

UNITED STATES PATENT AND TRADEMARK OFFICE

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BEFORE THE PATENT TRIAL AND APPEAL BOARD

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XENCOR, INC.,  
Petitioner

v.

MERUS N.V.,  
Patent Owner

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Case No. IPR2025-00605  
Patent No. 11,926,859

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**PATENT OWNER'S SUR-REPLY**

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**EXHIBIT LIST**

<b>Exhibit Number</b>	<b>Description</b>	<b>Previously Submitted</b>
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 Discovery 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	Amendment and Response to Final Office Action mailed in U.S. Pat. App. No. 12/700,618, dated August 25, 2011	X
EX2007	FAQs for Interim Processes for PTAB Workload Management, USPTO	X
EX2008	Xencor, Inc. Form 10-K for Fiscal Year ended Dec. 31, 2017	X
EX2009	International Application Publication No. WO 2011/028952 A1	X
EX2010	Declaration of Brian J. Sutton, Ph.D. In Support of Patent Owner's Preliminary Response	X
EX2011	<i>Curriculum Vitae</i> of Brian J. Sutton, Ph.D.	X
EX2012	U.S. Patent No. 8,216,805	X
EX2013	Presta Office Action Response – U.S. Patent App. No. 12/700,618	X
EX2014	14/155,344 Information Disclosure Statement, Jan. 14, 2014	X
EX2015	Deposition Transcript of Leonard G. Presta, Ph.D. Dec. 5, 2025	X

EX2016	Presta Deposition Exhibit 4001 (Brian W. Matthews, Studies on Protein Stability with T4 Lysozyme)	X
EX2017	Presta Deposition Exhibit 4002 (Jin & Zhu, The Design and Engineering of IgG-Like Bispecific Antibodies)	X
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## I. INTRODUCTION

Xencor's position that the claims of U.S. Patent No. 11,926,859 (the '859 Patent) are unpatentable turns on its argument that the patent is not entitled to its earliest priority date based on lack of adequate written description. In its Patent Owner Response ("POR"), Merus, relying on Dr. Sutton's declarations, demonstrated exactly why Xencor is wrong. Dr. Sutton provided a careful and detailed analysis of why a POSA would understand from the specification that the inventors were in possession of the claimed inventions.

Xencor's principal response is to accuse Merus and Dr. Sutton of undertaking an "obviousness-type" analysis instead of following written description law. But this is demonstrably incorrect. It is well-settled Federal Circuit law that a claimed invention can meet the written description requirement even if it is not described *in haec verba*; does not appear in any examples; and is not specifically identified as a preferred embodiment. What is necessary are blaze marks, and Dr. Sutton explained clearly why those in Provisional Application No. 61/635,935 ("the '935 Application") would have led a POSA directly to the Challenged Claims.

Xencor's fallback argument, that even if the patent is entitled to its earliest priority date the claims should still be found obvious, fares no better. Xencor bears the burden of proof, yet it has consistently failed to articulate any real motivation for a POSA to have modified Lazar either on its own or in combination with Kannan,

and has still provided no reason why a POSA would have had a reasonable expectation of success.

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

## **II. THE CHALLENGED CLAIMS ARE ENTITLED TO A PRIORITY DATE OF APRIL 20, 2012**

### **A. The '935 Application Provided Adequate Written Description Support for the '859 Patent Claims Under the Correct Legal Standard**

#### **1. Xencor Misconstrues the Federal Circuit Standard for Written Description**

Xencor argues in its Reply that Merus takes an “obviousness-style approach to written description.” Reply at 2. Xencor's argument betrays a fundamental misunderstanding of both written description law and Merus's arguments.

What Xencor characterizes as an “obviousness-style approach” is simply a straightforward application of the Federal Circuit's well-settled standard for written description. The case law is clear that the written description requirement can be satisfied without an “*in haec verba*” disclosure of the claim language; without specific examples covering the claim language; and without the inventors actually reducing their invention to practice. *Nalpropion Pharms., Inc. v. Actavis Labs. FL, Inc.*, 934 F.3d 1344, 1350 (Fed. Cir. 2019); *Immunex Corp. v. Sandoz Inc.*, 964 F.3d 1049, 1064 (Fed. Cir. 2020); *Falkner v. Inglis*, 448 F.3d 1357, 1366-1367 (Fed. Cir. 2006).

As the Federal Circuit has found, the written description requirement is satisfied if “‘the essence of the original disclosure’ conveys the necessary information – ‘regardless of *how* it’ conveys such information, and regardless of whether the disclosure’s ‘words [a]re open to different interpretation[s].’” *Inphi Corp. v. Netlist, Inc.*, 805 F.3d 1350, 1354-55 (Fed. Cir. 2015) (*quoting In re Wright*, 866 F.2d 422, 424-25 (Fed. Cir. 1989)); *see also Teva Pharm. Int’l GmbH v. Eli Lilly & Co.*, 2024-1094, 2026 WL 1025802, at \*4 (Fed. Cir. April 16, 2026) (“The ‘written description’ requirement states that the patentee must describe the invention; it does not state that every invention must be described in the same way.”) (*quoting Capon v. Eshhar*, 418 F.3d 1349, 1358 (Fed. Cir. 2005)). Written description support can be found anywhere within the “four corners of the specification.” *Teva*, 2026 WL 1025802 at \*4. A claimed invention is adequately described if there are “blaze marks within the disclosure that guide attention to the claimed species or subgenus.” *Regents of the Univ. of Minnesota v. Gilead Scis., Inc.*, 61 F.4th 1350, 1356 (Fed. Cir. 2023).

As set forth below and in the POR, this is exactly what Merus has demonstrated, and Merus’s argument is a proper application of written description, not obviousness, law.

**B. The '935 Application Reasonably Conveys to a POSA that the Inventors had Possession of the Subject Matter Claimed in the '859 Patent**

Xencor's attempts to refute Dr. Sutton's analysis of why the Challenged Claims have adequate written description support are based largely on attorney argument, are contrary to written description law, and should be rejected.

Xencor begins by arguing that Merus puts an "artificially narrow focus on Table 7" and that "the inventors' heterodimer testing confirms they were focused on other substitutions." Reply at 3. Xencor appears to be arguing that only those constructs specifically exemplified or identified as "preferred" can have adequate written description support. But, as discussed above, that is not the law. Even if not specifically described as "preferred," claimed subject matter can be adequately supported as long as the application contains "blazemarks as to what compounds, other than those disclosed as preferred, might be of special interest." *Fujikawa v. Wattanasin*, 93 F.3d 1559, 1571 (Fed. Cir. 1996); *Boston Sci. Corp. v. Johnson & Johnson*, 647 F.3d 1353, 1367-68 (Fed. Cir. 2011).

*Duke Univ. v. Sandoz Inc.*, 160 F.4th 1305, 1314 (Fed. Cir. 2025), cited by Xencor, is not to the contrary. See Reply at 3-4. In *Duke*, the specification described a genus of billions of compounds while the claim at issue covered a subgenus of a few thousand compounds. The Court found a lack of written description because "the *only* blaze marks provided by the specification" pointed away from the claimed

invention. *Duke*, 160 F.4th at 1314 (emphasis added). Here, to the contrary Dr. Sutton opined that the '935 Application contains blaze marks leading a POSA directly to the 364/368 pair of the Challenged Claims.

As Dr. Sutton explained, the '935 Application discloses to a POSA that the heterodimeric antibodies of the “present invention ... substitute[] non-charged CH3 amino acids for charged ones,” which “has the advantage that at least one additional charge-charge interaction on the CH3 interface is created.” EX2019 at ¶¶ 45-46; EX1030 at 23:28-24:9. A POSA therefore would have understood that the antibodies of the invention included a neutral-to-charged amino acid substitution on each chain, and that those amino acid residues provide an extra charge-charge interaction connecting the CH3 domains of each chain.

The data in Table 7 of Example 13 provides express guidance to a POSA as to which variants would be best for heterodimerization when combined with a second variant; *i.e.*, those that provided the most effective homodimerization inhibition (*i.e.*, prevent interaction between identical chains) when expressed alone. EX2019 at ¶¶ 50-53. As Dr. Sutton explained, the extent of homodimer formation shown in Table 7 is “one way of looking at the propensity for that mutation to be valuable in [the] production of a heterodimeric antibody.” EX1062 at 36:21-37:9. Dr. Sutton further explained that a POSA would have understood from the '935 Application that a variant identified in Table 7 would provide such a heterodimeric

antibody only in conjunction with its “matched pair,” *i.e.*, a second variant having an opposite charge at a contact residue associated with the position of the substituted amino acid of the first variant. EX2019 at ¶¶ 57-60.

Dr. Sutton also explained, and Xencor’s expert Dr. Presta acknowledged at deposition, that the inventor’s data in Table 7 teaches that one of the three single residue changes that have the greatest inhibition on homodimerization – and the only one of the three not expressly identified by the inventors as “problematic” – is S364K. EX2015 at 158:9-19; EX2019 at ¶¶ 37, 55-62. A POSA therefore would have immediately recognized the inventors possessed heterodimeric antibodies having a neutral-to-positive (*i.e.*, serine (S) to lysine (K)) substitution at position 364 of one chain, coupled with its corresponding “matched pair.” EX2019 at ¶ 58.

Finally, Dr. Sutton opined that a POSA would have understood the ’935 Application to have disclosed exactly what that “matched pair” would be. EX2019 at ¶¶ 58-59. In view of the inventors’ characterization of their invention as including neutral-to-charged substitutions that provide an additional charge-charge interaction (EX1030 at 23:28-24:9), a POSA would have understood that the “matched pair” must have a neutral-to-negative substitution at a contact residue associated with position 364. EX2019 at ¶¶ 60-62. Table A describes the exclusive and specific contact relationship between position 364 on one chain and positions 368 and 370 on the other chain at the CH3 interface. EX2015 at 161:4-6, 163:10-13; EX2019 at

¶¶ 37, 72. However, only one of these positions – position 368 – has a naturally occurring neutral charge that could be substituted with a negative charge. EX2019 at ¶¶ 60-62, 69. Accordingly, a POSA would have been immediately and directly led by the blaze marks set forth in the '935 Application to a heterodimeric antibody having a positive substitution at position 364 of the CH3 domain of one chain, and a negative substitution at position 368 of the other chain. EX1062 at 38:4-39:1, 59:4-20, 61:19-22, 62:1-6; EX2019 at ¶¶ 70-72.

**C. Dr. Sutton and Merus Have Not “Misread the Provisional”**

As discussed above and in the POR, Dr. Sutton provides a reasoned explanation as to why a POSA would have recognized, based on blaze marks in the specification, that the inventors possessed the 364+/368- pairing. EX2019 at ¶¶ 54-83. And, this explanation is entirely consistent with Federal Circuit precedent. As discussed in the Patent Owner Response, a POSA would have understood that the inventors of the '859 Patent possessed the claimed subject matter based on the disclosures in Table A and Table 7 of the '935 Application. In *Nalpropion*, the Federal Circuit affirmed a district court finding that data from two different tables in the specification provided adequate written description support for a claimed dissolution range. 934 F.3d at 1349-51. As the district court found, “there was nothing odd or invalidating” about basing written description support on data from two different disclosures in a specification. *Id.* at 1351.

Xencor attempts to avoid a similar outcome in this case by mischaracterizing Dr. Sutton's analysis as a "a seven-step chain of inferences" that "misreads the '935 provisional." Reply at 5, 6. These arguments should be rejected.

**Table 7.** Xencor first criticizes Merus's assertion that a POSA would have looked to Table 7 for guidance. Xencor asserts that Table 7 "does not show possession of a 'pair' of mutations as claimed because it is testing homodimer repulsion involving only identical heavy chains." Reply at 7. However, neither Merus nor Dr. Sutton allege that Table 7 by itself shows possession of the pair of mutations as claimed. POR at 18-21; EX2019 at ¶¶ 50-53. The '935 Application expressly states that the objective of the study that resulted in Table 7 "was to engineer the IgG CH3 region to result in the production of only heterodimers or only homodimers upon mixed expression of different IgG heavy chains in a single cell, wherein the novel engineered CH3 domains will not homo- or heterodimerize with known engineered CH3 domains, or with wildtype CH3 domains." EX2019 at ¶ 51; EX1030 at 51:1-14.

Xencor's criticism thus ignores the expressly stated objective of the study and is a misleading characterization of the '935 Application's disclosures. Moreover, Xencor's disagreement with Dr. Sutton's opinions concerning how a POSA would have understood Table 7 rests solely upon attorney argument, and these attorney arguments cannot take the place of objective evidence. IPR2023-00495, Paper 24,

Final Written Decision, 16 (citing *Gemtron Corp. v. Saint-Gobain Corp.*, 572 F.3d 1371, 1380 (Fed. Cir. 2009)); *see also Icon Health & Fitness, Inc. v. Strava, Inc.*, 849 F.3d 1034, 1043 (Fed. Cir. 2017).

**++ or +++ only.** Next, Xencor criticizes Merus's assertion that a POSA would look to the “++” or “+++” rating in Table 7 to identify the variants that best embodied the inventors' stated preference. Reply at 8. Xencor's criticism of a POSA's understanding of Table 7 is, again, based solely upon attorney arguments (Reply at 8), which cannot obviate the objective evidence provided by Dr. Sutton. IPR2023-00495, Paper 24, Final Written Decision at 16. Table 7's legend defines “+++” as “max inhibition.” EX1030 at Table 7; POR at 21; EX2019 at ¶ 52. A POSA looking at Table 7 would have understood these ratings to refer to variants that best inhibited homodimerization. As explained by Dr. Sutton, the '935 Application taught a POSA that inhibiting homodimerization was preferential for effectively producing heterodimeric antibodies. EX2019 at ¶¶ 47-49. Dr. Presta does not dispute that the '935 Application expressly states this preference. EX2015 at 157:4-22. Dr. Sutton's opinion that a POSA's attention would have been drawn specifically to those variants Table 7 identifies as having a relatively greater ability to prevent homodimerization therefore does not contradict the '935 Application, as Xencor nonsensically suggests. Reply at 8. It is dictated by the '935 Application's own express disclosure.

**Eliminating F405 and Y407.** Xencor cites to deposition testimony from Dr. Sutton and Dr. Presta in an attempt to undermine Merus's assertion that a POSA would have been led away from the F405 and Y407 variants. Reply at 9. Xencor's arguments ignore the express teachings of the '935 Application. It is undisputed that the '935 Application states the following concerning F405 and Y407:

[I]t is known that *residues F405 and Y407* have multiple interactions at the CH3-CH3 interface, including interactions with residues that are already charged, *which may be problematic* after introduction of multiple charge mutations among these interacting residues (see **Table A**).

EX1030 at 54:12-16. EX2019 at ¶ 54; EX2015 at 165:18-166:13, 176:13-18.

As Dr. Sutton explains, a POSA would have understood that from this explicit disclosure that the inventors were not focused on antibodies with these F405 and Y407 substitutions. EX2019 at ¶ 54. This is a clear-cut example of a blaze mark pointing a POSA in a particular direction – *i.e.*, away from the F405 and Y407 variants the inventors themselves identified as “problematic” – when trying to determine which embodiments the inventors “possessed.”

In a case of what appears to be unintentional irony, Xencor proffers a complicated obviousness-type argument that essentially says a POSA would have either ignored the inventors' express statement because they would have understood the inventors' concern was unfounded or would have applied the same reasoning to conclude that S364 would be similarly problematic. Reply at 9-11. But, as Xencor

repeatedly reminds the Board throughout its Reply, the relevant question here is *not whether a POSA would have found it obvious* to use S364 in an antibody, but whether there are adequate blaze marks in the '935 Application from which a POSA *would have understood the inventors were in possession* of antibodies containing the S364 variant. The inventors' explicit language is thus of the utmost importance. The '935 Application includes an express teaching pointing away from F405 and Y407, and does not include such a statement concerning S364. Xencor's attempt to introduce needless complexity to the inventors' unambiguous blaze mark pointing away from F405 and Y407 should be rejected.

**Frequency.** Xencor attempts to undermine Dr. Sutton's opinion that the '935 Application would guide a POSA to S364K because L351K appears more frequently in Table 7 than S364K. Reply at 11. Xencor mischaracterizes Dr. Sutton's and Merus's position. Dr. Sutton does not opine that simply because there are three variants that are rated either “+++” or “++” in Table 7 that a POSA would be directed to S364K. Dr. Sutton considers this as one of the factors in his blaze marks analysis. EX1062 at 94:2-21. For example, Dr. Sutton opined that a POSA would have further taken notice that S364K is the only variant in Table 7 (other than the “problematic” F405 and Y407 variants discussed above) to achieve at least a “++” rating as a single substitution. EX2019 at ¶ 56.

**T366.** Xencor asserts that “Merus ignores T366K without explanation.”

Reply at 12. This is incorrect. Merus did not “ignore[] T366K.” To the contrary, Dr. Sutton explicitly concluded that the inventors “had possession of, bispecific antibodies produced by engineering matched pairs for the *T366K and S364K variants* identified in Table 7.” EX2019 at ¶ 58 (emphasis added). And Merus related that specific opinion to the Board in its Patent Owner Response. POR at 23 (“A POSA reading this statement would have understood that the inventors invented, and had possession of, bispecific antibodies produced by engineering matched pairs for ... the T366K and S364K variants identified in Table 7”). At no point has Merus or Dr. Sutton alleged that the claimed antibodies are *the only antibodies* a POSA would have understood the inventors to have been in possession of.

**K370.** Contrary to Xencor’s assertion, Merus does not “carve” out and then “abandon” its position on K370. Reply at 12. Xencor attempts to undermine Merus’s blaze marks rationale by noting that K370 is part of a “particularly preferred” combination in the ’935 Application. However, even if a patent disclosure identifies an embodiment as “preferred,” written description for other embodiments may still be found to be adequate. In *Immunex Corp. v. Sandoz Inc.*, 964 F.3d 1049, 1053-54 (Fed. Cir. 2020), the claimed invention was a p75—IgG1 fusion protein. The patent challenger argued that there was a lack of written description because (1) the specification described a truncated sequence as

“preferred” and the claimed full sequence was “never-referenced” in the specification and (2) the priority application disclosed a range of immunoglobulin classes and provided no blaze marks that would have led a POSA to select the claimed IgG1. *Id.* at 1065. The Federal Circuit found that the claims nevertheless had adequate written description support. *Id.*

As discussed above, a POSA would have been directly led by the '935 Application's blaze marks to the naturally-occurring neutral amino acid at the 368 position as a matched pair for the S364K variant. Whether a mutated K370 was included as part of a “preferred” combination of variants without S364K is irrelevant to that analysis. Regardless, Merus did not “eliminate” K370 any more than it “ignored T366.” As explained in Patent Owner's Response and by Dr. Sutton, a POSA would have reasonably believed that the inventors had possession of the four matched pairs with the S364K substitution, including the mutated K370 Xencor accuses Merus of eliminating. POR at 24-26; EX2019 at ¶ 60.

### **III. THE CHALLENGED CLAIMS ARE NOT OBVIOUS OVER LAZAR ALONE OR LAZAR IN VIEW OF KANNAN**

#### **A. *Lazar* Alone Does Not Render the Challenged Claims Obvious**

In trying to convince the Board that Lazar alone renders the Challenged Claims obvious, Xencor attempts to equate the disclosure of the '935 Application for purposes of written description with the disclosure of Lazar for purposes of

obviousness. The disclosures and teachings of the two references, however, differ for significant reasons.

Most critically, unlike Lazar, the '935 Application specifically describes its invention as involving neutral to charged substitutions. For example, the '935 Application explains that “[t]he mutations according to the present invention are an inventive alternative to this approach, because now CH<sub>3</sub> amino acids that are non-charged or neutral in wildtype CH<sub>3</sub> are substituted with charged residues.” EX1030 at 23:32-24:1. And, it goes further, explaining exactly why such substitutions are beneficial. *Id.* at 24:6-9 (“In view of this additional charge-charge interaction on top of the existing charge-pairs in the CH<sub>3</sub>-CH<sub>3</sub> interface, the dimers according to the invention are generally more stable as compared to the wild type dimers.”).

A POSA, reading the '935 Application, would have therefore had a sufficient reason to focus specifically on neutral to charged substitutions when ascertaining the scope of the invention. By contrast, a POSA reading Lazar would have had no reason to appreciate the importance of neutral to charged substitutions when deciding which antibodies to pursue. Lazar does not even mention any relationship between amino acid charges and heterodimer formation, much less suggest the particular importance of neutral to charged substitutions. In other words, while the '935 Application draws a POSA's attention directly to substituting neutral amino

acid residues with charged ones, Lazar is, at best, agnostic with respect to amino acid charges.

Xencor's principal response to Merus's assertion that a POSA would not have been motivated to pick the 364/368 pair for further modification is a misreading of the case law. Xencor argues, citing *Cytiva BioProcess R&D AB v. JSR Corp.*, 122 F.4th 876, 884 (Fed. Cir. 2024) and *Guardant Health, Inc. v. Univ. of Wash.*, No. 2024-1129, 2026 WL 184334 (Fed. Cir. 2026), that it has no requirement in this case to show motivation to combine or modify. But *Cytiva* and *Guardant* have no relevance here.

In *Cytiva*, the claims required a particular amino acid substitution in a particular domain of Protein A, and two independent prior art references "expressly disclose[d]" the exact same substitution in the exact same domain as required by the claims. *Cytiva*, 122 F.4th at 882, 884-85. The Court rejected Patent Owner's contention that a finding of obviousness required a separate justification for selecting that domain as a starting point for modification, explaining that "[a] lead compound analysis is not required where the prior-art references expressly suggest the proposed modification." *Id.* at 884. Unlike the situation in *Cytiva*, Lazar does not "expressly suggest the proposed modification"; *i.e.*, it does not expressly suggest swapping the charges at the 364/368 position.

All that the Court found in *Guardant* was that “there is no need to show that a skilled artisan would have been motivated to modify a reference to perform two claim steps one after the other when the reference itself already discloses those limitations together in the same sequence required by the claims.” *Guardant*, 2026 WL 184334, at \*4. Here, there is no dispute that Lazar does not disclose the elements of claim 1 of the ’859 patent in a single embodiment; it discloses opposite charges on the 364/368 pair from those in the claims. EX1004 at ¶ 241 (tables 1 and 2).

Xencor’s fallback position is that motivation would have existed because of Lazar’s disclosure of the 364/368 pair as “preferred.” Reply at 17. But this begs the question: if the 364-/368+ pair was “preferred,” why would a POSA have been motivated to modify the charges to arrive at 364+/368-? Xencor has no answer to this question, and nothing in Lazar teaches or suggests modifying the variants disclosed in Table 1 for improvement. See EX1004 at ¶ 241 and Table 1; see also EX2019 at ¶ 128.

Xencor’s reliance on *Dembiczak* for the proposition that “motivation to combine may flow from the prior art references themselves” does not obviate its need to prove motivation to combine with actual evidence. Reply at 17 (quoting *In re Dembiczak*, 175 F.3d 994, 999 (Fed. Cir. 1999)). As *Dembiczak* clarifies, “[b]road conclusory statements regarding the teaching of multiple references, standing alone, are not evidence.” *In re Dembiczak* 175 F.3d at 999 (quotation

omitted). Xencor’s identification of 364-/368+ as “preferred,” without identifying a particular motivation for a POSA to have combined this pair with a teaching to swap these charges is insufficient to establish obviousness. *See id.* at 999-1000 (reversing obviousness rejection where the analysis was “limited to a discussion of the ways that the multiple prior art references can be combined to read on the claimed invention,” but “fail[ed] to demonstrate how the [prior art] references teach or suggest their combination”).

Moreover, Lazar Table 1 contains twenty-nine rows of variants and Table 2 contains fourteen rows of different variants, all of which are labeled “preferred.” Xencor does not explain why a POSA would have selected the 364/368 pair for modification over all the others that are identified as “preferred.” While Xencor makes much of Dr. Sutton’s testimony that the 364/368 variant “produced an improvement in heterodimer formation” (Reply at 17), the improvement was, as he noted, modest and far below that of other “preferred” variants. EX1062 at 209:1-210:8; EX1004 at Figure 5. In fact, as Merus noted in its POR, some variants achieved heterodimerization rates of 100%. POR at 50; EX2019 at ¶¶ 129, 130; EX1004 at Figures 5-7 (K370D/K392D/K409D and E356K/E357K/D399K).

**B. *Lazar* in View of *Kannan* Does Not Render the Challenged Claims Obvious**

*Kannan* does not remedy the deficiencies in Xencor’s obviousness analysis based on *Lazar* alone.

**No Motivation to Combine:** Merus demonstrated in its POR that a POSA would have had no motivation to combine Kannan with Lazar. Xencor's Reply does nothing to undermine that analysis. Although Xencor excerpts quotes from each reference, it fails to articulate how any of those teachings would have motivated a POSA to combine their teachings to arrive at the claimed invention. To the extent Xencor contends that there was a motivation to combine simply because Lazar and Kannan discuss similar technologies, that is insufficient to establish obviousness. *Sisvel Int'l S.A. v. Sierra Wireless, Inc.*, 82 F.4th 1355, 1364 (Fed. Cir. 2023) ("We agree with the Board that Cross-Appellant's first, second, and third reasons to combine were merely assertions that references were analogous art, which, without more, is an insufficient articulation for motivation to combine.").

While Xencor asserts that Kannan "teaches the benefits of charge-swapping in promoting heterodimerization," it does not even attempt to explain why a POSA would have been motivated to swap charges on a variant where a neutral-to-charged substitution has already been made that results in an increase in heterodimerization. Reply at 19 (citing EX1007 at 2:35-37; and EX1062 at 90:12-16, 89:19-22, 168:8-170-7). Indeed, Kannan is highly selective as to the locations of substitutions, and it does not teach charge swapping at positions 364 or 368. Rather, it teaches that "different combinations will have diverse effect[s] on the quaternary (homodimer/heterodimer) structure formation depending on surrounding residues at

the mutation site and role of water molecules.” *See* EX1007 at 10:6-10; *see also id.* 2:33-3:13. Xencor ignores these teachings.

**No Reasonable Expectation of Success:** Xencor’s Reply consists of an attempt to poke holes, based on attorney argument alone, in Dr. Sutton’s detailed analysis of why a POSA would not have had a reasonable expectation of success in modifying Lazar. Xencor’s attempts to rebut Merus’s arguments fail. More importantly, however, Xencor bears the burden of proof on this issue, and it provides no *affirmative reason* why a reasonable expectation of success would exist. It therefore has not met its burden.

**C. Merus’s Secondary Considerations Establish Nonobviousness of the Challenged Claims**

**1. Gunasekaran Teaches Away**

Dr. Sutton explained in his declaration that the Gunasekaran reference (EX1012) “clearly instructed POSAs not to modify the neutral residues in the hydrophobic core of the CH3 region or in the hydrophobic region of the CH3-CH3 interface.” EX2019 at ¶¶ 11,12. From this, Dr. Sutton concluded that Gunasekaran taught away from the claimed invention. *Id.* at ¶ 153. Xencor apparently disagrees, and alleges, without any expert analysis, that Gunasekaran “in no way discourages modification of neutral-to-charged substitutions.” Reply at 21. The Board should credit Dr. Sutton’s expert opinion over Xencor’s attorney argument.

Although Xencor suggests that because Kannan (EX1007), whose authors overlap with those of Gunasekaran, allegedly disclosed the possibility of using neutral-to-charged substitutions, Gunasekaran should not be understood to teach away from doing so. But this conclusion does not logically follow. Gunasekaran published more than a year after the application leading to Kannan was filed. It would therefore have been perfectly reasonable for a POSA – who is deemed to have been aware of the relevant prior art – to assume that the Gunasekaran authors only recognized the difficulties associated with modifications to the hydrophobic core after filing EX1007, but before drafting the Gunasekaran reference, thus leading to inclusion of the warning in the latter.

Xencor also suggests that, since Lazar incorporates by reference Gunasekaran and nevertheless “still made numerous neutral-to-charged substitutions in the hydrophobic core of the CH3 domain,” Gunasekaran cannot have taught away from doing so. Reply at 21. Such an inference similarly requires far too much speculation to be credited.

**D. The Dependent Claims Are Not Obvious Over *Lazar* and *Lazar* In View Of *Kannan***

Dependent Claims 2-7 include all of the elements of independent claim 1. For the same reasons that independent claim 1 is not obvious, none of dependent claims 2-7 is obvious. *See In re Fritch*, 972 F.2d 1260, 1266 (Fed. Cir. 1992).

#### IV. 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, 4,682 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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