

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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Patent No. 11,926,859

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**PETITION FOR *INTER PARTES* REVIEW  
OF U.S. PATENT NO. 11,926,859**

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EX1006	International Patent Application Publication No. WO 1998/050431 A2 to Arathoon <i>et al.</i> (“Arathoon”)
EX1007	International Patent Application Publication No. WO 2009/089004 A1 to Kannan <i>et al.</i> (“Kannan”)
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EX1011	<i>Excerpts from</i> Kenneth Murphy <i>et al.</i> , <i>Janeway’s Immunobiology</i> (7th ed. 2008)

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<sup>1</sup> Citations to non-patent publications are to the original page numbers of the publication, and citations to U.S. patents are to the column:line number of the patents.

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EX1013	Roland Kontermann, <i>Dual targeting strategies with bispecific antibodies</i> , MABS, 4(2), 182-197 (2012)
EX1014	<i>Reserved</i>
EX1015	John Ridgway <i>et al.</i> , “ <i>Knobs-into-holes</i> ” <i>engineering of antibody CH3 domains for heavy chain heterodimerization</i> , PROTEIN ENGINEERING, 9(7), 617-621 (1996)
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EX1017	A. Margaret Merchant <i>et al.</i> , <i>An efficient route to human bispecific IgG</i> , NATURE BIOTECH., 16(7), 677-81 (1998)
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EX1024	Hui F. Liu <i>et al.</i> , <i>Recovery and purification process development for monoclonal antibody production</i> , MABS, 2(5), 480-499 (2010)

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EX1027	Jonathan Marvin & Zhenping Zhu, <i>Recombinant approaches to IgG-like bispecific antibodies</i> , ACTA PHARMACOLOGICA SINICA, 26(6), 649-658 (2005)
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EX1035	U.S. Patent Application No. 13/866,747
EX1036	U.S. Patent No. 10,472,427 to Desjarlais <i>et al.</i> (“ <i>Desjarlais</i> ”)
EX1037	U.S. Provisional Patent Application No. 61/780,310
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EX1050	Bibliographic Data, U.S. Patent Application No. 13/866,747, Patent Center, USPTO

## I. INTRODUCTION

Petitioner Xencor, Inc. requests *inter partes* review of claims 1-7 of U.S. Patent No. 11,926,859 (“the ’859 patent”). According to PTO records, the ’859 patent is assigned to Merus N.V. (“Patent Owner” or “Merus”). The ’859 patent is generally directed to heterodimeric antibodies—antibodies made from two (“-dimeric”) different (“hetero-”) parts. Specifically, the ’859 patent claims heterodimeric antibodies with a positively charged amino acid substitution in one CH3 domain and a negatively charged amino acid substitution in the other CH3 domain at two precise positions—364 and 368, respectively.

But Merus did not disclose antibodies with such modifications at both the 364 and 368 positions on different CH3 domains until it belatedly attempted to claim them in the application that issued as the ’859 patent (Application No. 18/318,507 (“the ’507 application”). Because these limitations are not supported by any application to which the ’859 patent claims priority, these new claims—the challenged claims—are entitled to a filing date of no earlier than May 16, 2023, the actual filing date of the ’507 application.

By contrast, long before Merus attempted to claim (let alone disclose) modifications on the 364 and 368 positions on a first and second CH3 domain, respectively, Xencor disclosed such modifications in both: (1) an issued Xencor patent effectively filed ten years before the ’859 patent (“*Desjarlais*”), and (2) a

Xencor-authored scientific article published four years before the '859 patent was filed ("*Moore*"). Through the claims challenged in this proceeding, Merus has attempted to work backwards and capture Xencor's published work. But in doing so, Merus forfeits any priority entitlement and renders the copied Xencor work prior art. *Desjarlais* and *Moore* individually disclose each and every claim limitation, and thus both anticipate all claims in the '859 patent.

Moreover, even if Merus were allowed to stitch together disparate teachings in its priority applications in an attempt to show earlier written description support for its claims, every claim of the '859 patent remains unpatentable. An even earlier Xencor patent publication (*Lazar*) disclosed or suggested all of the limitations of the '859 patent claims, particularly when read in view of *Kannan*—a well-known reference that *Lazar* and the '859 patent itself both identify as teaching positively and negatively charged amino acid substitutions in the CH3 domain to promote heterodimerization. The combination of *Lazar* and *Kannan* thus renders obvious all claims in the '859 patent. (EX1002, ¶¶98-102.)

Xencor requests that the Board institute a trial and find all challenged claims unpatentable.

## II. MANDATORY NOTICES

**Real Parties-in-Interest:** Pursuant to 37 C.F.R. § 42.8(b)(1), Petitioner identifies Xencor, Inc. as the real party-in-interest.

**Related Matters:** Pursuant to 37 C.F.R. § 42.8(b)(2), Petitioner states that the '859 patent is being asserted in the following pending litigation: *Merus N.V. v. Xencor, Inc.*, C.A. No. 24-913-CFC (D. Del.). In the district court litigation, Merus also asserts U.S. Patent No. 9,358,286, which is a patent family member to the '859 patent, as well as U.S. Patent No. 9,944,695. Petitioner is concurrently filing an IPR petition challenging U.S. Patent No. 9,358,286.

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### **III. PAYMENT OF FEES**

The PTO is authorized to charge any fees due during this proceeding to Deposit Account No. 50-2613.

#### IV. GROUNDS FOR STANDING

Petitioner certifies that the '859 patent is available for review and that Petitioner is not barred or estopped from requesting review on the grounds identified herein.

#### V. PRECISE RELIEF REQUESTED AND GROUNDS RAISED

Petitioner respectfully requests review of claims 1-7 of the '859 patent on the following grounds:

**Ground 1:** Claims 1-7 are anticipated by *Desjarlais* (EX1036).

**Ground 2:** Claims 1-7 are anticipated by *Moore* (EX1038).

**Ground 3:** Claims 1-7 are unpatentable as obvious over *Lazar* (EX1004) alone or in view of *Kannan* (EX1007).

*Desjarlais*, *Lazar*, and *Kannan* qualify as prior art under at least 35 U.S.C. §§ 102(a)(1) and 102(a)(2), and *Moore* qualifies as prior art under at least § 102(a)(1). (Sections VIII.A-D.)<sup>2</sup>

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<sup>2</sup> According to PTO records, the '859 patent is an AIA patent. (EX1050.) Merus acknowledged this during prosecution of an ancestor application for the '859 patent by noting it included claims not entitled to an earlier priority date. (EX1045, 4 (Application Data Sheet filed with Application No. 13/866,747).)

## VI. BACKGROUND

### A. Technology Overview

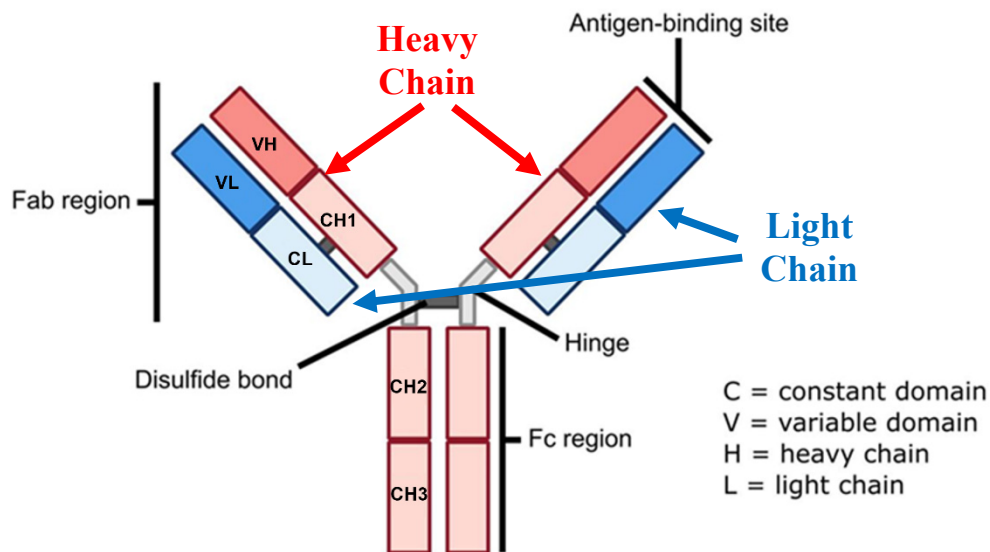
Antibodies are proteins made by the body, including in response to infection. (EX1002, ¶¶19-23.) Their role in the immune system is to seek out and bind to particular portions (“epitopes”) of particular targets (“antigens”), thereby neutralizing disease-causing agents (“pathogens”). (EX1002, ¶23.) Antibodies typically bind very specifically to the target, meaning they do not indiscriminately bind other molecules. (EX1002, ¶21.) These pathogen-neutralizing and binding-specificity characteristics make antibodies attractive for use as therapeutic agents. (EX1002, ¶¶21-22.)

For these reasons, antibody-based therapeutics have been in development for decades. (*E.g.*, EX1004, ¶¶3-4; EX1002, ¶¶20-36.) By the 2012 timeframe (*i.e.*, earliest alleged priority date of the ’859 patent), antibody engineering and production had progressed significantly, such that antibody therapeutics had already become widely utilized to treat a variety of diseases, including cancers and other disorders. (EX1001, 1:41-55; EX1002, ¶¶20-40.)

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Even if the ’859 patent were a pre-AIA patent, however, *Lazar* and *Kannan* would qualify as prior art under at least pre-AIA § 102(a), (b), and (e).

The most common class of antibodies (also referred to as “immunoglobulins”) is immunoglobulin G, or “IgG.” The basic structure of natural IgG comprises four protein chains—two identical heavy chains (shown in red) and two identical light chains (shown in blue)—which are arranged in a Y-shaped configuration:

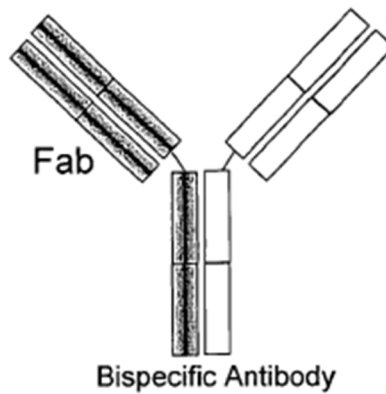


(EX1013, 112-13; EX1002, ¶¶23-31.) These four amino acid chains are generated within a cell and self-assemble to form the antibody. (EX1002, ¶¶26-31.) The top two arms of the Y include antigen binding sites, which is why those portions are called the “Fab” (Fragment antigen-binding) region. (EX1013, 112-15, Fig. 3.3; EX1002, ¶28.) The lower portion of the Y is the “Fc” (Fragment crystallizable) region. (EX1002, ¶29.) As shown above, this Fc portion in natural IgG is comprised of two pairs of Constant Heavy domains—CH2 and CH3. (EX1002,

¶¶28-29.) The CH3 domains, specifically, play a critical role in the pairing of the two heavy chains, called “dimerization” or “Fc dimerization” in the context of the CH3 domain—part of the Fc region—pairing. (EX1002, ¶30.) The pairing of the light chains to the heavy chains can occur before or after this heavy chain dimerization. (EX1002, ¶31.)

Because the two halves of the common antibody structure shown above (one heavy chain + one light chain) are identical, this is known as a “homodimeric” antibody. (EX1002, ¶¶26-27.) Furthermore, because the two Fab regions and antigen binding sites are identical, this is a “monospecific” antibody—meaning it binds to only one target. (EX1002, ¶27.) At the relevant time, the industry had also built other antibody constructs from this basic structure to improve antibody therapeutics and develop new uses thereof. (EX1002, ¶¶32-36; EX1013, Figure 2.)

One of those improvements was bispecific antibodies, which were well known in the art by 2012. (*See, e.g.*, EX1036, Fig. 1; EX1038, Fig. 1; EX1007, Fig. 2; EX1002, ¶¶32-39.) As their name suggests, these antibodies are capable of simultaneously engaging two targets. (EX1004, ¶38; EX1006, 1, 10; EX1013, 183; EX1002, ¶32.) One, non-limiting example of a bispecific antibody structure is shown below:



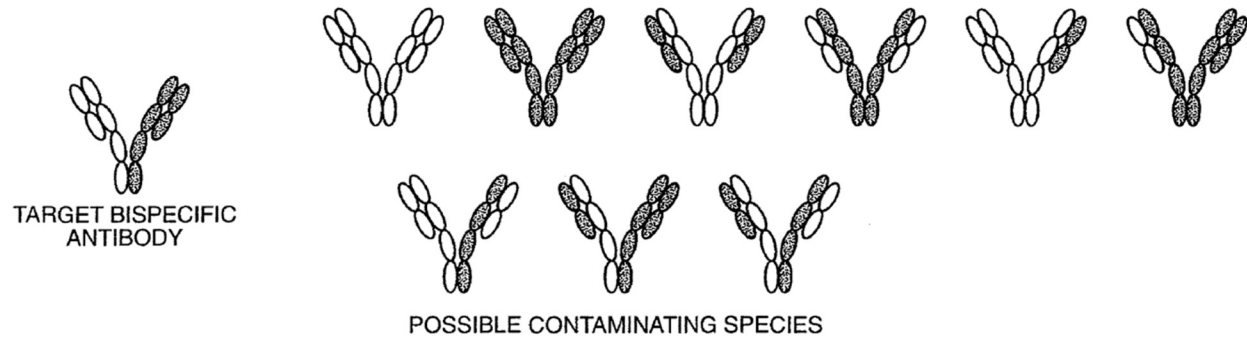
(EX1007, Fig. 2)

In the structure above, the antigen binding regions at the end of each tip at the top of the “Y” are different. One way this can be accomplished is by including one heavy and light chain pair from one antibody with specificity for a particular antigen with a heavy and light chain pair from a different antibody with specificity for a different antigen, as shown above. (EX1002, ¶33.)

The capability of bispecific antibodies to simultaneously bind different targets allowed for new therapeutic mechanisms and provided an attractive area for research and development by the 2012 timeframe. (EX1002, ¶¶34-36; EX1013, 184-185, Table 1 (describing a variety of bispecific antibody therapies in development by March 2012), Figure 2 (instructing that “more than 45 different [bispecific antibody formats] have been established” in this timeframe.)

One area of particular focus was achieving high yields for bispecific antibody production, which was limited primarily by undesired interactions

between heavy chains and light chains. (EX1002, ¶¶41-45.) As illustrated in the graphic below, two main undesired interactions during self-assembly in cells can occur: (1) mismatching of the heavy chains; and (2) mismatching of the light chain to the heavy chain.



(EX1006, Fig. 1A.)

By 2012, there were several strategies known in the art to mitigate these mismatch problems. (EX1002, ¶¶41-58.) To address heavy chain mismatching, one set of techniques involved modifying the CH3 domains in the Fc region of the heavy chains to favor mixed-chain pairing (heterodimerization) and disfavor same-chain pairing (homodimerization). (EX1002, ¶¶44-45; EX1013, 184; EX1017, 677.) Early efforts included a “knob-into-hole” (KIH) strategy, which involved introducing a protuberance (knob) in one CH3 domain and a corresponding cavity (hole) in the complementary CH3 domain of the second heavy chain to achieve a lock-in-key mechanism. (EX1001, 4:49-5:2; EX1007, 2:5-21; EX1002, ¶¶46-49.) As research progressed, scientists also introduced electrostatic interactions, which

involved replacing residues within the two different CH3 regions with oppositely charged amino acid residues, such that mixed-chain pairing was electrostatically favored and same-chain pairing disfavored (also referred to herein as “electrostatic engineering” or “electrostatic steering”). (EX1007, 2:33-3:13; EX1012, 19637; EX1016, 188-190; EX1002, ¶¶52-58.) As discussed below, *Desjarlais*, *Moore*, *Lazar*, and *Kannan* all disclose such CH3-domain modification techniques. (EX1002, ¶¶71-97.)

## **B. '859 Patent Overview**

The '859 patent, titled “Methods and Means for the Production of Ig-Like Molecules,” issued on March 12, 2024 from U.S. Patent Application No. 18/318,507, which was filed on May 16, 2023. (EX1001, Cover; EX1002, ¶¶59-70.) The '859 patent purports to claim priority through a chain of continuation applications to Application No. 13/866,747, filed on April 19, 2013, which further purports to claim priority to a provisional application filed on April 20, 2012.<sup>3</sup> As

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<sup>3</sup> As noted above, Merus recognized during prosecution of the '747 application that the '747 application included claims not supported by the provisional application, and hence the continuation '859 patent is also an AIA patent. Furthermore, because the '859 patent is not entitled to the priority it claims (Section X), its effective date is after March 16, 2013, making it an AIA patent.

discussed below, however, the claims of the '859 patent are not entitled to the benefit of these earlier applications. (Section X.)

Generally speaking, the '859 patent concerns “Ig-like molecules” and “antibod[ies],” which it defines broadly as not only including the native antibody structures, but also “functional derivative[s] and/or fragment[s]” of any of the Ig isotypes known in the art (such as IgG1). (*Id.*, 11:39-48.)

The Background section of the '859 patent acknowledges that “it is well-known that the CH3-CH3 interaction is the primary driver for Fc dimerization.” (*Id.* at 4:21-22.) According to the '859 patent, it was also “well-known” that the CH3 domains of interacting heavy chains “meet in a protein-protein interface which comprises ‘contact’ residues.” (*Id.*, 4:24-28.) Those contact residues are described as “known,” having “been identified” previously in the prior art, with the '859 patent listing those contact residues in Table A. (*Id.*, 12:44-13:61; *see also* EX1007, 3-4 (Table 1).)

The '859 patent also recites known strategies for increasing heterodimer formation through engineering CH3 domains, including knob-into-hole engineering and electrostatic engineering, among others. (EX1001, 4:46-6:3.) These various methods, according to the '859 patent, could be combined to “achieve said further improved percentages of desired (bispecific) antibodies.” (*Id.*, 6:10-14.)

The '859 patent claims heterodimeric antibodies that use electrostatic engineering. (*Id.*, 69:33-70:44.) And although the '859 patent admits that “electrostatic engineering” was known in the prior art, it attempts to distinguish prior-art techniques as supposedly being limited to a “charge reversal strategy” (*i.e.*, modifying an already-charged amino acid residue to the opposite charge). (*Id.*, 5:34-49 (citing *Kannan* (“WO2009/089004”)), 18:35-38.) According to the '859 patent, “[t]he present invention . . . does not exchange charged contact amino acids by amino acids of opposite charge[,] but substitutes non-charged CH<sub>3</sub> amino acids for charged ones.” (*Id.*, 18:42-45; *see also id.*, 13:33-49.) The '859 patent contends these neutral-to-charged mutations to be “an inventive alternative to” the prior art. (*Id.*, 18:39-45; *but see* Sections XI.A.1.ii, XI.B.1.ii, XI.C.1.ii.) However, as discussed below, *Kannan*—along with *Desjarlais* and *Moore*—expressly teaches applying its electrostatic techniques to “uncharged residues” as well. (Section VIII.D; EX1007, 10:16-18.)

The sole independent claim in the '859 patent recites a “heterodimeric antibody comprising a first human CH<sub>3</sub> domain comprising a positively charged amino acid residue at position 364 . . . and a second human CH<sub>3</sub> domain comprising a negatively charged amino acid residue at position 368 . . . .” (*Id.*, Claim 1.) But the '859 patent (and each of its parent applications) lacks any

disclosure of a heterodimeric antibody having this claimed pair of amino acid modifications.

**C. '859 Patent Prosecution History**

Merus filed the application leading to the '859 patent on May 16, 2023, over 10 years after the filing of the provisional application to which the '859 patent purports to claim priority. (EX1001.) With that application, Merus filed a preliminary amendment, replacing all pending claims with nine new claims. (EX1029, 174-75.)

Of those nine new claims, seven (claims 29-31 and 34-37) became the issued claims in the '859 patent and two (claims 32-33) were cancelled. (*Compare id.*, 174-75 (claims 29-37) *with* EX1001, (claims 1-7).) In the preliminary amendment, Merus did not attempt to point to written description support for each claim individually, and instead argued that “[s]upport for the new claims can be found throughout the specification, *inter alia*, at Example 13 and Table 7, and in the claims as originally filed.” (*Id.*, 176.)

The Examiner issued only one office action during prosecution. (*Id.*, 217-24.) In that office action, the Examiner did not reference or analyze any prior art, but instead rejected all claims on several double patenting grounds. (*Id.*) The Examiner rejected claims 29, 34, 35, and 37 for statutory double patenting over four claims in the parent application. (*Id.*, 217-19.) The Examiner also noted that

even if claim 29 had been allowable, claims 32-33 would have been rejected for being “substantial duplicate[s].” (*Id.*, 220.) Finally, the Examiner rejected all pending claims for nonstatutory double patenting over four issued Merus patents and provisionally rejected the claims over the parent patent application that was still pending. (*Id.*, 222-24.)

Merus overcame these rejections by cancelling certain claims in the parent application, canceling claims 32 and 33, and filing a terminal disclaimer. (*Id.*, 249-51 (terminal disclaimer), 255-59 (claim amendment and applicant remarks).) The ’859 patent issued thereafter. (*Id.*, 260-63.)

## **VII. LEVEL OF ORDINARY SKILL**

A person of ordinary skill in the art at the time of the alleged invention (“POSA”) would have at least an advanced degree (*e.g.*, a Master’s or Ph.D.) in biochemistry, process chemistry, protein chemistry, chemical engineering, molecular and structural biology, biochemical engineering, or similar disciplines; several years of post-graduate training or related experience (including industry experience) in one or more of these areas; and two or more years of experience in the production of bispecific antibodies. (EX1002, ¶¶16-18.)

## VIII. PRIOR ART OVERVIEW

### A. *Desjarlais* (EX1036)

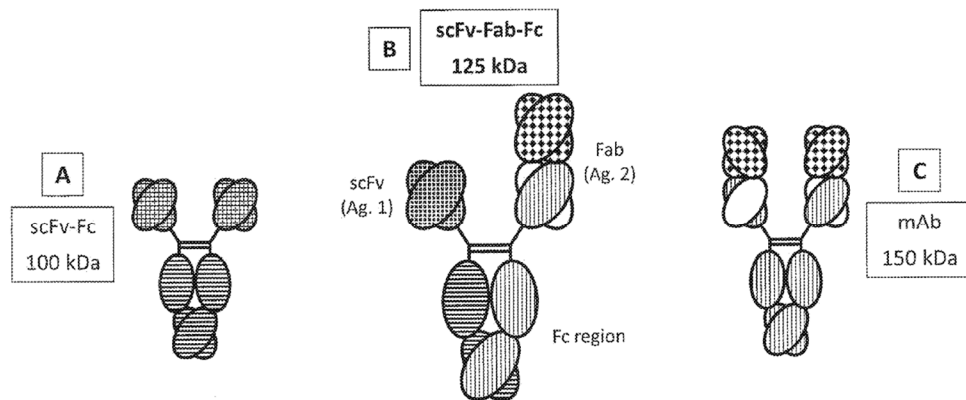
*Desjarlais* is a Xencor issued patent titled “Heterodimeric Proteins,” filed on June 26, 2017. (EX1036, Cover.) *Desjarlais* issued on November 12, 2019 as U.S. Patent No. 10,472,427. (*Id.*) *Desjarlais* claims priority to, *inter alia*, U.S. Provisional Application No. 61/780,310, which was filed on March 13, 2013 and contains the same disclosures as those relied on in *Desjarlais* in this petition. (*Id.*; EX1037.) *Desjarlais* thus is prior art to the ’859 patent under at least 35 U.S.C. §§ 102(a)(1) and 102(a)(2).

*Desjarlais* is directed to “novel immunoglobulin compositions” that “utilize heterodimeric Fc regions,” which can be used “for therapeutic purposes.” (*Id.*, 1:34-40; EX1002, ¶¶71-78.) *Desjarlais* discloses certain “heterodimerization variants,” which are specific amino acid modifications made to the Fc region that favor heterodimerization. (EX1036, 3:36-4:2; *see also id.*, Figs. 4-5; EX1002, ¶¶74-76.)

Several of *Desjarlais*’ heterodimerization variants include mutations to two heavy chains, modifying the 364 position in one chain to a positive residue (lysine (K)) and modifying the 368 position in another chain to a negative residue (either aspartic acid (D) or glutamic acid (E)). (EX1036, 3:45-4:2; *see also* Figs. 4, 5;

EX1002, ¶¶74-76.) Each of these variants are identified by *Desjarlais* as “preferred” variants. (EX1036, Figs. 4, 5.)

*Desjarlais* teaches that these variants are useful for generating bispecific antibodies—“antibody formats that engage two different antigens.” (EX1036, 1:51-53, 3:37-4:2, 52:61-63; *see also id.*, Figs. 4, 5; EX1002, ¶73.) These variants can be applied to various bispecific formats, such as the following illustrated in Figure 1:<sup>4</sup>



(EX1036, Figs. 1A-C.)

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<sup>4</sup> *Desjarlais* also teaches the use of these heterodimerization variants in a wide variety of other multispecific formats, such as those shown in Figures 2 and 3. (EX1036, Figs. 2-3.)

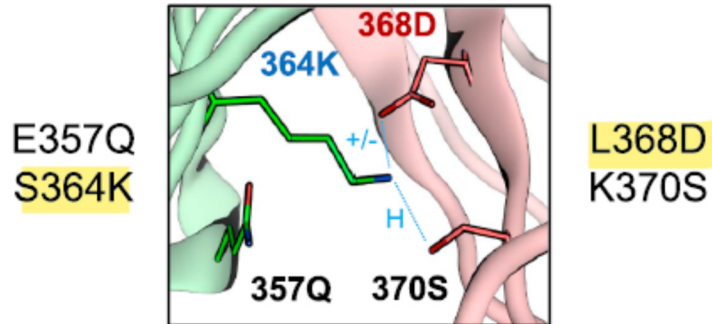
**B. *Moore* (EX1038)**

*Moore* is a peer-reviewed article authored by Xencor scientists titled, “A robust heterodimeric Fc platform engineered for efficient development of bispecific antibodies of multiple formats.” (EX1038, 38.) *Moore* published in the journal *Methods* and was publicly available as of October 23, 2018. (*Id.*) *Moore* thus is prior art to the '859 patent under at least 35 U.S.C. § 102(a)(1).

Like *Desjarlais*, *Moore* describes making bispecific, heterodimeric antibodies by modifying amino acids in the Fc region. (*Id.*, Abstract; EX1002, ¶¶79-83.) Specifically, *Moore* teaches “a robust heterodimeric Fc platform, called the XmAb<sup>®</sup> bispecific platform,” which was “engineered for efficient development of bispecific antibodies and Fc fusions of multiple formats.” (*Id.*, 39.) *Moore* teaches that “design of a heterodimeric Fc” involves the “design of two complementary CH3 domains” which have a “strong preference for pairing with each other” (*i.e.*, forming heterodimers) as opposed to “pairing with themselves” (*i.e.*, forming homodimers). (*Id.*)

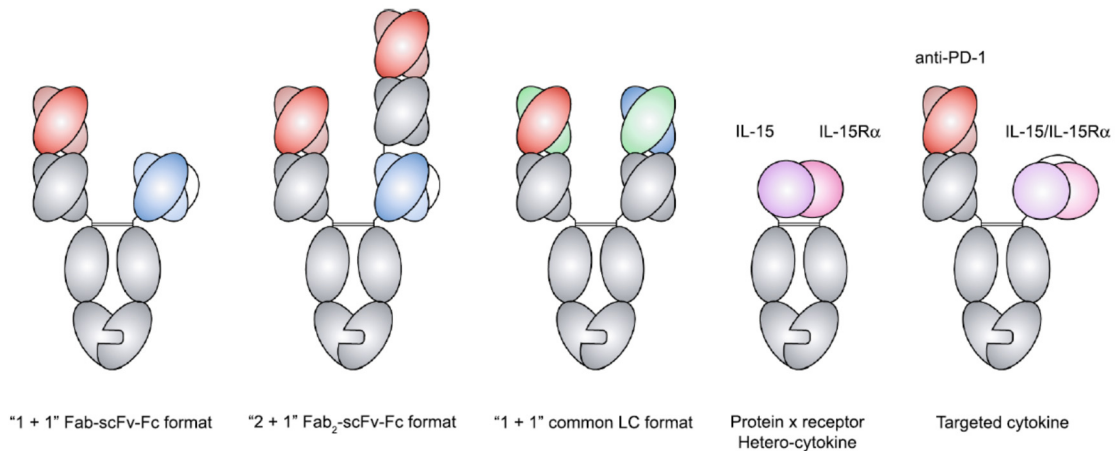
*Moore* teaches introducing amino acid substitutions into native IgG1, which includes inserting the positively charged lysine (K) at position 364, and the negatively charged aspartic acid (D) at position 368. (*Id.*, 39, 43, Figure 5.) Two additional mutations, a glutamine (Q) at position 357 and a serine (S) at position

370 were also introduced, leading to the combination variant E357Q/S364K-L368D/K370S. (*Id.*, 43.)



(*Id.*, Figure 5.)

*Moore* teaches that its XmAb platform can be used in a variety of bispecific formats:



(EX1038, Fig. 1; 45 (“a robust heterodimeric Fc region enables a wide variety of possible formats (Fig. 1)”), 49.)

*Moore* further discloses using the XmAb platform to produce several heterodimeric, bispecific antibodies that are being studied in the clinic. (*Id.*, 49

(“Our Fc heterodimer technology has proven to be an efficient component to rapidly enable multiple clinical bispecific candidates.”.)

**C. *Lazar* (EX1004)**

*Lazar* is a publication of a patent application filed by Xencor on September 10, 2010, titled “Compositions and Methods for Simultaneous Bivalent and Monovalent Co-engagement of Antigens.” (EX1004, Cover.) *Lazar* published on March 3, 2011. (*Id.*) *Lazar* thus is prior art to the ’859 patent under at least 35 U.S.C. §§ 102(a)(1) and 102(a)(2). *Lazar*, like *Desjarlais* and *Moore*, teaches methods for producing bispecific, heterodimeric antibodies. (EX1004, Abstract.)

*Lazar* discloses “Fc Modifications,” which are amino acid substitutions at certain locations on the Fc region of the heavy chains—specifically on the CH3 domain. (*Id.*, ¶¶114-25; EX1002, ¶¶84-91.) *Lazar* discloses a number of different amino acid positions for modifications, teaching and experimentally testing particular substitutions. (EX1004, ¶123, Figs. 5-7; EX1002, ¶¶90-91.) *Lazar* teaches modifications where neutral amino acids are replaced with charged ones, such as lysine (K) or arginine (R) for positive charges, and aspartic acid (D) or glutamic acid (E) for negative charges. (EX1004, ¶¶52, 123.) *Lazar* discloses that positions 364 and 368 in the Fc region can have amino acid substitutions:

In one embodiment of the invention, said variant Fc regions comprise at least one substitution at a position selected from the group consisting

of 349, 351, 354, 356, 357, **364**,<sup>5</sup> 366, **368**, 370, 392, 394, 395, 396, 397, 399, 401, 405, 407, 409, 411, and 439, wherein numbering is according to the EU index as in Kabat.

(EX1004, ¶¶52, 123.)

*Lazar* also teaches modifying positions 364 and 368 in tandem—on a first and second CH3 domain—in a single heterodimeric antibody, as shown below.

(*Id.*, ¶123.)

TABLE 1

Preferred CH3 domain variants that favor Fc heterodimerization.	
Variant 1	Variant 2
F405A	T394F
S364D	Y349K
<b>S364E</b>	<b>L368K</b>
S364E	Y349K
S364F	K370G
S364H	Y349K
S364H	Y349T
S364Y	K370G
T411K	K370E
V397S/F405A	T394F
K370R/T411K	K370E/T411E
L351E/S364D	Y349K/L351K
L351E/S364E	Y349K/L351K
L351E/T366D	L351K/T366K
P395T/V397S/F405A	T394F
S364D/K370G	S364Y/K370R
S364D/T394F	Y349K/F405A
S364E/F405A	Y349K/T394F
S364E/F405S	Y349K/T394Y
S364E/T411E	Y349K/D401K
S364H/D401K	Y349T/T411E
S364H/F405A	Y349T/T394F
S364H/T394F	Y349T/F405A
Y349C/S364E	Y349K/S354C
L351E/S364D/F405A	Y349K/L351K/T394F
L351K/S364H/D401K	Y349T/L351E/T411E
S364E/T411E/F405A	Y349K/T394F/D401K
S364H/D401K/F405A	Y349T/T394F/T411E
S364H/F405A/T411E	Y349T/T394F/D401K

(EX1004, ¶241 (Table 1).)

<sup>5</sup> All emphasis added unless otherwise noted.

**D. *Kannan* (EX1007)**

*Kannan* is a publication of an international patent application titled “Method for Making Antibody Fc-Heterodimeric Molecules Using Electrostatic Steering Effects.” (EX1007, 1.) *Kannan* was filed on January 6, 2009, and published on July 16, 2009, making it prior art under at least 35 U.S.C. §§ 102(a)(1) and 102(a)(2). (*Id.*, Cover.)

*Kannan* teaches “Fc heterodimeric molecules” with CH3 domain variations allowing for electrostatic steering effects to promote heterodimerization. (EX1007, Title, 2:33-3:13; EX1002, ¶¶92-97.) As *Kannan* describes, “by replacing one or more residues that make up the CH3-CH3 interface in both CH3 domains with a charged amino acid . . . homodimer formation [becomes] electrostatically unfavorable but heterodimerization [becomes] electrostatically favorable.” (*Id.*, 2:35-37.) The first step was to identify the CH3-CH3 interface, which *Kannan* did in Figure 4 and Table 1 “based on the IgG1 human Fc crystal structure.” (EX1007, 5:13-16, 7:19-8:7.) *Kannan* also identified the residues on the CH3 domain interface that naturally formed a charged pair. (EX1007, 7:19-8:7 (Table 7 bolding those pairs).) In one embodiment, *Kannan* teaches reversing the charges of the pair of interface positions.

Table 2a: List of some possible pair-wise charge residue mutations to enhance heterodimer formation<sup>a</sup>

Position in the First Chain	Mutation in the First Chain	Interacting Position in the Second Chain	Corresponding Mutation in the Second Chain
Lys409	Asp or Glu	Asp399'	Lys or Arg <sup>b</sup>
Lys392	Asp or Glu	Asp399'	Lys or Arg <sup>b</sup>
Lys439	Asp or Glu	Asp356'	Lys or Arg <sup>b</sup>
Lys370	Asp or Glu	Glu357'	Lys or Arg <sup>b</sup>
Asp399	Lys or Arg <sup>b</sup>	Lys409'	Asp or Glu
Asp399	Lys or Arg <sup>b</sup>	Lys392'	Asp or Glu
Asp356	Lys or Arg <sup>b</sup>	Lys439'	Asp or Glu
Glu357	Lys or Arg <sup>b</sup>	Lys370'	Asp or Glu

<sup>a</sup>Combinations of the above pair-wise charge residue mutations could also be used. For example Lys409 --- Asp399' interaction pair mutations could be combined with Lys439 --- Asp356' pair mutations.

(EX1007, 9 (Table 2a).)

As one example of its disclosed charge-reversal embodiment, as shown above in Table 2a, *Kannan* teaches changing a negative aspartic acid (D or “Asp”) at position 356 to a positive residue, either lysine (K or “Lys”) or arginine (R or “Arg”). (*Id.*) And *Kannan* teaches modifying the positive lysine (K) in the corresponding 439 position on the other chain to a negative residue, either aspartic acid (D) or glutamic acid (E or “Glu”). (*Id.*) This charge-reversal technique—and *Kannan* itself (identified as “WO2009/089004”)—was expressly referenced by the '859 patent. (EX1001, 5:34-49.) *Kannan*, however, was not limited to this charge reversal embodiment, and instead taught more broadly that “[t]his strategy can also

be extended to modifying uncharged residues to charged residues at the CH3 domain interface.” (EX1007, 10:16-18.)

*Kannan* also teaches that an “important application of Fc heterodimeric molecules is the generation of bispecific antibodies (BsAbs).” (EX1007, 1:29-35.)

*Kannan* describes that such “heterodimeric proteins may be particularly useful in therapeutic compositions” such as those containing a “pharmaceutically acceptable buffer.” (EX1007, 4:23-25, 30 (Claim 82).)

## **IX. CLAIM CONSTRUCTION**

Claim terms need only be construed “to the extent necessary to resolve the controversy.” *Vivid Techs., Inc. v. Am. Sci. & Eng’g, Inc.*, 200 F.3d 795, 803 (Fed. Cir. 1999). Petitioner submits that no terms of the ’859 patent require construction to resolve the challenges in this Petition. (EX1002, ¶¶103-04.)

## **X. THE CHALLENGED CLAIMS ARE NOT ENTITLED TO CLAIM PRIORITY BEFORE THEIR ACTUAL FILING DATE**

The ’859 patent, on its face, claims priority to a continuation chain of five non-provisional patent applications and one provisional application. (EX1001, Cover.) In order to be entitled to an effective filing date as of the filing of those prior applications, “each previous application in the chain must comply with the written description requirement of 35 U.S.C. § 112(a).” *L.A. Biomedical Rsch. Int. v. Eli Lilly & Co.*, 849 F.3d 1049, 1057 (Fed. Cir. 2017). “Patent claims are awarded priority on a claim-by-claim basis based on the disclosure in the priority

applications.” *Lucent Techs., Inc. v. Gateway, Inc.*, 543 F.3d 710, 718 (Fed. Cir. 2008).

The challenged claims contain subject matter first introduced with Merus’s preliminary amendment filed on May 16, 2023. (EX1029, 172-77.) The challenged claims do not have written description support in any application to which the ’859 patent claims priority, and thus are not entitled to an effective filing date before May 16, 2023. As such, *Desjarlais* and *Moore* are prior art under 35 U.S.C. § 102(a)(1) because they published more than a year before Merus filed the ’859 patent’s claims. *See Parus Holdings, Inc. v. Google LLC*, 70 F.4th 1365, 1373 (Fed. Cir. 2023) (“Because [Patent Owner] asserted that Kurnagov-262 is not prior art by claiming priority from the application from which it stems, the Board needed to determine whether the challenged claims satisfied the written description requirement.”); *Motorola Mobility LLC v. Largan Precision Co., Ltd.*, IPR2022-01156, Paper 13, 9 (Jan. 4, 2023) ; *Daiichi Sankyo Co., Ltd. v. Alethia Biotherapeutics, Inc.*, IPR2015-00291, Paper 75, 6-19 (Jun. 14, 2016) (finding in IPR proceedings that the “challenged claims [were] not entitled to the benefit of priority” of earlier applications where parent application failed to enable or “adequately describe the subject matter of the challenged claims”); 35 U.S.C.

§ 100(i)(1)(A); *Dr. Reddy's Labs. S.A. v. Indivior UK Ltd.*, IPR2019-00329,  
Paper 21 at 14, 23-26 (June 3, 2019).<sup>6</sup>

**A. The Written Description Standard**

Section 112 requires that “[t]he specification shall contain a written description of the invention . . . in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains . . . to make and use the same.” 35 U.S.C. § 112(a). That is, “the specification must describe an invention understandable to that skilled artisan and show that the inventor actually invented the invention claimed.” *Ariad Pharms., Inc. v. Eli Lilly & Co.*, 598 F.3d 1336, 1351 (Fed. Cir. 2010) (en banc).

“[T]he purpose of the written description requirement is to ‘ensure that the scope of the right to exclude, as set forth in the claims, does not overreach the scope of the inventor’s contribution to the field of art as described in the patent specification.’” *ICU Med., Inc. v. Alaris Med. Sys., Inc.*, 558 F.3d 1368, 1376-77 (Fed. Cir. 2009) (alteration in original) (quoting *Univ. of Rochester v. G.D. Searle & Co.*, 358 F.3d 916, 927 (Fed. Cir. 2004)). The requirement “is satisfied only if

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<sup>6</sup> To be clear, Petitioner does not concede the challenged claims have adequate written description support in any application, as Petitioner cannot challenge the claims as invalid under § 112 in an IPR.

the inventor convey[s] with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention, and demonstrate[s] that by disclosure in the specification of the patent.” *Biogen Int’l GmbH v. Mylan Pharms. Inc.*, 18 F.4th 1333, 1341-42 (Fed. Cir. 2021) (internal quotation marks omitted) (quoting *Nuvo Pharm. (Ir.) Designated Activity Co. v. Dr. Reddy’s Labs. Inc.*, 923 F.3d 1368, 1376-77 (Fed. Cir. 2019)). “[I]t is the specification itself that must demonstrate possession.” *Ariad*, 598 F.3d at 1352.

“While the written description requirement does not require that the specification recite the claimed invention in any particular way, pointing to an ‘amalgam of disclosures’ from which an artisan could have created the claimed invention does not satisfy this requirement.” *Flash-Control, LLC v. Intel Corp.*, No. 20-2141, 2021 WL 2944592, at \*3 (Fed. Cir. July 14, 2021) (quoting *Novozymes A/S v. DuPont Nutrition Biosciences APS*, 723 F.3d 1336, 1349 (Fed. Cir. 2013) and citing *Ariad*, 598 F.3d at 1352). “Instead, the specification must present each claim as an ‘integrated whole.’” *Id.* (quoting *Novozymes*, 723 F.3d at 1349). “A patent owner cannot show written description support by picking and choosing claim elements from different embodiments that are never linked together in the specification.” *Id.* at \*4.

The Federal Circuit has rejected that “a ‘laundry list’ disclosure” of every possible aspect of every possible limitation “would constitute a written description

of every species in the genus,” because “such a disclosure would not ‘reasonably lead’ those skilled in the art to any particular species.” *Fujikawa v. Wattanasin*, 93 F.3d 1559, 1571 (Fed. Cir. 1996); *see also Purdue Pharma L.P. v. Faulding Inc.*, 230 F.3d 1320, 1326-27 (Fed. Cir. 2000). And “a description that merely renders the invention obvious does not satisfy the requirement.” *Ariad*, 598 F.3d at 1352.

### **B. New Limitations in the ’859 Patent Claims**

The ’859 patent claims heterodimeric antibodies with specific substitutions made in two distinct CH3 domains to encourage heterodimerization using electrostatic engineering. (EX1002, ¶¶105-08.) The claims recite a heterodimeric antibody made up of two individual heavy chains—each incorporating an amino acid mutation at a precise position (positions 364 and 368 on a first and second chain) made to create an oppositely charged pair of chains. (EX1001, Claim 1.) In particular, the claimed heterodimeric antibody requires that position 364 on a first CH3 domain is mutated to include a positively charged amino acid (“364+”) *and* that position 368 on a second CH3 domain is mutated to include a negatively charged amino acid (“364-”). (*Id.*) Claim 2 requires a more limited set of mutations at that pair of locations (either 364K or 364R and 368D or 368E), and claim 3 requires specific mutations at those locations (364K and 368D). (EX1001, Claims 2 & 3.)

As discussed below, none of the Merus prior applications listed on the face of the '859 patent describes the antibody recited in claim 1 having a positive charge at position 364 on one CH3 domain *and* a negative charge at 368 on a second, distinct CH3 domain, nor did they teach the more particular modifications recited in claims 2 and 3. (EX1002, ¶¶109-22.) The remaining dependent claims 4-7 also lack written description support due to their dependency from claim 1. *See Stored Value Sols., Inc. v. Card Activation Techs., Inc.*, 499 F. App'x. 5, 14 (Fed. Cir. 2012).

**C. No Support in Provisional Application No. 61/635,935**

The earliest priority date claimed on the face of the '859 patent is April 20, 2012, the filing date of Provisional Application No. 61/635,935 (“the '935 Provisional”). (EX1001, Cover; EX1030.) The '935 provisional, however, does not disclose a heterodimeric antibody with the pair of mutations required in claim 1 (364+ and 368-), nor does it disclose the particular species recited in claims 2 and 3 (*e.g.*, 364K and 368D). (EX1002, ¶¶109-19.) In fact, even after providing a prior-art table listing known CH3 domain interface residues that includes positions 364 and 368 (EX1030, 17 (Table A)), the '935 provisional never mentions positions 364 and 368 together as a pair of positions for potential mutations on two chains—not in the written description, in the figures, or in the originally filed claims. (EX1002, ¶¶109-19.)

In the preliminary amendment for the '859 patent, Merus pointed to “Example 13 and Table 7” as purportedly supporting the new claims. (EX1029, 176.) Example 13 and Table 7 are the same in the '859 patent specification and the '935 provisional. (*Compare* EX1001, 39:63-43:40, *with* EX1030, 51-57.) Neither describes an amino acid mutation at position 364 of a first CH3 domain *and* an amino acid mutation at position 368 of a second, different CH3 domain in a heterodimeric antibody, let alone the more specific pair of mutations recited in claims 2 and 3. (EX1002, ¶¶109-19.)

Example 13 regards an “identification of novel charge pair mutants” based on engineered CH3 domains. (EX1030, 51.) None of the identified “pair mutants” involve both positions 364 *and* 368. In fact, none of the tested pairs in Example 13 involved *either* position 364 or 368. (*Id.*, 57 (Table 10, described in more detail below).)

Example 13 describes, as a “first step,” testing modifications in “many interface contact residues in the IgG CH3 domain” to determine if they “would result in repulsion of *identical* heavy chains – i.e., reduced homodimer formation - via electrostatic interactions.” (*Id.*, 51.) In other words, this first step involved testing one type of antibody heavy chain to see if it would inhibit the formation of pairing amongst identical chains—it did not involve a pair of different heavy chains, as the '859 patent claims require. (EX1002, ¶¶111-18.) The results of this

first-step testing are shown in Table 7. (EX1030, 52-54.) Although Table 7 discloses individual “constructs” (*i.e.*, modified heavy chains) with mutations at the 364 and/or 368 positions (including 364K (shown below) and 368D (one of the mutations in construct 42, not shown below)), neither Table 7 nor Example 13 teaches or describes combining *one heavy chain* with a 364 modification *with another chain* with a 368 modification. (EX1002, ¶¶1111-18.)

AA substitutions in CH3	construct #	Effect on homodimer formation (- = no effect; +++ = max. inhibition; NT= not tested on gel)
Q347K	8	-
Y349D	9	+-
Y349K	10	+-
T350K	11	-
T350K, S354K	12	+-
L351K, S354K	13	+-
L351K, T366K	14	++
L351K, P352K	15	+-
L351K, P353K	16	++
S354K, Y349K	17	++
D356K	18	-
E357K	19	-
S364K	20	++
T366K, L351K	21	++
T366K, Y407K	22	+++
L368K	23	NT
L368K, S364K	24	++
N390K, S400K	25	+-
T394K, V397K	26	+

(EX1030, 52 (Table 7, truncated).)

Instead, from this first-step testing, Example 13 identifies “promising” candidate positions for further testing—“Q347, S354, Y349, L351, K360, T366,

T394, and V397.” (*Id.*, 54.) Not one of these includes a substitution at positions 364 or 368 (either alone or individually). From those “promising” positions, Example 13 created seven new constructs (Table 8) and tested those constructs in combination with certain constructs from Table 7—test results shown in Table 10. (EX1030, 56-57; EX1002, ¶¶114-18.) Again, not one of the tested mutation pairs involved a mutation at either the 364 or 368 position. (EX1002, ¶¶114-18.) Table 10 shows the tested pairs of transfection “vectors” containing nucleotide sequences:

Transfection of	Transfection code (ratio)	Expected species	AA found (%)	AC found (%)	CC found (%)	Half A found (%)	Half C found (%)	other (%)
XIII + XVI	ZO (1:1)	AC	0	69	7	24	0	0
	ZT (3:1)	AC	10	45	16	27	0	0
	ZU (1:1)	AC	5	61	10	13	0	0
	ZV (1:3)	AC	3	61	23	13	0	0
	ZW (1:1)	AC	0	88.3	2.4	7	0	2.3
XIV + XVII	ZP	AC	30	52	13	0	0	5
XII + XVIII	ZQ	AC	4	51	33	2	1	8
XV + XIX	ZR	AC	20	42	11	0	1	26
XI + XX	ZS	AC	34	41	15	0	0	10

(EX1030, 57 (Table 10) (annotation added).) As seen above, the tested pairs of vectors involve vectors eleven (XI) to twenty (XX). Table 9 shows the “constructs” within each transfection vector (XI-XX):

Vector	VH gene	Antigen specificity	VH mass (Da)	Cloned in construct #
XI	IGHV 1.08	Tetanus (A)	13703	8
XII	IGHV 1.08	Tetanus (A)	13703	17
XIII	IGHV 1.08	Tetanus (A)	13703	43
XIV	IGHV 1.08	Tetanus (A)	13703	61
XV	IGHV 1.08	Tetanus (A)	13703	62
XVI	IGHV 3.30	Fibrinogen (C)	12794	63
XVII	IGHV 3.30	Fibrinogen (C)	12794	64
XVIII	IGHV 3.30	Fibrinogen (C)	12794	65
XIX	IGHV 3.30	Fibrinogen (C)	12794	66
XX	IGHV 3.30	Fibrinogen (C)	12794	67

(EX1030, 56 (Table 9) (annotation added).) As seen above, the constructs involved in the vectors that were tested in pairs were 8, 17, 43, 61, 62, 63, 64, 65, 66, 67. Tables 7 and 8 provide the mutations within each of those constructs.

(EX1030, 52-56 (Tables 7 & 8).) A summary of the relevant constructs, vectors, and substitutions is given below:

Construct #	Vector	AA substitutions in CH3
8	XI	Q347K
17	XII	S354K, Y349K
43	XIII	T366K
61	XIV	L351K
62	XV	T394K
63	XVI	L351D
64	XVII	T366D
65	XVIII	S354D, Y349D
66	XIV	V397D
67	XX	K360D

(EX1002, ¶118.)

As shown in the table above, while this portion of example 13 *did* involve two chains with different modifications (rather than identical heavy chains), none of these tested construct pairs involved mutations at either the 364 or 368 positions, and certainly not together.

None of these disclosures in the '935 provisional would have conveyed to a POSA that the purported inventors were in possession of a heterodimeric antibody comprising a pair of 364+ *and* a 368- modifications in two different chains, let alone the more specific modifications in claims 2 and 3. (EX1002, ¶119.) And, contrary to Merus's statement in its preliminary amendment, Example 13 would not have led a POSA toward a 364 / 368 pairing, considering that Merus tested mutations at those positions on an individual basis and did not even include them among those it called "promising for further testing." (EX1030, 54; EX1002, ¶¶114-19.)

The '935 provisional also describes "preferred embodiment[s]" describing pairs of mutations on two different chains, most of which revolved around a T366K mutation on one chain and a L351D mutation on another chain. (*See, e.g.*, EX1030, 24-31.) None of those preferred embodiments involved a 364 / 368 pair of modifications. (EX1002, ¶¶114-19.) Likewise, Table B "provides an overview of mutations that can be introduced in CH3 domains as preferred means for

preferential pairing,” but, as shown below, no mutation involved position 364 at all, let alone pairing a 364 / 368 set of modifications. (EX1030, 30.)

AA substitutions in CH3	Construct #	Preferentially pairs with
- (wildtype)	-	Wildtype
E356K, D399K	1	Construct 2 or 3
K392D, K409D	2	Construct 1
K392D, K409D, K439D	3	Construct 1
K392D, D399K, K409D	4	Construct 4
E356K, E357K, K439D, K370D	5	Construct 5
T366W	6	Construct 7
T366S, L368A, Y407V	7	Construct 6
T366K	43	Construct 63, 69, 70, 71, 73
L351D	63	Construct 43, 68
T366K, L351K	68	Construct 63, 69, 70, 71, 72, 75
L351D, L368E	69	Construct 43, 68
L351E, Y349E	70	Construct 43, 68
L351D, Y349E	71	Construct 43, 68
L351D, R355D	72	Construct 43, 68
L351D, Y349E, L368E	73	Construct 43
L351D, Y349D, R355D	75	Construct 68

(EX1030, 31 (Table B).)

Similarly, the remaining examples in the '935 provisional disclose numerous pairs of CH3 domain mutations, but never disclose a 364 / 368 pairing. (*Id.*, 38 (Table 1), 59-60 (Table 11), 61 (Table 12), 62-64 (Example 16 disclosing “mutations around T366K/L351'D”), 66-67 (Table 15).)

The original claims filed with the '935 provisional also do not disclose a 364 / 368 pairing. (EX1030, 72-75.) The only particular sets of modifications

mentioned in those original claims are in claim 25 (T366K on one chain and L351D and L368E on another) and claim 26 (T366K and L351K on one chain and L351D and L368E on another). (*Id.*, 75.)

Without any “blaze marks” to the particular pair of mutations for a heterodimeric antibody that Merus claimed ten years later in the ’859 patent, the ’935 provisional’s disclosure of a “forest” of potential individual mutations cannot satisfy the written description requirement. *See Purdue Pharma L.P. v. Faulding Inc.*, 230 F.3d 130, 1326-27 (Fed. Cir. 2000).

**D. No Support in Any Non-Provisional Application**

The ’859 patent also claims priority from five non-provisional applications that share a specification with the ’859 patent: U.S. Patent Application Nos. 16/934,925, 16/417,379, 15/155,743, 14/081,848, and 13/866,747. (EX1001, Cover; EX1031; EX1032; EX1033; EX1034; EX1035.) None of these applications, including their originally filed claims, discloses a 364 / 368 pair of modifications, as recited in the ’859 patent claims. (EX1002, ¶¶120-22.) As mentioned above, Merus’s preliminary amendment pointed to Example 13 and Table 7 as purported support for the ’859 patent claims. (EX1030, 176.) But this example and table are the same as described above for the ’935 provisional, and thus fail to provide sufficient written description for the same reasons. (EX1002, ¶¶109-19.)

Although the five non-provisional applications include additional disclosure over the '935 provisional, nothing in that additional disclosure teaches the claimed 364 / 368 pair of modifications. (EX1002, ¶¶120-22.) Specifically, the shared specification of the non-provisional applications (which is also the specification of the '859 patent) additionally discloses examples 19-24 and figures 18-29. (EX1001, 52:30-67:2, Figs. 18-29.)<sup>7</sup> But the only places in this additional disclosure mentioning sets of modifications on two different chains do not disclose a 364 / 368 pair. (*See, e.g.*, EX1001, 52:30-57:56 (Examples 19-20 testing stability of combinations listed in Table 15 from Example 17), 57:58-61:60 (Examples 21-22 testing “DEKK” combinations with T366K and L351K mutations on one chain and L351D and L368E mutations on another chain), 61:62-65:46 (Example 23 testing multiple pairs of mutations in a single cell), 65:48-67:2 (Example 24 testing DEKK combinations in mice), Fig. 20; EX1002, ¶¶120-22.) Similarly, none of the original claims filed with any of the five non-provisional applications disclose a 364 / 368 pair—in fact, none of the original claims even mention position 364.

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<sup>7</sup> The '935 provisional also includes a partial disclosure of Example 23, including the title and first paragraph, but labelling it “Example 20.” (EX1030, 69-70; EX1001, 61:46-67.)

(EX1031, 100-03; EX1032, 100-03; EX1033, 104-07; EX1034, 103-06; EX1035, 97-100.)

For these reasons, the five non-provisional applications do not add any disclosures to the '935 provisional that would have allowed a POSA to discern that the alleged inventors possessed the heterodimeric antibody comprising a 364+ and 368- modification pair, or more specifically the pairs of mutations recited in claims 2 and 3. (EX1002, ¶¶109-22.) Thus, the earliest effective filing date for all claims in the '859 patent is the actual date of filing of the claims—May 16, 2023.

## **XI. DETAILED EXPLANATION OF GROUNDS**

### **A. Ground 1: *Desjarlais*<sup>8</sup> Anticipates Claims 1-7**

*Desjarlais* discloses each limitation in every claim of the '859 patent as arranged therein, thus anticipating all challenged claims. (EX1002, ¶123; Section X.)

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<sup>8</sup> *Desjarlais* was filed on June 26, 2017, and claims priority to U.S. Provisional Application No. 61/780,310 (“the *Desjarlais* provisional”), filed on March 13, 2013. (EX1036, Cover.) Because the portions of *Desjarlais* relied upon in this petition are also disclosed in the *Desjarlais* provisional (EX1037), *Desjarlais*'s effective filing date stretches back to at least March 13, 2013, to the extent needed.

**1. Claim 1**

**i) [1.pre] “A heterodimeric antibody comprising”**

Regardless of whether the preamble is limiting, *Desjarlais* discloses heterodimeric antibodies with the claimed modifications. (EX1036, Abstract; 3:24-4:2; EX1002, ¶¶124-27.)

**ii) [1.a] “a first human CH3 domain comprising a positively charged amino acid residue at position 364 according to the EU numbering system, and a second human CH3 domain comprising a negatively charged amino acid residue at position 368 according to the EU numbering system”**

*Desjarlais* discloses “a first human CH3 domain comprising a positively charged amino acid residue at position 364” and a “second human CH3 domain comprising a negatively charged amino acid residue at position 368.” (EX1002, ¶¶128-35.) *Desjarlais* teaches a number of different “heterodimerization variants” and “novel steric variants” in Figure 4. (EX1036, 3:37-39, 4:55-60, 21:4-8, 21:29-67; *see also id.*, 4:61-62, Fig. 5B (“heterodimerization variants that find particular use in the present invention”).) Figure 4 discloses several variants with a pair of mutations at the 364 and 368 positions on two distinct CH3 domains. (EX1002, ¶131.) For instance, as shown below, Figure 4 discloses an L368D / S364K variant

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*See Penumbra Inc. v. Rapidpulse, Inc.*, IPR2021-01466, Paper 34 at 29-35 ( Mar. 10, 2023).

as well as a number of L368E / S364K variants, all of which anticipate claim 1. A POSA would have known that aspartic acid (D) and glutamic acid (E) (in red below) are negatively charged amino acids and that lysine (K) (in green below) is a positively charged amino acid. (EX1002, ¶¶131-33; *see also* EX1007 at 8:9-10; EX1001 at 13:35-49 (listing amino acid charges).))<sup>9</sup>

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<sup>9</sup> Even if a POSA would not have known this (but they would have), “[i]nsufficient prior understanding of the inherent properties of a known composition does not defeat a finding of anticipation.” *Atlas Powder Co. v. IRECO Inc.*, 190 F.3d 1342, 1349 (Fed. Cir. 1999).

Figure 4A

Preferred steric variants that favor Fc heterodimerization.

Monomer 1	Monomer 2
F405A	T394F
S364D	Y349K
S364E	L368K
S364E	Y349K
S364F	K370G
S364H	Y349K
S364H	Y349T
S364Y	K370G
T411K	K370E
V397S/F405A	T394F
K370R/T411K	K370E/T411E
L351E/S364D	Y349K/L351K
L351E/S364E	Y349K/L351K
L351E/T366D	L351K/T366K
P395T/V397S/F405A	T394F
S364D/K370G	S364Y/K370R
S364D/T394F	Y349K/F405A
S364E/F405A	Y349K/T394F
S364E/F405S	Y349K/T394Y
S364E/T411E	Y349K/D401K
S364H/D401K	Y349T/T411E
S364H/F405A	Y349T/T394F
S364H/T394F	Y349T/F405A
Y349C/S364E	Y349K/S354C
L351E/S364D/F405A	Y349K/L351K/T394F
L351K/S364H/D401K	Y349T/L351E/T411E
S364E/T411E/F405A	Y349K/T394F/D401K
S364H/D401K/F405A	Y349T/T394F/T411E
S364H/F405A/T411E	Y349T/T394F/D401K
Y349T	S364H
T394F	F405A
Y349T/T394F	S364H/F405A
K370E	T411K
K370E/T411D	T411K
K370E/T411E	K370R/T411K
L368E/K409E	L368K
Y349T/T411E	S364H/D401K
Y349T/T394F/S354C	S364H/F405A/Y349C
T411E	D401K
T411E	D401R/T411R
Q347E/K360E	Q347R
L368E	S364K
L368E/K370S	S364K
L368E/K370T	S364K
L368E/D401R	S364K
L368E/D401N	S364K
L368E	E357S/S364K
L368E	S364K/K409E
L368E	S364K/K409V
L368D	S364K

(EX1036, Fig. 4A.)

Figure 4B

Specifically preferred steric variants that favor Fc heterodimerization.

Variant 1	Variant 2
F405A	T394F
S364D	Y349K
S364E	Y349K
S364H	Y349T
L351K	L351E
D401K	T411E
S364D/T394F	Y349K/F405A
S364E/F405A	Y349K/T394F
S364H/D401K	Y349T/T411E
S364H/F405A	Y349T/T394F
S364H/T394F	Y349T/F405A
L351K/S364H/D401K	Y349T/L351E/T411E
S364H/D401K/F405A	Y349T/T394F/T411E
S364H/F405A/T411E	Y349T/T394F/D401K
Y349T	S364H
T394F	F405A
Y349T/T394F	S364H/F405A
K370E	T411K
K370E/T411D	T411K
K370E/T411E	K370R/T411K
L368E/K409E	L368K
Y349T/T411E	S364H/D401K
Y349T/T394F/S354C	S364H/F405A/Y349C
T411E	D401K
T411E	D401R/T411R
Q347E/K360E	Q347R
L368E	S364K
L368E/K370S	S364K
L368E/K370T	S364K
L368E/D401R	S364K
L368E/D401N	S364K
L368E	E357S/S364K
L368E	S364K/K409E
L368E	S364K/K409V
L368D	S364K

(EX1036, Fig. 4B.) Thus, each highlighted pair discloses the claimed 364+ and 368- modifications. In fact, the *Desjarlais* patent claims are directed to this L368D / S364K variant, identified by a red box above. (EX1036, Claims 1-14.)

Furthermore, *Desjarlais* expressly teaches that the disclosed mutation positions are numbered “according to the EU index.” (EX1036, 12:64-67.) For these reasons, a POSA would have understood *Desjarlais*’s teaching of an L368D and S364K variant to disclose the claimed “positively charged amino acid residue

at position 364” and “negatively charged amino acid residue at position 368 according to the EU numbering system.” (EX1002, ¶134.)

Regarding the “human CH3 domain” limitation, a POSA would have understood the variants taught in Figure 4 to disclose variations made from “human CH3 domains,” as recited. (EX1002, ¶135.)<sup>10</sup> Indeed, *Desjarlais* discloses that “in some embodiments the parent polypeptide, for example an Fc parent polypeptide, is a *human* wild type sequence, such as the Fc region from IgG1, IgG2, IgG3 or IgG4,” as recited in claim 1. (*Id.*; EX1002, ¶135.)

2. **Claim 2: “The heterodimeric antibody of claim 1, wherein said positively charged amino acid residue at position 364 comprises a lysine (K) or an arginine (R) residue, and wherein said negatively charged residue at position 368 comprises an aspartic acid (D) or glutamic acid (E) residue.”**

As described above, *Desjarlais* teaches a heterodimeric antibody variant with an L368D modification on one chain and a S364K modification on the other

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<sup>10</sup> To the extent any claim’s recitation of a “human CH3 domain,” a “human IgG,” or a “human IgG1” (discussed in any ground herein) requires entirely human residues—*i.e.*, an antibody with an unaltered CH3 domain or human IgG sequence—the claims would be indefinite because the claims *do* require non-natural modifications. (EX1002, ¶¶135, 144.)

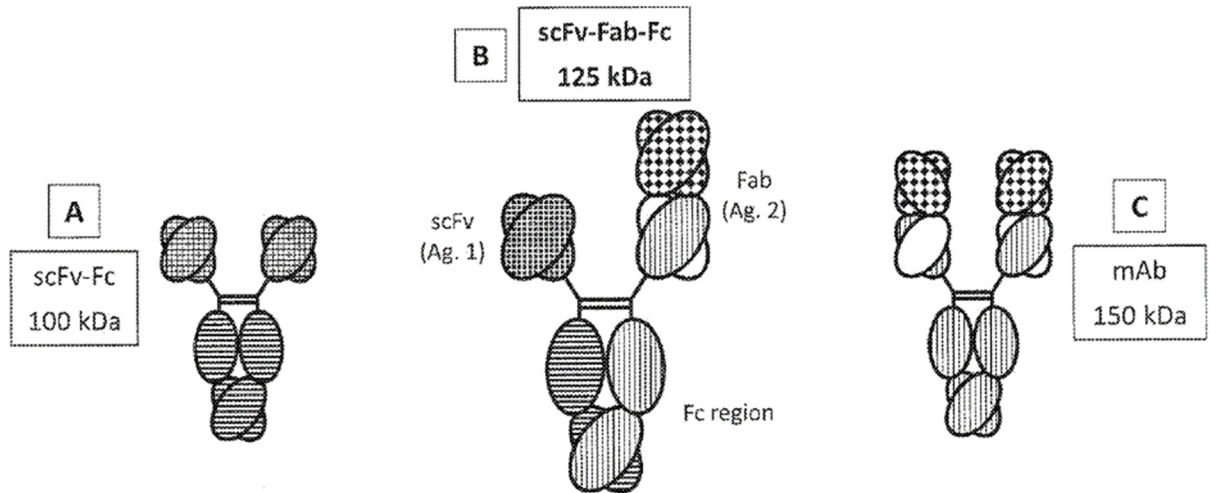
chain. (EX1036, Figs. 4A, 4B; *see also id.*, Fig. 5B, Claims 1-14.) This variant discloses the claimed “positively charged amino acid residue at position 364 comprises a lysine (K) . . . and [the] negatively charged residue at position 368 comprises an aspartic acid (D).” (EX1002, ¶¶136-37.) Additionally, *Desjarlais* discloses heterodimeric antibody variants with L368E and S364K modifications on two different CH3 domains. (EX1036, Figs. 4A, 4B; *see also id.*, Fig. 5B.) This satisfies the claim limitation that the “positively charged amino acid residue at position 364 comprises a lysine (K) . . . and [the] negatively charged residue at position 368 comprises . . . glutamic acid (E).” (EX1002, ¶¶136-37.)

**3. Claim 3: “The heterodimeric antibody of claim 2, wherein said positively charged amino acid residue at position 364 comprises a lysine (K) residue, and wherein said negatively charged amino acid residue at position 368 comprises an aspartic acid (D).”**

As described above, *Desjarlais* teaches a heterodimeric antibody variant with an L368D modification on one chain and a S364K modification on the other chain. (EX1036, Figs. 4A, 4B; *see also id.*, Fig. 5B; Claims 1-14.) This variant discloses the claimed heterodimer comprising a “positively charged amino acid residue at position 364 comprises a lysine (K) residue, and wherein said negatively charged residue at position 368 comprises an aspartic acid (D).” (EX1002, ¶¶138-39.)

**4. Claim 4: “The heterodimeric antibody of claim 1, wherein said heterodimeric antibody is a bispecific antibody.”**

*Desjarlais* discloses heterodimeric antibodies with the modifications described above for claim 1 that are bispecific antibodies. (EX1036, 4:27-54, 8:11-13, Figs. 1-3; EX1002, ¶¶140-43.) For instance, *Desjarlais* teaches that the “present invention is directed to novel constructs to provide bispecific antibodies.” (EX1036, 8:11-13, 15:41-45 (“The present invention is directed to the generation of multispecific, particularly bispecific binding proteins . . .”).) *Desjarlais* describes that its techniques for promoting heterodimerization are used in its inventive “triple F” (also called “bottle-opener”) bispecific antibody formats. (EX1036, 8:34-48 (explaining that, in these formats, “the two chains are brought together by the use of amino acid variants in the constant regions . . . that promote the formation of heterodimeric antibodies as is described more fully below”), 52:37-40 (“[T]he Fc region can be modified by amino acid substitution to promote the formation of the ‘triple F’ heterodimer.”).) Specifically, *Desjarlais* links the “triple F” format bispecific antibodies with the variants disclosed in Figure 4, which include L368D / S364K—“For example, see FIG. 4 for a list of substitutions that can be made in Fc monomer 1 and Fc monomer 2 to ‘skew’ production toward the ‘triple F’ heterodimer.” (EX1036, 52:61-63.) *Desjarlais* also describes that its variants are used in other bispecific formats as well:



(EX1036, Fig. 1, 4:27-34; *see also id.* Figs. 2-3 (additional multispecific formats).)<sup>11</sup>

For all of these reasons, a POSA would have understood *Desjarlais* to disclose bispecific heterodimeric antibodies with the CH3 modifications recited in claim 1. (EX1002, ¶¶140-43.)

**5. Claim 5: “The heterodimeric antibody of claim 1, wherein said heterodimeric antibody is human IgG.”**

As described above for claim 1, *Desjarlais* discloses a heterodimeric antibody with the CH3 domain modifications of claim 1 that is human IgG. (Section XI.A.1.ii; EX1002, ¶¶.) *Desjarlais* discloses that the “present invention is

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<sup>11</sup> A POSA would have understood that “Ag. 1” and “Ag. 2” in Fig. 1B refer to a first and second antigen, and thus Figure 1B is illustrating a bispecific antibody. (EX1002, ¶143.)

directed to the IgG class,” including “IgG1.” (EX1036, 15:63-66.) And as explained above, the CH3 mutations described in Figure 4—which are used in both *Desjarlais*’s “triple F” format as well as other bispecific formats (Section XI.A.4; EX1036, 4:27-34)—are made from parent polypeptides that are “human wild type,” specifically IgG1. (Section XI.A.1.ii; EX1036, 12:39-34; EX1002, ¶¶144-46.)

More specifically, *Desjarlais* discloses parent polypeptides that are “human wild type sequence, such as the Fc region from IgG1 . . . .” (EX1036, 12:29-34; EX1002, ¶144.) Thus, a POSA would have understood *Desjarlais* to disclose a heterodimeric antibody with the claimed CH3 mutations that “is human IgG.” (EX1002, ¶¶144-46.)

**6. Claim 6: “The heterodimeric antibody of claim 1, wherein said heterodimeric antibody is human IgG1.”**

*Desjarlais* discloses the “heterodimeric antibody of claim 1, wherein said heterodimeric antibody is human IgG1” for the reasons explained above for claim 5. (Section XI.A.5; EX1036, 12:29-34, 15:63-66, Figs. 4-5; EX1002, ¶¶147-48.)

**7. Claim 7: “A pharmaceutical composition comprising the heterodimeric antibody according to claim 1, and a pharmaceutically acceptable carrier.”**

*Desjarlais* discloses that the heterodimeric antibodies of the “present invention” are used in pharmaceutical compositions that expressly include

“pharmaceutically acceptable carriers.” (EX1036, 47:40-48:52 (describing “Antibody Compositions for In Vivo Administration,” including “pharmaceutically acceptable carriers, excipients or stabilizers,” listing many such exemplary components); EX1002, ¶¶149-52.)

**B. Ground 2: *Moore* Anticipates Claims 1-7**

Like *Desjarlais*, *Moore* discloses each limitation in the challenged claims, and thus anticipates those claims. (EX1002, ¶153; Section X.)

**1. Claim 1**

**i) [1.pre] “A heterodimeric antibody comprising”**

Regardless of whether the preamble is limiting, *Moore* discloses heterodimeric antibodies with the claimed modifications. (EX1038, Abstract (disclosing “[b]ispecific formats containing a heterodimeric Fc region”); EX1002, ¶¶154-55.) Specifically, *Moore* discloses a framework for generating heterodimeric antibodies (using a “novel set of Fc substitutions”) that can be used to develop several types of bispecific antibodies. (*Id.*, Abstract (“We present a robust heterodimeric Fc platform, called the XmAb® bispecific platform, engineered for efficient development of bispecific antibodies and Fc fusions of multiple formats.”).)

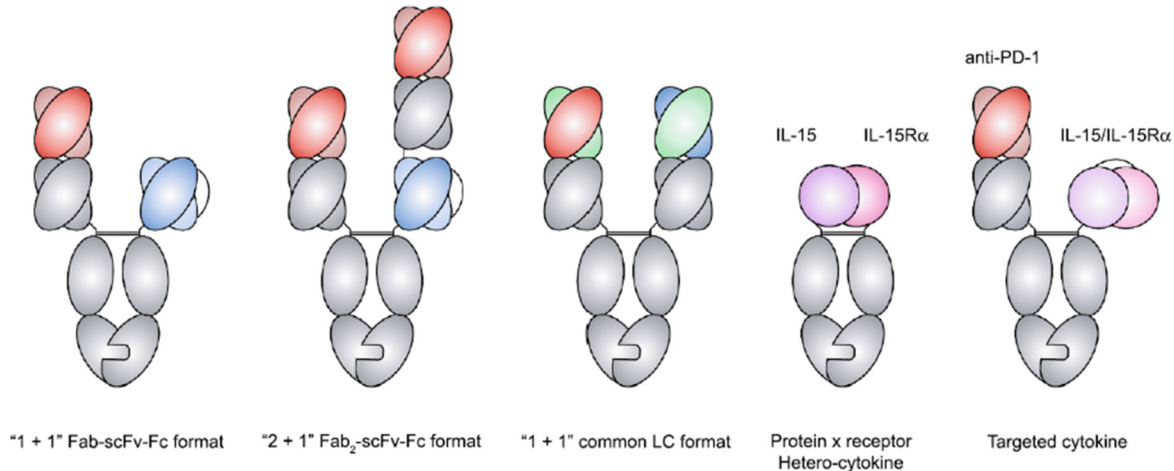
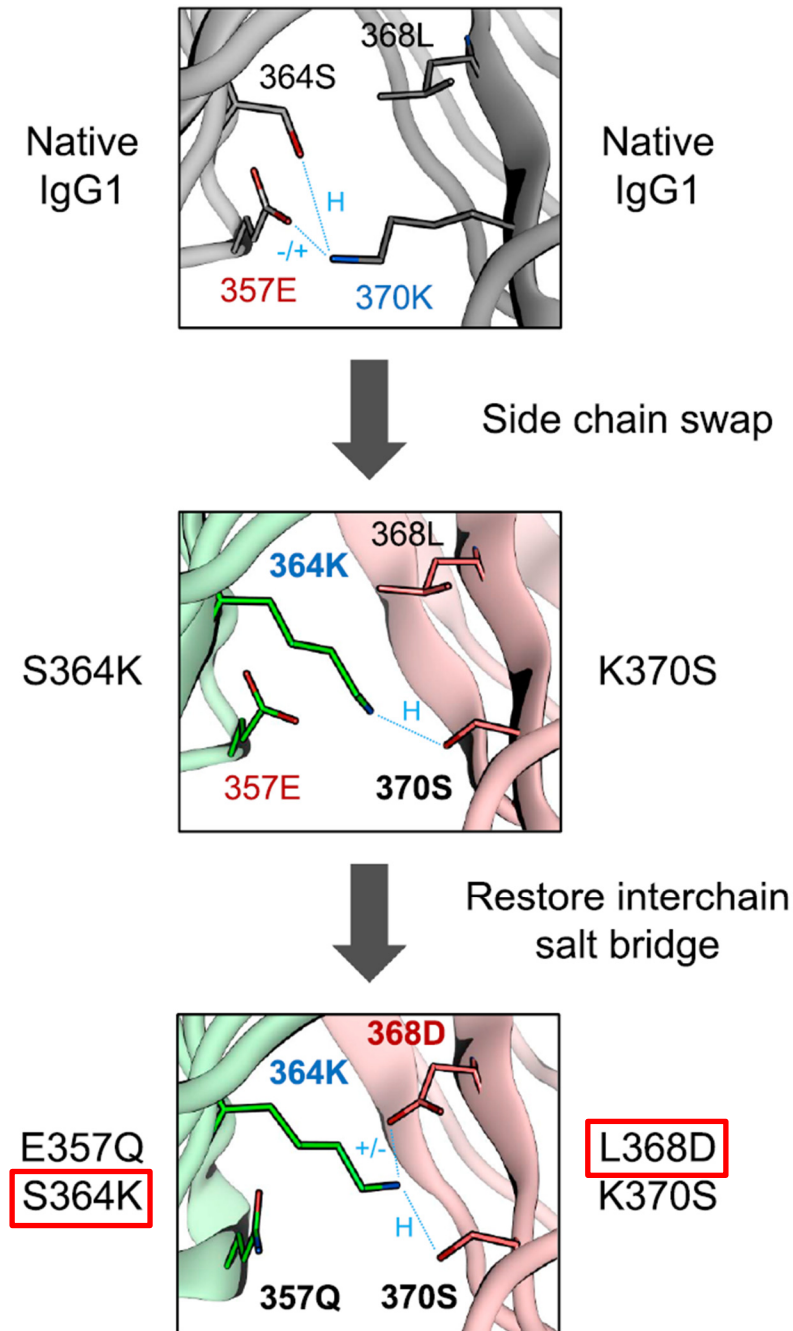


Fig. 1. Examples of bispecific antibody, hetero-cytokine, and targeted cytokine formats enabled by heterodimeric Fc technology.

(EX1038, Fig. 1 (illustrating various bispecific formats “enabled by heterodimeric Fc technology,” as disclosed in *Moore*).

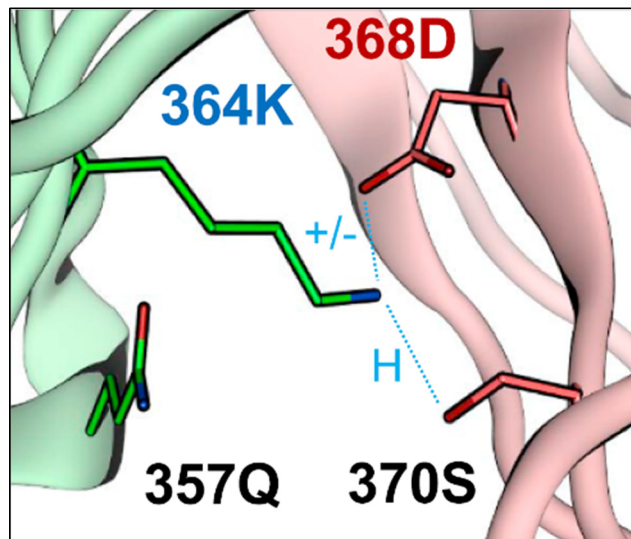
- ii) [1.a] “a first human CH3 domain comprising a positively charged amino acid residue at position 364 according to the EU numbering system, and a second human CH3 domain comprising a negatively charged amino acid residue at position 368 according to the EU numbering system”

*Moore* discloses “a first human CH3 domain comprising a positively charged amino acid residue at position 364” and a “second human CH3 domain comprising a negatively charged amino acid residue at position 368.” (EX1002, ¶¶156-58.) Specifically, *Moore* teaches a pair of modifications including S364K on a first CH3 domain and L368D on a second CH3 domain:



(EX1038, Fig. 5.) *Moore* describes this as the “E357Q/S364K-L368D/K370S” combination variant and shows it was made starting with “Native IgG1.” (EX1038, 42-44.) Additionally, like with *Desjarlais*, the “[p]ositions are numbered according to the EU index.” (EX1038, 39.)

As noted above, a POSA would have known that aspartic acid (D) is a negatively charged amino acid and that lysine (K) is a positively charged amino acid. (Section XI.A.1.ii.) In fact, *Moore* expressly discloses the claimed “positively charged amino acid residue at position 364” on a first CH3 domain and “negatively charged amino acid residue at position 368” on a second CH3 domain. *Moore*’s color coding in Figure 5 shows just that, with *Moore*’s Figure 5 legend indicating “[t]ext color indicates amino acid charge (blue, positive; red, negative), and bold text font indicates amino acid substitution.” (EX1038, 42.)



(EX1038, Fig. 5.)

Regarding the “human CH3 domain” limitation, Figure 5 shows that *Moore*’s E357Q/S364K-L368D/K370S combination variant is created from “native IgG1.” (*Id.*) And *Moore* explains that its constructs were created using “native human IgG1.” (*Id.*, 39.) From these disclosures, a POSA would have understood

that the S364K and L368D substitutions were made on “human CH3 domains,” as recited in claim 1. (EX1002, ¶158.)

2. **Claim 2: “The heterodimeric antibody of claim 1, wherein said positively charged amino acid residue at position 364 comprises a lysine (K) or an arginine (R) residue, and wherein said negatively charged residue at position 368 comprises an aspartic acid (D) or glutamic acid (E) residue.”**

As described above, *Moore* teaches a heterodimeric antibody with an Fc variant that has an L368D modification on one chain and a S364K modification on the other chain. (EX1038, Fig. 5.) This variant discloses the claimed “positively charged amino acid residue at position 364 comprises a lysine (K) . . . and [the] negatively charged residue at position 368 comprises an aspartic acid (D).”

(Section XI.A.1.ii; EX1002, ¶¶159-60.)

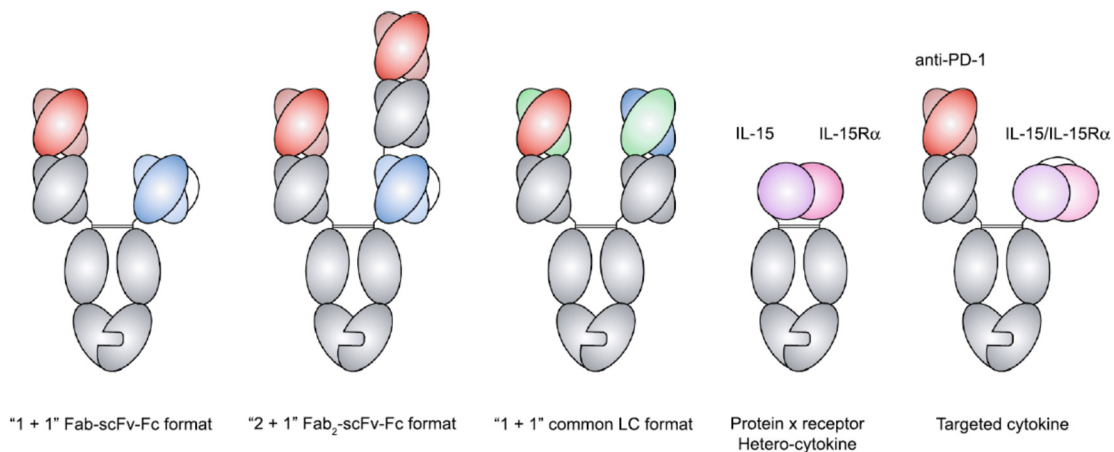
3. **Claim 3: “The heterodimeric antibody of claim 2, wherein said positively charged amino acid residue at position 364 comprises a lysine (K) residue, and wherein said negatively charged amino acid residue at position 368 comprises an aspartic acid (D).”**

As described above, *Moore* teaches a heterodimeric antibody with an Fc variant that has an L368D modification on one chain and a S364K modification on the other chain. (EX1038, Fig. 5.) This variant discloses the claimed “positively charged amino acid residue at position 364 comprises a lysine (K), and wherein said negatively charged residue at position 368 comprises an aspartic acid (D).”

(Section XI.A.1.ii; EX1002, ¶¶161-62.)

**4. Claim 4: “The heterodimeric antibody of claim 1, wherein said heterodimeric antibody is a bispecific antibody.”**

*Moore* discloses a robust heterodimeric Fc, known as the “XmAb bispecific platform,” which was engineered to facilitate the efficient development of bispecific antibodies. (EX1038, 47; EX1002, ¶¶163-65.) *Moore* teaches various “[e]xamples of bispecific antibod[ies]” that are “enabled by heterodimeric Fc technology” (e.g., the XmAb platform), as shown in Figure 1:



(EX1038, Fig. 1, 39, 45 (“a robust heterodimeric Fc region enables a wide variety of possible formats (Fig. 1)”)), 49 (explaining that these “[n]ewer formats” in Figure 1 had been “produced” and that *Moore*’s “Fc heterodimer technology has proven to be an efficient component to rapidly enable multiple clinical bispecific candidates”).)

**5. Claim 5: “The heterodimeric antibody of claim 1, wherein said heterodimeric antibody is human IgG.”**

As described above, *Moore* teaches that its E357Q/S364K-L368D/K370S combination variant is derived from human IgG (specifically, “native human IgG1”). (EX1038, B.1.ii; EX1038, 39, Fig. 5; EX1002, ¶¶166-67.)

**6. Claim 6: “The heterodimeric antibody of claim 1, wherein said heterodimeric antibody is human IgG1.”**

As described above, *Moore* teaches that its E357Q/S364K-L368D/K370S combination variant is derived from “native IgG1” (specifically, “native human IgG1”). (Section X.B.1.ii; EX1038, 39, Fig. 5; EX1002, ¶168.)

**7. Claim 7: “A pharmaceutical composition comprising the heterodimeric antibody according to claim 1, and a pharmaceutically acceptable carrier.”**

*Moore* discloses that the heterodimeric antibodies are purified by chromatography and eluted (*e.g.*, isolated) using a buffer, either “50 mM Tris, pH 8.5” or “50 mM MES, pH 6.0.” (EX1038, 40.) A POSA would understand this disclosure of elution in a buffer to be teaching a pharmaceutically acceptable carrier, particularly in light of the extremely broad definition of “pharmaceutically acceptable carrier” in the ’859 patent specification. The specification states:

As used herein, such ‘pharmaceutically acceptable carrier’ includes *any and all* solvents, salts, dispersion media, coatings, antibacterial and antifungal agents, isotonic and

absorption delaying agents, and the like that are physiologically compatible.

(EX1001, 29:12-17; EX1002, ¶¶169-73.) *Moore* further discloses that its “heterodimeric Fc” technology has been used in clinical candidates. (EX1038, 49.) A POSA would understand that the heterodimeric antibodies necessarily need to be formulated in a pharmaceutical composition in order to be studied as a clinical candidate. (EX1002, ¶¶171-72.)

**C. Ground 3: *Lazar* Alone or in view of *Kannan* Renders Obvious Claims 1-7<sup>12</sup>**

*Lazar* alone or in view of *Kannan* renders obvious all of the challenged claims. (EX1002, ¶¶174-80; Section X.)

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<sup>12</sup> Petitioner is not aware of any secondary indicia of nonobviousness, and reserves the right to respond to any attempted showing by Patent Owner. *See, e.g., Fox Factory, Inc. v. SRAM, LLC*, 944 F.3d 1366, 1378 (Fed. Cir. 2019) (Patent Owner “bear[s] the burden of proving. . . evidence of secondary considerations”); *see also Arctic Cat, Inc. v. Polaris Indus. Inc.*, IPR2017-00433, Paper 17 at 10 (July 5, 2017) (no requirement “to address secondary considerations, not previously presented to the Office, in the Petition”).

**1. Claim 1**

**i) [1.pre] “A heterodimeric antibody comprising”**

Regardless of whether the preamble is limiting, *Lazar* discloses heterodimeric antibodies with the claimed modifications. (EX1004, ¶¶2, 38, 39, 85; EX1002, ¶¶181-82.) *Kannan* also discloses heterodimeric antibodies with similar electrostatic steering modifications. (EX1007, Title (“Method for Making Antibody Fc-Heterodimeric Molecules Using Electrostatic Steering Effects”); EX1002, ¶183.)

**ii) [1.a] “ a first human CH3 domain comprising a positively charged amino acid residue at position 364 according to the EU numbering system, and a second human CH3 domain comprising a negatively charged amino acid residue at position 368 according to the EU numbering system”**

*Lazar* alone, or at least the combination of *Lazar* and *Kannan*, discloses the claimed pair of 364+ and a 368- mutations. (EX1002, ¶¶184-206.)

*Lazar* discloses several CH3 domain variants, including one with a charge pair at the 364 and 368 positions:

TABLE 1

Preferred CH3 domain variants that favor Fc heterodimerization.	
Variant 1	Variant 2
F405A	T394F
S364D	Y349K
S364E	L368K
S364E	Y349K
S364F	K370G
S364H	Y349K
S364H	Y349T
S364Y	K370G
T411K	K370E
V397S/F405A	T394F
K370R/T411K	K370E/T411E
L351E/S364D	Y349K/L351K
L351E/S364E	Y349K/L351K
L351E/T366D	L351K/T366K
P395T/V397S/F405A	T394F
S364D/K370G	S364Y/K370R
S364D/T394F	Y349K/F405A
S364E/F405A	Y349K/T394F
S364E/F405S	Y349K/T394Y
S364E/T411E	Y349K/D401K
S364H/D401K	Y349T/T411E
S364H/F405A	Y349T/T394F
S364H/T394F	Y349T/F405A
Y349C/S364E	Y349K/S354C
L351E/S364D/F405A	Y349K/L351K/T394F
L351K/S364H/D401K	Y349T/L351E/T411E
S364E/T411E/F405A	Y349K/T394F/D401K
S364H/D401K/F405A	Y349T/T394F/T411E
S364H/F405A/T411E	Y349T/T394F/D401K

(EX1004, ¶241 (Table 1) (annotation added); *see also id.* at Figures 5-6 (disclosing the same S364E/L368K charge pair, as well as a S364D/L368K charge pair).)

As an initial matter, a POSA would have understood the variants taught in *Lazar* to disclose variations made from “human CH3 domains,” as recited.

(EX1004, ¶123 (“substitution at a position in a CH3 domain”); EX1002, ¶193.)

Example 2 of *Lazar*—which contains Table 1, shown above—discloses its

modifications were made “using wild-type IgG1 Fc regions.” (EX1004, ¶239.)

*Lazar* further explains that “the Fc variants disclosed herein are based on *human* IgG sequences.” (EX1004, ¶118; *see also id.*, ¶¶66-67, 77-79, 90, 133; EX1002, ¶193.) A POSA would have understood such IgG sequences and IgG1 Fc regions contain a CH3 domain. (EX1002, ¶193.)

Although the charges in the annotated example are reverse (referred to herein for convenience as a “reverse charge pair”) to the recited 364+ and 368- claim limitation, *Lazar*’s 364- and 368+ example would have conveyed to a POSA a preference for a heterodimer variant with a charge pair at position 364 in one chain and position 368 in another. (EX1002, ¶¶185-89.) In addition, a POSA would have understood from *Lazar*’s teachings that the charges in this example could have been swapped.

For example, *Lazar* teaches several preferred locations in the CH3 domain for making amino acid substitutions, including numerous locations known to be on the CH3 domain interface, such as positions 364 and 368. (EX1004, ¶¶52, 121, 123.) *Lazar* teaches specific modifications for both the 364 and 368 positions, including both positive (green) and negative (red) substitutions at both positions:

Hetero-Fc variants herein preferably comprise at least one substitution at a position in a CH3 domain selected from the group consisting of 349, 351, 354, 356, 357, 364, 366, 368, 370, 392, 394, 395, 396, 397, 399, 401, 405, 407, 409, 411, and 439, wherein numbering is according

to the EU index as in Kabat. In a preferred embodiment, hetero-Fc variants comprise at least one CH3 domain substitution per heavy chain selected from the group consisting of 349A, 349C, 349E, 349I, 349K, 349S, 349T, 349W, 351 E, 351K, 354C, 356K, 357K, 364C, 364D, 364E, 364F, 364G, 364H, 364R, 364T, 364Y, 366D, 366K, 366S, 366W, 366Y, 368A, 368E, 368K, 368S, 370C, 370D, 370E, 370G, 370R, 370S, 370V, 392D, 392E, 394F, 394S, 394W, 394Y, 395T, 395V, 396T, 397E, 397S, 397T, 399K, 401 K, 405A, 405S, 407T, 407V, 409D, 409E, 411 D, 411 E, 411K, and 439D. Each of these variants can be used individually or in any combination for each heavy chain Fc region.

(EX1004, ¶123.) Thus, while the annotated example above in Table 1 makes use of 364E (negative) and 368K (positive) (a “reverse charge pair” to the substitutions recited in claim 1), a POSA reading *Lazar* would have understood that the opposite also would have been possible (*e.g.*, 364H or 364R, as shown in green above, and 368E, as shown in red above). (EX1002, ¶¶188-89.) As such, *Lazar* expressly teaches “a positively charged amino acid residue at position 364” (364H and 364R, above) on one chain and a “negatively charged amino acid residue at position 368” (368E, above) on a second chain—also mentioning the “numbering is according to the EU index.” (*Id.*) And *Lazar* in fact identifies these modifications in the context of creating “[h]etero-Fc variants” for the purpose of “favor[ing] heterodimerization and disfavor[ing] homodimerization.” (EX1004, ¶¶119-125.)

Indeed, additional teachings from *Lazar* would have further motivated a POSA, when selecting a positive-negative charge pair, to utilize amino acid residue substitutions causing a given position (A) to be positive and the other position (B) to be negative (a charge pair, A+/B-), as well as a reverse charge pair thereto (*i.e.*, A-/B+). (EX1002, ¶¶194-99.) In particular, Figures 5-7 of *Lazar* depict various heterodimers made with modifications on two separate chains (and indeed Table 1 above is derived from these figures). (EX1004, ¶¶240-241.) For instance, Figure 5 shows a S364D/K370R (-/+) charge pair (Lane 14), but also a S364R/K370D (+/-) reverse charge pair (Lane 17). (EX1004, Fig. 5.) In fact, there are multiple heterodimers in Figures 5-7 that explored inserting charge pairs (and reverse charge pairs) at interface positions, reinforcing the desirability of testing both +/- and -/+ amino acid substitutions at known contact residues. (EX1004, Fig. 5.) Exemplary such heterodimers taught and tested in *Lazar* (in Figures 5-7) are depicted in the table below:

<b>CH3 Domain A Substitution</b>	<b>CH3 Domain B Substitution</b>
S364D (-)	K370R (+)
S364R (+)	K370D (-)
S364E (-)	L368K (+)
S364R (+)	K370E (-)
T411E (-)	K370R (+)
T411K (+)	K370E (-)
T411K (+)	K370D (-)

(EX1004, Figs. 5-7.)

In view of the above disclosures, *Lazar* itself teaches or suggests limitation 1.a. Patent Owner may nonetheless argue that *Lazar*'s disclosures are insufficient because they disclose the preferred modifications in a list (EX1004, ¶123), and because the specific 364 / 368 preferred pairing in *Lazar* is the opposite of the charges recited in claim 1 (*id.*, ¶241 (Table 1)). As an initial matter, such an argument would critically undermine written description support for the '859 patent claims as well as any arguments for an earlier filing date than the actual filing of the '859 patent. (Section X.) This is because the '859 patent specification and the priority applications merely individually list S364K and L368D and L368E modifications as examples in Table 7. (EX1001, 41:17-63; EX1030, 52-54.) And the '859 patent specification and priority applications do not even list 364 and 368 as a preferential pair of positions for mutations on two separate chains to make a charge pair, unlike *Lazar*.<sup>13</sup> (Section X.) In any event, however, limitation 1.a is rendered obvious by the additional teachings of *Kannan*.

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<sup>13</sup> To the extent that Patent Owner contends a lead compound analysis—focusing on the 364 / 368 charge pair recited in claim 1—is required, such contention would be legally erroneous. *See Cytiva BioProcess R&D AB v. JSR Corp.*, 122 F.4th 876,

*Kannan* teaches the benefits of modifying amino acids at the CH3-CH3 domain interface to have positive-negative pairs for electrostatic steering. (EX1002, ¶¶190-92, 200-04.) *Kannan* first discloses CH3-CH3 domain interface residues, including positions 364 and 368, in its “Table 1”—a table that Merus largely copied in the ’859 patent’s specification’s Table A:

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884 (Fed. Cir. 2024). And regardless, *Lazar* teaches the charge pair at 364/368 as a preferred species, so to the extent a lead compound analysis were required (and it is not), such an analysis would be satisfied here. Moreover, any argument from Patent Owner regarding the sufficiency of *Lazar*’s disclosure would only confirm that the ’859 patent is not entitled to a priority date of any earlier than its actual filing, particularly where the applications related to the ’859 patent (unlike *Lazar*) fail to identify a 364 / 368 charge pair on a first and second CH3 domain, as discussed above. (Section X.)

<i>Interface Res. in Chain A</i>	<i>Contacting Residues in Chain B</i>
GLN A 347	LYS B 360'
TYR A 349	SER B 354' ASP B 356' GLU B 357' LYS B 360'
THR A 350	SER B 354' ARG B 355'
LEU A 351	LEU B 351' PRO B 352' PRO B 353' SER B 354' THR B 366'
SER A 354	TYR B 349' THR B 350' LEU B 351'
<i>ARG A 355<sup>b</sup></i>	THR B 350'
<b>ASP A 356</b>	TYR B 349' <b>LYS B 439'</b>
<b>GLU A 357</b>	TYR B 349' <b>LYS B 370'</b>
<i>LYS A 360<sup>b</sup></i>	GLN B 347' TYR B 349'
SER A 364	LEU B 368' LYS B 370'
THR A 366	LEU B 351' TYR B 407'
LEU A 368	SER B 364' LYS B 409'
<b>LYS A 370</b>	<b>GLU B 357'</b> SER B 364'
ASN A 390	SER B 400'
<b>LYS A 392</b>	LEU B 398' <b>ASP B 399'</b> SER B 400' PHE B 405'
THR A 394	THR B 394' VAL B 397' PHE B 405' TYR B 407'
PRO A 395	VAL B 397'
VAL A 397	THR B 393' THR B 394' PRO B 395'
<b>ASP A 399</b>	<b>LYS B 392'</b> <b>LYS B 409'</b>
SER A 400	ASN B 390' LYS B 392'
PHE A 405	LYS B 392' THR B 394' LYS B 409'
TYR A 407	THR B 366' THR B 394' TYR B 407' SER B 408' LYS B 409'
<b>LYS A 409</b>	LEU B 368' <b>ASP B 399'</b> PHE B 405' TYR B 407'
<b>LYS A 439</b>	<b>ASP B 356'</b>

(EX1007, 7:19-8:4 (Table 1); *see also id.*, 5:13-16 (noting the identified “CH3-CH3 domain interaction” positions were “identified based on the IgG1 human Fc crystal structure”), Fig. 4; EX1001, 13:6-31 (Table A).)

*Kannan*'s Table 1 emphasizes (in bold) the positions at which the natural IgG1 interface residues on two chains formed a charged pair and suggested swapping the charges. (EX1007, 8:15-10:14 (discussing “four unique charge residue pairs”—356 / 439, 357 / 370, 392 / 399, and 399 / 409); EX1002, ¶¶200-04.) For instance, for the first pair of bolded charges above (“ASP A 356”

and “LYS B 439”), *Kannan* teaches changing the negatively charged aspartic acid (Asp or D) at the 356 position for positively charged lysine (Lys or K) or arginine (Arg or R) and changing the negatively charged lysine (Lys or K) at the 439 position for positively charged aspartic acid (Asp or D) or glutamic Acid (Glu or E). This modification is shown in Table 2a, below:

Table 2a: List of some possible pair-wise charge residue mutations to enhance heterodimer formation<sup>a</sup>

Position in the First Chain	Mutation in the First Chain	Interacting Position in the Second Chain	Corresponding Mutation in the Second Chain
Lys409	Asp or Glu	Asp399'	Lys or Arg <sup>b</sup>
Lys392	Asp or Glu	Asp399'	Lys or Arg <sup>b</sup>
Lys439	Asp or Glu	Asp356'	Lys or Arg <sup>b</sup>
Lys370	Asp or Glu	Glu357'	Lys or Arg <sup>b</sup>
Asp399	Lys or Arg <sup>b</sup>	Lys409'	Asp or Glu
Asp399	Lys or Arg <sup>b</sup>	Lys392'	Asp or Glu
Asp356	Lys or Arg <sup>b</sup>	Lys439'	Asp or Glu
Glu357	Lys or Arg <sup>b</sup>	Lys370'	Asp or Glu

<sup>a</sup>Combinations of the above pair-wise charge residue mutations could also be used. For example Lys409 --- Asp399' interaction pair mutations could be combined with Lys439 --- Asp356' pair mutations.

(EX1007, 9 (Table 2a).) *Kannan* expressly teaches these are “pair-wise charge residue mutations.” (*Id.*) In other words, this boxed example above is teaching the following pairs of modifications:

- D356K and K439D
- D356K and K439E
- D356R and K439D

D356R and K439E

(EX1002, ¶¶202-04.) Each of these mutation pairs are changing a 356- and 439+ pair to a 356+ and 439- pair—*i.e.*, charge reversal. And of *Kannan*'s “pair-wise charge residue mutations” made at known CH3 interface residues, *Lazar* expressly teaches the insertion of charged amino acids at positions 364/368, specifically.

(EX1004, ¶241, Tables 1-2; EX1002, ¶¶89-90, 201.)

Therefore, *Lazar* together with the teachings of *Kannan* renders obvious swapping the charges in *Lazar*'s “[p]referred” S364E / L368K pair (or its S364D / L368K pair). (EX1002, ¶¶184-206.) A POSA would have recognized that this would have involved only a combination of known prior art elements according to known methods, including: *Lazar*'s teaching of charge pairing at the specific 364/368 positions; its teachings of alternative, oppositely charged substitutions at these locations (such as 364H, 364R, and 368E); and the fact that *Lazar* made a number of “charge pairs” and “reverse charge pairs.”

The claimed amino acid modifications also would have been obvious to try given the finite number of potential substitutions at positions 364 and 368 that would reverse the charge pair in *Lazar*'s preferred variant. (EX1004, ¶123.) In particular, a POSA would have known to use any of the finite number of positive amino acids (R/K/H) and negative amino acids (D/E) in making this charge

reversal. (EX1002, ¶¶194-204.) This would result in only six<sup>14</sup> potential combinations, each of which would have been obvious to try:

S364K, L368D

S364R, L368D

S364H, L368D

S364K, L368E

S364R, L368E

S364H, L368E

(EX1002, ¶¶220-23.) Here, “there are a finite number of identified, predictable solutions,” any one of which would have been obvious to try. *Valeant Pharms. Int’l, Inc. v. Mylan Pharms. Inc.*, 955 F.3d 25, 34 (Fed. Cir. 2020) (quoting *KSR Int’l Co. v. Teleflex Inc.*, 550 U.S. 398, 421 (2007)).

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<sup>14</sup> *Kannan* warns that insertion of the positively charged amino acid histidine (H) for a negatively charged residue “will lead to increase in side chain volume which may cause steric issues.” (EX1007, 10:11-12.) *Kannan*’s teaching therefore would have provided a POSA with good reason to utilize lysine (K) or arginine (R) as the positively charged amino acid to be inserted at position 364. (EX1002, ¶222.)

A POSA would have been motivated to apply the disclosures of *Lazar*, including together with the disclosures of *Kannan*, to manufacture the heterodimeric antibody of claim 1. That is, a POSA would have had good reason to swap the charges in *Lazar*'s “[p]referred” S364E / L368K pair (or its S364D / L368K pair) as of April 2012. (EX1002, ¶¶194-204.)

Moreover, with respect to the changes to the 364 and 368 positions that are claimed, *Lazar* teaches that the 364 and 368 positions are preferential locations for substitution by a variety of amino acid residues. (EX1002, ¶198.) This is shown by the number of different modifications for each of those points that *Lazar* lists as preferred: 364C, 364D, 364E, 364F, 364G, 364H, 364R, 364T, 364Y, and 368A, 368E, 368K, 368S. (EX1004, ¶¶52, 123.) This includes mutations that would be charge complements, such as 364H or 364R and 368E. (*Id.*) And this includes either positive or negative charges at either location (positive 364H, 364R, 368K; negative 364D, 364E, 368E). (*Id.*)

In addition, *Lazar* expressly incorporates *Kannan* by reference, teaching that “[o]ther Fc variants that favor heterodimerization” (such as those in *Kannan*) “may find use in the creation of the antibody analogs of the invention” in *Lazar*. (EX1004, ¶125.) This is not surprising, as *Lazar* and *Kannan* have analogous teachings and are highly compatible. (EX1002, ¶¶176-80.) For instance, *Lazar* and *Kannan* are both directed to modifying amino acid sequences in the CH3

domains of two heavy chains to promote heterodimerization. (*See, e.g.*, EX1004, ¶¶119-125; EX1007, 2:33-3:13.) And both *Lazar* and *Kannan* teach these CH3 domain modifications are beneficial for the creation of bispecific antibodies. (*See, e.g.*, EX1004, ¶¶3-7; EX1007, 1:29-2:21.)

*Kannan* further would have provided good reason for a POSA to swap the charges in *Lazar*'s “[p]referred” S364E / L368K pair (or its S364D / L368K pair) as of April 2012. *Kannan* teaches the heterodimer-promotion “can be achieved by replacing one or more residues that make up the CH3-CH3 interface in both CH3 domains with a charged amino acid such that homodimer formation is electrostatically unfavorable but heterodimerization is electrostatically favorable.” (EX1007, 2:35-37.) To do so, *Kannan* instructs that a “charged amino acid in each CH3 domain is replaced with an amino acid with an opposite charge. For example, a positive-charged amino acid may be replaced with a negative charged amino acid in the first CH3 domain and a negative charged amino acid may be replaced with a positive-charged amino acid in the second CH3 domain.” (*Id.*, 3:1-4.) So, *Kannan*'s charge-swap teaching would have motivated a POSA to **flip** the negative charge at position 364 of *Lazar*'s “[p]referred” S364E / L368K pair (or its S364D / L368K pair), as well as the positive charge at position 368—yielding a heterodimer comprising a **positively charged** amino acid residue at position 364 on one CH3

domain and a *negatively charged* amino acid residue at position 368 on a second CH3 domain as of April 2012.

Additionally, a POSA would have had a reasonable expectation of success in applying the teachings of *Lazar* (together with the teachings of *Kannan*) to make the heterodimeric antibody of claim 1. (EX1002, ¶¶205-06.) As an initial matter, claim 1 is directed only to a composition, and a person of ordinary skill in the art would have recognized that applying the teachings of *Lazar* (and *Kannan*) would have involved only a combination of known prior art elements according to known methods, including: *Lazar*'s teaching of charge pairing at the specific 364/368 positions, as well as its teachings of alternative, oppositely charged substitutions at these locations (such as 364H, 364R, and 368E). Moreover, as discussed above, *Lazar* demonstrates the successful creation of heterodimers incorporating charge pair and reverse charge pair amino acid mutations. (EX1002, ¶206.) So too does *Kannan*. (EX1002, ¶206.)

Equally, *Lazar* and *Kannan* both teach their CH3 domain modifications were compatible with other techniques. (*Id.*) For instance, *Lazar* teaches its variants “can be used individually or in any combination” and “can comprise different numbers of substitutions.” (EX1004, ¶123; *see also id.*, ¶124 (discussing “combination variants”).) *Lazar* further teaches that “[o]ther Fc variants that favor heterodimerization [] may find use in the creation of the antibody analogs of the

invention,” including those describing KIH variations as well as electrostatic steering (including *Kannan*). (EX1004, ¶125 (citing EX1007; EX1015; EX1021).) Likewise, *Kannan* teaches that an “Fc region may contain additional alterations,” such as “mutation in a glycosylation site, inclusion of unnatural amino acid, or a ‘knobs-into-holes’ mutation” and “still remain within the scope of” *Kannan*. (EX1007, 3:27-31.)

2. **Claim 2: “The heterodimeric antibody of claim 1, wherein said positively charged amino acid residue at position 364 comprises a lysine (K) or an arginine (R) residue, and wherein said negatively charged residue at position 368 comprises an aspartic acid (D) or glutamic acid (E) residue.”**

As discussed above (Section XI.C.1), *Lazar* expressly discloses heterodimeric antibodies with substitutions creating a charge pair at positions 364 and 368. (EX1004, Table 1; EX1002, ¶¶207-17.) As also discussed above, *Lazar*’s exemplary charge pairs recite the opposite charges of what is claimed (S364E/L368K and S364D/L368K), but *Lazar* provides teachings that would have suggested to a POSA to switch the charges (*e.g.*, providing for S364K/L368E or S364K/L368D). (Section XI.C.1.ii.) Thus, for the reasons discussed above (Section XI.C.1.ii), *Lazar* teaches or at least suggests the limitations of claim 2.

At a minimum, for the reasons described above, it would have been obvious to apply *Kannan*’s charge-reversal technique to flip the charges in

*Lazar*'s 364 / 368 examples. (Section XI.C.1.ii; EX1002, ¶¶209-16.) In implementing the *Kannan* charge reversal, a POSA looking at *Lazar* would have immediately identified the six possibilities noted above, four of which would satisfy this claim limitation: S364K / L368D; S364K / L368E; S364R / L368D; and S364R / L368E. (EX1004, ¶¶52, 123; EX1002, ¶¶209-22.) *See Valeant*, 955 F.3d at 34 (quoting *KSR*, 550 U.S. at 421). Furthermore, as described above (Section XI.C.1.ii), a POSA would have had a reasonable expectation of success in making this combination, given *Lazar*'s teachings of numerous substitutions that could be made on each of the 364 and 368 positions, including both positive and negative substitutions, given *Lazar*'s express incorporation by reference of *Kannan* in describing other variants that could be used with *Lazar*'s antibodies (EX1004, ¶125), and given *Kannan*'s teachings that are compatible with *Lazar*. (EX1002, ¶¶176-80.) All the more so where *Lazar* demonstrates that a range of heterodimers with charge pair modifications were actually designed, made, and screened. (EX1004, ¶241.)

3. **Claim 3: “The heterodimeric antibody of claim 2, wherein said positively charged amino acid residue at position 364 comprises a lysine (K) residue, and wherein said negatively charged amino acid residue at position 368 comprises an aspartic acid (D).”**

As discussed above, *Lazar* teaches heterodimeric antibodies with substitutions creating a charge pair at positions 364 and 368. (Section XI.C.1.ii;

EX1004, Table 1, ¶¶52, 123; EX1002, ¶¶218-23.) As also discussed above, *Lazar* discloses an example charge pair reciting the opposite charges of what is claimed (S364D/L368K), but *Lazar* provides teachings that would have suggested to a POSA to switch the charges (*e.g.*, providing for S364K/L368D). (Section XI.C.1.ii.) Thus, for the reasons discussed above (Section XI.C.1.ii), *Lazar* teaches or at least suggests the limitations of claim 3.

At a minimum, for the reasons described above, it would have been obvious to apply *Kannan*'s charge-reversal technique to flip the charges in *Lazar*'s 364 / 368 example. (Section XI.C.1.ii; EX1002, ¶¶219-22.) In implementing the *Kannan* charge reversal, a POSA looking at *Lazar* would have immediately identified the six possibilities noted above, including the claimed S364K / L368D combination, rendering it obvious. (EX1004, ¶¶52, 123; EX1002, ¶¶220-22.) *See Valeant*, 955 F.3d at 34 (quoting *KSR*, 550 U.S. at 421). Furthermore, as described above (Section XI.C.1.ii), a POSA would have had a reasonable expectation of success in making this combination, given *Lazar*'s teachings of numerous substitutions that could be made on each of the 364 and 368 positions, including both positive and negative substitutions, given *Lazar*'s express incorporation by reference of *Kannan* in describing other variants that could be used with *Lazar*'s antibodies (EX1004, ¶125), given that *Lazar* successfully made heterodimers with

“reverse charge pairs,” and given *Kannan*’s teachings that are compatible with *Lazar*. (EX1002, ¶223.)

**4. Claim 4: “The heterodimeric antibody of claim 1, wherein said heterodimeric antibody is a bispecific antibody.”**

At the relevant time, the antibody therapeutic industry was interested in producing bispecific antibodies due to their ability to bind distinct targets, which allowed for novel and more efficient therapeutic applications. (Sections VI.A; EX1002, ¶¶224-30.) Both *Lazar* and *Kannan* are directed to such bispecific antibodies. (EX1004, Abstract, ¶¶3, 99; EX1007, 1.)

*Lazar* teaches bispecific antibody characteristics and some of the features that make them attractive as therapeutic agents. (EX1004, ¶¶3-7, 38-56, 242.) *Lazar* describes multiple improvements, two of which are (1) novel variations to Fc regions to promote purity during heterodimeric antibody production and (2) a “novel antibody format referred to as mAb-Fv or mAb-Fab.” (EX1004, Figs. 5-8, ¶¶46, 52.) *Lazar* teaches its novel, Fc-region mutations are broadly applicable to “antibody analogs,” including both the mAb-Fv and mAb-Fab bispecific constructs, and more broadly “bispecific antibodies.” (EX1004, ¶¶98-125 (sections regarding “Antibody Analogs” and “Fc Modifications”); *see also id.*, ¶¶38, 46, 52, 85.)

*Kannan* likewise discloses Fc modifications for promoting purity during heterodimeric antibody production, via electrostatic steering, for use in the production of “bispecific antibodies (BsAbs),” as well as a variety of other antibody formats. (EX1007, 1:29-3:13, 4:17-20, 5:1-6.) *Kannan* describes its Figure 2 (below) as “depict[ing] some of the embodiments that include Fc-heterodimeric molecules,” specifically referencing “bispecific antibodies (hav[ing] specificity for two or more antigens).” (EX1007, 5:1-6; *see also id.*, 25-26 (Claims 34, 70).)

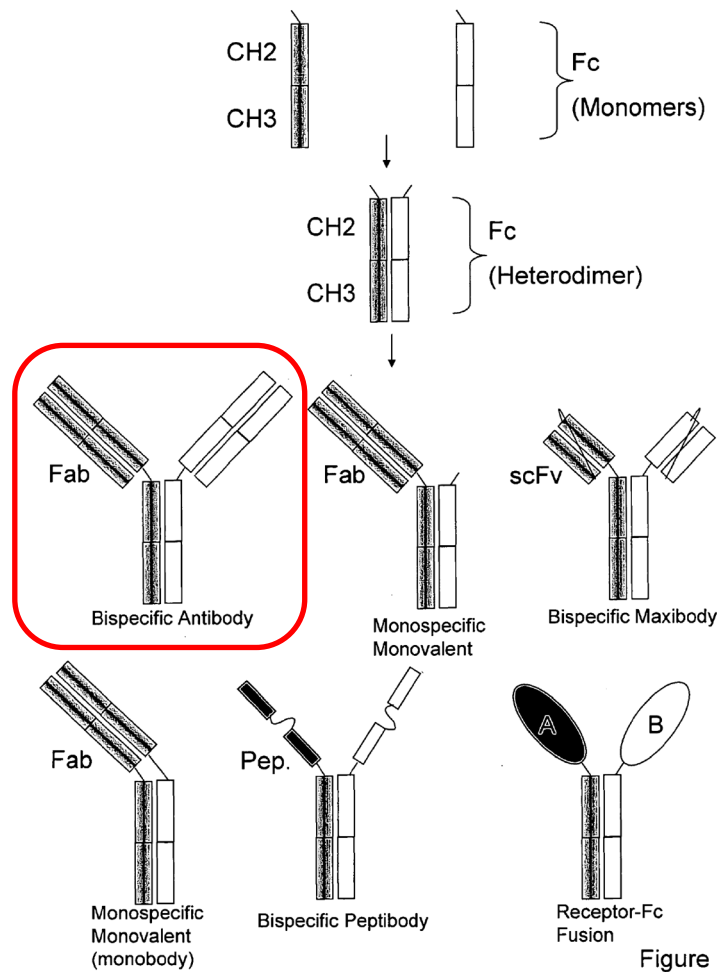


Figure 2

(EX1007, Fig. 2 (annotation added).)

For these reasons, and those discussed above for claim 1 (Section XI.C.1), *Lazar* alone or *Lazar* and *Kannan* render obvious creating a bispecific heterodimeric antibody with the claimed 364+ and 368- modifications. (EX1002, ¶¶224-30.)

**5. Claim 5: “The heterodimeric antibody of claim 1, wherein said heterodimeric antibody is human IgG.”**

As described above, both *Kannan* and *Lazar* taught their heterodimeric-promoting modifications would be applied using human IgG antibodies. (Section XI.C.1; EX1002, ¶¶231-35.) *Lazar* teaches that the “antibodies of embodiments disclosed herein may be substantially encoded by immunoglobulin genes belonging to any of the antibody classes”—expressly referencing “the IgG class of antibodies.” (EX1004, ¶90; *see also id.*, ¶¶66-67, 77-79; EX1002, ¶233.) Further, Example 2 of *Lazar* expressly applies “preferred” amino acid substitutions on heterodimers that incorporate an IgG1 antibody (*i.e.*, a human IgG) heavy chain, and demonstrates the successful creation of heterodimers incorporating a wide range of charge pair substitutions. (EX1004, ¶¶ 238-39, Table 1, Figs. 4-6; *see also* EX1004, ¶133.)

Likewise, the foundation of *Kannan*’s teachings—modifying charges on the CH3-CH3 domain interface—was based on identifying interface residues “based

on the IgG1 human Fc crystal structure.” (EX1007, 5:14-16, Fig. 4; *see also id.* 7:21-8:7; EX1002, ¶234.) And *Kannan* specifically teaches embodiments in which “the CH3-containing polypeptide comprises an IgG Fc region, preferably derived from a wild-type human IgG Fc region.” (*Id.*, 3:25-26, Claim 5; EX1002, ¶234.)

For these reasons, and those discussed above for claim 1 (Section XI.C.1), *Lazar* alone or *Lazar* and *Kannan* render obvious creating an IgG heterodimeric antibody with the claimed 364+ and 368- modifications. (EX1002, ¶235.)

**6. Claim 6: “The heterodimeric antibody of claim 1, wherein said heterodimeric antibody is human IgG1.”**

For the same reasons described above for claim 5 (Section XI.C.5), and those discussed above for claim 1 (Section XI.C.1), *Lazar* alone or *Lazar* and *Kannan* render obvious creating an IgG1 heterodimeric antibody with the claimed 364+ and 368- modifications. (EX1007, 5:14-16, 7:21-8:7, Fig. 4; EX1004, ¶¶90, 133, 238-39; EX1002, ¶¶236-39.)

**7. Claim 7: “A pharmaceutical composition comprising the heterodimeric antibody according to claim 1, and a pharmaceutically acceptable carrier.”**

Both *Lazar* and *Kannan* teach formulating their heterodimeric antibodies into pharmaceutical compositions comprising pharmaceutically acceptable carriers. (EX1002, ¶¶240-45.) *Lazar* teaches that the “present invention provides compositions comprising antibody analog peptides described herein, and a physiologically or *pharmaceutically acceptable carrier* or diluent.” (EX1004,

¶55.) *Lazar* lists many such carriers as being useful for “[f]ormulations of the immunoglobulins disclosed herein,” including buffers (phosphate, citrate, acetate), sugars/carbohydrates (glucose, mannose, dextrans, sucrose, mannitol, trehalose, sorbitol), non-ionic surfactants (TWEEN™, PLURONICS™, polyethylene glycol (PEG)), among others. (EX1004, ¶214; EX1002, ¶242.) Similarly, *Kannan* teaches its “heterodimeric proteins may be particularly useful in therapeutic compositions” that “may be formulated in a composition that includes one or more pharmaceutically acceptable buffer or excipient.” (EX1007, 4:23-25, 30 (Claim 82).)

For these reasons, and those discussed above for claim 1 (Section XI.C.1), *Lazar* alone or *Lazar* and *Kannan* would have rendered obvious creating a pharmaceutical composition comprising heterodimeric antibodies with the claimed 364+ and 368- modifications and a pharmaceutically acceptable carrier. (EX1002, ¶¶240-45.)

## **XII. DISCRETIONARY DENIAL IS NOT APPROPRIATE**

### **A. Discretionary Denial under 35 U.S.C. § 325(d) Is Not Appropriate**

The Board should not exercise its discretion under 35 U.S.C. § 325(d) to deny this Petition. Regarding part one of the *Advanced Bionics* framework, *Desjarlais* and *Moore* were not considered during the prosecution of the ’859 patent or any related patent (EX1001, Cover); and while the PCT publication of

*Lazar* was considered by the Examiner, it was never discussed in any office action. See *TCL Corp. v. Lexington Luminance LLC*, IPR2017-01780, Paper 8 (Jan. 2, 2018) (describing *Fox Factory, Inc. v. SRAM, LLC*, IPR2016-01876, Paper 8 (Apr. 3, 2017), as “declining to exercise discretion based on § 325(d) where the prior art was merely ‘cited on an IDS [and] there is no evidence that it was considered by the Examiner’”). And although the Examiner applied a subsequent U.S. Publication of *Kannan* (U.S. Publication No. 2010/0286374) in a brief § 102(b) rejection of a parent application to the ’859 patent—which issued as the ’286 patent and is the subject of a separate *inter partes* review submission submitted herewith—(EX1008, 218-20), they never analyzed the teachings of *Kannan* under obviousness. (*Id.*) For written description issues, although Merus asserted in a preliminary amendment that “[s]upport for the new claims can be found throughout the specification, *inter alia*, at Example 13 and Table 7, and in the claims as originally filed” (EX1029, 176), the Examiner never addressed the issues raised in the current petition regarding lack of disclosure of modifications at position 364 in one chain and at position 368 in another chain. (Section X.). During the ’859 patent prosecution, the Examiner did not apply any prior art or discuss any § 112 issues, and instead rejected all claims over various double-patenting grounds in the sole office action. (EX1029, 217-24.).

Regarding part two of the *Advanced Bionics* framework, even if the Board determines part one of the framework is satisfied—which it is not—the Office did not have the benefit of the teachings, arguments, obviousness combinations, and evidence presented in this Petition. (Sections X-XI.) For example, during the prosecution history for the '859 patent, the Examiner did not consider any of the clear teachings in the *Desjarlais* and *Moore* prior art individually disclosing heterodimeric antibodies using the claimed amino acid modifications. Nor did the Examiner discuss *Lazar*'s similar teachings in any office actions.

For *Kannan*, even in the parent application to the '859 patent, the Examiner never analyzed *Kannan* in the context of obviousness, let alone in combination with *Lazar*, as it is presented in this petition. (Section XI.C.) Additionally, the Examiner entirely overlooked *Kannan*'s teaching that its charge modification “strategy can also be extended to modifying uncharged residues to charged residues at the CH3 domain interface” (EX1007, 10:16-18), which led the Examiner to erroneously allow the ancestor claims on the basis that “the prior art does not teach or suggest replacing a neutral amino acid . . . with a positively charged amino acid in the CH3 domain” and instead “teaches changing positively charged residues . . . with other charged residues.” (EX1008, 274.) Finally, the Office also erred by not considering any combination of the references relied on by Petitioner, particularly in view of the expert testimony submitted with this petition.

Thus, discretionary denial under 35 U.S.C. § 325(d) is inappropriate.

**B. The Board Should Not Deny Institution under *Fintiv***

The six *Fintiv* factors do not justify denying institution.

The first factor (stay) favors institution. Petitioner plans to seek a stay of the district court case upon institution. Because the district court case is in an early stage (there is no case schedule as of the filing of this petition), there is a strong likelihood that such a stay will be granted.

The second factor (trial proximity) favors institution. Trial has not been scheduled. (EX1048.) The most recent statistics regarding the average time to trial in the District of Delaware is 32.2 months. (EX1046, 14.) A final written decision would thus likely precede trial.

The third factor (investment in parallel proceeding) also favors institution. The district court case is in its early stages, with Petitioner's early motion to dismiss currently pending. (EX1048.) Fact discovery, claim construction briefing, expert discovery, and substantive motion practice are yet to come. Thus, remaining investments substantially outweigh those already incurred.

The fourth factor (overlap) favors institution. Petitioner has not yet presented invalidity contentions, and thus there is no present overlap that could counsel in favor of discretion.

Under the fifth factor (same parties), Petitioner and Patent Owner are the same parties in the district court, but that is true in the vast majority of IPRs.

The sixth factor (other circumstances) favors institution. There is a significant public interest against “leaving bad patents enforceable.” *Thryv, Inc. v. Click-To-Call Techs., LP*, 140 S. Ct. 1367, 1374 (2020). Indeed, the merits of this petition are compelling and the evidence in support is substantial. That “alone demonstrates that the PTAB should not discretionarily deny institution under *Fintiv*.” (EX1047, 5.)

**XIII. CONCLUSION**

Petitioner requests institution of IPR for claims 1-7 of the '859 patent based on the grounds specified in this Petition.

Respectfully submitted,

Dated: February 11, 2025

By: /Naveen Modi/  
Naveen Modi (Reg. No. 46,224)  
Counsel for Petitioner

## CERTIFICATE OF COMPLIANCE

Pursuant to 37 C.F.R. § 42.24(d), the undersigned certifies that the foregoing Petition for *Inter Partes* Review of U.S. Patent No. 11,926,859 contains, as measured by the word-processing system used to prepare this paper, 13,736 words. This word count does not include the items excluded by 37 C.F.R. § 42.24 as not counting towards the word limit.

Respectfully submitted,

Dated: February 11, 2025

By: /Naveen Modi/  
Naveen Modi (Reg. No. 46,224)  
Counsel for Petitioner

## CERTIFICATE OF SERVICE

I hereby certify that on February 11, 2025, I caused a true and correct copy of the foregoing Petition for *Inter Partes* Review of U.S. Patent No. 11,926,859 and supporting exhibits to be served via express mail on the Patent Owner at the following correspondence address of record as listed on Patent Center:

STERNE, KESSLER, GOLDSTEIN & FOX P.L.L.C.  
1101 K Street, NW, 10th Floor  
WASHINGTON, DC 20005

A courtesy copy was also sent electronically to Patent Owner's litigation counsel listed below:

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