

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

XENCOR, INC.,
Petitioner

v.

MERUS N.V.,
Patent Owner

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

PATENT OWNER'S SUR-REPLY

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EXHIBIT LIST

Exhibit Number	Description	Previously Submitted
EX2001	FDA Grants Accelerated Approval to Zenocutuzumab-zbco for Non-Small Cell Lung Cancer and Pancreatic Adenocarcinoma	X
EX2002	Petosemtamab Granted Breakthrough Therapy Designation by the U.S. FDA for 1L PD-L1 Positive Head and Neck Squamous Cell Carcinoma, Feb. 18, 2025	X
EX2003	Incyte and Merus Announce Global Strategic Research Collaboration to Discover and Develop Bispecific Antibodies, Dec. 21, 2026	X
EX2004	Lilly and Merus NV Announce Collaboration to Discovery Novel T-Cell Re-Directing Bispecific Antibodies, Jan. 19, 2021	X
EX2005	Memorandum Regarding Interim Processes for PTAB Workload Management, Mar. 26, 2025	X
EX2006	FAQs for Interim Processes for PTAB Workload Management, USPTO	X
EX2007	Xencor, Inc. Form 10-K for Fiscal Year ended Dec. 31, 2017	X
EX2008	Declaration of Brian J. Sutton, Ph.D. In Support of Patent Owner's Preliminary Response	X
EX2009	<i>Curriculum Vitae</i> of Brian J. Sutton, Ph.D.	X
EX2010	U.S. Patent No. 9,493,579	X
EX2011	14/155,344 Information Disclosure Statement, Jan. 14, 2014	X
EX2012	Transcript of Deposition of Leonard G. Presta, Ph.D., Dec. 5, 2025	X
EX2013	Presta Deposition Exhibit 4001 (Brian W. Matthews, Studies on Protein Stability with T4 Lysozyme)	X
EX2014	Presta Deposition Exhibit 4002 (Jin & Zhu, The Design and Engineering of IgG-Like Bispecific Antibodies)	X
EX2015	Presta Deposition Exhibit 4003 (U.S. Patent No. 10,351,631 to Keyt et al.)	X
EX2016	Second Declaration of Brian J. Sutton, Ph.D. In Further Support of Patent Owner's Response	X

EX2017	R. R. Porter, Structural Studies of Immunoglobins Nobel Lecture, DEP'T OF BIOCHEMISTRY, U. OF OXFORD, ENG. (Dec. 12, 1972)	X
EX2018	R. R. Porter, <i>The Structure of Antibodies</i> , 217 SCI. AM. 81 (1967).	X
EX2019	Roitt, Brostoff and Male, <i>Immunology</i> , 3rd Edition, Chapter 4, (1994).	X
EX2020	Thomas J. Kindt et al., Kuby Immunology Ch. 4 76-104 (6th ed. 2007). <i>Antibodies: Structure and Function</i>	X
EX2021	A.K. Abbas, <i>Cellular and Molecular Immunology</i> 476-505 (5th Ed. 2001).	X
EX2022	Branden and Tooze, <i>Introduction to Protein Structure</i> , Chapter 12, Garland Publishing, (1991).	X
EX2023	Krapp et al., <i>Structural Analysis of Human IgG-Fc Glycoforms Reveals a Correlation Between Glycosylation and Structural Integrity</i> , 325 J. MOL. BIOL. 979-989 (2003)	X

I. INTRODUCTION

The question of patentability turns largely on the construction of “heavy chain.” The Board noted in its Institution Decision that there was no record evidence that the ’286 patent uses the term “in any way deviating from its ordinary and customary meaning in the art.” Institution Decision, 17. That conclusion remains correct.

Xencor’s Reply does not dispute that Merus’s proposed construction 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 regions (CH) and the hinge region, reflects the ordinary and customary meaning of the term. Nor did it propose any alternative construction. Instead, relying exclusively on attorney argument, it claims that the plain meaning of “heavy chain” is inconsistent with the specification. But Xencor points to nothing in the specification evidencing a clear intent for this term to have something other than its standard meaning. Xencor’s arguments should be rejected.

Xencor’s argument concerning the term “interacts” fares no better. Xencor does not dispute that Merus’s proposed construction is consistent with the ordinary and customary meaning of the term. Instead, it asserts that “interacts” is not a limitation at all. Xencor’s position is contrary to caselaw and inconsistent with the claims and specification. Xencor’s backup position that Merus’s proposed

construction is unduly narrow is devoid of any expert support and should likewise be rejected.

Once the challenged claims are properly construed, Xencor is left cobbling together disparate pieces of prior art references and challenging Dr. Sutton's opinions with attorney argument. But nothing in the prior art discloses or even suggests the combination of specific limitations required by the claimed inventions.

II. THE BOARD SHOULD ADOPT MERUS'S PROPOSED CONSTRUCTIONS

A. The Board Should Reject Xencor's Arguments on "Heavy Chain"

Xencor does not contend that the ordinary and customary meaning of "heavy chain" is anything other than the definition proffered by Dr. Sutton and Merus. Indeed, Xencor offers no expert testimony or documentary evidence to rebut the standard literature references that Dr. Sutton cited in support of his opinion that the term "heavy chain" would have been well understood by a POSA to refer to the entire polypeptide chain from the N-terminus to the C-terminus. EX2016, ¶26; POR, 18-20.

Xencor's allegation that the ordinary and customary meaning "is not supported by the intrinsic record" (Reply, 2) is easily disposed of. Xencor argues first that Merus's construction renders other claim language superfluous. Reply, 2-3. According to Xencor, "Claim 1 recites that the 'antibody comprises two heavy chains with CH3 domains.'" *Id.* If "heavy chain" itself already required a CH3

domain, Xencor contends, then the “with CH3 domains” language would be superfluous. *Id.* But Xencor’s argument is based on a misleadingly truncated quote. The claim actually qualifies “two heavy chains with CH3 domains” with the language “***that are capable of forming an interface.***” (emphasis added). The limitation is not providing a structural requirement that the heavy chain include a CH3 domain, as Xencor asserts, but is providing a functional requirement that the CH3 domains – which are part of the “heavy chains” – “are capable of forming an interface.” Thus, unlike in *Wasica Fin. GmbH v. Cont’l Augo. Sys., Inc.*, 853 F.3d 1272, 1288 n.10 (Fed. Cir. 2017), cited by Xencor, Merus’s construction does not make any claim limitation “optional,” “redundant,” or “superfluous.”

Xencor next tries and fails to rebut Merus’s argument that dependent claim 8, which recites “wherein each variable region of the 1st and 2nd antibody heavy chains recognizes a different target epitope,” confirms that the “heavy chains” of claim 1 require variable regions. POR, 16-17; EX2016, ¶¶33-34. According to Xencor, claim 8 “simply limits the scope of such variable regions ***when they are present.***” Reply, 3 (emphasis in original). But Xencor fails to offer any evidence, or even any explanation, as to why its tortured reading of the claim language is correct, and there is nothing in claim 8 (or any other claim) that supports it. The simplest and correct reading of claim 8 is that it narrows the scope of claim 1 by requiring that each variable region of the heavy chains recognizes a different target epitope.

Xencor also points to the specification to support its argument, but the specification cannot be used to alter the plain meaning of a claim term unless the patentee has “clearly set forth a definition of the disputed claim term” *and* “clearly express[ed] an intent to define the term.” *GE Lighting Solutions, LLC v. AgiLight, Inc.*, 750 F.3d 1304, 1308-09 (Fed. Cir. 2014); *see also Thorner v. Sony Comput. Ent’mt Am. LLC*, 669 F.3d 1362, 1365-66 (Fed. Cir. 2012) (“It is not enough for a patentee to simply disclose a single embodiment or use a word in the same manner in all embodiments, the patentee must ‘clearly express an intent’ to redefine the term.”) There is simply nothing in the ’286 specification that provides a special meaning for “heavy chain,” let alone a clear intent to redefine the term.

The only thing Xencor points to in the specification to support its argument is the following statement:

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

EX1001, 5:17-26. Xencor asserts that one of the six references listed, Gunasekaran, includes CH3 domain mutations only in constructs that do not meet Merus’s

definition of “heavy chain.” Reply, 3-5. Xencor is incorrect on both the facts and the law.

To begin with, Xencor provides no expert support for its interpretation of Gunasekaran, and its attorneys’ argument has no evidentiary value. *See Icon Health & Fitness, Inc. v. Strava, Inc.*, 849 F.3d 1034, 1043 (Fed. Cir. 2017); IPR2023-00495, Paper 24, Final Written Decision, 11-12, 16 (citing *Gemtron Corp. v. Saint-Gobain Corp.*, 572 F.3d 1371, 1380 (Fed. Cir. 2009)). Even if it did, their argument is incorrect. As Dr. Sutton testified, Figure 4a of Gunasekaran does describe a heavy chain consistent with Merus’s construction:

Q: Does figure 4A have a heavy chain as defined – as used within the ’286 patent?”

A: Yes.

EX1062, 142:19-143:2. Xencor’s contention that “Dr. Sutton admitted during deposition that none of [Gunasekaran’s] constructs has modifications in **two** ‘heavy chains’ under Merus’s construction” is therefore a red herring. Reply, 4 (emphasis added). Its erroneous attorney argument on this point should be disregarded.

Xencor’s argument that Merus’s claim construction “improperly omits antibody fragments” is equally unavailing. Reply, 4-5. Xencor misreads Dr. Sutton’s testimony to suggest that his construction is only applicable to “intact antibod[ies].” Reply, 4-5. While Dr. Sutton acknowledged that the definition of “heavy chain” applies to “complete intact antibodies,” he never said that it does not

also apply to antibody fragments. As he explained, a chain in an antibody fragment may be either a “heavy chain” or a truncated chain (typically referred to as Fv, Fab, Fc, Fab’, F(ab’)₂, Fc’, pFc’, and Fd, depending upon which domains are present). EX2016, ¶¶25-26; EX1062, 142:11-21. Indeed, as discussed above, Dr. Sutton acknowledged that Gunasekaran’s Figure 4a construct – which is not an intact antibody – includes a “heavy chain.” EX1062, 142:11-21. While the specification may define the term “antibody” broadly to include fragments, the plain language of the claim limits “antibody” to one that “comprises two heavy chains.”

Finally, Xencor improperly discounts the prosecution history. During prosecution, the patentee narrowed the scope of the claims during prosecution by replacing the term “CH3-domain comprising polypeptide chain” with the narrower term “antibody heavy chain” to overcome a prior art rejection over art disclosing molecules comprising “a first polypeptide and a second polypeptide.” POR, 18; EX2016, ¶40. As Dr. Sutton explained, this amendment confirms that “heavy chain” is used in the claims in accordance with its plain and ordinary meaning rather than more broadly to refer to any polypeptide chain. EX2016, ¶¶40-43.

Xencor suggests that this amendment does not support Merus’s construction because the patentee did not expressly state to the Examiner that this amendment “created any patentable distinction over the prior art.” Reply, 5. Xencor again misapplies the law. First, one may disavow claim scope by narrowing amendment

alone, so long as the disavowal is unambiguous. *See Schindler Elevator Corp. v. Otis Elevator Co.*, 593 F.3d 1275, 1285 (Fed. Cir. 2010) (“[P]rosecution disclaimer attaches where an applicant, whether by amendment or by argument, ‘unequivocally disavowed a certain meaning to obtain his patent.’”) (*quoting Omega Eng’g, Inc. v. Raytek Corp.*, 334 F.3d 1314, 1324 (Fed. Cir. 2003)). Second, and, more to the point, Merus never suggested that this amendment served to narrow “heavy chain” beyond its ordinary and customary meaning. To the contrary, the amendment replacing “polypeptide” with “heavy chain” supports adoption of the plain meaning of heavy chain because it demonstrates that the term was used consistently with its plain meaning during prosecution. *See Phillips v. AWH Corp.*, 415 F.3d 1303, 1317 (Fed. Cir. 2005) (*en banc*) (“Like the specification, the prosecution history provides evidence of how the PTO and the inventor understood the patent.”).

B. The Board Should Reject Xencor’s Arguments on “Interacts”

1. The Term “Interacts” Should Be Given Patentable Weight

Xencor’s argument that “interacts” should not be given patentable weight should be rejected. Although a “wherein” clause may, in certain circumstances, merely state an intended result, when it “states a condition that is material to patentability, it cannot be ignored in order to change the substance of the invention.” *Allergan Sales, LLC v. Sandoz, Inc.*, 935 F.3d 1370, 1376 (Fed. Cir. 2019) (quotation and citation omitted). That is the case here.

Claim 1 of the '286 patent requires that the positively charged amino acid residue substituted in the CH3 domain of the first heavy chain “interacts” with the negatively charged amino acid residue substituted in the CH3 domain of the second heavy chain “to produce a heterodimeric antibody.” As explained in the POR and by Dr. Sutton, the intrinsic record makes clear that the specific interaction between the substituted residues must play a role in producing the claimed heterodimeric antibody. POR, 21-23; EX2016, ¶¶45-58. If those substituted residues do not interact, then a heterodimeric antibody may still be produced (*e.g.*, if the CH3 domains form an interface solely via interactions between other amino acids), but would not fall within the claim. EX2016, ¶¶45-54; EX2012, 52:10-53:20.

Notably, the specification emphasizes the importance of the “additional charge-charge interaction on top of the existing charge pairs in the CH3 interface” to the patentability of the invention. EX1001, 18:10-20; *see also id.*, 10:38-39 (“Through these mutations novel specific interactions are formed between two CH3 domains.”). And, as explained in Patent Owner’s Response, the “interacts” limitation was added during prosecution, and relied upon to overcome a prior art rejection. POR, 22-23. Xencor attempts to discount the relevancy of this amendment by asserting that Merus did not argue that the limitation “introduced any ‘structural’ or ‘but-for’ cause of heterodimerization to the claims.” Reply, 8-9. But it is undisputed that Merus added this limitation in response to a rejection, and relied

on it in arguing to the Examiner that the prior art did not teach the claimed invention “in which two substituted amino acids interact within the CH3 interface.” EX1008, 239, 245.

The cases Xencor relies upon do not support its position. In *Minton v. NASD, Inc.*, 336 F.3d 1373, 1381 (Fed. Cir. 2003), the Court found that the term “‘efficiently’ on its face does not inform the mechanics of how the trade is executed.” *Minton*, 336 F.3d at 1381. Similarly, in *Bristol-Myers Squibb Co., v. Ben Venue Lab’ys., Inc.*, 246 F.3d 1368, 1374-76 (Fed. Cir. 2001), the Court found that the limitation at issue “does not result in a manipulative difference in the steps.” Here, “interacts” informs exactly “the mechanics” of how the heterodimeric antibody is produced (*i.e.*, via interaction between the two identified residues), and meeting this limitation “result[s] in a manipulative difference in the steps” (*e.g.*, selecting specific amino acid substitutions that will interact with one another to form a heterodimeric antibody). It is thus not merely an intended result of the other steps, which could be carried out with or without such a specific interaction.

The “interacts” limitation in this case is thus more akin to the wherein clauses in *Allergan*. Indeed, *Allergan* distinguished *Bristol-Myers* on the ground that the “wherein” clause in the latter was only added to the claim after allowance, while in the former, the “wherein” clause was relied upon during prosecution to distinguish the claims over the prior art. *Allergan*, 935 F.3d at 1376.

2. Merus's Construction of the "Interacts" Limitation is Correct

As with "heavy chain," Xencor does not take issue with Dr. Sutton's opinion on the "ordinary and customary meaning of "interacts," and does not offer a competing construction. Instead, it contends that the ordinary meaning is inconsistent with the specification. Reply, 7. It is not.

"Interacts" appears in the specification in the context of the definition of interface: "'interface,' as used herein, refers to the association between two CH3 domains of separate CH3-domain comprising polypeptides that is a result of *interacting amino acid residues*, i.e. at least *one interaction between an amino acid of a first CH3 domain and an amino acid of a second CH3 domain*." EX1001, 13:18-29 (emphasis added); EX2016, ¶50; POR, 21-22. Thus, the specification explains that CH3 domains may form an interface when at least one amino acid residue on each CH3 domain "interact" with each other. Based on the specification, a POSA would understand exactly which amino acid residues must "interact" to produce the claimed heterodimeric antibody: the positive and negative substituted residues specifically required by the claim. EX2016, ¶46; *Phillips*, 415 F.3d at 1314 ("[T]he claims themselves provide substantial guidance as to the meaning of particular claim terms.").

Accordingly, as Dr. Sutton explained, one may produce a heterodimeric antibody by making a neutral-to-positive substitution in one CH3 domain and a

neutral-to-negative charge in the other. EX2016, ¶¶45, 54. If the positive and negative substituted residues required by the claim interact to form an interface, the limitation is satisfied. *Id.* But if the interface forms **exclusively** due to interactions between **other** amino acids (*i.e.*, not the neutral-to-charged substitutions), then the “interacts” limitation is not satisfied. *Id.* Contrary to Xencor’s assertions, this does not mean that claim 1 requires the substituted amino acids to be the **only** amino acids that interact to produce the antibody. *See* Reply, 8-9. Accordingly, Xencor’s contention that Merus’s construction renders the claim indefinite is baseless. Reply, 9.

Xencor does not rely on expert testimony to support its argument that Merus’s definition “narrows the claims to only a subset of the broad, non-limiting description of ‘interaction’ in the specification,” (Reply, 7) and the opinions of its attorneys should be afforded no weight. *Icon*, 849 F.3d at 1043; IPR2023-00495, Paper 24, Final Written Decision, 11-12 and 16. Significantly, Xencor does not identify any interactions that are described in the specification and are outside the scope of Merus’s construction.

Xencor also sets up a strawman by arguing that Merus’s construction requires “a certain quality” interaction that, “by itself, causes heterodimerization.” Reply, 8. But Merus’s proposed construction includes no such requirement. Although Dr. Sutton opines that the substituted amino acid must themselves “interact,” neither he

nor Merus ever suggested that this interaction must take any particular form or act alone in producing the antibody. Dr. Sutton's testimony that claim 1 does not describe "in any greater details the nature of the interaction," cited by Xencor, is thus entirely consistent with Merus's proposed construction. Reply, 8; EX1062, 153:1-154:21.

Xencor also attempts to discount the prosecution history because it claims that "Merus made no arguments during prosecution that this amendment introduced any 'structural' interactions or 'but-for' cause of heterodimerization to the claims." Reply, 9. Xencor's argument misses the point. As discussed, Merus's construction does not demand that the claimed "interact[ion]" be a "but-for" cause of heterodimerization. Moreover, Merus relies upon the prosecution history to support the plain meaning of "interacts," not to prove that the interaction is "structural." POR, 22-23. Regardless, Dr. Sutton opined that such an interaction would be structural, and his testimony remains unrebutted by any expert. EX2016, ¶ 57.

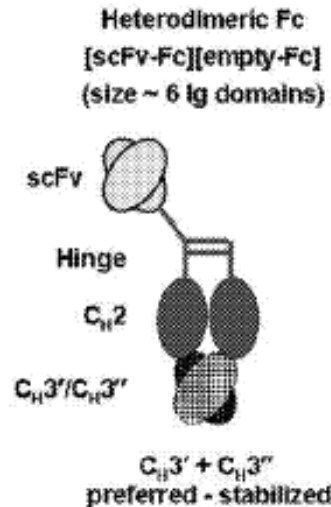
III. LAZAR AND CABRERA DO NOT ANTICIPATE THE CHALLENGED CLAIMS

A. Lazar Does Not Anticipate Any Claim of the '286 Patent

1. Lazar's Test Constructs Do Not Anticipate Claim 1

The only neutral to charge substitutions Xencor alleges are expressly disclosed by Lazar are in the context of scFv-Fc/empty-FC constructs. As explained in the POR, and as shown in the below figure, these constructs include two chains,

neither of which includes a CH1 domain, and one that does not even include a VH domain. POR, 27.



EX1004, Fig. 1. Thus Lazar's test constructs do not anticipate claim 1 because they do not contain "heavy chains" within the plain meaning of the term.

Xencor's contention that Lazar's constructs anticipate claim 1 because the '286 patent "describes Gunasekaran as disclosing 'mutations in the CH3 domains of heavy chains'" and "Gunasekaran uses the same construct as Lazar" (Reply, 11) is easily disposed of. As Dr. Sutton testified, while Figure 2a of Gunasekaran, the specific construct that Xencor compares to Lazar's, **does not** have a "heavy chain," the construct in Figure 4a of Gunasekaran, which Xencor ignores, **does**. EX.2012, Fig. 4a; EX.1062, 139:18-140:11. The general statement in the '286 patent about Gunasekaran therefore indicates nothing about whether Lazar's construct has a "heavy chain," and Xencor's misleading argument should be rejected.

Xencor's backup assertion that even if Merus's construction is adopted Lazar still anticipates claim 1 (Reply, 11-14), is meritless. Xencor's anticipation argument relies on cobbling together multiple, distinct portions of Lazar, which cannot amount to anticipation under Federal Circuit precedent. As the Federal Circuit has found, anticipation cannot be proven by "multiple, distinct teachings that the artisan might somehow combine to achieve the claimed invention." *Microsoft Corp. v. Biscotti, Inc.*, 878 F.3d 1052, 1069 (Fed. Cir. 2017). That is exactly what Xencor does here.

Xencor's reliance on *Purdue Pharma L.P. v. Epic Pharma, LLC*, 811 F.3d 1345, 1358-59 (Fed. Cir. 2016) and *Kennametal, Inc. v. Ingersoll Cutting Tool Co.*, 780 F.3d 1376, 1383 (Fed. Cir. 2015) does not support a different conclusion.

Purdue Pharma provides that combining disclosures in a prior art reference to establish anticipation may be permissible when the disclosures are "directly related." 811 F.3d at 1358-59. In *Purdue*, the prior art provided a detailed description of the preferred embodiment, which included all the limitations of the claimed pharmaceutical formulation except for the therapeutic compound, which the Court found was "directly related." *Id.* at 1359. In *Kennametal*, the Court found that the prior art "effectively teaches 15 combinations, one of which anticipates pending claim 1." *Kennametal*, 780 F.3d at 1383.

Unlike *Purdue* and *Kennametal*, the disclosures that Xencor attempts to combine in Lazar are not "directly related," and are not limited to a small number of

combinations such that the claimed combination would be “immediately apparent” to a POSA. Xencor points to Lazar’s disclosure that its “invention provides antibody analogs,” couples that with a separate disclosure of a definition of “antibody” – not “antibody analog” – as including “full length antibodies,” and combines this with yet another disclosure that Fc variants are “of particular benefit to the immunoglobulins of the invention.” Reply, 12 (quoting EX1004). Xencor then takes all these disclosures, and combines them with arbitrarily selected Fc variants listed in a Table of preferred Fc variants that just so happens to include neutral to charged substitutions. *Id.*, 12-13. Notably, Xencor has no expert testimony supporting its complicated analysis.

While Xencor notes that “antibodies” includes “full length antibodies,” (Reply, 12) it glosses over the fact that “antibodies” also refers to “antibody fragments,” among other things. EX1004, 99. And the language Xencor relies on states that these variants are of particular benefit to the “immunoglobulins” of the invention,” not to the “antibodies” of the invention. Lazar defines an “immunoglobulin” as any “protein consisting of one or more polypeptides substantially encoded by immunoglobulin genes” and as “not limited to antibodies.” *Id.*, ¶66. Thus, the possible universe of immunoglobulins referred to by Lazar is enormous. Xencor provides no explanation for why a POSA would have understood

Lazar's Fc variant disclosure to be directly related to full-length antibodies or any particular constructs as opposed to some other immunoglobulin(s).

In an effort to convince the Board that a POSA would “at once envisage” the claimed substitutions, Xencor artificially narrows the enormous universe of potential combinations of Fc variants and immunoglobulins disclosed by Lazar to just two - the mAb-Fv and mAb-Fab constructs- purportedly because the specification says that these formats are “particularly suited for the use of variants that favor Fc heterodimerization and disfavor homodimerization.” Reply, 14 (citing EX1004 at ¶107). But the specification says the same thing about immunoglobulins in general, which Xencor itself relies upon elsewhere in its brief. Reply, 12 (citing EX1004, ¶120); EX1004, ¶120). Xencor provides no expert opinion that a POSA would have focused on these particular constructs – as opposed to the entire universe of immunoglobulins – in combination with Fc variants. Moreover, Xencor's position is contradicted by its own Petition, which stated that Lazar's “Fc-region mutations are broadly applicable to ‘antibody analogs,’ which are ***not limited to the mAb-Fv and mAb-Fab constructs.***” Petition, 44 (emphasis added). Xencor's attempt to reduce the number of possible combinations disclosed by Lazar to align more closely with its cited caselaw should be rejected.

Moreover, Lazar expressly discloses that “[h]eterodimeric Fc variants are not a necessity” for the mAb-Fv and mAb-Fab structures Xencor relies upon as

containing heavy chains. EX1004, ¶108. This is because, as Dr. Sutton explains, these antibody formats do not need CH3 heterodimerization because Lazar adds an additional binding site at the C- termini of wild-type IgG. EX2016, ¶91; EX1004, ¶46. A POSA reading Lazar would therefore not have understood that the Fc variants were directly related to these constructs. EX2016, ¶¶61-72, 90-96.

Furthermore, even if one were to assume that Lazar did disclose the Fc variants as beneficial to full-length antibodies, a POSA still would not have considered this a disclosure of neutral to charge substitutions on the heavy chains of such antibodies. At no point does Lazar even mention, much less emphasize, neutral to charge substitution. Xencor's assertion that a POSA would have envisaged the few particular variants that coincidentally include such substitutions on full-length antibodies is incorrect.

2. *Lazar Does Not Anticipate Dependent Claims 7, 21, 22, 24, 26, 28, 30 and 32*

For at least the reasons discussed above with respect to claim 1, Lazar does not anticipate claims 7, 21, 22, 24, 26, 28, 30, and 32. Lazar does not anticipate for the additional reasons below.

a. *Claim 7*

Lazar does not disclose the additional limitation that “the presence of contaminating homodimers is less than 5%” because none of the Lazar experiments using a scFv-Fc/empty-Fc construct with neutral to charged substitutions comes

close to this purity. POR, 29; EX2016, ¶¶111, 166-168; EX1004, Figs. 5-7. Xencor points to Lazar's alleged teachings that its "hetero-Fc variants" may increase the heterodimer population to 95%, or that a POSA would have understood that Lazar's "hetero-Fc variants" could be combined with other heterodimerization techniques to boost purity "to meet the expressly taught '95%' in Lazar." Reply, 15.

Xencor's conclusory arguments are insufficient to prove anticipation. That "hetero-Fc variants" (generally), and not any specific neutral-to-charged substitution, "may" increase heterodimer population to 95% is not an express or inherent disclosure of the limitations recited in claim 7. Xencor fails to articulate its anticipation theory with particularity, including how Lazar anticipates claim 7 under Merus's claim construction.

b. Claims 21, 24, and 32

Each of claims 21, 24, and 32 depends, either directly or indirectly, from claim 1, and further requires that the "antibody is human IgG." Claim 32 also requires that the "antibody is IgG1." Xencor alleges that "Lazar's test construct itself is based on IgG1," but, as discussed above, those test constructs do not include "heavy chains" and therefore cannot anticipate these claims. Reply, 15. Lazar's disclosure that "[i]n certain embodiments, the Fc variants disclosed herein are based on human IgG sequences" does not teach including neutral-to-charged substitutions in a human IgG antibody, much less an IgG1 antibody, specifically. *Id.* As discussed above, a POSA

would not have at once envisaged neutral-to-charged substitutions into Lazar's alternative constructs. And Xencor does not even allege that such constructs are IgG1 antibodies.

B. Cabrera Does Not Anticipate Any Claim of the '286 Patent

1. Cabrera Does Not Anticipate Claim 1

Xencor claims that Cabrera's disclosure of the AZ34 variant, which includes (among several other modifications) a neutral to positive substitution on one heavy chain (N390R) and a neutral to negative substitution on the other (S400E) anticipates claim 1. Xencor is wrong because these amino acid residues do not "interact," as required by claim 1. POR, 30-33; EX2016, ¶¶73-86.

As explained by Dr. Sutton, Cabrera disclosed two, nearly identical variants: (1) AZ34, which included the substitutions noted above along with three other substitutions on each chain; and (2) AZ33, which included the exact same substitutions as AZ34, except it did not include N390R and S400E:

TABLE 1-continued

CH3 domain amino acid modifications for the generation of Fc variant heterodimers.								
Variant	Chains	Fc Mutations						
AZ33	A	L351Y	F405A	Y407V	-	-	-	-
	B	T366I	K392M	T394W	-	-	-	-
AZ34	A	L351Y	S400E	F405A	Y407V	-	-	-
	B	T366I	N390R	K392M	T394W	-	-	-

EX2016, ¶75; EX1005, 39. In other words, the only difference between these two variants is that AZ34 includes the N390R and S400E amino acid residues that must “interact” for claim 1 to be anticipated.

Dr. Sutton further explained that if these N390R and S400E amino acid residues in fact interacted, then one would expect such interaction to be reflected by an increase in melting point from AZ33 to AZ34. EX2016 at ¶81. However, Cabrera disclosed melting point data demonstrating just the opposite – that making these neutral to charge substitutions **decreased** the melting point:

Variant	T _m °C
AZ29	70
AZ30	71
AZ31	68
AZ32	71.5
AZ33	74
AZ34	73.5

EX2016, ¶77; EX1005, Table 3. Dr. Sutton concluded from these data that, not only are the N390R and S400E amino acid residues of AZ34 not interacting to produce a heterodimer, they are actually interfering with its production. EX2016, ¶81. Xencor posits no alternative explanation for these data, and offers no expert testimony to the contrary.

Instead, Xencor contends – through attorney argument alone – that Merus’s melting temperature argument conflates stability with promoting

heterodimerization. Reply, 17. But Xencor misunderstands the issue. Neither Merus nor Dr. Sutton suggested that the melting temperature of a construct on its own indicates heterodimerization. Rather, it is the comparison of two melting temperatures, with one variant having the identified substitution and the other not, that shows whether the identified substitutions interact. Xencor's focus on melting temperatures in other constructs of Cabrera and the '286 patent are irrelevant.

Dr. Sutton also explained exactly why there would be no interaction between the N390R and S400E amino acid residues, based on the literature. POR, 31-32; EX2016, ¶¶77-78. Xencor's attorneys' casual dismissal of Dr. Sutton's interpretation of scientific literature as "pure conjecture" should be ignored.

Moreover, Xencor has never even attempted to affirmatively demonstrate that the N390R and S400E amino acid residues interact in Cabrera's AZ34 construct, leaning instead on possibilities that they may do so. Reply, 19-20 ("capable of interacting"; "expected to interact"; "expected to form a salt bridge"). Possibilities are no substitute for proof, particularly in the face of Cabrera's own affirmative melting point evidence to the contrary. Xencor has therefore not met its burden of establishing that Cabrera anticipates claim 1.

2. *Cabrera Does Not Anticipate Dependent Claims 2, 7, 21, 22, 24, 26-28, and 30-32*

For at least the reasons discussed above with respect to claim 1, Lazar does not anticipate claims 2, 7, 21, 22, 24, 26-28, and 30-32.

IV. LAZAR IN VIEW OF ARATHOON OR ARATHOON AND CABRERA DOES NOT RENDER THE CHALLENGED CLAIMS OBVIOUS

A. Independent Claims

Despite its decision to allege obviousness grounds based on a combination of references, Xencor contends that it does not need to identify “a motivation to select” the neutral-to-charged variants in Lazar. Reply, 21. Xencor relies on *Guardant Health, Inc. v. Univ. of Washington*, No. 2024-1129, 2026 WL 184334, at *4 (Fed. Cir. 2026) and *Cytiva BioProcess R&D AB v. JSR Corp.*, 122 F.4th 876, 884 (Fed. Cir. 2024). But neither case supports its position. *Guardant* stands for the uncontroversial proposition that “[w]hen the disputed elements of a claim are disclosed in a single embodiment in a single reference, no finding regarding a motivation to combine to arrive at those claimed elements is required.” 2026 WL 184334 at *4. But Xencor does not allege that any of the Challenged Claims are obvious over Lazar alone or that all the elements of any challenged claim are disclosed in a single embodiment in Lazar. Reply, 21-24. *Cytiva* is similarly inapposite as it is focused on “[a] lead-compound analysis.” 122 F.4th at 884. Merus has never argued that a lead compound analysis is required here.

That a lead compound analysis is not required does not, however, absolve Xencor of establishing a “motivation to combine or modify the teachings in the prior art.” See *Regents of Univ. of California v. Broad Inst., Inc.*, 903 F.3d 1286, 1291 (Fed. Cir. 2018). And, as explained in the POR, Xencor has failed to identify any

reason why a POSA, faced with all the possible choices for making heterodimers available in the prior art, would have specifically chosen to incorporate a neutral to charged substitution tested by Lazar on its scFv-empty-Fc constructs into an antibody having two heavy chains. POR, 42-44. This is particularly problematic in view of Lazar's own disclosure that other Fc variants yielded more favorable results. Just because a POSA *could have* stitched together these disparate disclosures to make a heterodimeric antibody does not mean they *would have* had any reason to do so.

Nor did Merus "completely avoid[] Lazar's disclosure that those Fc variants would be used in full-length antibodies." Reply, 21-22. Even if Lazar included full-length antibodies amongst a laundry list of potential constructs, as Xencor asserts, Xencor has still articulated no reason why a POSA would have specifically included neutral to charge variants in such antibodies. And, with regard to Lazar's mAb-Fv and mAb-Fab alternative constructs, Xencor has failed to explain why a POSA would have decided to introduce neutral-to-charged substitutions in such constructs when Lazar itself teaches that "[h]eterodimeric Fc variants are not a necessity, however, for generation and use of the mAb-Fv and mAb-Fab." EX1004, ¶108.

B. Dependent Claims

With respect to claims 2 and 8-20, Xencor erroneously alleges that Merus "incorrectly assumes Lazar's neutral-to-charged substitutions were limited to its test

constructs.” Reply, 24, 25-26, 28. In fact, Xencor points to no instance where Lazar incorporated neutral to charged variants into anything other than those test constructs. To the extent Xencor is referring to Lazar’s general disclosure that Fc variants that favor heterodimerization of the Fc region are of “particular benefit to the immunoglobulins of the invention,” this is a far cry from a disclosure of neutral to charged substitutions in any particular immunoglobulin. Reply, 12; EX2016, ¶162.

With regard to claim 7, Xencor acknowledges that the neutral-to-charged substitutions disclosed by Lazar resulted in 12% to 93% contaminating homodimer. Reply, 25, 28-29. Xencor suggests, however, that a POSA would have been motivated to combine these neutral-to-charged substitutions with other modifications already known to provide at least 95% purity, and would have expected that combination to result in the claimed purity. *Id.* But as Dr. Presta acknowledged, a POSA would have considered 95% heterodimeric purity to already be “very good.” EX2012, 126:24-127:2; EX2016, ¶133. As Dr. Sutton explained, including additional neutral-to-charged substitutions can actually decrease heterodimerization. EX2016, ¶169. A POSA would therefore have had no reason to incorporate Lazar’s neutral-to-charged substitutions into another heterodimer that already had 95% purity, and would have had no reason to expect such high purity to be maintained had they done so. *Id.*, ¶172.

Xencor needed to articulate why a POSA would have been motivated to combine distinct disclosures within Lazar and with other teachings in Arathoon or Cabrera to arrive at the claimed invention with a reasonable expectation of success. Xencor has failed to do so.

V. CONCLUSION

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

Dated: April 24, 2026

Respectfully submitted,

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CERTIFICATE OF COMPLIANCE

Pursuant to 37 C.F.R. § 42.24(d), the undersigned certifies that the foregoing PATENT OWNER'S SUR-REPLY contains, as measured by the word-processing system used to prepare this paper, 5,391 words. This word count does not include the items excluded by 37 C.F.R. § 42.24.

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The undersigned hereby certifies that pursuant to 37 C.F.R. § 42.6(e), a copy of the foregoing PATENT OWNER'S SUR-REPLY was delivered via electronic mail on April 24, 2026 to lead and backup counsel of record for the Petitioner as follows:

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