Of The Challenged Claims	30
i.	Claim 1	30
ii.	Claims 2, 7, 21, 22, 24, 28, And 32	33
iii.	Claims 26 And 27.....	34
iv.	Claims 30 And 31.....	34
VII.	OBVIOUSNESS ANALYSIS	34

A.	The <i>Graham</i> Factors.....	36
i.	Scope And Content Of The Prior Art	36
(1)	Lazar	36
(2)	Cabrera	37
(3)	Arathoon.....	38
ii.	Differences Between The Prior Art And The Challenged Claims	38
(1)	Lazar	38
(2)	Cabrera	39
(3)	Arathoon.....	39
iii.	Level Of Ordinary Skill In The Art	40
iv.	Secondary Considerations Of Non-Obviousness.....	40
(1)	Teaching Away / Skepticism.....	40
(2)	Unexpected Results	41
B.	The Challenged Claims Are Not Obvious Over Lazar	42
i.	A POSA Would Not Have A Reason To Modify Lazar To Achieve The Challenged Claims With A Reasonable Expectation Of Success	42
(1)	Claim 1	42
(2)	Claims 2, 7–24, 28, And 32.....	44
(3)	Claims 26 And 27.....	47
(4)	Claims 30 And 31.....	47
C.	The Challenged Claims Are Not Obvious Over Lazar View Of Arathoon.....	47
i.	A POSA Would Not Be Motivated To Combine Lazar And Arathoon To Achieve The Challenged Claims With A Reasonable Expectation Of Success	48
(1)	Claim 1	48
(2)	Claims 2, 7–24, 28, And 32.....	49

(3) Claims 26 And 27	52
(4) Claims 30 And 31	52
ii. Even If Combined, Lazar And Arathoon Together Fail To Disclose All Elements Of The Challenged Claims.....	52
D. The Challenged Claims Are Not Obvious Over Lazar In View Of Arathoon And Cabrera.....	53
i. A POSA Would Not Be Motivated To Combine Lazar, Arathoon, And Cabrera To Achieve The Challenged Claims With A Reasonable Expectation Of Success.....	53
(1) Claim 1	53
(2) Claims 2, 7–24, 28, And 32.....	56
(3) Claims 26 And 27	57
(4) Claims 30 And 31	57
ii. Even If Combined, Lazar And Arathoon Together Fail To Disclose All Elements Of The Challenged Claims.....	57
VIII. DR. PRESTA'S DECLARATION AND OPINIONS ARE UNRELIABLE AND SHOULD CARRY NO WEIGHT	58
A. Dr. Presta Used The Wrong Claim Constructions	58
B. Dr. Presta's Description Of The Art Is Inconsistent	60
IX. CONCLUSION	60

TABLE OF AUTHORITIES

	Page(s)
Cases	
<i>Allergan Sales, LLC v. Sandoz, Inc.</i> , 935 F.3d 1370 (Fed. Cir. 2019)	<i>passim</i>
<i>In re Arkley</i> , 455 F.2d 586 (C.C.P.A. 1972)	25
<i>Fox Factory, Inc. v. SRAM, LLC</i> , 944 F.3d 1366 (Fed. Cir. 2019)	40
<i>In re Gleave</i> , 560 F.3d 1331 (Fed. Cir. 2009)	25
<i>Graham v. John Deere Co.</i> , 383 U.S. 1 (1966)	<i>passim</i>
<i>Hoffer v. Microsoft Corp.</i> , 405 F.3d 1326 (Fed. Cir. 2005)	7, 24
<i>Hulu, LLC v. Sound View Innovations, LLC</i> , IPR2018-00582, Paper 34 (P.T.A.B. August 5, 2019)	35
<i>Intelligent Bio-Systems, Inc. v. Illumina Cambridge, Ltd.</i> , 821 F.3d 1359 (Fed. Cir. 2016)	35
<i>KSR Int'l Co. v. Teleflex Inc.</i> , 550 U.S. 398 (2007)	34
<i>Leo Pharm. Prods., Ltd. v. Rea</i> , 726 F.3d 1346 (Fed. Cir. 2013)	35
<i>Microsoft Corp. v. Biscotti, Inc.</i> , 878 F.3d 1052 (Fed. Cir. 2017)	25
<i>Nidec Motor Corp. v. Zhongshan Broad Ocean Motor Co.</i> , 868 F.3d 1013 (Fed. Cir. 2017)	14

<i>Phillips v. AWH Corp.</i> , 415 F.3d 1303 (Fed. Cir. 2005)	<i>passim</i>
<i>Precision Cancer Technologies Inc., v. Oncoustics Inc.</i> , IPR2025-00242, Paper 7 (P.T.A.B. June 3, 2025)	25
<i>Regents of Univ. of California v. Broad Inst., Inc.</i> , 903 F.3d 1286 (Fed. Cir. 2018)	35
<i>Ex parte Smith</i> , 2011-003337, Decision On Appeal (P.T.A.B. February 28, 2012).....	25
<i>Ex parte Thompson</i> , 2011-011620, Decision On Appeal (P.T.A.B. March 21, 2014).....	35
<i>Univ. of Strathclyde v. Clear-Vu Lighting LLC</i> , 17 F.4th 155 (Fed. Cir. 2021)	53, 58
<i>Ex Parte Whirlpool Corp.</i> , 2013-008232, Decision On Appeal (P.T.A.B. October 30, 2013)	35
Statutes	
35 U.S.C. § 102	25
Other Authorities	
37 C.F.R. § 42.100(b)	14

LIST OF EXHIBITS

Exhibit Number	Description
EX1001	'286 Patent
EX1002	Presta Declaration
EX1004	Lazar
EX1005	Cabrera
EX1006	Arathoon
EX1008	'286 Patent File History
EX1012	Gunasekaran Paper
EX1013	Kontermann
EX1017	Merchant
EX2012	Presta Transcript
EX2013	Presta Transcript EX4001 (Matthews)
EX2016	Second Sutton Declaration

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	Merus' U.S. Patent No. 9,358,286
POSA	Person of ordinary skill in the art
Gunasekaran Paper	Gunasekaran Kannan, et al., Enhancing antibody Fc heterodimer formation through electrostatic steering effects: applications to bispecific molecules and monovalent IgG. J Biol Chem. 2010 Jun 18;285(25):19637-46
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
Challenged Claims	'286 Patent claims 1 – 2, 7 – 24, 26 – 28, and 30 – 32
Second Sutton Declaration	Second Declaration of Brian J. Sutton, Ph.D.
Presta Declaration	Declaration of Leonard G. Presta, Ph.D.
Presta Transcript	Transcript from the Cross-Examination of Dr. Leonard G. Presta, Ph.D. (December 5, 2025)

I. INTRODUCTION

The Board should deny Xencor's petition to invalidate the Challenged Claims in its entirety. When properly construed, these claims are neither anticipated by, nor obvious over, Xencor's asserted references.

As shown by the parties' submissions to date and the Board's Decision Granting Institution (Paper 13), two claim terms are in controversy: (1) "heavy chain" in both singular and plural forms; and (2) "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 . . . to produce a heterodimeric antibody" (hereinafter, the "interacts" limitation). In granting institution, the Board stated that "[a]t this stage of the proceeding, we expressly construe no claim terms and give each claim term the ordinary and customary meaning it would have had to the person of ordinary skill in the art as of the invention date." *Id.* at 17. Xencor, however, did not use the ordinary and customary meaning of either of the disputed claim terms.

With respect to "**heavy chain**"—and despite asserting in his declaration that he used ordinary and customary meaning for all claim terms (EX1002 at ¶ 99)—Xencor's expert Dr. Presta admitted during cross-examination that he did not use a textbook, paper, or other reference to establish the ordinary and customary meaning

of “heavy chain.” Instead, Dr. Presta admitted that he used a personal, context-dependent definition of the term. Dr. Presta further admitted that he did not compare his personal, context-dependent definition of “heavy chain” to the specification, the other claims, or the prosecution history.

For example, Dr. Presta admitted that he did not consider dependent claim 8, which specifies that “each variable region of the 1st and 2nd antibody heavy chains recognizes a different target epitope.” This failure is significant, including because it directly impacts the Lazar Figure 1 construct. Dr. Presta’s personal definition does not require that each “heavy chain” have a variable region. Claim 8 clearly does.

As another example, Dr. Presta admitted that he did not review the prosecution history. This is another significant failure. During prosecution, applicants replaced “CH3-domain-containing polypeptide chain” with the narrower term “antibody heavy chain.” Dr. Presta’s personal definition of “heavy chain” includes any polypeptide chain with a CH3 domain, like those in the Lazar Figure 1 construct. The prosecution history contradicts that construction.

In short, cross-examination showed that Xencor and Dr. Presta used a personal, context-dependent definition of “heavy chain.” That *ad hoc* definition is neither the ordinary and customary meaning of “heavy chain” nor its proper construction given the specification, the other claims, and the prosecution history.

In the Second Declaration Of Brian J. Sutton, Ph.D. (EX2016) (“Second

Sutton Declaration”) submitted concurrently with Patent Owner’s Response, Merus’ expert Dr. Sutton analyzes and explains the ordinary and customary meaning of “heavy chain” to a POSA as of the invention date. Dr. Sutton reviews relevant textbooks and papers, as well as the specification, other claims, and prosecution history. As Dr. Sutton explains, these sources align and establish the ordinary and customary meaning of “heavy chain”: “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.”

In its institution decision, the Board noted that “IgG, IgA, and IgD classes of antibodies have three constant domains on their heavy chains” while “[o]ther classes of antibodies, e.g., IgM and IgE, have four constant domains (adding a CH4 domain).” Paper 13 at 5 fn.3. As Dr. Sutton explains, the Board’s observation is consistent with the ordinary and customary meaning of “heavy chain.” In their preliminary submissions, Merus and Dr. Sutton focused on the specification discussion of IgG antibodies and their component parts. The Board rejected that focus for independent claim 1. With that rejection in mind, Merus and Dr. Sutton provide a complete claim construction analysis that covers all Challenged Claims, all antibody classes, and all relevant sources for the ordinary and customary meaning of “heavy chain” to a POSA as of the invention date.

As Dr. Sutton explains, when “heavy chain” is properly construed, none of the Challenged Claims is anticipated by, or obvious over, the Lazar reference. As Dr. Sutton further explains, the dependent Challenged Claims have additional significant differences from Lazar regardless of the construction of “heavy chain.” For example, the neutral to charged Fc variants in Lazar do not even come close to meeting the claim 7 requirement that “the presence of contaminating homodimers is less than 5%.” Nor do the constructs with these Fc variants—which are part murine and which Lazar does not even call antibodies—come close to being IgG or IgG1 antibodies, as required by claims 21, 24, and 32, or suitable for inclusion in a pharmaceutical composition, as required by claim 28.

With respect to the **“interacts” limitation**—Xencor uses an improper construction that: (a) is not the ordinary and customary meaning of the term; and (b) Dr. Presta contradicted during cross-examination. Specifically, Xencor construes this term such that any CH3 domain interaction is sufficient to satisfy it. Xencor’s construction is contradicted by the plain language of the term, which requires a specific interaction between the “at least one positively charged amino acid residue substituted in the CH3 domain of said 1st antibody heavy chain” and the “at least one negatively charged amino acid residue substituted in the CH3 domain of said 2nd antibody heavy chain.” Xencor’s construction was further contradicted by Dr. Presta during cross-examination, when he admitted that not just any

interaction between these substituted amino acids is sufficient to satisfy the claims—it must be an interaction that produces a heterodimeric antibody:

Q As you read the claim, the substituted positively charged amino acid residue from the first antibody heavy chain interacts with the negatively charged amino acid residue in the second heavy chain, and that interaction, according to the claim, produces a heterodimeric antibody, right?

A "Produces a heterodimeric antibody." The problem I have is just because the two interact, that might not necessarily give you the heterodimeric antibody.

Q And to satisfy the claim, there has to be an interaction that does give you the heterodimeric antibody, right?

A Yes.

Q So if there's just an interaction between the positively charged amino acid substitution on the first antibody heavy chain and the negative amino acid substitution on the second antibody heavy chain, and those don't interact to produce a heterodimeric antibody, then that does not satisfy claim 1, correct?

A Correct.

EX2012 (Presta Transcript) at 52:10 – 53:5.

Dr. Sutton agrees with Dr. Presta on this issue. As Dr. Sutton explains in his Second Declaration, to satisfy the Challenged Claims, the two substituted residues must interact *and* must interact to produce a heterodimeric antibody. Residues that do not interact—or interact in a way that does not produce, or disrupts production

of, a heterodimeric antibody—are not sufficient to satisfy the claims.

Drs. Presta and Sutton agreeing on this issue is significant, including because it directly impacts AZ34 in Cabrera. Xencor's improper construction of the “interacts” limitation does not require that the neutral to charged substitutions in AZ34 interact to produce a heterodimeric antibody, only that the CH3 domains interact. But the plain language of the limitation and Drs. Presta and Sutton contradict that construction. The prosecution history further contradicts that construction, showing that the “interacts” limitation was added to distinguish prior art.

As Dr. Sutton explains in his Second Declaration, when the “interacts” limitation is properly construed, none of the Challenged Claims is anticipated by, or obvious over, the Cabrera reference. As Dr. Sutton further explains, the dependent claims have additional significant differences from Cabrera regardless of the construction of the “interacts” limitation. For example, the neutral to charged constructs in Cabrera do not meet the “each variable region . . . recognizes a different target epitope” requirement in claims 8 to 20 or the “pharmaceutical composition” requirement of claim 28.

In its institution decision, the Board stated that “[a]t this stage of the proceeding, neither party has provided an argument or evidence addressing whether this wherein clause, i.e., the ‘interacting’ claim element, should be given patentable

weight and, if so, why.” Paper 13 at 34. Merus provides that argument here and includes as evidence the Second Sutton Declaration, patent specification, and prosecution history. As Dr. Sutton explains, the “interacts” limitation produces a heterodimeric antibody when satisfied. The method of claim 1 would be incomplete if it were not given patentable weight. Claim 22—a composition of matter claim—would similarly be incomplete if the “interacts” limitation were not given patentable weight. Lastly, the “interacts” limitation was added during prosecution to overcome a prior art rejection. Federal Circuit precedent prohibits ignoring it now. *See Hoffer v. Microsoft Corp.*, 405 F.3d 1326, 1329 (Fed. Cir. 2005); *Allergan Sales, LLC v. Sandoz, Inc.*, 935 F.3d 1370, 1373-1376 (Fed. Cir. 2019).

In addition to using improper claim constructions, Xencor failed to apply the proper standard for anticipation. Especially in *Lazar*, Xencor picks and chooses from different disclosures and seeks to combine them as an alleged anticipation. But that is not the standard. As the Federal Circuit has explained, the standard for anticipation is whether a reference discloses all of the claim elements ***as arranged or combined in the claims***.

Xencor also failed to do a proper obviousness analysis. For example, Xencor failed to analyze all of the *Graham* factors. Xencor further failed to provide a credible reason why a POSA would combine its asserted references—which have incompatible structures and approaches—much less do so with a reasonable

expectation of success. As Dr. Sutton explains, a POSA would not find any of the Challenged Claims obvious over any of Xencor's cited references, whether alone or in combination.

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

II. STATE OF THE PRIOR ART

By April 20, 2012, researchers had investigated numerous ways to create bispecific antibodies for potential therapeutic uses. EX2016 (Second Sutton Declaration) at ¶ 7. Indeed, by that date, a POSA would have been aware of at least 45 different approaches for creating bispecific antibodies. *Id.* at ¶ 8; EX1013 (Kontermann) at Fig. 2. As Dr. Presta agreed during cross-examination, only **seven** of the 45 known approaches for creating bispecific antibodies involved modification of the antibody Fc region (which includes the CH3 domain), and only **one** of those seven approaches involved "charge pairs." See EX2012 (Presta Transcript) at 25:16 – 26:12; EX2016 (Second Sutton Declaration) at ¶ 9.

A POSA in 2012 would have had no reason to select for modification the one "charge pairs" approach to creating bispecific antibodies out of the 45 different approaches reported in the Kontermann paper (EX1013). EX2016 (Second Sutton Declaration) at ¶ 10. Indeed, Xencor fails to cite any evidence suggesting that the "charge pairs" approach was superior to other approaches as of the invention date.

Id. Even if a POSA were interested in modifying the Fc region to create bispecific antibodies, they would have investigated other well-known methods for creating bispecific antibodies—like knob-into-hole with disulfide bonds, which reported 95% heterodimeric purity—or been content to use the existing “charge pairs” approach, which reported producing the desired heterodimer “almost exclusively.” *Id.*; *see also* EX1017 (Merchant); EX1012 (Gunasekaran Paper). Dr. Presta used hindsight to single out the “charge pairs” approach for modification. *See* EX2016 (Second Sutton Declaration) at ¶ 10. A POSA on April 20, 2012, however, did not have any reason to do so. *Id.*

Even if they ignored the 44 other known approaches for creating bispecific antibodies, a POSA seeking to modify the “charge pairs” approach knew to avoid the neutral residues in the hydrophobic core of the CH3 domain. *Id.* at ¶ 11. This was well known to a POSA by the invention date, including because Dr. Gunasekaran Kannan had explained in a widely cited paper that these neutral residues play an important role in protein folding and stability and should not be modified. *Id.*; EX1012 (Gunasekaran Paper) at 4 (citing EX2013 (Matthews)).¹ Indeed, this concept was so well-accepted that the Gunasekaran Paper (EX1012) is

¹ EX1012 inadvertently switched author Gunasekaran Kannan's first and last names. Merus calls it the “Gunasekaran Paper” in this IPR for consistency.

incorporated into Lazar and Cabrera in its entirety. EX1004 (Lazar) at ¶ 125; EX1005 (Cabrera) at 129; EX2016 (Second Sutton Declaration) at ¶ 18. A POSA clearly understood on April 20, 2012—from at least the Gunasekaran Paper (EX1012) and the Matthews paper cited therein (EX2013)—that any charge modifications to improve heterodimerization should be made to the already charged residues at the periphery of the CH3 domain and not to neutral residues in the hydrophobic core. EX2016 (Second Sutton Declaration) at ¶ 12.

Dr. Presta's cross-examination testimony confirms that a POSA would not have been motivated to substitute the neutral residues in the hydrophobic core of the CH3 domain to promote heterodimerization. The Gunasekaran Paper explicitly states that the neutral residues in the hydrophobic core play an important role in protein folding. *Id.*; EX1012 (Gunasekaran Paper) at 4. According to Dr. Presta, a POSA at the relevant time was unlikely to "understand the intricacies of what controlled protein folding." EX2012 (Presta Transcript) at 87:16 – 88:1; EX2016 (Second Sutton Declaration) at ¶ 15. A POSA would be unlikely to modify a residue when they did not understand its role. EX2016 (Second Sutton Declaration) at ¶ 14.

Dr. Presta further testified that a POSA at the relevant time knew the antibody Fc region (which contains the CH3 domain) serves important biological functions and that a POSA would not want to interfere with those functions. *See id.* ¶¶ 16–17; EX2012 (Presta Transcript) at 42:1 – 43:8. It follows that a POSA would not want

to modify, and potentially destabilize, this critical domain. *See id.*; EX2016 (Second Sutton Declaration) at ¶ 16.

III. LEVEL OF ORDINARY SKILL IN THE ART

As explained by Dr. Sutton, a POSA at the time of the invention would have a Ph.D. in biochemistry, chemistry, molecular or structural biology, molecular biophysics, antibody engineering, immunology, or a related discipline and at least 2 years of related experience in academia or industry or a Masters degree in any of the above fields with at least 4 years of related experience in academia or industry. *Id.* at ¶ 6. As further explained by Dr. Sutton, the relevant analysis does not change if Dr. Presta's proposed level of ordinary skill in the art is used. *Id.*

IV. THE '286 PATENT

Independent claim 1 recites (with the disputed claim terms in bold):

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.

EX1001 ('286 Patent) (emphasis added).

Claims 2, 7–21, and 32 depend from independent claim 1 and require additional limitations, including that the host cell encode a common light chain (claim 2), that contaminating homodimers are kept below a certain level (claim 7), that “each variable region of the 1st and 2nd antibody heavy chains recognizes a different target epitope” (claims 8 – 20), and that the heterodimeric antibody is human IgG (claim 21) or human IgG1 (claim 32). *See id.* Claims 22 – 24 and 28 depend from independent claim 1 and claim a heterodimeric antibody obtained by the method of claim 1 (claim 22), that said heterodimeric antibody binds to different epitopes (claim 23), that said antibody is a human IgG (claim 24), and that said antibody is combined with a pharmaceutically acceptable carrier in a pharmaceutical composition (claim 28). *See id.*

Independent claim 26 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.

Id. (emphasis added). Claim 27 depends from independent claim 26 and includes all of its limitations and the additional limitation that the host cell encodes a common light chain. *See id.*

Independent claim 30 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.

Id. (emphasis added). Claim 31 depends from independent claim 30 and includes all of its limitations and the additional limitation that the host cell encodes a common light chain. *See id.*

Claims 1 – 2, 7 – 24, 26 – 28, and 30 – 32 are collectively the “Challenged Claims.” The remaining claims were not included in Xencor’s petition or the Board’s institution decision and are not part of this proceeding.

V. CLAIM CONSTRUCTION

The Board need only construe claim terms “that are in controversy, and only to the extent necessary to resolve the controversy.” *See Nidec Motor Corp. v. Zhongshan Broad Ocean Motor Co.*, 868 F.3d 1013, 1017 (Fed. Cir. 2017).² Here, there are two claim terms in controversy: (1) “heavy chain” in the singular and plural forms; and (2) “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 . . . to produce a heterodimeric antibody.” *See* EX2016 (Second Sutton Declaration) at ¶ 23.

In an IPR, the Board applies the claim construction standard articulated in *Phillips* and its progeny. *See* 37 C.F.R. § 42.100(b); *Phillips v. AWH Corp.*, 415 F.3d 1303 (Fed. Cir. 2005)(*en banc*). Under *Phillips*, the “words of a claim are generally given their ordinary and customary meaning” as would be understood by a POSA at the time of the invention. *Phillips*, 415 F.3d at 1312–13. Sources to determine the ordinary and customary meaning of a claim term include “the words of the claims themselves, the remainder of the specification, the prosecution history,

² Unless otherwise indicated, all internal case quotations and citations have been omitted.

and extrinsic evidence concerning relevant scientific principles, the meaning of technical terms, and the state of the art.” *Id.* at 1314.

The Federal Circuit has emphasized the importance of intrinsic evidence in claim construction. “[T]he claims themselves provide substantial guidance as to the meaning of particular claim terms,” and “[o]ther claims of the patent in question . . . can also be valuable sources of enlightenment as to the meaning of a claim term.” *Id.* The claims “must be read in view of the specification,” as the specification “is the single best guide to the meaning of a disputed term.” *Id.* at 1315. In addition to consulting the specification, the Board “should also consider the patent’s prosecution history,” which is “intrinsic evidence . . . of how the PTO and the inventor understood the patent.” *Id.* at 1317.

The Federal Circuit has also authorized reliance on extrinsic evidence to determine the general knowledge and understanding of a POSA at the relevant time. *See id.* Extrinsic evidence “consists of all evidence external to the patent and prosecution history, including expert and inventor testimony, dictionaries, and learned treatises.” *Id.*

An expert’s “conclusory, unsupported assertions” regarding claim construction, however, “are not useful.” *See id.* at 1318. The Board should discount any such assertions, especially if they are “clearly at odds with the claim construction mandated by the claims themselves, the written description, and the

prosecution history, in other words, with the written record of the patent.” *See id.*

A. “Heavy Chain”

Under the *Phillips* standard, the “ordinary and customary” meaning of the claim term “heavy chain” would be understood by a POSA at the time of the invention to be: “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.” EX2016 (Second Sutton Declaration) at ¶ 25.

This ordinary and customary meaning of “heavy chain” is confirmed by both the intrinsic and extrinsic evidence. Indeed, this meaning of “heavy chain” was documented and well understood by a POSA in 2012. *See id.* at ¶ 26. The other claims, specification, prosecution history, and extrinsic evidence further support this ordinary and customary meaning of “heavy chain.”

i. Other Claims Of The '286 Patent

Other claims of the '286 Patent confirm the ordinary and customary meaning of “heavy chain.” *See id.* at ¶¶ 32–34. For example, dependent claim 8 confirms that the correct construction of “heavy chain” requires a variable region. *Id.* at ¶ 34.

Dependent claim 8 reads: “The method of claim 1, wherein ***each variable region of the 1st and 2nd antibody heavy chains recognizes a different target epitope.***” EX1001 ('286 Patent) (emphasis added). The requirement in dependent

claim 8 that “***each variable region*** of the 1st and 2nd antibody heavy chains ***recognizes a different target epitope***” is persuasive evidence that the two heavy chains in independent claim 1 must each have a variable region. See EX2016 (Second Sutton Declaration) at ¶¶ 33–34. That is, a POSA reading claim 8 would understand that each heavy chain in independent claim 1 must have a variable region and that in claim 8 each of those variable regions must be different (*i.e.*, “recognize a different target epitope”). *Id.* at ¶ 34. Dependent claim 8 thus confirms the ordinary and customary meaning of “heavy chain” as including a variable region. *Id.*

ii. Specification Evidence

Dr. Sutton agrees with the Board's observation that the specification does not use the term “heavy chains” differently than its ordinary and customary meaning. *Id.* at ¶ 35. For example, for IgG antibodies, the specification describes each heavy chain as having “four domains, the variable heavy chain (VH) and three constant heavy chain domains (CH1, CH2, CH3).” See *id.* at ¶ 39; EX1001 ('286 Patent) at 11:58–66. That description is consistent with—and a subset of—the ordinary and customary meaning of “heavy chain” for all antibody classes. See EX2016 (Second Sutton Declaration) at ¶¶ 36–38.

For the dependent claims that require an IgG or IgG1 antibody—claims 21, 24, and 32—the specification discussion of an IgG “heavy chain” helps inform a

POSA of the exact antibody structure that is required to satisfy those claims. *See id.* at ¶ 39; EX1001 ('286 Patent) at 11:58–63. While this specification discussion may not constitute a clear definition for claim construction purposes, a POSA reading it would understand that—consistent with its ordinary and customary meaning—each “heavy chain” in an IgG or IgG1 antibody must have a variable region and three constant regions. *See* EX2016 (Second Sutton Declaration) at ¶ 39.

iii. Prosecution History Evidence

As Dr. Sutton explains, during prosecution claim 1 was amended to replace “CH3-domain comprising polypeptide chain” with “antibody heavy chain” to overcome a prior art rejection. *See id.* at ¶¶ 40–43; EX1008 ('286 Patent File History) at 217–218; 239–245. This was a narrowing amendment because the specification defines “polypeptides” broadly as “a chain of amino acids that are covalently joined together through peptide bonds.” *See* EX2016 (Second Sutton Declaration) at ¶¶ 40–43; EX1001 ('286 Patent) at 14:19–22. The prosecution history thus confirms the ordinary and customary meaning of “heavy chain,” *i.e.*, that a heavy chain requires more than just a string of amino acids containing a CH3 domain. *See* EX2016 (Second Sutton Declaration) at ¶ 43.

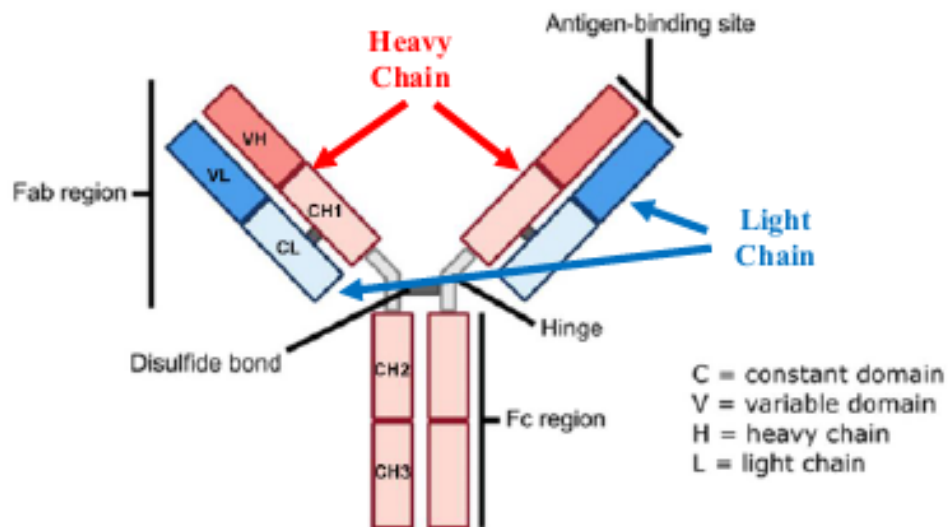
iv. Extrinsic Evidence

The term “heavy chain” was used in various prior art papers and textbooks that confirm its ordinary and customary meaning. *See id.* at ¶ 26. According to these

materials, a “heavy chain” is the entire polypeptide chain from the N- terminus to the C-terminus, including the variable VH domain and all CH domains. *See id.* at ¶¶ 25–26. Based on these disclosures, a POSA would have understood that an antibody fragment lacking a VH region or lacking a CH1 domain is not a “heavy chain.” *Id.* at ¶ 26.

While using a different, *ad hoc* definition of “heavy chain” in his analysis, Dr. Presta provides a depiction of a “naturally occurring antibody” with red arrows pointing to each antibody “heavy chain.”

Demonstrative 2 – Monoclonal Antibody Structure



See id. at ¶ 27; Presta Declaration (EX1002) at ¶ 25. According to Dr. Presta’s red arrows, each “heavy chain” has a variable region and, here, three constant domains (because the depicted antibody is an IgG). *See* Presta Declaration (EX1002) at ¶ 25.

Given the intrinsic and extrinsic evidence, a POSA would have understood the ordinary and customary meaning of “heavy chain” to be: “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.” See EX2016 (Second Sutton Declaration) at ¶¶ 24–43.

Dr. Presta admitted during cross-examination that he failed to analyze the ordinary and customary meaning of “heavy chain” under the *Phillips* standard. See EX2012 (Presta Transcript) at 26:22 – 30:4, 38:3–25. His declaration should thus be afforded no weight regarding its construction.

B. The “Interacts” Limitation

Under the *Phillips* standard, a POSA at the time of the invention would have understood the ordinary and customary meaning of the “interacts” limitation to contain two requirements: (1) that the two identified substituted residues interact; and (2) that the interaction of those residues produces a heterodimeric antibody. See EX2016 (Second Sutton Declaration) at ¶ 45. A POSA would have understood that if there is no “interaction” between the identified residues—or if any such “interaction” does not “produce a heterodimeric antibody” or disrupts heterodimeric antibody production—then the “interacts” limitation is not satisfied. *Id.* In such a situation, heterodimerization may still occur, but it would be the result of other

interactions at the CH3-CH3 interface and not the required interaction between identified residues. *Id.* at ¶¶ 45, 53.

Dr. Presta agrees with Dr. Sutton's understanding of the "interacts" limitation. *See id.* at ¶¶ 46–47. Indeed, Dr. Presta admitted during cross-examination that "just because the two [residues] interact, that might not necessarily give you the heterodimeric antibody." *Id.* at ¶ 46; EX2012 (Presta Transcript) at 52:16 – 53:5. According to both Dr. Presta and Dr. Sutton, the "interacts" limitation requires both interaction and production of a heterodimeric antibody. *Id.*; *see also* EX2016 (Second Sutton Declaration) at ¶ 47. Meeting only one of those two requirements is not enough to satisfy the limitation. *Id.*

The relevant evidence all supports this ordinary and customary meaning of the "interacts" limitation. *See* EX2016 (Second Sutton Declaration) at ¶¶ 45–47.

i. Specification Evidence

A POSA reading the specification would have understood that the "interacts" limitation requires both that the identified residues interact and that their interaction produces a heterodimeric antibody. *See id.* at ¶¶ 48–54. A POSA would have further understood that such interactions to produce a heterodimeric antibody could include, *e.g.*, formation of hydrogen bonds or salt bridges between the identified residues in the two CH3 domains. *Id.* at ¶ 48.

For example, the specification describes "interaction" of the substituted

residues at the “interface” as one or more atoms of the first substituted residue being in contact distance with one or more atoms of the second substituted residue, such as to form either a van der Waals interaction, hydrogen bond (directly or mediated by a water molecule) or salt bridge. *Id.* at ¶¶ 49–50; EX1001 ('286 Patent) at 13:18–29. The specification also provides specific examples of substituted residues “interacting” at the CH3/CH3 interface. EX2016 (Second Sutton Declaration) at ¶ 51; EX1001 ('286 Patent) at Figure 15. Based on these disclosures, a POSA would have understood that for two different heavy chains to form a heterodimeric antibody by means of an interaction between the two identified residues, there must be a strong interaction such as a salt bridge or hydrogen bonding. EX2016 (Second Sutton Declaration) at ¶ 52.

A POSA would have also understood that not all substituted residues would “interact[] . . . to produce a heterodimeric antibody.” *See id.* at ¶ 54. Some substituted residues would not interact at all, whereas other substituted residues would interact to disrupt heterodimerization. *Id.* As discussed below, these non-interacting or disruptive substitutions are what Xencor relies on for its invalidity arguments.

ii. Prosecution History Evidence

As Dr. Sutton explains, applicants amended claim 1 to add the “interacts” limitation in response to a prior art rejection. *See id.* at ¶¶ 55–58. Specifically, the USPTO cited Kannan *et al.* (US 2010/0286374) and stated it disclosed that “one or

more residues that make up the CH3-CH3 interface can be replaced with a charged amino acid such that the interaction between homodimers becomes electrostatically unfavorable.” *Id.* at ¶ 55; EX1008 (’286 Patent File History) at 218–220. Applicants overcame this rejection by amending the claims to add the “interacts” limitation. *See* EX2016 (Second Sutton Declaration) at ¶¶ 55–56; EX1008 (’286 Patent File History) at 239–246. This amendment is evidence that the “interacts” limitation requires an interaction between the identified residues that produces a heterodimeric antibody; an interaction that prevents homodimerization does not satisfy the limitation. *See* EX2016 (Second Sutton Declaration) at ¶ 57. A POSA would understand the same to be true for the ordinary and customary meaning of this limitation. *See id.* at ¶ 58.

iii. The “Interacts” Limitation Is Of Patentable Weight

The “interacts” limitation is of patentable weight. As discussed above, satisfying this limitation requires that specific residues interact and that their interaction produces a heterodimeric antibody. Without the “interacts” limitation, the claim 1 method would be incomplete, as there would be no interaction joining the heavy chains to produce a heterodimeric antibody. The heterodimeric antibody of claim 22 would be incomplete as well, because there would be no interaction, *e.g.*, a hydrogen bond or salt bridge, holding the heavy chains of the antibody together.

Dr. Presta agrees that neither the formation of a new salt bridge nor its role in producing the claimed heterodimeric antibody are inevitable results of substituting

known neutral contact residues to charged residues in the CH3 domain. This is at least because, according to Dr. Presta, it is not a given that the substituted residues will “interact,” even if the native residues are known to interact. *See* EX2012 (Presta Transcript) at 115:6–14. Furthermore, a charge interaction does not necessarily produce a heterodimeric antibody. *See id.* at 49:23 – 50:17, 52:10–19.

In short, the “interacts” limitation is not an inherent result of introducing neutral to charged substitutions to the CH3 domain and is an important requirement of the claimed methods and antibodies.

Confirming this fact, the “interacts” limitation was added during prosecution to overcome a prior art rejection. Federal Circuit precedent prohibits ignoring it now. *See Hoffer*, 405 F.3d at 1329; *Allergan Sales*, 935 F.3d at 1373–76 (finding “wherein” clauses were claim limitations because they “were neither unnecessary nor irrelevant, but were instead material to the Examiner’s patentability determination”).

Dr. Presta failed to analyze the ordinary and customary meaning of the “interacts” limitation under the *Phillips* standard. *See* EX2012 (Presta Transcript) at 26:22 – 28:3. His declaration should thus be afforded no weight regarding its construction.

VI. ANTICIPATION ANALYSIS

To anticipate, a single prior art reference must disclose all of the elements of

the claimed invention arranged or combined in the same way as in the claims. *See Microsoft Corp. v. Biscotti, Inc.*, 878 F.3d 1052, 1068 (Fed. Cir. 2017); *see also In re Gleave*, 560 F.3d 1331, 1334 (Fed. Cir. 2009); *Precision Cancer Technologies Inc., v. Oncoustics Inc.*, IPR2025-00242, Paper 7, at 5 (P.T.A.B. June 3, 2025) (“the prior art reference—in order to anticipate under 35 U.S.C. § 102—must not only disclose all elements of the claim within the four corners of the document, but must also disclose those elements arranged as in the claim”).

A prior art reference does not anticipate if “picking and choosing” disclosures from the reference is required to arrive at the claimed invention. *See Ex parte Smith*, 2011-003337, Decision On Appeal, at 7–8 (P.T.A.B. February 28, 2012) (informative) (citing *In re Arkley*, 455 F.2d 586, 587–88 (C.C.P.A. 1972)). Rather, to anticipate, a prior art reference “must clearly and unequivocally disclose the claimed compound or direct those skilled in the art to the compound without any need for picking, choosing, and combining various disclosures.” *In re Arkley*, 455 F.2d at 587–88.

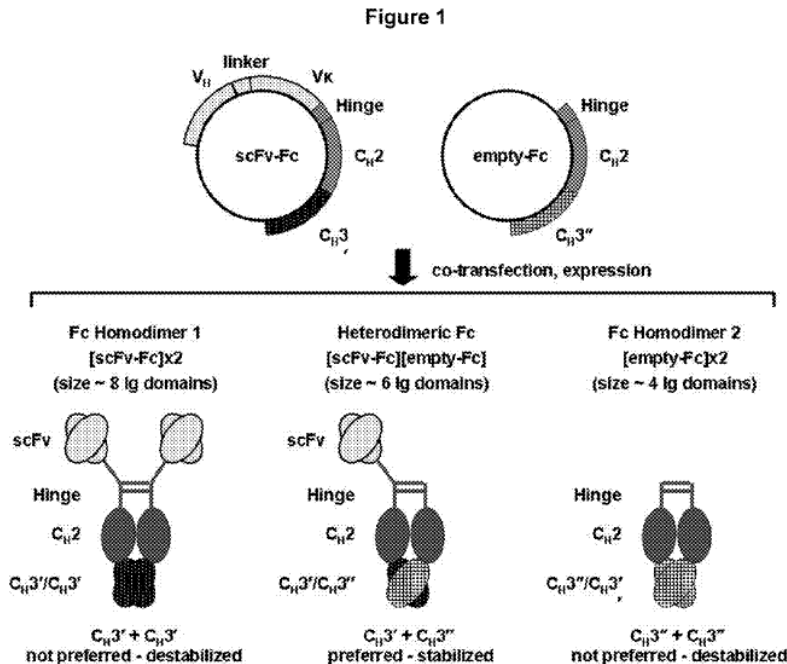
Neither Lazar nor Cabrera discloses all of the elements of any of the Challenged Claims arranged or combined as they are in the claims. EX2016 (Second Sutton Declaration) at ¶¶ 59–60. Xencor and Dr. Presta improperly pick, choose, and combine different pieces of information from these references in their anticipation analyses. *Id.* But that does not meet the legal standard for anticipation.

A. Lazar Does Not Anticipate Any Of The Challenged Claims

Lazar does not disclose all of the elements of any of the Challenged Claims, much less disclose them arranged as they are in those claims. *See id.* at ¶¶ 61–72. Lazar therefore does not anticipate any of the claims for which it is asserted. *Id.* at ¶ 72; Paper 13 at 9.

i. Claim 1

Lazar does not disclose producing a heterodimeric antibody using two heavy chains with neutral to charged substitutions that interact to produce the antibody, as required by claim 1. *See id.* at ¶¶ 61–62. The only disclosure of neutral to charged substitutions in Lazar is in Example 2, which is limited to discussing a truncated experimental construct that Lazar calls the “scFv-Fc/empty-Fc format” and depicts in Lazar Figure 1:



Id. at ¶¶ 62–63; EX1004 (Lazar) at Fig. 1. As Dr. Presta admitted during cross-examination, only the scFv-Fc/empty-Fc construct was used for Fc binding in Lazar. See EX2016 (Second Sutton Declaration) at ¶ 70; EX2012 (Presta Transcript) at 91:7 – 92:10, 94:7 – 95:5.

As depicted above and explained by Dr. Sutton, the scFv-Fc/empty-Fc construct in Lazar does not have even one “heavy chain” (as properly construed), much less two. See EX2016 (Second Sutton Declaration) at ¶¶ 62–64. Specifically, the scFv-Fc polypeptide lacks a CH1 domain, and the empty-Fc polypeptide lacks both a VH domain and a CH1 domain. *Id.* at ¶ 66. Thus, neither “half” of the Lazar scFv-Fc/empty-Fc construct is a “heavy chain” as required by claim 1. *Id.* Indeed, the Lazar inventors themselves did not call the scFv-Fc/empty-Fc construct an

antibody or suggest that it contained “heavy chains.” *See id.* at ¶¶ 67–69. And Dr. Presta admits that the empty-Fc half of the construct lacks a variable region. *See* EX2012 (Presta Transcript) at 78:10–20.

In an attempt to overcome these deficiencies, Dr. Presta resorts to picking and choosing certain substitutions in the scFv-Fc/empty-Fc construct—out of well over one hundred such substitutions—and combining them with a separate, general reference to IgG antibodies. *See* EX1004 Figs. 5–7; EX2016 (Second Sutton Declaration) at ¶¶ 62, 71–72. Dr. Presta's picking and choosing is not an anticipation. *See id.* Lazar uses only particular Fc substitutions in any antibody heavy chains, and none of them are neutral to charged substitutions of the kind required by claim 1. *See* EX2016 (Second Sutton Declaration) at ¶ 71.

Similarly, a POSA would not immediately “envisage” the invention of claim 1 based on the substitutions listed in Figures 5 to 7 of Lazar for the scFv-Fc/empty-Fc construct and the separate discussion in Lazar of full-length antibodies. Indeed, as discussed below, Lazar's full-length antibodies do not require any heterodimerization modifications and Lazar does not disclose any of them as having neutral to charged Fc substitutions.

For all these reasons, Lazar does not anticipate claim 1.

ii. Claims 7, 21, 22, 24, 26, 28, 30, And 32

Claims 7, 21, 22, 24, 26, 28, 30, and 32 depend from claim 1 and contain

additional limitations. *See id.* at ¶ 159. Because Lazar does not disclose all of the limitations of claim 1, Lazar likewise does not disclose all of the limitations of these dependent claims. *Id.* Moreover, Lazar does not disclose the additional limitations found in many of these dependent claims.

For claim 7, Lazar does not disclose the additional limitation that “the presence of contaminating homodimers is less than 5%.” *See id.* at ¶¶ 166–167. Indeed, none of the Lazar experiments using a scFv-Fc/empty-Fc construct with neutral to charged substitutions comes close to this required purity. *See id.* at ¶¶ 111, 168; EX1004 (Lazar) at Figures 5–7.

For claims 21, 24, 28, and 32, Lazar does not disclose the additional limitation of using any of the scFv-Fc/empty-Fc construct neutral to charged substitutions in a “human IgG” or “human IgG1” antibody, much less in a “pharmaceutical composition.” *See* EX2016 (Second Sutton Declaration) at ¶¶ 62–63, 65, 70–71, 181–182, 185–186.

For at least these reasons, Lazar does not anticipate any of claims 7, 21, 22, 24, 26, 28, 30, and 32.

iii. Claim 26

For at least the reasons discussed above with respect to claim 1, Lazar does not anticipate claim 26. *Id.* at ¶ 21.

iv. Claim 30

For at least the reasons discussed above with respect to claim 1, Lazar does not anticipate claim 30. *Id.*

B. Cabrera Does Not Anticipate Any Of The Challenged Claims

Cabrera does not disclose all of the elements of any of the Challenged Claims, much less disclose them arranged as they are in those claims. *See* EX2016 (Second Sutton Declaration) at ¶¶ 73–86. Cabrera therefore does not anticipate any of the claims for which it is asserted. *Id.* at ¶ 73; Paper 13 at 9.

i. Claim 1

Cabrera does not disclose producing a heterodimeric antibody using neutral to charged amino acid residue substitutions in the CH3 domains of heavy chains that interact to produce the antibody. *See* EX2016 (Second Sutton Declaration) at ¶ 73.

As discussed above, the ordinary and customary meaning of the “interacts” limitation has two requirements: (1) that the two substituted residues interact; and (2) that the interaction of those residues produces a heterodimeric antibody. *See id.* at ¶¶ 44–58. To anticipate, it is not enough for a reference to disclose a general interaction of the CH3-CH3 interface. *Id.* at ¶ 45. Indeed, Dr. Presta admitted as much during cross-examination. *See id.* at ¶ 47.

Cabrera discloses numerous IgG1 variants. *See id.* at ¶ 74; EX1005 (Cabrera) at Tables 1, 6–7. Not one of those variants, however, comprises neutral to charged

amino acid residue substitutions that interact to produce a heterodimeric antibody. EX2016 (Second Sutton Declaration) at ¶ 74. Indeed, the data in Cabrera shows that the only disclosed neutral to charged amino acid substitutions do not interact to produce—**and actually disrupt production of**—a heterodimeric antibody. *Id.*

Dr. Presta discusses Cabrera variant AZ34, which comprises neutral to charged amino acid residue substitutions S400E/N390R (among other substitutions). *Id.* at ¶ 75. The data in Cabrera, however, shows that these substitutions in AZ34 do not interact to produce a heterodimeric antibody and actually disrupt such production. *See id.* at ¶¶ 76–78. **First**, AZ34 has the same reported heterodimeric purity as AZ33—a variant with all of the same substitutions **except** S400E/N390R. *See id.* at ¶¶ 75–76; EX2012 (Presta Transcript) at 123:23 – 126:12. It follows that because the heterodimeric purity is the same between AZ33 and AZ34, substitutions S400E and N390R are not producing a heterodimeric antibody. EX2016 (Second Sutton Declaration) at ¶¶ 76, 83; EX2012 (Presta Transcript) at 125:23 – 126:12. **Second**, AZ33 has a higher melting temperature than AZ34, meaning that the S400E and N390R substitutions in AZ34 actually **weakened** the overall interaction between the two CH3 domains. EX2016 (Second Sutton Declaration) at ¶¶ 77, 81–85; EX1005 (Cabrera) at Tables 1, 3–4.

A POSA in 2012 would have understood the significance of this data in Cabrera and not been surprised by it. *See* EX2016 (Second Sutton Declaration) at

¶¶ 77–78. Specifically, a POSA would have known from the literature that wild-type residues S400 and N390 interact with each other at the edge of the CH3 domain interface to form a strong hydrogen bond between their side-chains. *Id.* A POSA would have understood that this hydrogen bond cannot form between the side-chains of the S400E and N390R substitutions for a simple reason: the substituted side-chains are larger. *See id.* As a result of their size, these side-chains are fully exposed to water, instead of only partially exposed to water like the wild-type side-chains in S400 and N390. *See id.* This full exposure to water prevents interaction for heterodimerization between the S400E and N390R substituted residues, much less an interaction that produces a heterodimeric antibody as required by claim 1. *See id.*

Even if a POSA did not understand why the S400E/N390R substitutions in AZ34 were destabilizing, they would have no doubt that they were destabilizing given the lower melting temperature for AZ34 as compared to AZ33. *See id.* at ¶¶ 77–79. In its institution decision, the Board noted a standard for melting temperature set by the Cabrera reference. *See id.* at ¶ 79. Respectfully, any such standard is irrelevant to claim 1. *Id.* The relevant question for claim 1 is whether the identified substitutions interact to produce a heterodimeric antibody. *See id.* at ¶¶ 80–81. When a variant with the identified substitutions melts at a lower temperature than a variant that is identical but for the identified substitutions, that is conclusive proof

that the identified substitutions are not interacting to produce a heterodimeric antibody. *See id.* at ¶ 81–82, 85. That is dispositive with respect to claim 1. Cabrera does not anticipate it. *See id.* at ¶ 86.

ii. Claims 2, 7, 21, 22, 24, 28, And 32

Claims 2, 7, 21, 22, 24, 28, and 32 depend from claim 1 and contain additional limitations. *See id.* at ¶ 159. Because Cabrera does not disclose all of the limitations of claim 1, Cabrera likewise does not disclose all of the limitations of these dependent claims. *Id.* Moreover, Cabrera does not disclose the additional limitations found in certain of the dependent claims.

For example, for claim 28, Cabrera does not disclose the additional limitation that the claimed heterodimeric antibody be part of a “pharmaceutical composition.” Cabrera requires at least three substitutions per antibody heavy chain, and the variants with neutral to charged substitutions have four substitutions per heavy chain. *See* EX1005 (Cabrera) at Tables 1, 6–7. As Dr. Sutton explains, and Dr. Presta agreed during cross-examination, modifying the Fc region can impact biological function, including antibody half-life and cell-mediated cytotoxicity. EX2016 (Second Sutton Declaration) at ¶ 16; EX2012 (Presta Transcript) at 42:1–16. Cabrera has no disclosure that introducing all of its changes to the Fc region would be suitable for a therapeutic antibody.

iii. Claims 26 And 27

For at least the reasons discussed above with respect to claim 1, Cabrera does not anticipate either of claims 26 or 27. EX2016 (Second Sutton Declaration) at ¶ 21.

iv. Claims 30 And 31

For at least the reasons discussed above with respect to claim 1, Cabrera does not anticipate either of claims 30 or 31. *Id.*

VII. OBVIOUSNESS ANALYSIS

The *Graham* factors analysis for determining alleged obviousness requires: (1) determining the scope and content of the prior art; (2) ascertaining the differences between the prior art and the claims at issue; (3) resolving the level of ordinary skill in the art; and (4) considering objective evidence indicating obviousness or non-obviousness (“secondary considerations”). See *KSR Int’l Co. v. Teleflex Inc.*, 550 U.S. 398, 406 (2007)(citing *Graham v. John Deere Co.*, 383 U.S. 1 (1966)).

Dr. Presta did not perform this analysis, including because he ignored the objective evidence *Graham* factor entirely. See, e.g., EX1002 (Presta Declaration) at ¶¶ 185, 188, 206 (alleged “Motivation to Combine and Reasonable Expectation of Success”). The Board must consider any objective evidence of non-obviousness, i.e., secondary considerations, because such evidence can establish that “an invention appearing to have been obvious in light of the prior art was not,” and may

be “the most probative and cogent evidence in the record.” *Ex Parte Whirlpool Corp.*, 2013-008232, Decision On Appeal, at 11–12 (P.T.A.B. October 30, 2013) (informative) (quoting *Apple Inc. v. Int’l Trade Comm’n*, 725 F.3d 1356, 1366 (Fed. Cir. 2013)); *see also Leo Pharm. Prods., Ltd. v. Rea*, 726 F.3d 1346, 1358 (Fed. Cir. 2013)(explaining that obviousness is not established by technical comparisons in isolation, but through a holistic inquiry that must account for objective indicia); *Ex parte Thompson*, 2011-011620, Decision On Appeal, at 5 (P.T.A.B. March 21, 2014) (informative) (“objective evidence of secondary considerations pertaining to nonobviousness must be considered”).

An obviousness determination under the *Graham* factors further requires a finding that a POSA would have been motivated to modify or combine the cited references to arrive at the claimed inventions and would have had a reasonable expectation of success in doing so. *See Regents of Univ. of California v. Broad Inst., Inc.*, 903 F.3d 1286, 1291 (Fed. Cir. 2018); *Intelligent Bio-Systems, Inc. v. Illumina Cambridge, Ltd.*, 821 F.3d 1359, 1367 (Fed. Cir. 2016); *Hulu, LLC v. Sound View Innovations, LLC*, IPR2018-00582, Paper 34, at 8–9 (P.T.A.B. August 5, 2019) (informative) (no claims unpatentable, insufficient reason to combine references).

Under this well-settled precedent, not one of the Challenged Claims is rendered obvious by Lazar, whether alone or in view of Arathoon and/or Cabrera. A POSA had no reason to modify or combine these references to arrive at the

Challenged Claims, much less any reasonable expectation of success in doing so. The Challenged Claims are further supported by various secondary considerations, including that the claimed inventions overcame skepticism and teaching away to provide unexpected results.

A. The *Graham* Factors

i. Scope And Content Of The Prior Art

(1) Lazar

As Dr. Sutton explains, the experiments in Lazar were directed to creating “alternative” bispecific moieties that allegedly improved upon “full length antibody-like formats.” EX2016 (Second Sutton Declaration) at ¶¶ 90–91; EX1004 (Lazar) at ¶ 7. As Lazar explains, however, these alternative formats do not require “heterodimeric Fc variants.” EX2016 (Second Sutton Declaration) at ¶ 91; EX1004 (Lazar) at ¶ 108.

As discussed above, Lazar used the scFv-Fc/empty-Fc format for screening purposes only. EX2016 (Second Sutton Declaration) at ¶ 92. The neutral to charged substitutions tested in the scFv-Fc/empty-Fc construct were *never* used in Lazar’s “alternative” bispecific moieties. *Id.* The only Fc substitutions used in the “alternative” bispecific moieties were Y349T/T394F and S364H/F405A, which do not include two neutral to charged substitutions. *See id.* at ¶¶ 92, 95. And no Fc substitutions of any kind were tested in “full length antibody-like formats,” including

in an IgG or IgG1 antibody. *Id.* at ¶ 92.

Fatal to Xencor's obviousness arguments, Lazar reported 0% contaminating homodimers for the charge-swap variant K370D/K392D/K409D and E356K/E357K/D399K. *Id.* at ¶ 96; EX1004 (Lazar) at Figure 6. Given that level of purity, a POSA would have had no reason to select for modification/combination any of the neutral to charged substitutions in Lazar's scFv-Fc/empty-Fc construct, which reported 12% or greater contaminating homodimers in Figures 5 to 7. EX2016 (Second Sutton Declaration) at ¶¶ 96, 111, 114, 118; EX1004 (Lazar) at Figure 6.

Notably, Lazar does not include charge-swap variant K370D/K392D/K409D and E356K/E357K/D399K—with its 100% heterodimeric purity—among its “preferred” or “most preferred” Fc heterodimerization options. EX2016 (Second Sutton Declaration) at ¶ 110. As Dr. Sutton explains, a POSA would notice this omission and focus on Lazar's heterodimeric purity data over its Fc heterodimerization lists. *Id.* at ¶¶ 112–114.

(2) Cabrera

As discussed above, Cabrera discloses numerous Fc variants. *See id.* at ¶ 97. Certain of these variants reportedly have over 90 to 95% heterodimeric purities, but none of them contains neutral to charged substitutions that meet the “interacts” limitation of the Challenged Claims. *Id.* at ¶ 86. Notably for secondary considerations,

none of Cabrera's variants are as stable as a wild-type antibody. *Id.* at ¶ 98.

(3) Arathoon

Arathoon discloses production of multi-specific antibodies using the knob-into-hole with disulfide bonds approach, as well as use of a common light chain. *Id.* at ¶ 99. Arathoon's common light chain will "pair with each of the variable heavy chains of the multi-specific antibody." *Id.*; EX1006 (Arathoon) at 6:24–26.

Dr. Presta agreed during cross-examination that Arathoon does not disclose heterodimerization via charge engineering. EX2012 (Presta Transcript) at 96:22–25; EX2016 (Second Sutton Declaration) at ¶ 99. Dr. Presta further admitted that Arathoon's common light chain "has nothing to do with the formation of the heterodimer." EX2012 (Presta Transcript) at 59:11–13; EX2016 (Second Sutton Declaration) at ¶ 99.

ii. Differences Between The Prior Art And The Challenged Claims

(1) Lazar

As discussed above and in Dr. Sutton's declarations, there are multiple differences between Lazar and the Challenged Claims. For example, Lazar does not disclose a heterodimeric antibody comprising two "heavy chains" (as properly construed) having neutral to charged substitutions. EX2016 (Second Sutton Declaration) at ¶ 100. Nor does Lazar disclose a heterodimeric antibody wherein

“each variable region” of the antibody “heavy chains” recognizes a different target epitope, as required by dependent claims 8 through 20. *See id.* at ¶¶ 173–175. Lazar similarly does not disclose that neutral to charged substitutions (in any construct) achieve the freedom from “contaminating homodimers” required by claim 7. *See id.* at ¶¶ 111, 166–168. Lazar further does not disclose that neutral to charged substitutions (in any construct) can be suitable for a “pharmaceutical composition” as required by claim 32 or part of a “human IgG” or “human IgG1” as required by claims 21, 24, and 28. *See id.* at ¶¶ 182–183, 185–186.

(2) Cabrera

As discussed above and in Dr. Sutton's declarations, there are several differences between Cabrera and the Challenged Claims. Most importantly, Cabrera does not disclose neutral to charged substitutions that meet the “interacts” limitation of claim 1. *Id.* at ¶ 101. Nor does Cabrera disclose any antibodies containing such substitutions suitable for inclusion in a “pharmaceutical composition,” as required by claim 28. *See id.* at ¶ 184.

(3) Arathoon

As discussed above and in Dr. Sutton's declarations, there are multiple differences between Arathoon and the Challenged Claims. For example, Arathoon discloses a totally different approach to heterodimerization. *See id.* at ¶ 102. As a result, Arathoon does not disclose anything about charge engineering, much less

disclose neutral to charged substitutions that interact to produce a heterodimeric antibody. *See id.*

iii. Level Of Ordinary Skill In The Art

See Section III, above.

iv. Secondary Considerations Of Non-Obviousness

Multiple secondary considerations support the non-obviousness of the Challenged Claims. The Board can and should accord substantial weight to these secondary considerations because there is a “legally and factually sufficient connection”—*i.e.*, a nexus—“between the evidence and the patented invention.” *See Fox Factory, Inc. v. SRAM, LLC*, 944 F.3d 1366, 1373 (Fed. Cir. 2019).

(1) Teaching Away / Skepticism

The field in 2012 was skeptical about promoting heterodimerization using neutral to charged substitutions. For example, the Gunasekaran Paper (EX1012) taught away from modifying the neutral residues of the hydrophobic core—the precise subject matter of the Challenged Claims. EX2016 (Second Sutton Declaration) at ¶ 153. This warning was so well known that Lazar and Cabrera incorporate the Gunasekaran Paper in its entirety by reference. *Id.* at ¶ 18; EX1004 (Lazar) at ¶ 125; EX1005 (Cabrera) at 129. Adding to the skepticism and teaching away, Lazar disclosed that neutral to charged substitutions in its scFv-Fc/empty-Fc construct led to a significant percentage of contaminating homodimers. *See* EX2016

(Second Sutton Declaration) at ¶¶ 111, 153; EX1004 (Lazar) at Figure 6. Similarly, Cabrera disclosed that neutral to charged substitutions lower the melting temperature of variants that are the same but for those substitutions, *i.e.*, these substitutions disrupt the production of a heterodimeric antibody. EX2016 (Second Sutton Declaration) at ¶¶ 84–85. Arathoon has no bearing on any charge engineering approach to heterodimerization and, as a result, does nothing to lessen the skepticism and teaching away discussed above. *See id.* at ¶¶ 99, 153.

(2) Unexpected Results

The Challenged Claims produced unexpected results, as shown by the specification and other evidence. *See id.* at ¶¶ 154–157. For example, the specification explains that due to the additional charge-charge interaction the heterodimeric antibodies of the invention are generally more stable than their wild-type counterparts. *See id.* at ¶ 155; EX1001 ('286 Patent) at 18:10–20. This stands in stark contrast with Cabrera, which reports that its neutral to charged substitutions actually lowered the melting temperature of the variants containing them. *See* EX2016 (Second Sutton Declaration) at ¶¶ 84–85. The specification further explains that the heterodimeric antibodies of the invention have very low levels of contaminating homodimers, reaching the point where such homodimers “are essentially absent.” EX1001 ('286 Patent) at 21:10–20. This stands in stark contrast with Lazar, which reports significant contaminating homodimers for any scFv-

Fc/empty-Fc construct with neutral to charged substitutions. See EX1004 at Figs 5–7.

B. The Challenged Claims Are Not Obvious Over Lazar

As discussed above, Lazar does not disclose various elements of the Challenged Claims. Moreover, as Dr. Sutton explains in his Second Declaration, a POSA did not have a reason to modify any of the disclosures in Lazar to arrive at any of the Challenged Claims, much less a reasonable expectation of success in doing so. In fact, Lazar teaches away from modifying its disclosures to arrive at the Challenged Claims, including because of: (1) the significant percentage of contaminating homodimers reported for the neutral to charged substitutions in its scFv-Fc/empty-Fc construct; (2) its failure to use any neutral to charged substitutions in any of its “alternative” antibody moieties or any full-length antibodies; and (3) its incorporation of the Gunasekaran Paper (EX1012) in its entirety by reference.

i. A POSA Would Not Have A Reason To Modify Lazar To Achieve The Challenged Claims With A Reasonable Expectation Of Success

(1) Claim 1

A POSA did not have a reason to modify Lazar to arrive at the subject matter of claim 1 with a reasonable expectation of success of doing so.

First, Lazar reports a significant percentage of contaminating homodimers for all of the neutral to charged substitutions in its scFv-Fc/empty-Fc construct, while

reporting 100% heterodimeric purity for a charge-swap variant. *See id.* at ¶¶ 108–111. Given this disparity, a POSA had no reason to modify the neutral to charged substitutions in Lazar's scFv-Fc/empty-Fc construct to achieve claim 1, as opposed to focusing on the charge-swap variant shown to have 100% heterodimeric purity. *Id.* at ¶ 108.

Second, as of 2012, a POSA would have known of challenges with introducing heterodimer variants from fragments like the Lazar scFv-Fc/empty-Fc construct to an antibody with “heavy chains.” *See id.* at ¶ 119. These challenges are attributable to, *e.g.*, differences in molecular weight and conformation between different formats. *Id.* This potential disconnect is acknowledged by Lazar Table 2, which specifically discloses the “[m]ost preferred CH3 domain variants that favor **Fc heterodimerization**” as distinct from heavy chain heterodimerization or antibody heterodimerization. *Id.* at ¶ 112; EX1002 (Presta Declaration) at ¶ 81 (emphasis added). This is another reason a POSA had no motivation to modify the neutral to charged substitutions in Lazar's scFv-Fc/empty-Fc construct to achieve claim 1, much less have a reasonable expectation of success in doing so.

Third, Lazar does not itself use any neutral to charged substitutions in any of its “alternative” antibody moieties or any full-length antibodies. EX2016 (Second Sutton Declaration) at ¶ 117. A POSA would not have a reason to modify the neutral to charged substitutions in Lazar's scFv-Fc/empty-Fc construct when the Lazar

inventors did not do so themselves, much less have a reasonable expectation of success in doing so. *See id.*

Fourth, Lazar incorporated the Gunasekaran Paper in its entirety by reference, including its warning not to modify the neutral residues in the hydrophobic core of the CH3 domain due to known negative impacts on protein folding and stability. *Id.* at ¶¶ 18, 104–107; EX1004 (Lazar) at ¶ 125; EX1012 (Gunasekaran Paper) at 4. Given this incorporated warning, a POSA had no reason to modify the neutral to charged substitutions in Lazar's scFv-Fc/empty-Fc construct to arrive at claim 1, much less a reasonable expectation of success in doing so. *See* EX2016 (Second Sutton Declaration) at ¶¶ 106–108.

For all these reasons, a POSA would not have been motivated to modify Lazar to achieve the subject matter of claim 1, much less have a reasonable expectation of success in doing so.

(2) Claims 2, 7–24, 28, And 32

Claims 2, 7–24, 28, and 32 depend from claim 1 and contain additional limitations. *Id.* at ¶ 159. For the same reasons as independent claim 1, a POSA did not have a motivation to modify Lazar to arrive at any of these dependent claims, much less with a reasonable expectation of success. *Id.* Moreover, a POSA did not have a reason to modify Lazar further to arrive at the additional limitations found in many of these dependent claims with a reasonable expectation of success. *Id.*

For claim 2, a POSA had no reason to modify Lazar's scFv-Fc/empty-Fc construct—which has only one variable region—to meet the additional requirement of having a “common light chain.” *Id.* at ¶¶ 160–162. A POSA similarly had no reasonable expectation of success in doing so: Lazar's scFv-Fc/empty-Fc construct lacks the two heavy chain variable regions needed for common light chain pairing. *Id.*

For claim 7, a POSA had no reason to modify Lazar's scFv-Fc/empty-Fc construct—which reports significant contaminating homodimers for neutral to charged substitutions, while reporting 100% heterodimeric purity for charge-reversal substitutions—to meet the additional requirement of having less than 5% contaminating homodimers. Indeed, as shown by Lazar's own data, the neutral to charged substitutions in its scFv-Fc/empty-Fc construct have from 12% to 93% contaminating homodimers. *See id.* at ¶¶ 111, 166–168; EX1004 (Lazar) at Figures 5 to 7. Given this data, a POSA had no reason to modify the neutral to charged substitutions in Lazar's scFv-Fc/empty-Fc construct to achieve claim 7, much less have a reasonable expectation of success in doing so. *See id.*

In this regard, a POSA would rely on the experimental heterodimer data in Lazar's Figures 5 to 7 rather than on Lazar's lists of “preferred” or “most preferred CH3 domain variants that favor Fc heterodimerization.” EX2016 (Second Sutton Declaration) at ¶¶ 112–114. Indeed, the inventors of Lazar themselves ignored these

lists for their “alternative” bispecific format and any full-length antibodies. *See id.* at ¶ 117. For example, Lazar used only one substitution—Y349T/T394F and S364H/F405A (“TF-HA”)—in its “alternative” bispecific moieties. *Id.* Neither the TF-HA variant—nor the K370D/K392D/K409D and E356K/E357K/D399K variant, which provides 100% heterodimeric purity—are on the lists of “preferred” or “most preferred variants that favor Fc heterodimerization.” *Id.* at ¶¶ 110, 117. Given these omissions, a POSA would have no reason to rely on the Fc heterodimerization lists to modify the neutral to charged substitutions in Lazar’s scFv-Fc/empty-Fc construct to achieve claim 7, much less have a reasonable expectation of success in doing so. *See id.* at ¶¶ 113, 172.

For claims 8 – 20, a POSA had no reason to modify Lazar’s scFv-Fc/empty-Fc construct—which has no heavy chains and only one variable region—to meet the additional requirement that “each variable region of the 1st and 2nd antibody heavy chains recognizes a different target epitope.” *See id.* at ¶¶ 173–175. A POSA similarly had no reasonable expectation of success in doing so: Lazar’s scFv-Fc/empty-Fc construct lacks the two heavy chain variable regions needed for modification such that “each variable region of the 1st and 2nd antibody heavy chains recognizes a different target epitope.” *Id.* at ¶ 175.

For claims 21, 24, 28 and 32, a POSA had no reason to modify Lazar’s scFv-Fc/empty-Fc construct—which is part murine, has no heavy chains, and has only

one variable region—to meet the additional limitations that the claimed antibody be part of a “pharmaceutical composition” or “human IgG.” *See id.* at ¶¶ 181–182, 184–186. A POSA similarly had no reasonable expectation of success in doing so: there is nothing in Lazar to indicate that such modifications are possible for the scFv-Fc/empty-Fc construct. *See id.*

(3) Claims 26 And 27

As discussed above for claims 1 and 2, a POSA had no reason to modify Lazar to arrive at claims 26 and 27 with a reasonable expectation of success. *Id.* at ¶ 21.

(4) Claims 30 And 31

As discussed above for claims 1 and 2, a POSA had no reason to modify Lazar to arrive at claims 30 and 31 with a reasonable expectation of success. *Id.*

C. The Challenged Claims Are Not Obvious Over Lazar View Of Arathoon

Lazar and Arathoon each fail to disclose various elements of the Challenged Claims. *See id.* at ¶¶ 100, 102. As Dr. Sutton explains in his Second Declaration, a POSA would not have been motivated to combine the teachings of Lazar and Arathoon to arrive at any of the Challenged Claims with a reasonable expectation of success in doing so. *See id.* at ¶¶ 103–128. Indeed, Lazar and Arathoon use totally different approaches to heterodimerization. *See id.* at ¶¶ 124–125. A POSA would have had no reason to combine them, much less a reasonable expectation of success

in making substitutions that satisfy the “interacts” limitation in the presence of knob-into-hole substitutions. *See id.* at ¶ 126.

i. A POSA Would Not Be Motivated To Combine Lazar And Arathoon To Achieve The Challenged Claims With A Reasonable Expectation Of Success

(1) Claim 1

A POSA would not have been motivated to combine Lazar and Arathoon to arrive at claim 1, much less have a reasonable expectation of success in doing so. In fact, 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. *See id.* at ¶¶ 123–126. For example, the Lazar scFv-Fc/empty-Fc construct and Arathoon knob-into-hole moieties each change the CH3 domain in different ways, while the Lazar “alternative” bispecific moieties seek to add an extra variable region where Arathoon adds a disulfide bond. *See id.*

Moreover, with Lazar's charge-reversal constructs reaching 100% heterodimeric purity and Arathoon's knob-into-hole with disulfide bond moieties reaching 95% heterodimeric purity, a POSA had no reason to try to harmonize their structural incompatibilities to combine them. *See id.*; Arathoon (EX1006) at 43, Tables 3–4. The heterodimeric purity of each approach was already sufficient. *See* EX2016 (Second Sutton Declaration) at ¶¶ 123–126.

In any event, a POSA would not reasonably expect success in combining Lazar and Arathoon to achieve claim 1. As discussed above, by incorporating the Gunasekaran Paper (EX1012), Lazar warns of the negative effects on protein folding and stability of disrupting the hydrophobic core. Arathoon does nothing to assuage that warning. Indeed, Arathoon discloses only neutral to neutral or charged to neutral substitutions. *See id.*

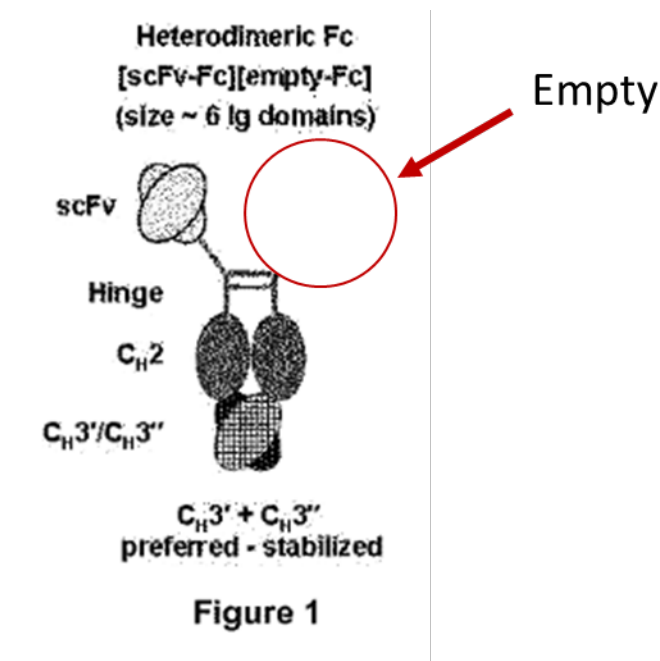
Based on Lazar and Arathoon, a POSA would have no reasonable expectation of success in using neutral to charged substitutions in heavy chain CH3 domains that interact with each other to produce heterodimeric antibodies. *See id.* As discussed above, Lazar teaches away from that approach by incorporating the Gunasekaran Paper (EX1012) and reporting poor heterodimeric purity data for such changes in its scFv-Fc/empty-Fc construct. Nothing in Arathoon contradicts that teaching.

(2) Claims 2, 7–24, 28, And 32

Claims 2, 7–24, 28, and 32 depend from claim 1 and contain additional limitations. For the same reasons as independent claim 1, a POSA did not have a motivation to combine Lazar and Arathoon to arrive at any of these dependent claims, much less with a reasonable expectation of success. Moreover, a POSA did not have a reason to combine Lazar and Arathoon further to arrive at the additional limitations found in several of these dependent claims with a reasonable expectation of success. *See id.* at ¶ 159.

For claim 2, a POSA had no reason to combine Lazar's scFv-Fc/empty-Fc construct—which has only one variable region—with Arathoon to meet the additional requirement of having a “common light chain.” *See id.* at ¶¶ 164–165. A POSA similarly had no reasonable expectation of success in doing so: Lazar's scFv-Fc/empty-Fc construct lacks the two heavy chain variable regions needed for common light chain pairing. *See id.*

As discussed above, 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 heterodimeric antibody.” *Id.* at ¶ 99; EX1006 (Arathoon) at 6:24–26. Lazar's scFv-Fc/empty-Fc construct, however, does not have two heavy chain variable regions to which a common light chain can attach:



See EX1004 (Lazar) at Figure 1; EX2016 (Second Sutton Declaration) at ¶¶ 93–94.

Lazar's "alternative" bispecific constructs (*i.e.*, mAb-Fv, mAb-Fab, Fab-Fv, and Fab-Fab) similarly do not include two different variable regions to which a common light chain can attach to enhance the production of the "desired heteromultimeric antibody." See EX2016 (Second Sutton Declaration) at ¶ 94. As Dr. Sutton explains, these alternative constructs do not need a common light chain to enhance the production of bispecific antibodies because they do not suffer from the same mispairing issues as traditional bispecific antibodies. See *id.*

For claim 7, a POSA had no reason to combine Lazar's scFv-Fc/empty-Fc construct—which reports significant contaminating homodimers for neutral to charged substitutions, while reporting 100% heterodimeric purity for charge-reversal substitutions—with Arathoon's knob-into-hole with disulfide bond moieties to meet the additional requirement of having less than 5% contaminating homodimers. Indeed, Arathoon reported heterodimeric purity for its moieties was lower than Lazar's reported 100% heterodimeric purity for charge-reversal substitutions. *Id.* at ¶ 123. And as Dr. Presta admitted during his cross-examination, Arathoon's common light chain does **not** improve heterodimer yield; it merely reduces the number of possible dimers. *Id.* at ¶ 99; EX2012 (Presta Transcript) at 59:6–13. Given these facts, a POSA had no reason to combine the neutral to charged substitutions in Lazar's scFv-Fc/empty-Fc construct with any of the Arathoon

disclosures to achieve claim 7, much less have a reasonable expectation of success in doing so. *See* EX2016 (Second Sutton Declaration) at ¶¶ 123 –126.

(3) Claims 26 And 27

For at least the reasons discussed above for claims 1 and 2, a POSA would not have been motivated to combine Lazar and Arathoon to arrive at claims 26 and 27 with a reasonable expectation of success. *Id.* at ¶ 21.

(4) Claims 30 And 31

For at least the reasons discussed above for claims 1 and 2, a POSA would not have been motivated to combine Lazar and Arathoon to arrive at claims 30 and 31 with a reasonable expectation of success. *Id.*

ii. Even If Combined, Lazar And Arathoon Together Fail To Disclose All Elements Of The Challenged Claims

Even if combined using hindsight, Lazar and Arathoon still fail to disclose all of the elements of the challenged claims. *See id.* at ¶ 127. As discussed above, Lazar does not disclose neutral to charged amino acid residue substitutions in the CH3 domains of “heavy chains.” *See id.* Arathoon similarly does not disclose any such substitutions. *See id.* Instead, Arathoon uses the knob-into-hole approach to promote heterodimerization, potentially with a disulfide bond. *Id.* at ¶ 99. As a result, even if combined, Lazar and Arathoon do not disclose using neutral to charged amino acid residue substitutions in the CH3 domains of “heavy chains” to

produce a heterodimeric antibody. *See id.* at ¶ 127. Their combination thus cannot render any of the Challenged Claims obvious. *See Univ. of Strathclyde v. Clear-Vu Lighting LLC*, 17 F.4th 155, 160 (Fed. Cir. 2021) (citing *PAR Pharm., Inc. v. TWI Pharms., Inc.*, 773 F.3d 1186, 1194 (Fed. Cir. 2014)).

D. The Challenged Claims Are Not Obvious Over Lazar In View Of Arathoon And Cabrera

As discussed above, Lazar, Arathoon, and Cabrera each fail to disclose various elements of the Challenged Claims. Moreover, as Dr. Sutton explains in his Second Declaration, a POSA would not have been motivated to combine Lazar, Arathoon, and Cabrera to arrive at any of the Challenged Claims, much less with a reasonable expectation of success in doing so. *See* EX2016 (Second Sutton Declaration) at ¶¶ 129–130. Indeed, Lazar, Arathoon, and Cabrera have structural incompatibilities. *See id.* at ¶¶ 93–94, 119, 142, 161–163. Moreover, even if they were combined, these references still fail to disclose all of the elements of the Challenged Claims. Lazar, Arathoon, and Cabrera thus cannot render any of the Challenged Claims obvious.

i. A POSA Would Not Be Motivated To Combine Lazar, Arathoon, And Cabrera To Achieve The Challenged Claims With A Reasonable Expectation Of Success

(1) Claim 1

A POSA would not have been motivated to combine Lazar, Arathoon, and

Cabrera to achieve independent claim 1. As discussed above, a POSA would not combine Lazar and Arathoon. Nor would a POSA add Cabrera to any such combination. For example, as Dr. Sutton explains in his Second Declaration, Cabrera and Lazar disclose incompatible antibody formats. *Id.* at ¶ 142.

Moreover, a POSA would have no reason to believe that Lazar's scFv-Fc/empty-Fc construct or "alternative" bispecific moieties would benefit from the introduction of Cabrera's heterodimerization technology. *Id.* Those Lazar disclosures either already had reported 100% heterodimeric purity—for the charge-reversal scFv-Fc/empty-Fc construct—or did not need Fc heterodimerization—for the "alternative" bispecific moieties. *Id.* at ¶¶ 96, 115. Likewise, a POSA would have no reason to believe that Cabrera's IgG constructs would benefit from the introduction of the neutral to charged substitutions in Lazar's scFv-Fc/empty-Fc construct. *Id.* at ¶¶ 132–133. For example, Cabrera discloses that variant AZ34, which has neutral to charged substitutions, and AZ33, which does not have such substitutions, both achieve more than 95% heterodimer purity and that the AZ34 variant had a lower melting temperature indicating reduced stability. *See id.*

As Dr. Presta admitted during cross-examination, a POSA in 2012 would have been happy with 95% heterodimeric purity (and in fact would still be happy with that number today). *See id.*; EX2012 (Presta Transcript) at 126:19 – 127:2. A POSA would thus have been satisfied with charge-reversal scFv-Fc/empty-Fc constructs in

Lazar—with their reported 100% heterodimeric purity—or the Cabrera AZ33 IgG heterodimer—with its reported heterodimeric purity of greater than 95% and a higher melting temperature than AZ34. *See id.* Given this data, a POSA had no reason to combine Lazar and Cabrera to achieve claim 1.

A POSA would furthermore not reasonably expect success in combining Lazar, Arathoon, and Cabrera to achieve claim 1. For the reasons discussed above, a POSA would not arrive at claim 1 with a reasonable expectation of success based on Lazar alone or Lazar in combination with Arathoon. These references generally teach a POSA to use charge-reversal or knob-into-hole substitutions rather than neutral to charged substitutions, as in claim 1. This deficiency is not remedied by the addition of Cabrera. *See* EX2016 (Second Sutton Declaration) at ¶ 131. That is, Cabrera does not change or contradict the teachings of Lazar and Arathoon against using neutral to charged substitutions.

In fact, Cabrera corroborates Lazar and Arathoon in this respect and undermines any suggestion that neutral to charged substitutions will improve antibody heterodimerization and stability. *See id.* at ¶¶ 132–136. For example, as of April 20, 2012, a POSA would understand from Cabrera's data (*e.g.*, the AZ33 and AZ34 melting temperature and molecular dynamic simulation data) that neutral to charged substitutions in heavy chains **do not** interact to produce a heterodimeric antibody. *See id.* A POSA would have understood that the poor heterodimerization

data for Lazar's neutral to charged scFv-Fc/empty-Fc construct is likely due to this lack of interaction. *See id.* at ¶ 118.

Cabrera discloses another example—variants AZ28 and AZ29—that again show that neutral to charged substitutions do not interact to produce a heterodimeric antibody. *See id.* at ¶¶ 134–135. A POSA would understand from the melting temperatures for these variants—like the melting temperatures for AZ33 and AZ34—that the neutral to charged substitutions are actually disrupting the production of a heterodimeric antibody. *See id.*

Like Lazar, Cabrera also teaches away from the subject matter of claim 1 by incorporating the Gunasekaran Paper (EX1012) in its entirety by reference. *See id.* at ¶ 137; EX1005 (Cabrera) at 129. As discussed above, the Gunasekaran Paper discourages substitutions in the hydrophobic core of the CH3 domain. *See* EX2016 (Second Sutton Declaration) at ¶ 137. Indeed, a POSA would recognize that Cabrera's discouraging data for the AZ34 and AZ28 variants with neutral to charged substitutions comports with the Gunasekaran Paper's warning. *See id.* at ¶ 138.

(2) Claims 2, 7–24, 28, And 32

For at least the reasons discussed above with respect to claims 1, 2, 7–24, 28, and 32 for Lazar, Lazar and Arathoon, and/or Lazar, Arathoon, and Cabrera, a POSA would not have been motivated to combine Lazar, Arathoon, and Cabrera to achieve claims 2, 7–24, 28, and 32 or had a reasonable expectation of success in doing so.

As discussed above, a POSA in 2012 would understand that Lazar, Arathoon, and Cabrera each discourage use of neutral to charged substitutions in heavy chain CH3 domains. A POSA would understand this teaching away to extend to all antibodies of the Challenged Claims, including human IgG (claims 21, 24, and 32). *See id.* at ¶ 183. Based on these references, a POSA would also understand that the relatively unstable neutral to charged heterodimeric antibodies are likely unsuitable for use in pharmaceutical compositions (claim 28). *See id.* at ¶¶ 184–186.

(3) Claims 26 And 27

For at least the reasons discussed above for claims 1, 2, 26, and 27 for Lazar, Lazar and Arathoon, and/or Lazar, Arathoon, and Cabrera, a POSA would not have been motivated to combine Lazar, Arathoon, and Cabrera to achieve claims 26 and 27 with a reasonable expectation of success in doing so. *Id.* at ¶ 21.

(4) Claims 30 And 31

For at least the reasons discussed above for claims 1, 2, 30, and 31 for Lazar, Lazar and Arathoon, and/or Lazar, Arathoon, and Cabrera, a POSA would not have been motivated to combine Lazar, Arathoon, and Cabrera to achieve claims 30 and 31 with a reasonable expectation of success in doing so. *Id.*

ii. Even If Combined, Lazar And Arathoon Together Fail To Disclose All Elements Of The Challenged Claims

Even if combined using hindsight, Lazar, Arathoon, and Cabrera still fail to

disclose all of the elements of the Challenged Claims. *See id.* at ¶ 145. As discussed above, Lazar and Arathoon do not disclose all of the elements of the Challenged Claims. Cabrera does not provide the missing elements. *See id.* For example, not one of these references discloses substituted neutral to charged amino acid residues in the CH3 domains of “heavy chains” that “interact . . . to produce a heterodimeric antibody.” *See id.* at ¶¶ 146–150. Their combination thus cannot render any of the Challenged Claims obvious. *See Univ. of Strathclyde*, 17 F.4th at 160.

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

Dr. Presta's cross-examination showed that his declaration and opinions are unreliable and should carry no weight. Indeed, as cross-examination revealed, Dr. Presta spent shockingly little time drafting his 175-page declaration, did not review key documents like the prosecution history, and did not use the ordinary and customary meaning of the disputed claim terms in his analysis. *See* EX2012 (Presta Transcript) at 10:12 – 11:2 (spent “[p]robably 16” hours on this matter); 27:22 – 28:3, 111:3–25 (failure to review prosecution history); 35:3–17 (failure to use ordinary and customary meaning), 38:20–25 (failure to review extrinsic evidence). The Board should not credit his declaration or opinions in this proceeding.

A. Dr. Presta Used The Wrong Claim Constructions

Dr. Presta used the wrong claim constructions in his declaration. Although

Dr. Presta alleges he assigned the claim terms their “ordinary and customary meaning” in his declaration, his cross-examination revealed that he instead ascribed them a legally and factually erroneous, “context-dependent” meaning. *See id.* at 35:3–17. When asked, Dr. Presta could not explain the relevant “context” for any claim term or what “context-dependent” analysis he undertook. *Id.* at 38:3–14. What Dr. Presta could confirm was that he did not discern the “ordinary and customary meaning” of “heavy chain” to a POSA from papers, textbooks, or other evidence. *Id.* at 38:16–25.

Among multiple fatal flaws, Dr. Presta’s *ad hoc* claim construction failed to consider all of the claims. For example, as discussed above, Dr. Presta did not consider that dependent claim 8 is directed to “each” of the variable regions of the “heavy chains” of independent claim 1. *Id.* at 29:5 – 30:4. Dr. Presta also failed to closely consider the specification in his claim construction analysis. Instead, Dr. Presta admits that he focused mostly on the “wording in the claims.” *Id.* at 39:1–13.

Dr. Presta also admits that he failed to consider the prosecution history (EX1008) in his analysis. Despite it being one of Xencor’s exhibits, Dr. Presta admits that he had never seen the prosecution history prior to his cross-examination. *Id.* at 111:3–10. Had Dr. Presta reviewed the prosecution history, he would have learned that his *ad hoc* construction of “heavy chain” is contradicted by the narrowing amendment that added that term to the claims.

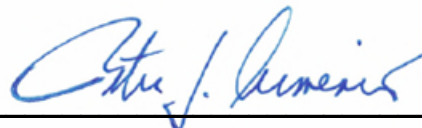
B. Dr. Presta's Description Of The Art Is Inconsistent

While Dr. Presta asserts that the claimed heterodimerization inventions were obvious in 2012, Dr. Presta represented to the USPTO that heterodimerization was difficult in 2013. For example, Dr. Presta stated in his own patent application filed in September 2013—well after the April 20, 2012, priority date here—that prior heterodimerization efforts “have been fraught with difficulty.” *Id.* at 130:5–21. This inconsistent statement undermines Dr. Presta's obviousness analysis.

IX. CONCLUSION

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

Dated: January 9, 2026



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

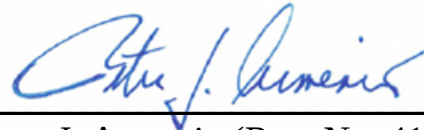
Counsel for Patent Owner Merus N.V.

CERTIFICATE OF COMPLIANCE

Pursuant to 37 C.F.R. § 42.24(d), the undersigned certifies that the foregoing **PATENT OWNER'S RESPONSE** contains, as measured by the word-processing system used to prepare this paper, 13,138 words. This word count does not include the items excluded by 37 C.F.R. § 42.24 as not counting towards the word limit.

Dated: January 9, 2026

Respectfully submitted,



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

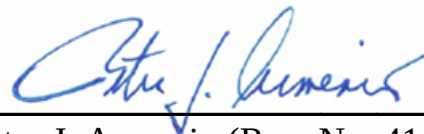
Counsel for Patent Owner Merus N.V.

CERTIFICATE OF SERVICE

I hereby certify that I caused to be served a true and correct copy of the foregoing: **PATENT OWNER'S 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 January 9, 2026, in its entirety on the following:

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

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



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

Counsel for Patent Owner Merus N.V.