

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

XENCOR, INC.,
Petitioner,

v.

MERUS N.V.,
Patent Owner.

IPR2025-00605
Patent 11,926,859 B2

Before ZHENYU YANG, TAWEN CHANG, and RYAN H. FLAX,
Administrative Patent Judges.

CHANG, *Administrative Patent Judge.*

DECISION
Granting Institution of *Inter Partes* Review
35 U.S.C. § 314

I. INTRODUCTION

Xencor, Inc. (“Petitioner”) filed a Petition for *inter partes* review of claims 1–7 of U.S. Patent No. 11,926,859 B2 (Ex. 1001, “the ’859 patent”). Paper 1 (“Pet.”). Merus N.V. (“Patent Owner”) filed a Preliminary Response.¹ Paper 7 (“Prelim. Resp.”).

We have authority under 35 U.S.C. § 314(a), which provides that an *inter partes* review may not be instituted “unless . . . there is a reasonable likelihood that the petitioner would prevail with respect to at least 1 of the claims challenged in the petition.” For the reasons discussed below, we determine Petitioner has demonstrated a reasonable likelihood that at least one challenged claim of the ’859 patent is unpatentable. Accordingly, we institute an *inter partes* review of all challenged claims on each of the Grounds raised in the Petition. *See SAS Inst., Inc. v. Iancu*, 138 S. Ct. 1348, 1359–60 (2018).

¹ In addition, Patent Owner filed a Request for Discretionary Denial of Institution under 35 U.S.C. §§ 314(a) and 324(a) on May 30, 2025 (Paper 6), to which Petitioner filed an Opposition on June 30, 2025. The parties further filed, with authorization (Ex. 3101), a Reply and a Sur-Reply regarding Patent Owner’s Request for Discretionary Denial on July 9, 2025 and July 11, 2025, respectively. Papers 10, 11. On July 17, 2025, the Acting Director denied Patent Owner’s Request for Discretionary Denial and referred the Petition to the Board “to handle . . . in the normal course, including by issuing a decision on institution addressing the merits and other non-discretionary considerations, as appropriate.” Paper 12, 4.

A. Real Parties-in-Interest

Petitioner and Patent Owner each identifies itself as the real party-in-interest. Paper 1, 2; Paper 4,² 1.

B. Related Proceedings

Petitioner and Patent Owner each identifies *Merus N.V. v. Xencor, Inc.*, C.A. No. 24-913-CFC (D. Del.) as a pending district court litigation in which the '859 patent is being asserted. Pet. 3; Paper 4, 1. The parties note that in the same district court litigation Patent Owner also asserts U.S Patent No. 9,358,286 ("'286 patent"), which is in the same family as the '859 patent, and U.S. Patent No 9,944,695. Pet. 3; Paper 4, 1. Petitioner has concurrently filed an IPR petition, IPR2025-00604, challenging the '286 patent. Pet. 3; Paper 4, 1.

C. The '859 Patent and Relevant Background

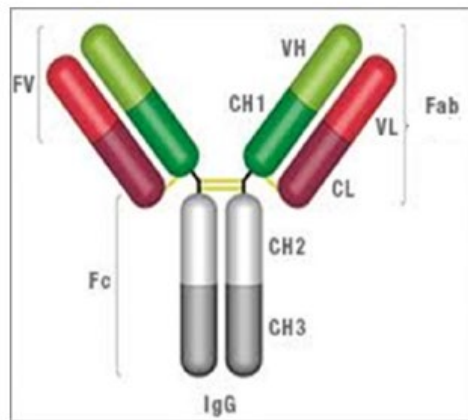
1. *Antibody Function and Structure*

Immunoglobulins (Ig) are proteins involved in the bodies' immune response and are produced naturally by B cells in the body. *See, e.g.*, Ex. 1011, 111. They may be membrane-bound on the surface of the B-cell as B-cell receptors or secreted as antibodies. *Id.* The secreted antibodies bind specifically to portions (i.e., epitopes) of molecules (i.e., antigens) from pathogens that elicited the immune response and, once bound, perform the effector function of recruiting other cells and molecules to destroy the

² Paper 4 is not paginated. We refer to the pages as if numbered sequentially starting with the first page after the cover page.

pathogen. *Id.* The antigen-binding region, which “varies extensively between antibody molecules,” is referred to as the variable (V) region. *Id.* In contrast, the region of the antibody molecules that engages in the effector function is known as the constant (C) region. *Id.* Antibodies are classified into five classes (IgM, IgD, IgG, IgA, and IgE) based on the form of their constant region. *Id.* at 112.

Naturally occurring antibodies generally have a Y shape consisting of two identical light (L) chains and two identical heavy (H) chains, as shown in the figure below:



Ex. 2010 ¶ 24; *see also* Ex. 1002³ ¶ 26 (Demonstrative 2); Ex. 1011, 112–113 (Figs. 3.1 & 3.2). The figure above is a schematic from the Sutton Declaration⁴ showing the general structure of an IgG antibody, which is the

³ Declaration of Leonard G. Presta, Ph.D. (“Presta Declaration,” Ex. 1002).

⁴ Declaration of Brian J. Sutton, Ph.D., filed in support of Patent Owner’s Preliminary Response (Ex. 2010, “Sutton Declaration”). Throughout the Preliminary Response, Patent Owner refers to Exhibit 1010 when citing to

most common type of antibody found in human blood. Ex. 2010 ¶ 23; Ex. 1002 ¶ 23. As shown in the figure above and explained in the declaration,

[e]ach IgG heavy chain consists of one variable domain (VH) and three constant domains (CH1, CH2, and CH3). Each light chain consists of one variable domain (VL) and one constant domain (CL). The CH2 and CH3 domains of the heavy chains interact to form the “fragment crystallizable” or Fc region. The VH and VL domains form the Fv fragment, which binds antigen, and together with the CL and CH1 domains forms the “fragment antigen-binding” or Fab region.

Id. ¶ 24; *see also* Ex. 1002 ¶ 26 (Demonstrative 2). The two respective heavy and light chains of the immunoglobulin molecules are joined by disulfide bonds (shown as the yellow horizontal bars in the figure above) such that “each heavy chain is linked to a light chain and the two heavy chains are linked together.” Ex. 1011, 113, Fig. 3.2; *see also* Ex. 2010 ¶ 25, Ex. 1002 ¶ 26 (Demonstrative 2).

“For antibodies, . . . the CH3-CH3 interaction is the primary driver for Fc dimerization,” and “when two CH3 domains interact with each other they meet in a protein-protein interface” comprising “contact” or “interface” amino acids or residues, which may interact with each other via, e.g., Van der Waals forces, hydrogen bonds, electrostatic forces, disulfide bonds, or interactions between side chains. Ex. 1001, 4:21–39.

the Sutton Declaration. However, we understand these to be typographical errors and that Patent Owner intends to cite Exhibit 2010.

2. The '859 Patent

The '859 patent, entitled “Methods and Means for the Production of Ig-Like Molecules,” was filed as U.S. Patent Application No. 18/318,507 ('507 application) on May 16, 2023, and indicates priority to U.S. Patent Application No. 16/934,925 ('925 application), filed on July 21, 2020; U.S. Application No. 16/417,379 ('379 application, now U.S. Patent No. 10,752,929), filed on May 20, 2019; U.S. Application No. 15/155,743 ('743 application, now U.S. Patent No. 10,329,596), filed on May 16, 2016; U.S. Application No. 14/081,848 ('848 application, now U.S. Patent No. 9,358,286), filed on November 15, 2013; U.S. Application No. 13/866,747 ('747 application, now U.S. Patent No. 9,248,181), filed on April 19, 2013; and U.S. Provisional Application No. 61/635,935 ('935 Provisional), filed on April 20, 2012. Ex. 1001, codes (54), (21), (22), (63), (60), 1:7–19.

The '859 patent teaches that monoclonal antibodies, which bind to a single epitope, may be less therapeutically effective than polyclonal antibody preparations. Ex. 1001, 1:41–2:25. However, polyclonal antibody preparations, whether derived from serum or by combining two monoclonal antibodies, have their own limitations relating to availability, cost, reproducibility, and/or potential risk of infectious disease transmission. Ex. 1001, 26:45–3:12.

The '859 patent teaches that bispecific antibodies, in which a single immunoglobulin binds to two different epitopes on the same or different targets, “have emerged as an alternative to the use of combinations of [two] antibodies.” Ex. 1001, 3:13–22. According to the '859 patent, development

of bispecific antibodies may be less complex “[f]rom a technological and regulatory perspective,” because it involves only a single molecule. *Id.* at 3:27–31.

The ’859 patent teaches that “[b]ispecific antibodies based on the IgG format, consisting of 2 heavy and 2 light chains[,] have been produced by,” e.g., “fusing two antibody-secreting cell lines to create a new cell line or by expressing two antibodies in a single cell using recombinant DNA technology.” Ex. 1001, 3:35–40. However, these approaches produce an antibody mixture that also contains monospecific dimers (i.e., homodimers) and heavy and light chain mis-pairs, such that the bispecific antibodies of interest must be purified from the mixture. *Id.* at 3:40–52.

The ’859 patent teaches that different methods have been used to increase the percentage of bispecific antibodies in the antibody mixture. Ex. 1001, 3:57-63. In particular, “[s]pecific engineering in the CH3 domains was applied in order to favour heterodimerization over homodimerization.” *Id.* at 4:47–49. Examples of such engineering include “introduction of complementary protuberance and cavity mutations, also known as ‘knob-into-hole’ approaches,” and “electrostatic engineering of contact residues within the CH3-CH3 interface,” wherein “naturally occurring charged amino acid contact residues are replaced by amino acid residues of opposite charge (i.e., a charge reversal strategy).” *Id.* at 4:49–54, 5:34–49.

According to the ’859 patent, its invention uses electrostatic engineering technology to achieve “further improved percentage of desired bispecific antibodies.” Ex. 1001, 6:6–14.

D. Overview of Challenged Claims

Petitioner challenges claims 1–7 (all claims) of the '859 patent.

Claim 1, reproduced below, is the sole independent claim:

1. A heterodimeric antibody comprising 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.

Ex. 1001, 69:33–38.

Claims 2–6 depend directly or indirectly from independent claim 1 and recite additional features of the claimed antibody. Ex. 1001, 69:39–45, 70:33–41. Claim 7 recites “[a] pharmaceutical composition comprising the heterodimeric antibody according to claim 1, and a pharmaceutically acceptable carrier.” *Id.* at 70:42–44.

E. Asserted Grounds of Unpatentability

Petitioner asserts the following grounds of unpatentability (Pet. 4):

Ground ⁵	Claims Challenged	35 U.S.C § ⁶	Reference(s)/Basis
1	1–7	102	Desjarlais ⁷
2	1–7	102	Moore ⁸
3a	1–7	103	Lazar ⁹

⁵ Ground 3 in the Petition challenges claims 1–7 of the '859 patent as obvious over Lazar “alone or in view of” Kannan. Pet. 4. For clarity, we designate the challenge relying on Lazar alone as Ground 3a, and the challenge relying on Lazar and Kannan as Ground 3b.

⁶ The Leahy-Smith America Invents Act (“AIA”), Pub. L. No. 112-29, 125 Stat. 284, 287–88 (2011), amended 35 U.S.C. §§ 102 and 103, effective March 16, 2013. AIA § 3(b)–(c). Because Patent Owner previously represented that the '747 application, to which the '859 patent claims priority, “contains, or contained at any time, a claim to a claimed invention that has an effective filing date on or after March 16, 2013” (Ex. 1045, 4), the AIA versions of §§ 102 and 103 apply to the '859 patent. AIA § 3(n)(1)(B); *see also* Pet. 4 n.2 (pointing out Patent Owner’s representation to the Patent Office). Our Decision will not change, however, if the pre-AIA versions of 35 U.S.C. §§ 102 and 103 apply.

⁷ Desjarlais et al., US 10,472,427 B2, issued Nov. 12, 2019 (Ex. 1036, “Desjarlais”).

⁸ Moore, A Robust Heterodimeric Fc Platform Engineered for Efficient Development of Bispecific Antibodies of Multiple Formats, 154 METHODS 38 (2019) (Ex. 1038, “Moore”).

⁹ Lazar et al., US 2011/0054151 A1, published Mar. 3, 2011 (Ex. 1004, “Lazar”).

Ground ⁵	Claims Challenged	35 U.S.C § ⁶	Reference(s)/Basis
3b	1-7	103	Lazar, Kannan ¹⁰

Petitioner further relies, *inter alia*, on the Presta Declaration.

II. ANALYSIS

A. Principles of Law

“In an [*inter partes* review], the petitioner has the burden from the onset to show with particularity why the patent it challenges is unpatentable.” *Harmonic Inc. v. Avid Tech., Inc.*, 815 F.3d 1356, 1363 (Fed. Cir. 2016). The burden of persuasion never shifts to Patent Owner. *Dynamic Drinkware, LLC v. Nat’l Graphics, Inc.*, 800 F.3d 1375, 1378 (Fed. Cir. 2015).

However, Patent Owner has the burden of production to show that a claim is entitled to a filing date prior to the date of the alleged prior art. *See Tech Licensing Corp. v. Videotek, Inc.*, 545 F.3d 1316, 1327 (Fed. Cir. 2008). Our reviewing court has explained that “[t]he burden of production cannot be met without some combination of citing the relevant record evidence with specificity and explaining the significance of the produced material in briefs.” *Parus Holdings, Inc. v. Google LLC*, 70 F.4th 1365, 1372 (Fed. Cir. 2023).

¹⁰ Kannan et al., WO 2009/089004 A1, published July 16, 2009 (Ex. 1007, “Kannan”).

Pursuant to 35 U.S.C. § 120, a patent application is entitled to assert priority to the filing date of a prior application only “for an invention disclosed [in the prior application] in the manner provided by [35 U.S.C. §] 112(a) (other than the requirement to disclose the best mode).” Section 112(a) in turn requires the specification to (1) contain a written description of the claimed invention and (2) enable a skilled artisan to make and use the same without undue experimentation. *Ariad Pharms., Inc. v. Eli Lilly & Co.*, 598 F.3d 1336, 1340 (Fed. Cir. 2010) (en banc).

The test for sufficiency of a written description under 35 U.S.C. § 112(a) is whether the earlier application’s disclosure “reasonably conveys to those skilled in the art that the inventor had possession of the claimed subject matter as of the filing date.” *Ariad*, 598 F.3d at 1351. That “test requires an objective inquiry into the four corners of the specification from the perspective of a person of ordinary skill in the art.” *Id.* “[T]he level of detail required to satisfy the written description requirement varies depending on the nature and scope of the claims and on the complexity and predictability of the relevant technology.” *Id.* (citing *Capon v. Eshhar*, 418 F.3d 1349, 1357–58 (Fed. Cir. 2005)).

To anticipate under 35 U.S.C. § 102, each and every claim element, arranged as in the claim, must be found in a single prior art reference. *Net MoneyIN, Inc. v. VeriSign, Inc.*, 545 F.3d 1359 (Fed. Cir. 2008). It is permissible to consider not only the literal teachings of an alleged anticipatory prior art reference, but also the inferences a person of ordinary

skill in the art would draw from the reference. *Eli Lilly and Co. v. Los Angeles Biomedical Res. Inst.*, 849 F.3d 1073, 1074–75 (Fed. Cir. 2017).

In general, a claim is unpatentable under 35 U.S.C. § 103 if the differences between the claimed invention and the prior art are such that the claimed invention as a whole would have been obvious before the effective filing date of the claimed invention to a person having ordinary skill in the art to which the claimed invention pertains. *See KSR Int’l Co. v. Teleflex Inc.*, 550 U.S. 398, 406 (2007). The question of obviousness is resolved on the basis of underlying factual determinations including: (1) the scope and content of the prior art; (2) any differences between the claimed subject matter and the prior art; (3) the level of ordinary skill in the art; and (4) objective evidence of nonobviousness (or obviousness), if any. *Graham v. John Deere Co.*, 383 U.S. 1, 17–18 (1966).

We address Petitioner’s challenges with these standards in mind, and in view of the definition of the skilled artisan and the claim constructions discussed below.

B. Person of Ordinary Skill in the Art

Factual indicators of the level of ordinary skill in the art include “the various prior art approaches employed, the types of problems encountered in the art, the rapidity with which innovations are made, the sophistication of the technology involved, and the educational background of those actively working in the field.” *Jacobson Bros., Inc. v. U.S.*, 512 F.2d 1065, 1071 (Ct. Cl. 1975); *see also Orthopedic Equip. Co. v. U.S.*, 702 F.2d 1005, 1011 (Fed. Cir. 1983) (quoting with approval *Jacobson Bros.*).

Petitioner asserts that

[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.

Pet. 14.

Patent Owner asserts that

[a] POSA at the time of the invention of April 20, 2012 would have a Ph.D. in biochemistry, chemistry, molecular or structural biology, molecular biophysics, antibody engineering, immunology, or related discipline and at least 2 years of related experience in academia or industry or a Master’s degree in any of the above fields with at least 4 years of related experience in academia or industry.

Prelim. Resp. 8.¹¹ However, Patent Owner states that, “[f]or purposes of the Preliminary Response, Patent Owner applies Petitioner’s proposed definition of a POSA. Under either definition of POSA . . . , [Petitioner] still fails to meet its burden for IPR institution.” *Id.*

¹¹ The Preliminary Response ascribes the above definition of a POSA to “Petitioner” and cites to paragraph 17 of Ex. 1010 as support. We understand the definition to be proposed by Patent Owner and further understand that Patent Owner intends to cite to paragraph 17 of Ex. 2010, rather than Ex. 1010, as support.

On the current record, for purposes of this Decision, we accept Petitioner’s proposed definition, as it appears to be consistent with the level of skill in the art reflected in the prior art of record and the disclosure of the ’859 patent, and because Patent Owner applied the same definition for purposes of the Preliminary Response. *See Okajima v. Bourdeau*, 261 F.3d 1350, 1355 (Fed. Cir. 2001) (“the prior art itself [may] reflect[] an appropriate level” as evidence of the ordinary level of skill in the art) (quoting *Litton Indus. Prods., Inc. v. Solid State Sys. Corp.*, 755 F.2d 158, 163 (Fed. Cir. 1985)). Our Decision will not change, however, even if we were to adopt Patent Owner’s proposed definition.

C. Claim Construction

We construe claims “using the same claim construction standard that would be used to construe the claim in a civil action under 35 U.S.C. [§] 282(b).” 37 C.F.R. § 42.100 (2021). Therefore, we construe the challenged claims under the framework set forth in *Phillips v. AWH Corp.*, 415 F.3d 1303, 1312–19 (Fed. Cir. 2005) (en banc). Under this framework, claim terms are given their ordinary and customary meaning, as would be understood by a person of ordinary skill in the art, at the time of the invention, in light of the language of the claims, the specification, and the prosecution history of record. *Id.*

Furthermore, “we need only construe terms ‘that are in controversy, and only to the extent necessary to resolve the controversy.’” *See Nidec Motor Corp. v. Zhongshan Broad Ocean Motor Co.*, 868 F.3d 1013, 1017 (Fed. Cir. 2017) (noting that “we need only construe terms ‘that are in

controversy, and only to the extent necessary to resolve the controversy” (quoting *Vivid Techs., Inc. v. Am. Sci. & Eng’g, Inc.*, 200 F.3d 795, 803 (Fed. Cir. 1999))).

The parties do not propose express construction for any claim term. *See* Pet. 23; Prelim. Resp. 7. However, Patent Owner’s arguments regarding obviousness appear to depend at least partially on particular constructions of the claim limitations of “heterodimeric antibody” and “CH3 domain.” Prelim. Resp. 20 (citing Ex. 2010 ¶ 57). We therefore provide preliminary constructions for these terms below. Further argument on claim construction by the parties at trial is permitted, but it should be provided in a designated section of briefing, rather than merely mingled with arguments on the merits of patentability challenges. Any final written decision entered in this case may include final claim constructions that differ from these preliminary constructions, or from any discussion of claim scope provided in our analysis below. Any final claim constructions will be based on the full trial record.

1. Heterodimeric antibody

Patent Owner asserts that, “[b]ased on the Specification of the ’859 Patent, a POSA would understand that the ’859 Patent is directed to a heterodimeric antibody with two heavy chains with four domains, VH, CH1, CH2, and CH3, and two Fab arms each with a different binding site specificity.” Prelim. Resp. 19–20 (citing Ex. 2010 ¶¶ 54–56).

To the extent Patent Owner intends this argument to be a proposed construction of “heterodimeric antibody,” we do not adopt the proposed

construction for the reasons discussed below.

The '859 patent provides an explicit definition for “antibody”:

The term ‘antibody’ as used herein means a proteinaceous molecule belonging to the immunoglobulin class of proteins, containing one or more domains that bind an epitope on an antigen, where such domains are derived from or share sequence homology with the variable region of an antibody. Antibodies are known in the art and include several isotypes, such as IgG1, IgG2, IgG3, IgG4, IgA, IgD, IgE, and IgM. An antibody according to the invention may be any of these isotypes, or a functional derivative and/or fragment of these. In a preferred embodiment, Ig-like molecules are produced that are antibodies of the IgG isotype because IgG antibodies e.g. have a longer half-life as compared to antibodies of other isotypes.

Ex. 1001, 11:39–52.

Our reviewing court explained in *Phillips* that, where a patentee provides a definition of a claim term in the specification, that meaning governs even if it differs from the meaning the language would otherwise possess. 415 F.3d at 1316. We thus adopt the construction set forth in the Specification (and reproduced above as the first sentence in the quoted passage) for the term “antibody,” and apply the construction in view of the context provided by the rest of the passage.

The '859 patent does not provide an explicit definition of “immunoglobulin class.” Nevertheless, we do not construe that term to require “two heavy chains with four domains, VH, CH1, CH2, and CH3, and two Fab arms.”

As an initial matter, the Specification teaches that antibodies include,

e.g., IgE and IgM — which have an additional CH4 domain in their heavy chains — as well as functional derivatives and/or fragments of known antibody isotypes. Ex. 1001, 11:44–48. Patent Owner’s proposed construction, which limits antibodies to those having two Fab arms and “two heavy chains with four domains, VH, CH1, CH2, and CH3,” excludes these embodiments and cannot be correct. Moreover, the ’859 patent defines antibody as containing “*one* or more domains” that bind an epitope on an antigen. Ex. 1001, 11:39–44. Thus, an antibody does not require two Fab arms as in a native immunoglobulin molecule.¹² The ’859 patent also describes a preferred embodiment as “Ig-like molecules.” *Id.* at 11:49–52. Thus, we look to the definition of “Ig-like molecule” in the ’859 patent, i.e., “a proteinaceous molecule that possesses at least one immunoglobulin (Ig) domain,” to inform our understanding of the phrase “immunoglobulin class of proteins.” Ex. 1001, 11:4–6. Accordingly, we further construe “immunoglobulin class of proteins” to mean proteinaceous molecules comprising at least one domain that is derived from or shares sequence homology with an immunoglobulin domain.

The ’859 patent likewise does not provide an explicit definition of “heterodimeric.” Accordingly, we look to the “ordinary and customary meaning” of the term, “as would be understood by a person of ordinary skill in the art, at the time of the invention, in light of the language of the claims,

¹² Native immunoglobulin molecules are made up of two identical heavy and light chains, thus providing the molecule with two identical antigen-binding sites. Ex. 1011, 113, 113, Fig. 3.2.

the specification, and the prosecution history of record.” *Phillips*, 415 F.3d at 1312–19.

We agree with Petitioner’s declarant that the ordinary and customary meaning of “hetero” is “different,” and the ordinary and customary meaning of dimer is “made up of two.” Ex. 1002 ¶ 33. These meanings are further consistent with the way the term “heterodimeric” is used in the Specification. For instance, the Specification describes “heterodimeric Fc technology that supports the design of bispecific and asymmetric fusion proteins by devising strand-exchange engineered domain (SEED) CH3 heterodimers, the so-called SEED-bodies.” Ex. 1001, 5:23–33. Thus, contrary to Patent Owner’s apparent suggestion that heterodimers must be bispecific (*see, e.g.*, Ex. 2010 ¶ 54), “heterodimeric” in the context of the ’859 patent retains its plain and ordinary meaning of a molecule comprising two different polypeptide chains (e.g., two different CH3 domains).

Accordingly, for the purposes of this Decision, we construe the claim language “heterodimeric antibody” to mean

a proteinaceous molecule comprising two different polypeptide chains and including (1) at least one domain derived from or sharing sequence homology with an immunoglobulin domain and (2) one or more domains that bind an epitope on an antigen, where such domains are derived from or share sequence homology with the variable region of an antibody.

Finally, we note the above construction is consistent with the portion of the Specification, reproduced below, that is cited in the Sutton

Declaration as support for Patent Owner's apparent claim construction:

Bispecific antibodies based on the IgG format, consisting of 2 heavy and two light chains have been produced by a variety of methods. For instance, bispecific antibodies may be produced by fusing two antibody-secreting cell lines to create a new cell line or by expressing two antibodies in a single cell using recombinant DNA technology. These approaches yield multiple antibody species as the respective heavy chains from each antibody may form monospecific dimers (also called homodimers), which contain two identical paired heavy chains with the same specificity, and **bispecific dimers (also called heterodimers) which contain two different paired heavy chains with different specificity.**

Ex. 2010 ¶ 54 (quoting Ex. 1001, 3:35–46 and adding emphasis).

The cited portion of the Specification explains, consistent with our preliminary definition of the claim term “heterodimeric,” that bispecific dimers are heterodimers because they “contain two different paired heavy chains with different specificity” — i.e., they comprise two different chains. In our view, on the current record, it does not suggest the converse, i.e., that all heterodimers must also be bispecific. Indeed, such a construction would render dependent claim 4 superfluous, because it depends from claim 1 and further recites that the “heterodimeric antibody is a bispecific antibody,” which suggests that the heterodimeric antibody claim 1 is broader than a bispecific antibody. Ex. 1001, 70:36–37.

2. *CH3 domain*

In its arguments regarding obviousness, Patent Owner asserts Lazar does not disclose or suggest the claimed CH3 domain because the CH3

domains of Lazar's constructs "are not CH3 domains in heavy chains with four domains as defined in the Specification of the []'859 Patent." Prelim. Resp. 21. To the extent Patent Owner is proposing that "CH3 domain" should be construed to require it to be part of a heavy chain with four domains, we do not adopt this construction for the following reason. *Id.*

Patent Owner cites to the Sutton Declaration for support. Prelim. Resp. 21 (citing, e.g., Ex. 2010 ¶ 59). In his Declaration, Dr. Sutton relies on the following passage in the Specification regarding CH3 domain:

The term "**CH3 domain**" is well known in the art. The IgG structure has four chains, two light and two heavy chains; each light chain has two domains, the variable and the constant light chain (VL and CL) and **each heavy chain has four domains, the variable heavy chain (VH) and three constant heavy chain domains (CH1, CH2, CH3).**

Ex. 2010 ¶ 55 (quoting Ex. 1001 and adding emphasis). However, this passage merely explains the structure of an immunoglobulin in the IgG class; it neither constitutes a definition of a CH3 domain nor requires a CH3 domain to be part of a heavy chain with four domains. Indeed, as noted above, the '859 patent specification defines "Ig-like molecule" as "a proteinaceous molecule that possesses at least one immunoglobulin (Ig) domain" and further states that preferably such a molecule "comprises" a sequence comprising the function of at least an immunoglobulin CH3 domain." Ex. 1001, 11:4–9. In other words, the '859 patent contemplates CH3 domains as part of an "Ig-like molecule" that possesses a single

immunoglobulin domain rather than all of the domains in an IgG immunoglobulin heavy chain.

Accordingly, we construe “CH3 domain” to mean “a domain derived from or sharing sequence homology with the CH3 domain of an immunoglobulin molecule.”

D. Overview of References Asserted

1. Overview of Desjarlais (Exhibit 1036)

Desjarlais is a United States Patent, U.S. 10,472,427 B2, entitled “Heterodimeric Proteins,” which was issued on November 12, 2019. Ex. 1036, codes (12), (10), (45), (54). Desjarlais was filed as U.S. Patent Application No. 15/633,629 on June 26, 2017, and claims the benefit of U.S. Application No. 14/155,344, filed on January 14, 2014 (now U.S. Patent No. 9,701,759) and three U.S. provisional applications, including U.S. Provisional No. 61/780,310, filed on March 13, 2013. Ex. 1036, codes (21), (22), (63), (60), 1:5–11.

Desjarlais teaches that various approaches have been explored to improve clinical efficacy of antibody-based therapeutics. Ex. 1036, 1:44–2:40. These approaches include “non-native or alternate antibody formats that engage two different antigens,” which are often referred to as bispecifics. *Id.* at 1:48–53. Desjarlais teaches that bispecifics made by fusing two cell lines each producing a single monoclonal antibody require extensive purification to isolate the desired antibody, whereas bispecifics made from antibody fragments “clear rapidly in vivo and can present manufacturing obstacles,” in large part because they “lack the constant

region of the antibody with its associated functional properties.” *Id.* at 1:64–2:23. Desjarlais teaches that “[m]ore recent work . . . to address the shortcomings of fragment-based bispecifics by engineering dual binding into full length antibody-like formats” has the drawback that, “because they build new antigen binding sites on top of the homodimeric constant chains, binding to the new antigen is always bivalent.” *Id.* at 2:24–40.

According to Desjarlais, the above problems were solved by its heterodimeric antibodies comprising a first heavy chain comprising (1) a first Fc domain and a single chain Fv region that binds a first antigen, and (2) a second heavy chain comprising a second Fc domain, a first variable heavy chain and a first variable light chain, wherein the first and second Fc domains are different.” Ex. 1036, 3:18–30.

Desjarlais teaches that its heterodimeric antibodies may comprise heterodimerization variants according to its Figures 4, 5, 6, 20, 21, and 22. Ex. 1036, 3:37–39. Figures 4A and 4B of Desjarlais are entitled, respectively, “Preferred steric variants that favor Fc heterodimerization” and “**Specifically** preferred steric variants that favor Fc heterodimerization.” *Id.* at Figs. 4A, 4B. These figures list amino acid residues of antibody Fc regions and indicate mutations to change existing amino acids to other amino acids at various positions, as well as identifying “‘corresponding’ monomer pairs or ‘sets.’” *Id.* at 4:55–60, 13:43–46, 16:46–50, 52:61–63, Figs. 4A, 4B. For example, Fig. 4A discloses L368E and S364K as a set, corresponding to a variant having one monomer with a negative glutamic

acid at residue 368 and a second monomer having a positive lysine at residue 364. *Id.* at Fig. 4A.

2. Overview of Moore (*Exhibit 1038*)

Moore is an article entitled, “A robust heterodimeric Fc platform engineered for efficient development of bispecific antibodies of multiple formats,” which appears to have been published in the journal *Methods* in 2019. *Ex. 1038*.

Moore teaches that “[b]ispecific monoclonal antibodies [(mAbs)] can bind two protein targets simultaneously and enable therapeutic modalities inaccessible by traditional mAbs.” *Ex. 1038, Abstract*. Moore teaches that “[b]ispecific formats containing a heterodimeric Fc region are of particular interest,” because a heterodimeric Fc “empowers bispecificity” while retaining “the developability and druggability of a monoclonal antibody.” *Id.* Moore teaches that “[d]esign of a heterodimeric Fc can be stated as the design of two complementary CH3 domains that show a strong preference for pairing with each other versus pairing with themselves, resulting in a significantly higher yield of heterodimer versus homodimeric or monomeric side products.” *Id.* at 39, left col.

Moore presents a “heterodimeric Fc platform” for “development of bispecific antibodies and Fc fusions.” *Ex. 1038, Abstract*. As part of this platform, Moore discloses “a novel set of Fc substitutions capable of achieving heterodimer yields over 95% with little change in thermostability.” *Id.* More particularly, Moore teaches a “newly designed combination variant” of Fc heterodimer, E357Q/S364K-L368D/K370S, in

which serine (S) is replaced with a positive lysine (K) in residue 364 of the first chain of the Fc heterodimer and leucine (L) is replaced with a negative aspartic acid (D) in residue 368 of the second chain. *Id.* at 43, right col.

Moore teaches that “a robust heterodimeric Fc region enables a wide variety of possible formats” of bispecific antibodies and Fc fusions. Ex. 1038, 45, right col. (citing Fig. 1); *see also id.* at 39, Fig. 1. Moore provides a case study of tumor-associated antigen (TAA) x CD3 bispecifics using its heterodimeric Fc platform. *Id.* at 45–46.

3. *Overview of Lazar (Exhibit 1004)*

Lazar is a U. S. Patent Publication, US 2011/0054151 A1, entitled “Compositions and Methods for Simultaneous Bivalent and Monovalent Co-engagement of Antigens,” which was published on March 3, 2011. Ex. 1004, codes (19), (12), (10), (43), (54). Lazar is the publication of U.S. Patent Application No. 12/875,010, filed on September 2, 2010, and claims the benefit of U.S. Provisional Application No. 61/239, 316, filed on September 2, 2009. *Id.* at codes (21), (22), (60), ¶ 1.

Lazar teaches that bispecifics (i.e., a single immunoglobulin that co-engages two different antigens) produced using antibody fragments suffer shortcomings caused by the lack of the constant region with its associated functional properties. Ex. 1004 ¶ 4. Lazar describes attempts to address these shortcomings by “engineering dual binding into full length antibody-like formats,” but notes that, because these formats “build new antigen binding sites on top of the homodimeric constant chains, binding to the new antigen is always bivalent.” *Id.* ¶ 5. Lazar teaches that this is a significant

drawback because “engag[ing] co-target antigens multivalently in the absence of the primary target antigens” may lead to “nonspecific activation and potentially toxicity.” *Id.* ¶¶ 6–7.

Lazar teaches that its invention solves this problem by “introducing a novel set of bispecific formats that enable the simultaneous bivalent and monovalent co-engagements of distinct target antigens.” Ex. 1004 ¶ 7. Lazar’s Figure 8, reproduced below, illustrates some of these bispecific formats:

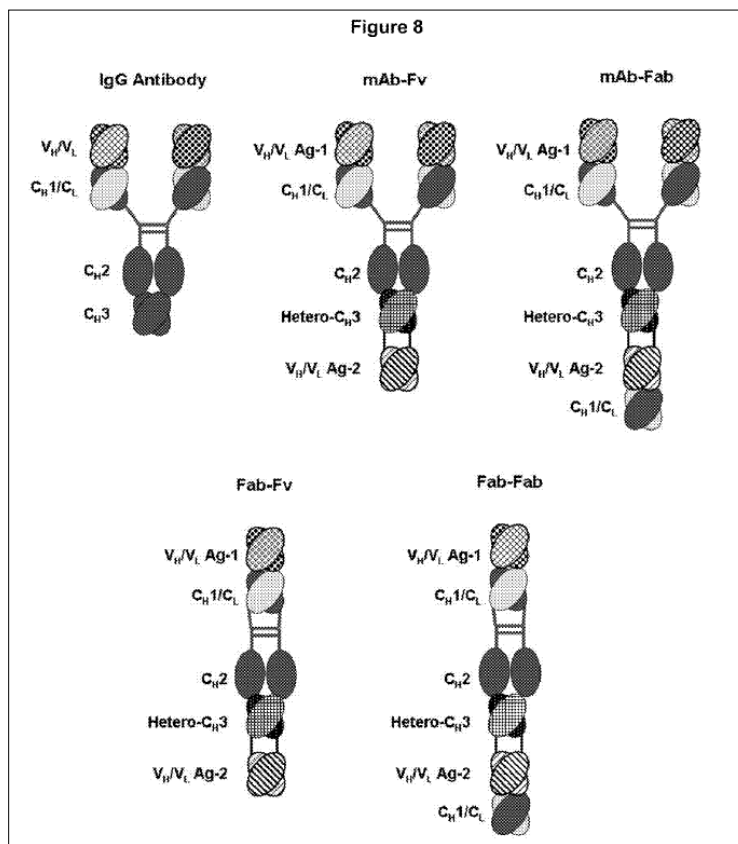


Figure 8 provides an illustration of mAb-Fv and mAb-Fab immunoglobulin formats, with the native IgG antibody (top row, left) provided as a reference. *Id.* ¶ 16. As Lazar explains, the formats in the top row, center and right,

show “[b]ivalent binding to antigen-1 (Ag-1) . . . mediated by the N-terminal VH/VL pairs (Fv-1)” and “monovalent binding to antigen-2 (Ag-2) . . . mediated by the C-terminal VH/VL pair (Fv-2).” *Id.*¹³ In addition, Figure 8 shows the Fab-Fv and Fab-Fab analogs (bottom row) that monovalently bind both antigen-1 and antigen-2. *Id.*

Lazar teaches that its immunoglobulins preferably have heterodimeric Fc regions. Ex. 1004, Abstract. The heterodimeric regions are labeled as “Hetero-CH3” in Figure 8 above. Lazar further teaches a “[h]eterodimeric Fc region proof-of-concept system” in which “DNA constructs encoding two different immunoglobulin polypeptides were designed: (i) scFv-Fc (VH-

¹³ The difference between the mAb-Fv (top row, center) and mAb-Fab (top row, right) formats is that mAb-Fab format includes the CH1 and CL (labeled CH1 and CL) domains in its antigen-2 binding portion whereas the mAb-Fv format does not. Ex. 1004, Fig. 8.

linker-V κ -Hinge-CH2-CH3') and (ii) empty-Fc (Hinge-CH2-CH3")." *Id.*

¶ 9. Figure 1 of Lazar, reproduced below, illustrates this proof-of-concept:

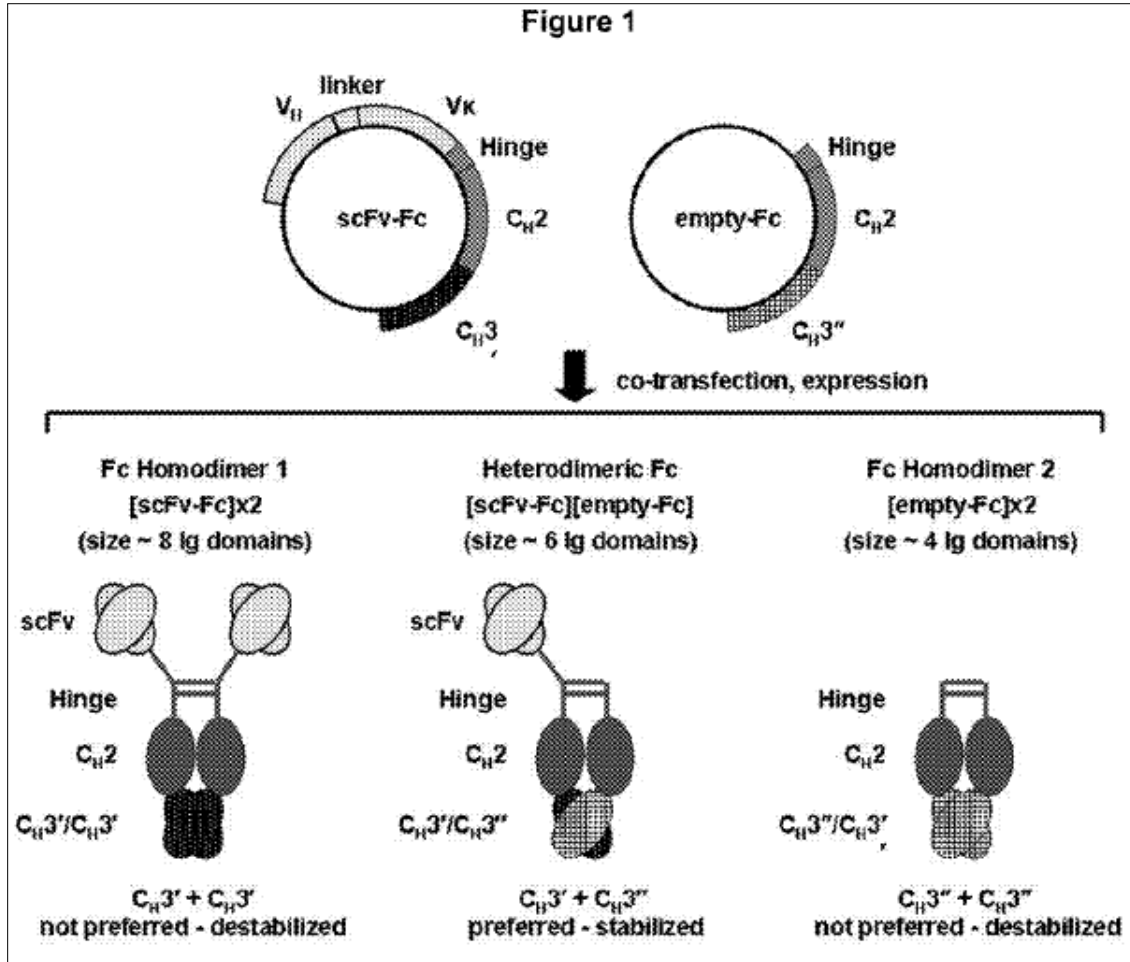


Figure 1 of Lazar shows the three possible dimers that can be formed from co-transfection and expression of the two polypeptides. *Id.* Lazar teaches that “[t]he two different CH3 domains, CH3' (prime) and CH3'' (double prime), can be designed to promote heterodimer formation and discourage homodimer formation.” *Id.* Lazar teaches that, in one preferred embodiment where amino acid modifications stabilize a heterodimeric Fc region while destabilizing homodimeric Fc regions, the variant Fc regions

comprise at least one substitution at particular amino acid positions. *Id.*
¶ 52. Lazar teaches another preferred embodiment where the variant Fc regions comprise at least one of the enumerated substitutions. *Id.*

4. Overview of Kannan (Exhibit 1007)

Kannan is an International Patent Publication, WO 2009/089004 A1, published under the Patent Cooperation Treaty (PCT) on July 16, 2009. Ex. 1007, codes (10), (12), (43). Kannan claims the benefit of U.S. Provisional Application Nos. 61/019,569 and 61/120,305, filed January 7, 2008 and December 5, 2008, respectively.

Kannan teaches that, “[i]n certain instances, it is desirable to create a molecule that contains the Fc portion of an antibody but comprises a heterodimer,” and that “[a]n important application of Fc heterodimeric molecules is the generation of bispecific antibodies (BsAbs).” Ex. 1007 1:29–31. Kannan “describes a strategy for altering the interaction of antibody domains, e.g., altering a CH3 domain to reduce the ability of the domain to interact with itself, i.e., form homodimers.” *Id.* at 2:33–35.

More particularly, Kannan teaches

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. In certain embodiments, 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. By reversing the charge of the amino acid, homodimer formation is reduced. When the replacements are coordinated properly, the reversed charges are electrostatically favorable, i.e., opposing charges in the interface, for heterodimerization formation.

Ex. 1007, 2:35–3:7.

Kannan also discloses a “[l]ist of CH3 domain interface residues in the first chain (A) and their contacting residues in the second chain (B), including SER 364 and LEU 368 in chain A and their respective contacting residues in chain B (i.e., LEU 368’ LYS 370’ for SER 364, and SER 364’ LYS 409’ for LEU 368). Ex. 1007, 7:19–8:4.

E. Priority Date

A foundational issue for Petitioner’s first two asserted grounds of unpatentability, anticipation by Desjarlais and/or Moore, is whether Desjarlais and Moore qualify as prior art, which in turn depends on the priority date to which the challenged claims are entitled.

Citing *PowerOasis, Inc. v. T-Mobile USA, Inc.*, 522 F.3d 1299, 1304 (Fed. Cir. 2008), Patent Owner first argues that it is “entitled to the April 20, 2012 priority date” because it is the priority date afforded by the Examiner, who “must receive deference as they are presumed to perform their duties and responsibilities . . . , understand the cited reference, and issue only valid patents.” Prelim. Resp. 10. However, *PowerOasis* actually explains that, “[i]n the absence of an interference or rejection which would require the PTO to make a determination of priority, the PTO does not make such

findings as a matter of course in prosecution.” *PowerOasis*, 522 F.3d at 1305.

Instead, once a challenger has established that the prior art was anticipatory, the burden is on the patentee to “come forward with evidence to prove entitlement to claim priority to an earlier filing date.” *PowerOasis*, 522 F.3d at 1305; *see also Dynamic Drinkware*, 800 F.3d at 1379–80 (explaining that, once Petitioner has satisfied its initial burden of production, the burden of production shifts to Patent Owner to argue or produce evidence that either the prior art does not actually anticipate, or it is not prior art because the challenged claims were entitled to an earlier filing date).

As further discussed below, Patent Owner additionally asserts that the claims are entitled to an effective filing date of April 20, 2012, based on the disclosures in the ’935 provisional. Prelim. Resp. 11. Petitioner argues that the challenged claims are entitled to an effective filing date no earlier than the ’859 patent’s actual filing date, i.e., May 16, 2023, because none of the applications in the ’859 patent’s priority chain adequately describe the heterodimeric antibodies recited in the challenged claims. Pet. 23–24.¹⁴

¹⁴ Although the ’507 application that issued as the ’859 patent claims priority to several applications, Patent Owner presents arguments only with respect to the ’935 provisional filed April 20, 2012. Thus, for purposes of institution, we limit our analysis to whether the challenged claims are entitled to a priority date of April 20, 2012.

1. Petitioner's Position

Petitioner asserts that “none of the . . . prior applications listed on the face of the '859 patent describes the antibody recited in claim 1 having a positive charge at 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,” and “[t]he remaining dependent claims 4–7 also lack written description support due to their dependency from claim 1.” Pet. 28.

2. Patent Owner's Position

Patent Owner relies on the following portions of the '935 provisional, and Dr. Sutton's testimony regarding what an ordinarily skilled artisan would have understood based on these disclosures, to show that the inventors of the '859 Patent had possession of all the elements of the claimed heterodimeric antibodies as of April 20, 2012:

- Disclosures of bispecific dimers and CH3 domains, Prelim. Resp. 12 (citing Ex. 2010 ¶¶ 42–43); Ex. 2010 ¶¶ 42–43 (quoting Ex. 1030, 4:5–13, 5:28–31);
- Statements that the '935 provisional is an “inventive alternative” to the prior art because it “does not exchange charged contact amino acids by amino acids of opposite charge but substitutes non-charged CH3 amino acids for charged ones” and that this approach “provides not only a method for efficiently steering the dimerization of CH3 domains but also has the advantage that at least one additional charge-charge interaction in the CH3 interface

is created,” resulting in greater stability as compared to wildtype dimers and “surprisingly . . . increas[ing] the proportion of . . . Ig-like molecules of interest in a mixture even further,” Prelim. Resp. 12 (citing Ex. 2010 ¶ 44); Ex. 2010 ¶ 44 (quoting Ex. 1030, 23:28–24:13);

- The identification of charged and neutral residues, Prelim. Resp. 12 (citing Ex. 2010 ¶ 45); Ex. 2010 ¶ 45 (quoting Ex. 1030, 17);
- Table A, reproduced in the Sutton Declaration with portions highlighted:

Table A: List of CH3 domain interface residues

Interface residue in chain A	Contacting residues in chain B
Q347	K360
Y349	S354, D356, E357, K360
T350	S354, R355
L351	L351, P352, P353, S354, T366
S354	Y349, T350, L351
R355	T350
D356	Y349, K439
E357	Y349, K370
K360	Q347, Y349
S364	L368, K370
T366	L351, Y407
L368	S364, K409
K370	E357, S364
N390	S400
K392	L398, D399, S400, F405
T394	T394, V397, F405, Y407
P395	V397
V397	T394, P395
D399	K392, K409
S400	N390, K392
F405	K392, T394, K409
Y407	T366, T394, Y407, K409
K409	L368, D399, F405, Y407
K439	D356

Ex. 2010 ¶ 47 (reproducing Table A of the ’935 provisional with residues recited in ’859 patent claim 1 (residues 364 and 368) highlighted);

- Table 7, partially reproduced in Dr. Sutton’s declaration with portions highlighted:

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	+
T394K, F405K	27	+++
T394K, Y407K	28	+++
P395K, V397K	29	+-
S400K	30	-
F405K	31	+++
Y407K	32	++
Q347K, V397K, T394K	33	+
Y349D, P395K, V397K	34	+
T350K, T394K, V397K	35	NT
L351K, S354K, S400K	36	+
S354K, Y349K, Y407K	37	+-
T350K, N390K, S400K	38	+-
L368K, F405K	39	++
D356K, T366K, L351K	40	+++
Q347K, S364K	41	+++
L368D , Y407F	42	+
T366K	43	+
L351K, S354K, T366K	44	+
Y349D, Y407D	45	+
Y349D, S364K	46	+

Ex. 2010 ¶ 48 (partially reproducing Table 7 with S364K and L368D highlighted).

Patent Owner relies on Dr. Sutton’s testimony that, based on the disclosures in the ’935 provisional, an ordinarily skilled artisan would reasonably “understand that substituting neutral residues in the CH3 domain with charged residues would result in the production of the claimed heterodimer antibody,” and, more particularly, “substituting known contacting pairs 364 and 368 with a lysine (K) or an arginine (R) residue at

position 364 and an aspartic acid (D) or glutamic acid (E) residue at position 368 would produce the claimed heterodimeric antibody in Claims 1 – 3 of the '859 patent.” Prelim. Resp., 12–13 (citing Ex. 2010 ¶¶ 45–49). Patent Owner further relies on Dr. Sutton’s testimony that such a skilled artisan would further reasonably understand that “the inventors were in possession of such an invention.” *Id.* at 13 (citing Ex. 2010 ¶ 49).

3. *Analysis*

The crux of the parties’ dispute is whether the '935 provisional adequately describes a heterodimeric antibody comprising the recited charged residues at the recited positions of the CH3 domains, i.e., “a positively charged amino residue at position 364” at a first CH3 domain and “a negatively charged amino acid residue at position 368” of the second CH3 domain. Having considered the evidence of record at this preliminary stage of the proceeding, and for the reasons set forth below, we are persuaded that Petitioner has shown sufficiently, for purposes of institution, that the '935 provisional does not provide adequate written description support for claim 1 of the '859 patent and that, accordingly, Desjarlais and Moore qualify as prior art to that claim.

As Petitioner points out, the cited disclosure in the '935 provisional does not “mention[] positions 364 and 368 together as a pair of positions for potential mutations on two chains.” Pet. 28 (citing Ex. 1002 ¶¶ 109–19). Although Patent Owner is correct that examples or actual reduction to practice are not required for adequate written description and “[a] specification may . . . contain a written description of a broadly claimed

invention without describing all species that [the] claim encompasses,” Prelim. Resp. 15 (quoting *Ariad Pharms.*, 598 F.3d at 1352 and *Cordis Corp. v. Medtronic AVE Inc.*, 339 F.3d 1352, 1365 (Fed. Cir. 2003)), the ’935 provisional must still “reasonably convey[] to those skilled in the art that the inventor[s] had possession of the claimed subject matter” as of the relevant date. *Regeneron Pharms., Inc. v. Mylan Pharms. Inc.*, 127 F.4th 896, 914 (Fed. Cir. 2025); *Ariad*, 598 F.3d at 1351.

In this case, Table A of the ’935 provisional discloses a list of CH3 domain interface residues and identifies, for each interface residue in heavy chain A, the contacting residue in the corresponding chain B. Ex. 1030, 17, Table A. Table A does not, however, describe any particular substitutions or pairs of substitutions that should be made to the CH3 domains. *See, e.g.*, Pet. 28 (citing Ex. 1002 ¶¶ 109–119).

Table 7 of the ’935 provisional does identify specific amino acid substitutions in CH3 domains, including substitutions resulting in a positively charged residue at position 364 (e.g., S364K) and a negatively charged residue (e.g., L368D) at position 368. Ex. 1030, 52, Table 7. Patent Owner argues that this table “discloses specific positions for ‘identification of novel charge pair mutants.’” Prelim. Resp. 13 (citing Ex. 2010 ¶ 48). As Petitioner points out, however, while Example 13 of the ’935 provisional relates to identification of novel charge pair mutants, Table 7 itself was only a “first step” in this identification process. Ex. 1030, 51:6–17. In this step, “many interface contact residues in the IgG CH3 domain were scanned one by one or in groups for substitutions that would result in repulsion of

identical heavy chains” so that identified substitutions can then be used to generate antibodies “by engineering matched pairs of CH3 residues in one or more IgG heavy chains – CH3 regions” in follow up experiments. *Id.*

Accordingly, Table 7 does not appear to describe heterodimer combinations, such as those that would result from a pairing of chains with different substitutions. Pet. 29–30 (citing, e.g., Ex. 1002 ¶¶ 111–118). As Petitioner further points out, the follow up experiments testing the matched pairs of CH3 residues did not include paired substitutions at positions 364 and 368. *Id.* at 29–31.

Patent Owner points to disclosure in the ’935 provisional describing, as a distinguishing feature of its invention, the substitution of non-charged or neutral amino acids in wildtype CH3 with charged residues, which according to the ’935 provisional has the “advantage that at least one additional charge-charge interaction in the CH3 interface is created.” Prelim. Resp. 12 (citing, e.g., Ex. 2010 ¶¶ 42–48). For the same reasons discussed above, Petitioner has sufficiently established, for purposes of institution, that such disclosure would not reasonably convey to an ordinarily skilled artisan that the inventors had possession of the entire genus of heterodimeric antibodies comprising CH3 domains wherein a non-charged amino acid is replaced with a charged residue so as to create an additional charge-charge interaction in the CH3 interface. In this regard, we also note that “a description that merely renders the invention obvious does not satisfy the [written description] requirement.” *Ariad*, 598 F.3d at 1352.

Finally, Patent Owner asserts that Petitioner’s declarant, Dr. Presta,

“has obtained patents on similar subject matter while arguing that he was in possession of his invention based on *the same type of* disclosure he seeks to criticize here.” Prelim. Resp. 16. However, the adequacy of the written description in Dr. Presta’s patents is not at issue in this proceeding. To the extent Patent Owner alleges that Dr. Presta’s statements during the prosecution of his own patents is relevant to this proceeding, Patent Owner may explore the issue during Dr. Presta’s cross-examination at trial, should Patent Owner choose to depose the witness.

F. Ground 1: Anticipation by Desjarlais

Petitioner has mapped the disclosures in Desjarlais to each limitation of claim 1. Pet. 38–42.

Petitioner asserts Desjarlais teaches a heterodimeric antibody as evidenced by, e.g., its abstract, and further discloses “a number of different ‘heterodimerization variants’ and ‘novel steric variants’ in Figure 4.” Pet. 38. Petitioner asserts Figure 4 discloses “several variants with a pair of mutations at the 364 and 368 positions on two distinct CH3 domains” and points specifically to a L368D/S364K variant and a number of L368E and S364K variants, where the leucine (L) in residue 368 is substituted with negative residues aspartic acid (D) or glutamic acid (E) and serine (S) in residue 364 is substituted with positive residue lysine (K). *Id.* at 38–41. Petitioner notes Desjarlais “expressly teaches that the disclosed mutation positions are numbered ‘according to the EU index’” and teaches embodiments where the Fc parent polypeptide is a human wild type sequence. *Id.* at 41.

In its Preliminary Response, Patent Owner does not argue that Desjarlais fails to teach a heterodimeric antibody meeting all the limitations of claim 1, but argues that Desjarlais is not prior art because the claims of the '859 patent are entitled to an April 20, 2012 priority date. Prelim. Resp. 10–18.

As discussed above, we find on this record that Petitioner has established, sufficient for purposes of institution, that Desjarlais qualifies as prior art. We further find, based on Petitioner's evidence and arguments summarized above, that Petitioner has established a reasonable likelihood that it will prevail in showing that Desjarlais anticipates claim 1 of the '859 patent.

G. Ground 2: Anticipation by Moore

Petitioner has mapped the disclosures in Moore to each limitation of claim 1. Pet. 47–51.

Petitioner asserts Moore teaches a heterodimeric antibody as evidenced by, e.g., its abstract, and further teaches “a pair of modifications including S364K on a first CH3 domain and L368D on a second CH3 domain,” i.e., a positively charged amino acid residue (K, for lysine) at position 364 and a negatively charged amino acid residue (D, for aspartic acid) at residue 368. Pet. 48–50. Petitioner notes Moore discloses creating its constructs using native human IgG1 and that the amino acid residue positions are “numbered according to the EU index.” *Id.* at 49–50.

In its Preliminary Response, Patent Owner does not argue that Moore fails to teach a heterodimeric antibody meeting all the limitations of claim 1,

but argues that Moore is not prior art because the claims of the '859 patent are entitled to an April 20, 2012 priority date. Prelim. Resp. 10–18.

As discussed above, we find Petitioner has established, sufficient for purposes of institution, that Moore qualifies as prior art. We further find, based on Petitioner's evidence and arguments summarized above, that Petitioner has established a reasonable likelihood that it will prevail in showing that Moore anticipates claim 1 of the '859 patent.

H. Ground 3: Obviousness over Lazar or Lazar and Kannan

1. *Petitioner's Position*

Petitioner asserts that each of Lazar and Kannan teaches heterodimeric antibodies with electrostatic steering modifications. Pet. 55 (citing, e.g., Ex. 1002 ¶¶ 181–83). Petitioner asserts that Lazar “discloses several CH3 domain variants, including one with a charge pair at the 364 and 368 positions.” *Id.* at 55–56 (citing Ex. 1004 ¶ 241 (Table 1, showing, as one of the preferred CH3 domain variants that favor Fc heterodimerization, a “Variant 1” of S364E and “Variant 2” of L368K)). Petitioner asserts that Lazar teaches that its Fc variants are based on human IgG sequences and that the numbering is according to the EU index. *Id.* at 57, 58.

Petitioner acknowledges that the example of S364E/L368K discloses a negatively charged residue (E, or glutamic acid) at the 364 position and a positively charged residue (K, or Lysine) at the 368 position, which is the opposite of what is recited in claim 1 (i.e., positively charged residue at position 364 and negatively charged residue at position 368). Pet. 57.

Petitioner argues, however, that this 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.” *Id.* (citing Ex. 1002 ¶¶ 185–89). Petitioner further argues that “a POSA would have understood from *Lazar*’s teachings that the charges in this example could have been swapped.” *Id.*; *see also id.* at 58.

Petitioner points to *Lazar*’s teaching of “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,” as well as “specific modifications for both the 364 and 368 positions, including both positive . . . and negative . . . substitutions at both positions.” Pet. 57 (citing Ex. 1004 ¶¶ 52, 121, 123). Petitioner notes that *Lazar* “identifies these modifications in the context of creating ‘[h]etero-Fc variants’ for the purposes of ‘favor[ing] heterodimerization and disfavor[ing] homodimerization.’” *Id.* at 58 (citing Ex. 1004 ¶¶ 119–125). Petitioner points out that *Lazar* disclosed “multiple heterodimers . . . 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.” *Id.* at 59–60 (citing Ex. 1004, Figs. 5–7.)

Petitioner asserts that the limitation of “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” is rendered further obvious by the additional teachings of Kannan. Pet. 60.

Petitioner notes Kannan discloses CH3-CH3 domain interface residues, including positions 364 and 368, which were identified based on human IgG1 Fc crystal structure, and teaches the benefits of modifying these residues to have positive-negative pairs for electrostatic steering. Pet. 61 (citing, e.g., Ex. 1002 ¶¶ 190–192, 200–204; Ex. 1007, 5:13–16, 7:19–8:4 (Table 1)). Petitioner further notes Kannan “emphasizes . . . the positions at which the natural IgG1 interface residues on two chains formed a charged pair and suggested swapping the charges” — i.e., changing the negatively charged residue to a positively charged residue at one of the positions in the charged pair and the positively charged residue to a negatively charged residue at the other position in the charged pair. *Id.* at 62–63.

Petitioner asserts that Kannan’s teaching of such “pair-wise charge residue mutations,” when combined with Lazar’s teaching of inserting charged amino acids at positions 364/368, renders obvious “swapping” the charges in Lazar’s preferred S364E/L368K pair (or the also disclosed S364D/L368K pair). Pet. 64 (citing, e.g., Ex. 1002 ¶¶ 184–206). Petitioner asserts an ordinarily skilled artisan would have had reason to combine the teachings of Lazar and Kannan to arrive at the claimed invention, because such combination “would have involved only a combination of known prior art elements according to known methods,” and Lazar and Kannan “both teach their CH3 domain modifications were compatible with other techniques.” *Id.* at 64, 68.

2. *Patent Owner's Position*

Patent Owner asserts that neither of the constructs disclosed in Lazar — the “scFv-Fc/empty-Fc format” and the “alternative bispecific format” — is a “heterodimeric antibody” or comprises a “CH3 domain,” as those terms are used in the claims. Prelim. Resp. 19–23. Patent Owner further asserts that neither Lazar nor Kannan discloses a positively charged amino acid residue at position 364 and a negatively charged amino acid residue at position 368, as recited in the claims, and Lazar in fact teaches away from the combination. *Id.* at 23–33. Patent Owner asserts that a person of ordinary skill in the art would not have had reason to modify or combine the teachings of Lazar (alone or together with Kannan) to arrive at the claimed invention. *Id.* at 30–33.

3. *Analysis*

Having considered the evidence of record at this preliminary stage of the proceeding, and for the reasons set forth below, we are persuaded that Petitioner has shown sufficiently, for purposes of institution, that claim 1 of the '859 patent is obvious over Lazar or Lazar in combination with Kannan.

(1) *Heterodimeric Antibody Comprising a CH3 Domain*

Patent Owner's arguments that Lazar does not disclose a heterodimeric antibody comprising CH3 domains appear to be based on its claim construction of “heterodimeric antibody” and “CH3 domain.” As we have explained above in the section on claim construction, we do not adopt Patent Owner's constructions of these terms.

Instead, we have construed “heterodimeric antibody” as a proteinaceous molecule comprising two different polypeptide chains and including (1) at least one domain derived from or sharing sequence homology with an immunoglobulin domain and (2) one or more domains that bind an epitope on an antigen, where such domains are derived from or share sequence homology with the variable region of an antibody.

We have further construed “CH3 domain” as “a domain derived from or sharing sequence homology with the CH3 domain of an immunoglobulin domain.”

In view of the above claim constructions, both the constructs used in Lazar’s heterodimeric Fc region “proof-of-concept” system (Figure 1) and Lazar’s bispecific formats (Figure 8) are “heterodimeric antibodies” comprising a “CH3 domain,” as recited in claim 1.

For example, as shown in Figure 1, the molecule used as heterodimeric Fc region “proof-of-concept” in Lazar comprises “two different immunoglobulin polypeptides” — i.e., the “scFv-Fc chain” having the structure of VH-linker-Vκ-Hinge-CH2-CH3’ and the “empty-Fc” chain having the structure of Hinge-CH2-CH3.” Ex. 1004 ¶ 9, Fig. 1. The molecule also includes various domains derived from or sharing sequence homology with an immunoglobulin domain (e.g., VH, Vκ, CH2, CH3’, and CH3”), including CH3 domains and a domain, derived from or sharing sequence homology with the variable region of an antibody, that binds an epitope on an antigen (e.g., VH and Vκ).

Likewise, Lazar's bispecific formats, illustrated in Figure 8, comprise two different immunoglobulin peptides at least because they comprise a "Hetero-CH₃" region (i.e., a heterodimeric CH₃ region) and thus differ in their CH₃ domains. They also include various domains derived from or sharing sequence homology with an immunoglobulin domain (e.g., VH, VL, CH1, CL, CH2, and CH3) and VH/VL domains that bind to epitopes on antigens (e.g., Ag-1 and Ag-2).

(2) *Positively Charged Residue at Position 364 and
Negatively Charged Residue at Position 368*

Patent Owner asserts that neither Kannan nor Lazar discloses "a heterodimeric antibody with a positively charged amino acid residue at position 364 in one CH₃ domain and a negatively charged amino acid residue at position 368 in the other CH₃ domain." Prelim. Resp. 19, 23–24. Patent owner asserts that, in fact, Lazar discloses the paired mutations of S364E & L368K, the opposite of what is claimed, i.e., a negatively charged amino acid residue at position 364 and a positively charged amino acid residue at position 368. *Id.* at 19, 24. Patent Owner asserts that, while S364E & L368K is describes as "[p]referred CH₃ domain variants," the "charge-swapped" version of this — i.e., where there is a positively charged residue at position 364 and a negatively charged residue at position 368 — is not so listed. *Id.* at 28. Patent Owner asserts "a POSA would *not* swap the substitutions disclosed by Lazar because there is no teaching, suggestion or motivation to do so." *Id.* at 24.

We acknowledge that Lazar does not disclose a specific example of a heterodimeric antibody comprising CH3 domains having positively charged residue at position 364 in one domain and negatively charged residue at position 368 in the other. Nevertheless, as Petitioner points out, Lazar teaches preferred embodiments in which amino acid modifications stabilize a heterodimeric Fc region while destabilizing homodimeric Fc region, and specifically teaches embodiments wherein the variant Fc region comprise at least one substitution selected from a group consisting of, among others, 364C, 364D, 364E, 364F, 364G, 364H, 364R, 364T, 364Y, 368A, 368E, 368K, and 368S. Pet. 57; Lazar ¶¶ 52, 123. Among these substitutions 364H and 364R would result in a positively charged residue at position 364, and 368E would result in a negatively charged residue at position 368. Together with Petitioner's citation to Lazar's disclosure of an example of a heterodimeric antibody with paired substitutions at positions 364 and 368 (albeit with a negative charge at position 364 and a positive charge at position 368), we are persuaded Petitioner has shown a reasonable likelihood that Lazar's combined teachings render the claimed heterodimeric antibody obvious.

Patent Owner criticizes Petitioner's reliance on Lazar's disclosure of "charge swapped" substitution pairs in, e.g., Figure 5, in particular S364R/K370D and S364D/K370R, in arguing the obviousness of claim 1. Ex. 1002 ¶ 198; Prelim. Resp. 25–26. Patent Owner argues that "positions 364 and 370 are self-evidently not the same as positions 364 and 368" and "cannot be directly compared." *Id.* at 25 (citing Ex. 2010 ¶ 75). Patent

Owner also points out that the substitution of K to D or R in position 370 is a “neutral to charged mutation,” which further distinguishes the substitution pairs at positions 364 and 370 with the claimed substitution pairs of 364 and 368. *Id.* at 27 (citing Ex. 2010 ¶ 78). Patent Owner asserts that, in any event, an ordinarily skilled artisan would understand that “charge swapping could have a significant, likely negative, effect upon heterodimerization” based on the data in Lazar regarding the paired mutations at positions 364 and 370. *Id.* at 25 (citing Ex. 2010 ¶ 75).

However, “[a] person of ordinary skill is also a person of ordinary creativity, not an automaton.” *KSR*, 550 U.S. at 421. Thus, the fact that there are differences between the claimed substitution pairs at positions 364 and 368 and the substitution pairs at positions 364 and 370 does not preclude our consideration of Lazar’s teachings regarding the latter for purposes of determining obviousness. What an ordinarily skilled person would understand when considering Lazar’s disclosure relating to the substitution pair at positions 364 and 370 — in view of the other disclosures in Lazar — is a fact intensive issue that would benefit from further development at trial.

In a related vein, Patent Owner argues that the data in Lazar showed a higher fraction of heterodimers when residues 364 and 370 are each modified with a neutral-to-neutral substitution (S364F and K370G, where neutral, or non-charged, residues are substituted for other neutral residues), which would suggest to a POSA that “substitution of neutral residuals to neutral residues is preferred to neutral to charged substitutions.” *Id.* at 26 (citing Ex. 2010 ¶ 75). Patent Owner asserts that Lazar “neither highlights,

nor do the data support, any particular advantage of neutral to charged substitutions.” *Id.* at 28.

Patent Owner’s arguments are unavailing, because a prior art reference may be relied upon for all that it teaches, and is not limited to its preferred embodiments or working examples. *See Merck & Co., Inc. v. Biocraft Labs., Inc.*, 874 F.2d 804, 807 (Fed. Cir. 1989). In this case, as noted above, Lazar teaches that preferred variant Fc regions include those having a positive charge at 364 (e.g., 364H and 364R) as well as those having a negative charge at 368 (e.g., 368E). All of these substitutions would involve a substitution of a neutral amino acid (Serine (S) in position 364 and Leucine (L) in position 368) with a charged amino acid residue. Moreover, even assuming these substitutions were not the most preferred, they are still relevant to our obviousness analysis. *See In re Lamberti*, 545 F.2d 747, 750 (CCPA 1976) (“[A]ll disclosures of the prior art, including unpreferred embodiments, must be considered.”).

For the reasons above, and based on the current record, we also do not agree with Patent Owner’s argument that Lazar teaches away from the claimed residue pair. Prelim. Resp. 26. Patent Owner argues that “Lazar and the state of the art at the time of the invention taught against making neutral to charged substitutions as the result is capable of destabilizing the Fc region.” Prelim. Resp. 24 (citing Ex. 2010 ¶¶ 31, 91). Patent Owner also points out Lazar states that “CH3 domain modifications to yield ‘[h]eterodimeric Fc variants are not a necessity’ for generation of the alternative bispecific formats.” *Id.* at 29.

“[I]n general, a reference will teach away if it suggests that the line of development flowing from the reference’s disclosure is unlikely to be productive of the result sought by the applicant.” *Baxter Intern., Inc. v. McGaw, Inc.*, 149 F.3d, 1321, 1328 (Fed. Cir. 1998) (quoting *In re Gurley*, 27 F.3d 551, 553 (Fed. Cir. 1994)). In this case, however, Lazar explicitly suggests several substitutions in which neutral residues are replaced with charged residues in the context of stabilizing a heterodimeric Fc region. Ex. 1004 ¶¶ 52, 123. Likewise, although Lazar teaches that CH3 domain modifications are optional, Lazar also teaches that such modifications are preferred in some embodiments. *Id.* ¶ 42. Accordingly, we do not find Patent Owner’s arguments persuasive in this regard.

Finally, Patent Owner asserts that Lazar in combination with Kannan does not disclose or suggest the claimed amino acid residues. Because we find Petitioner has shown, for purposes of institution, that claim 1 is reasonably likely to be obvious over the combined teachings of Lazar, we need not, and do not, decide whether claim 1 is further obvious over the combination of Lazar and Kannan.

I. Dependent claims 2–7

In *SAS*, the Supreme Court held the following:

Section 314(a) [of Title 35] does not require the Director to evaluate every claim individually. Instead, it simply requires him to decide whether the petitioner is likely to succeed on “at least 1” claim. Once that single claim threshold is satisfied, it doesn’t matter whether the petitioner is likely to prevail on any additional claims; the Director need not even consider any other claim before

instituting review. Rather than contemplate claim-by-claim institution, then, the language anticipates a regime where a reasonable prospect of success on a single claim justifies review of all.

SAS, 138 S. Ct. at 1356. Thus, because we determine, based on the arguments and evidence on the present record, that there is a reasonable likelihood Petitioner would prevail with respect to claim 1, we institute an *inter partes* review of all challenged claims under each Ground presented in the Petition. *Id.*; *see also* 37 C.F.R. § 42.108(a) (“When instituting *inter partes* review, the Board will authorize the review to proceed on all of the challenged claims and on all grounds of unpatentability asserted for each claim.”).

III. CONCLUSION

For the reasons provided above, we find that Petitioner has demonstrated a reasonable likelihood of showing at trial that at least one of the challenged claims of the ’859 patent is unpatentable under at least one ground. Accordingly, we institute *inter partes* review of all challenged claims based on all the Grounds presented in the Petition.

We emphasize that our determination in this Decision is not a final determination on the construction of any claim term or the patentability of any challenged claim and, thus, leaves undecided any factual issues necessary to determine whether sufficient evidence supports Petitioner’s contentions by a preponderance of the evidence in the final written decision. *See TriVascular, Inc. v. Samuels*, 812 F.3d 1056, 1068 (Fed. Cir. 2016) (noting that “there is a significant difference between a petitioner’s burden to

establish a ‘reasonable likelihood of success’ at institution, and actually proving invalidity by a preponderance of the evidence at trial”) (quoting 35 U.S.C. § 314(a) and comparing § 316(e)).

The Board will deem forfeited any issue not raised by Patent Owner in a timely response to the Petition, or as permitted in another manner during trial, even if asserted in the Preliminary Response or discussed in this Decision.

Nothing in this Decision authorizes Petitioner, in a manner not otherwise permitted by the Board’s rules, to supplement the information pertaining to any ground advanced in the Petition.

IV. ORDER

In consideration of the foregoing, it is hereby:

ORDERED that, pursuant to 35 U.S.C. § 314(a), an *inter partes* review of claims 1–7 of U.S. Patent No. 11,926,859 B2 is instituted with respect to all challenged claims and all grounds set forth in the Petition;

FURTHER ORDERED that, pursuant to 35 U.S.C. § 314(c) and 37 C.F.R. § 42.4, notice is hereby given of the institution of a trial, which will commence on the entry date of this decision.

IPR2025-00605
Patent 11,926,859 B2

FOR PETITIONER:

Naveen Modi
Eric Dittmann
Isaac Ashkenazi
Daniel Zeilberger
Michael Wolfe
Ashley Mays-Williams
PAUL HASTINGS LLP
naveenmodi@paulhastings.com
ericdittmann@paulhastings.com
isaacashkenazi@paulhastings.com
danielzeilberger@paulhastings.com
michaelwolfe@paulhastings.com
ashleymayswilliams@paulhastings.com

FOR PATENT OWNER:

Peter Armenio
Colleen James
CAHILL GORDON & REINDEL LLP
parmenio@cahill.com
ctracyjames@cahill.com