

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

XENCOR, INC.,
Petitioner,

v.

MERUS N.V.,
Patent Owner.

IPR2025-00604
Patent 9,358,286 B2

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

FLAX, *Administrative Patent Judge.*

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

I. INTRODUCTION

Merus N.V. (“Patent Owner”) is the owner of U.S. Patent 9,358,286 B2 (Ex. 1001, “the ’286 patent”). Paper 3, 1 (Patent Owner Mandatory Notices). On February 11, 2025, Xencor, Inc. (“Petitioner”) filed a Petition for *inter partes* review challenging the patentability of claims 1, 2, 7–24, 26–28, and 30–32 of the ’286 patent. Paper 1, 1 (“Pet.”). On June 30, 2025, Patent Owner filed a Preliminary Response to the Petition. Paper 7 (“Prelim. Resp.”). On July 17, 2025, the Acting Director declined to discretionarily deny institution in this proceeding and referred the case to the Board. Paper 12.

Under 37 C.F.R. § 42.4(a), we have authority to determine whether to institute trial in an *inter partes* review. We may institute an *inter partes* review if the information presented in the petition filed under 35 U.S.C. § 311, and any preliminary response filed under § 313, shows that there is a reasonable likelihood that Petitioner would prevail with respect to at least one of the claims challenged in the petition. 35 U.S.C. § 314.

After reviewing the parties’ submissions in view of the existing record, we conclude that Petitioner demonstrates a reasonable likelihood it would prevail in showing that at least one challenged claim of the ’286 patent is unpatentable under the presented grounds. *See* Pet. Therefore, we grant institution of *inter partes* review. Our reasoning is discussed below.

A. REAL PARTIES-IN-INTEREST

“Petitioner identifies Xencor, Inc. as the real party-in-interest.” Pet. 2. “Patent Owner identifies Merus N.V. as the real party-in-interest.” Paper 3, 1.

B. RELATED MATTERS

Regarding related matters,

Petitioner states that the '286 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. 11,926,859 (which claims priority to the challenged '286 patent through a series of continuations), as well as U.S. Patent No. 9,944,695. Petitioner is concurrently filing an IPR petition challenging U.S. Patent No. 11,926,859.

Pet. 2. Regarding related matters, Patent Owner identifies the same litigation. Paper 3, 1.

C. THE '286 PATENT AND RELEVANT BACKGROUND

The '286 patent, titled "METHODS AND MEANS FOR THE PRODUCTION OF IG-LIKE MOLECULES," issued on March 1, 2022, from U.S. Application 14/081,848, which was filed on November 15, 2013. Ex. 1001, codes (10), (21), (22), (45), (54). The '286 patent indicates priority as a continuation application of U.S. Application 13/866,747 (filed on April 19, 2013), and to an earliest-filed U.S. Provisional Application 61/635,935, which was filed on April 20, 2012.¹ *Id.* at codes (60), (63).

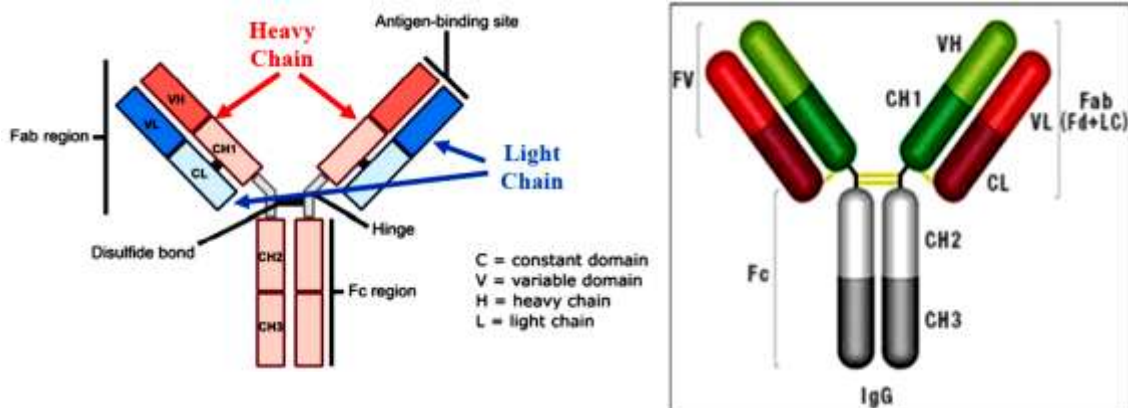
The '286 patent relates to antibodies; therefore, we include a brief overview of these biological structures. The parties agree, and Petitioner explains, through witness testimony, that "[a]ntibodies are proteins made by

¹ Petitioner identifies that Patent Owner, during the prosecution of parent U.S. Application 13/866,747, acknowledged that the application included claims not supported (under § 112) by the disclosure of the provisional application, and Petitioner disputes that the challenged claims of the '286 patent are entitled to priority to the provisional application's 2012 filing date, but uses the provisional's April 20, 2012, filing date as the priority date of the '286 patent for the purposes of this proceeding. Pet. 12–13 n.3.

the body, including in response to infection. (EX1002, ¶¶ 19–22.)” Pet. 4; *see also* Prelim. Resp. 3 (agreeing). “Antibodies . . . are also referred to as immunoglobulins or Igs.” Ex. 2008 ¶ 19.

Natural or wild type Igs have a particular structure made of two identical light (L) chains and two identical heavy (H) chains. *See* EX2008 at ¶ 23. Each Ig heavy chain consists of three constant domains (CH1, CH2, and CH3) and one variable domain (VH), which is also consistent with the definition of heavy chain in the ’286 Patent. *See* EX2008 at ¶ 24; EX1001 at 11:58–66.

Prelim. Resp. 3–4; *see also* Pet. 5 (agreeing). A typical antibody (IgG) structure is illustrated by the parties with the following illustrations:



Both images above are drawings showing the general components of a typical immunoglobulin G (IgG) antibody, with Petitioner’s figure on the left and Patent Owner’s figure on the right. Pet. 5–6; Prelim. Resp. 4. Each figure shows an antibody having two pairs of chains (amino acid polypeptides)², one a heavy chain and the other a light chain (respectively,

² Amino acids (naturally occurring) include: alanine (Ala, A), arginine (Arg, R), asparagine (Asn, N), aspartic acid (Asp, D), cysteine (Cys, C), glutamic acid (Glu, E), glutamine (Gln, Q), glycine (Gly, G), histidine (His, H),

pink and blue colored in Petitioner's figure; respectively gray, green and red in Patent Owner's figure). Pet. 5–6. The light chains are composed of a constant domain (CL) and a variable domain (VL). The heavy chains are composed of three constant domains (CH1, CH2, and CH3) and one variable domain (VH), where CH2 and CH3 make up an Fc (fragment crystallizable) region, and CH1 and VH (with the light chain VL and CL domains) make up a Fab (fragment antigen-binding) region. See Ex. 1002 ¶¶ 25–28; see also Ex. 2008 ¶¶ 23–25 (Patent Owner's expert agreeing with this characterization).

The variable regions of the antibody contain the antigen-binding sites and determine target complementarity. Ex. 1016, 170. The Fab and Fc regions of each heavy chain are connected at a hinge, where a disulfide bond connects the two heavy chains to each other (the connected version is termed “dimerized”). See Ex. 1002 ¶¶ 25–28. When IgG antibodies³ are discussed in the art, it is the structure above that is typically referenced and identified. See, e.g., Ex. 1016, 170; Ex. 1018, 48.

In addition to the disulfide bond at the antibody's connecting hinge, the heavy chains of an antibody are also associated with each other via

isoleucine (Ile, I), leucine (Leu, L), lysine (Lys, K), methionine (Met, M), phenylalanine (Phe, F), proline (Pro, P), selenocysteine (Sec, U), serine (Ser, S), threonine (Thr, T), tryptophan (Trp, W), tyrosine (Tyr, Y), and valine (Val, V). See, e.g., Ex. 1001, 13:3–17 (some amino acids are charged (e.g., Arg(R)+, His(H)+, Lys(K)+, Asp(D)-, Glu(E)-) and some are neutral (e.g., Ala(A), Gln(Q), Gly(G), Leu(L))); Ex. 2010, 30:15–23.

³ IgG, IgA, and IgD classes of antibodies have three constant domains on their heavy chains, as discussed above. See, e.g., Ex. 1018, 48. Other classes of antibodies, e.g., IgM and IgE, have four constant domains (adding a CH4 domain). *Id.*

interactions between domains of their Fc region; in IgG, the most extensive site of interaction occurs between the CH3 domains. *See* Pet. 6; Ex. 1018, 48–49; *see also* Ex. 2008 ¶ 25 (explaining the same interactions).

Furthermore, there are a number of pairs of specific amino acid sites (residues) in the CH3 domain known to be sites of such (electrostatic) interaction between heavy chains. *See, e.g.*, Ex. 1007, 7 (Table 1) (list of complementary CH3 interface residues, including charged residues); Ex. 1016, 186–190 (studying position 407); Ex. 1018, 49–50 (Fig. 1), 51 (Fig. 5), 54 (studying positions 366 and 407; modeling replacing amino acids to provide attractive charges).

When the two halves of an antibody on either side of the disulfide bond (the respective heavy and light chains) are identical and bind the same target, the antibody is homodimeric and monospecific, meaning it has mirrored polypeptides and binds a single antigen. *Id.* When the two Fab regions are different and each capable of binding a different target, either on the same or different antigens, and the heavy chains are not identical, the antibody is heterodimeric and bispecific. *Id.* ¶¶ 25–57; *see also* Prelim. Resp. 4–6; *and* Ex. 1001, 3:28–3:59 (Background).

The '286 patent indicates that its invention relates to: “means and methods for producing one or more Ig-like molecules in a single host cell. Novel CH3 mutations enabling the production of monospecific and/or bispecific Ig-like molecules of interest are also provided,” and also that “[t]he invention relates to the fields of molecular biology, medicine and biological therapeutics. It particularly relates to the field of therapeutic antibodies for the treatment of various diseases.” Ex. 1001, Abstract, 1:21–24.

The Specification states that, “[f]or antibodies, it is well-known that the CH3-CH3 interaction is the primary driver for Fc dimerization” and “[i]t is furthermore well known that when two CH3 domains interact with each other they meet in a protein-protein interface which comprises ‘contact’ residues (also called contact amino acids, interface residues or interface amino acids).” *Id.* at 4:5–12. The Specification identifies that the residue interaction is understood to be via “electrostatic forces” or “other forces known to one skilled in the art.” *Id.* at 4:20–22.

Further to these understandings, the Specification identifies a known “approach for the production of a given bispecific antibody of interest is based on electrostatic engineering of contact residues within the CH3-CH3 interface that are naturally charged,” where “mutations in the CH3 domains of heavy chains wherein naturally occurring charged amino acid contact residues are replaced by amino acid residues of opposite charge (i.e. a charge reversal strategy)” so as to “create[] an altered charge polarity across the Fc dimer interface such that co-expression of electrostatically matched Fc chains support favorable attractive interactions thereby promoting desired Fc heterodimer formation.” *Id.* at 5:17–32.

Further, the Specification describes:

The present invention provides novel engineered CH3 domains as well as novel combinations of CH3 mutations. Before the present invention, charged contact amino acids of CH3 domains that[] were known to be involved in CH3-CH3 pairing were substituted by amino acids of opposite charge (charge reversal), thereby influencing the CH3-CH3 pairing. The mutations according to the present invention are an inventive alternative to this approach, because now CH3 amino acids that are non-charged or neutral in wildtype CH3 are substituted with charged residues. The present invention in this

embodiment does not exchange charged contact amino acids by amino acids of opposite charge but substitutes non-charged CH3 amino acids for charged ones. The approach of the present invention 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[.] [I]n view of this additional charge-charge interaction on top of the existing charge pairs in the CH3-CH3 interface, the dimers according to the invention are generally more stable as compared to the wild type dimers (the wildtype dimer [being] defined as a bispecific IgG (AB) without CH3 engineering in contrast to its parental homodimers (AA or BB)). . . . [And,] [q]uite surprisingly, the present inventors have succeeded in introducing mutations that further enhance the proportion of an Ig-like molecule of interest in a mixture.

Id. at 17:65–18:34.

The '286 patent concludes with thirty-two claims, of which claims 1, 25, 26, and 30 are independent claims. Claim 1 is reproduced below:

1. A method for producing a heterodimeric antibody from a single cell, wherein said antibody comprises two heavy chains with CH3 domains that are capable of forming an interface, said method comprising:
 - a. providing a host cell comprising
 - (i) a first nucleic acid molecule encoding a 1st antibody heavy chain comprising at least one substitution of a neutral amino acid residue in the CH3 domain by a positively charged amino acid residue, and
 - (ii) a second nucleic acid molecule encoding a 2nd antibody heavy chain comprising at least one substitution of a neutral amino acid residue in the CH3 domain by a negatively charged amino acid residue;
 - b. culturing said host cell and allowing for expression of said two nucleic acid molecules to produce said 1st antibody heavy chain and said 2nd antibody heavy chain, wherein the at

least one positively charged amino acid residue substituted in the CH3 domain of said 1st antibody heavy chain interacts with the at least one negatively charged amino acid residue substituted in the CH3 domain of said 2nd antibody heavy chain in the interface between said 1st and 2nd antibody heavy chains to produce a heterodimeric antibody; and

c. harvesting said heterodimeric antibody from the culture.

Ex. 1001, 71:38–74:41 (claims).

D. PETITIONER’S ASSERTED GROUNDS FOR UNPATENTABILITY

Petitioner asserts the following grounds for unpatentability:

Ground	Claims Challenged	35 U.S.C. § ⁴	Reference(s)/Basis
1	1, 7, 21, 22, 24, 26, 28, 30, 32	102	Lazar ⁵
2	1, 2, 7–24, 26–28, 30–32	103	Lazar, Arathoon ⁶
3	1, 2, 7, 21, 22, 24, 26–28, 30–32	102	Cabrera ⁷
4	1, 2, 7–24, 26–28, 30–32	103	Lazar, Arathoon, Cabrera

⁴ 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). Petitioner asserts that the ’286 patent is an AIA patent, which Patent Owner does not dispute in the Preliminary Response. *See* Pet. 12–13; *see generally* Prelim. Resp. Thus, for the purposes of this Institution Decision, AIA §§ 102 and 103 apply, but our decision would not change based on either version of the Patent Act.

⁵ G.A. Lazar and G.L. Moore, US 2011/0054151 A1, pub. Mar. 3, 2011. Ex. 1004 (“Lazar”).

⁶ R. Arathoon et al., WO 98/50431 A2, pub. Nov. 12, 1998. Ex. 1006 (“Arathoon”).

⁷ E.E. Cabrera et al., WO 2012/058768 A1, pub. May 10, 2012. Ex. 1005 (“Cabrera”).

Pet. 3–4. In support of these grounds for unpatentability, Petitioner submits, *inter alia*, the Declaration of Leonard G. Presta, PhD. Ex. 1002. In support of the positions taken in the Preliminary Response, Patent Owner submits, *inter alia*, the Declaration of Brian J. Sutton, PhD. Ex. 2008. At this point, we have no concerns over the qualifications of these witnesses to testify as to the subject matter of their declarations.

II. DISCUSSION AND ANALYSIS

A. LEGAL STANDARDS

“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) (citing 35 U.S.C. § 312(a)(3) (requiring *inter partes* review petitions to identify “with particularity . . . the evidence that supports the grounds for the challenge to each claim”)). This burden of persuasion never shifts to Patent Owner.⁸ *See Dynamic Drinkware, LLC v. Nat’l Graphics, Inc.*, 800 F.3d 1375, 1378 (Fed. Cir. 2015) (discussing the burden of proof in *inter partes* review).

An *inter partes* review may be instituted if the information presented by a petitioner in the petition, in view of the patent owner’s preliminary response and the preliminary record, shows that there is a reasonable likelihood that the petitioner would prevail with respect to at least one of the claims challenged in the petition. 35 U.S.C. § 314.

⁸ Although at times we refer to Patent Owner’s arguments as unpersuasive, it is in the context of the record as a whole and we never shift the ultimate burden of proof in this proceeding from Petitioner.

“[A] prior art reference will anticipate [under 35 U.S.C. § 102] if it ‘disclose[s] each and every element of the claimed invention . . . arranged or combined in the same way as in the claim.’” *Blue Calypso, LLC v. Groupon, Inc.*, 815 F.3d 1331, 1341 (Fed. Cir. 2016) (quoting *In re Gleave*, 560 F.3d 1331, 1334 (Fed. Cir. 2009) (alteration by Federal Circuit)). “However, a reference can anticipate a claim even if it ‘d[oes] not expressly spell out’ all the limitations arranged or combined as in the claim, if a person of skill in the art, reading the reference, would ‘at once envisage’ the claimed arrangement or combination.” *Id.* (quoting *Kennametal, Inc. v. Ingersoll Cutting Tool Co.*, 780 F.3d 1376, 1381 (Fed. Cir. 2015) (alteration by Federal Circuit); *In re Petering*, 301 F.2d 676, 681 (CCPA 1962)).

The Supreme Court in *KSR International Co. v. Teleflex Inc.*, 550 U.S. 398 (2007), reaffirmed the framework for determining obviousness under 35 U.S.C. § 103 initially set forth in *Graham v. John Deere Co.*, 383 U.S. 1 (1966). The *KSR* Court summarized the following four factual *Graham* (383 U.S. at 17–18) factors to apply in determining obviousness under § 103: (1) determine the scope and content of the prior art; (2) ascertain the differences between the prior art and the claims at issue; (3) resolve the level of ordinary skill in the art;⁹ and (4) consider objective evidence indicating obviousness or non-obviousness.¹⁰ *KSR*, 550 U.S. at 406. “The combination of familiar elements according to known methods is likely to be obvious when it does no more than yield predictable results.” *Id.* at 416. “[W]hen the question is whether a patent claiming the combination

⁹ See *infra* Section II.B.

¹⁰ There is no evidence of record regarding objective indicia of obviousness or non-obviousness. See, Pet. 34 n.12; see *generally* Prelim. Resp.

of elements of prior art is obvious,” the answer depends on “whether the improvement is more than the predictable use of prior art elements according to their established functions.” *Id.* at 417.

B. ORDINARY SKILL IN THE ART

Petitioner contends:

A POSA at the time of the alleged invention 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, ¶¶16-17.)

Pet. 15. Patent Owner states, “[f]or purposes of the Preliminary Response, Patent Owner applies Petitioner’s proposed definition of a POSA.” Prelim. Resp. 10.

At this point, we accept and use Petitioner’s proposed, and unopposed, definition of the ordinarily skilled artisan. It appears that Petitioner’s proposed definition comports with the level of skill in the art reflected in the prior art of record and the ’286 patent, itself. *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)).

C. CLAIM CONSTRUCTION

Our claim construction positions herein are preliminary. Further argument by the parties is permitted, but should be explicitly made and set forth in a designated section of briefing.

The Board interprets claim terms in an *inter partes* review using the same claim construction standard used to construe patent claims in a civil action in federal district court. 37 C.F.R. § 42.100(b). In construing claims, district courts and the Board here, by default, give claim terms their ordinary and customary meaning, which is “the meaning that the term would have to a person of ordinary skill in the art in question at the time of the invention.” *Phillips v. AWH Corp.*, 415 F.3d 1303, 1312–13 (Fed. Cir. 2005) (en banc).

“[W]e need only construe terms ‘that are in controversy, and only to the extent necessary to resolve the controversy.’” *Nidec Motor Corp. v. Zhongshan Broad Ocean Motor Co.*, 868 F.3d 1013, 1017 (Fed. Cir. 2017) (quoting *Vivid Techs., Inc. v. Am. Sci. & Eng’g, Inc.*, 200 F.3d 795, 803 (Fed. Cir. 1999)).

Should claim terms require express construction, sources for claim interpretation include “the words of the claims themselves, the remainder of the specification, the prosecution history [i.e., the intrinsic evidence], and extrinsic evidence concerning relevant scientific principles, the meaning of technical terms, and the state of the art.” *Id.* at 1314 (quoting *Innova/Pure Water, Inc. v. Safari Water Filtration Sys., Inc.*, 381 F.3d 1111, 1116 (Fed. Cir. 2004)). “[T]he claims themselves [may] provide substantial guidance as to the meaning of particular claim terms.” *Id.*

However, the claims “do not stand alone,” but are part of “‘a fully integrated written instrument’ . . . consisting principally of a specification that concludes with the claims,” and, therefore, the claims are “read in view of the specification.” *Id.* at 1315 (quoting *Markman v. Westview Instruments, Inc.*, 52 F.3d 967, 978–79 (Fed. Cir. 1995) (en banc)). Any special definition for a claim term must be set forth in the specification “with

reasonable clarity, deliberateness, and precision.” *In re Paulsen*, 30 F.3d 1475, 1480 (Fed. Cir. 1994). Without such a special definition, however, limitations may not be read from the specification into the claims. *In re Van Geuns*, 988 F.2d 1181, 1184 (Fed. Cir. 1993).

“Petitioner submits that no terms of the ’286 patent require construction to resolve the challenges in this Petition, but reserves the right to respond to any constructions advanced by Patent Owner. (EX1002, ¶¶98-99.)” Pet. 21.

Patent Owner asserts:

Petitioner does not propose any claim constructions and ignores the explicit definition of “heavy chains” in the Specification of the ’286 Patent. A POSA would understand that the ’286 Patent is directed to producing bispecific antibodies with two “heavy chains” with VH, CH1, CH2, and CH3 domains and two Fab arms each with a different binding site specificity. Petitioner and its expert’s failure to apply the correct construction for “heavy chains” is fatal to its Petition. The Board need not construe any other claim term for the purpose of deciding to deny institution.

Prelim. Resp. 9–10. However, other than this statement, Patent Owner’s claim construction argument neither specifically cites supporting disclosure in the ’286 patent nor provides the “explicit definition” Patent Owner asserts is in the Specification. *Id.*

We address the parties’ positions below.

1. “heavy chains”

The language “heavy chains” (or “heavy chain”) is recited in claims 1, 3–6, 8, 26, and 30. Ex. 1001, 71:38–74:41. As noted above, Petitioner takes no position on the meaning of “heavy chains.” Pet. 21. And, Patent Owner

asserts the term is defined by the '286 patent's Specification, but does not identify how or where this is so. Prelim. Resp. 9–10.

“Absent claim language carrying a narrow meaning, the [US]PTO should only limit the claim based on the specification or prosecution history when those sources expressly disclaim the broader definition.” *In re Bigio*, 381 F.3d 1320, 1325 (Fed. Cir. 2004). “When the specification explains and defines a term used in the claims, without ambiguity or incompleteness, there is no need to search further for the meaning of the term.” *Multiform Dessicants, Inc. v. Medzam, Ltd.*, 133 F.3d 1473, 1478 (Fed. Cir. 1998).

And,

While [we] may look to the specification and prosecution history to interpret what a patentee meant by a word or phrase in a claim, extraneous limitations cannot be read into the claims from the specification or prosecution history. . . . In other words, [we] may not read into a claim a limitation from a preferred embodiment, if that limitation is not present in the claim itself.

Bayer AG v. Biovail Corp., 279 F.3d 1340, 1348 (Fed. Cir. 2002).

The '286 patent expressly defines several terms, for example, “preferential pairing . . . ,” “Ig-like molecule,” “antibody,”¹¹ “antigen,”

¹¹ When defining “antibody,” a term used in every claim, the '286 patent states:

The term ‘antibody’ as used herein means a proteinaceous molecule belonging to the immunoglobulin class of proteins, containing one or more domains that bind 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, IgE, and IgM. An antibody according to the invention may be any of these

“contact residue,” and “charged residue,” and in each case does so similarly by indicating that the respective term “as used herein” means something specifically. *See* Ex. 1001 *passim*. Thus, it is apparent that Patent Owner understood how — and had a particular linguistic style — to expressly define technical terms in the ’286 patent, when desired.

The ’286 patent uses the term “heavy chain” or “heavy chains” repeatedly; however, we find no express definition of the term. *See generally* Ex. 1001. Rather, the ’286 patent uses the term “heavy chain” in relation to antibody structure in a way that suggests the term is standard and well known in the art. *See, e.g., id.* at 3:19–59 (Background). The parties’ briefing on the technology reinforces this fact. *See* Pet. 5–14 (“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, ¶¶23-30.)”); Prelim. Resp. 3–4 (“Natural or wild type Igs have a particular structure made of two identical light (L) chains and two identical heavy (H) chains. *See* EX2008 at ¶ 23. Each Ig heavy chain consists of three constant domains (CH1, CH2, and CH3) and one variable domain (VH), which is also

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, 11:9–21. As noted above (*see supra* Section I.C), IgG antibodies’ heavy chains have three constant domains, but IgE and IgM have four. Thus, Patent Owner’s argument that *heavy chain* means one variable and three constant domains, and two differently-binding Fab arms, ignores embodiments of the invention.

consistent with the definition of heavy chain in the '286 Patent. See EX2008 at ¶ 24; EX1001 at 11:58–66.”). This is also how the '286 patent generally uses the term. See Ex. 1001, 11:58–12:1. But, the Specification does not limit its embodiments to only IgG antibodies because it also describes that the invention may be “IgG1, IgG2, IgG3, IgG4, IgA, IgE, and IgM” type antibodies, and fragments. Ex. 1001, 11:9–21; *see also supra* n.10 (quoting the '286 patent’s definition of *antibody*). Other embodiments would not necessarily have the *heavy chains* as argued by Patent Owner.

There is no evidence of record that the '286 patent’s claims or the Specification generally use or limit the term “heavy chains” (or “heavy chain”) in any way deviating from its ordinary and customary meaning in the art. Therefore, at this stage of the proceeding, we decline to expressly interpret this claim language.

2. Summary on Claim Construction

At this stage of the proceeding, we expressly construe no claim terms and give each claim term the ordinary and customary meaning it would have had to the person of ordinary skill in the art as of the invention date. See *Nidec Motor Corp.*, 868 F.3d at 1017. If either party intends to further argue claim construction at trial, they should do so in a clearly designated section of their briefing so as to expressly identify such arguments. See, e.g., 37 C.F.R. § 42.104(b)(3) (content of petition); *see also* Board’s Consolidated Trial Practice Guide (CTPG) at 46, 48–45 (Nov. 2019).¹² Claim construction arguments should not be relegated to patentability arguments on the facts.

¹² Available at www.uspto.gov/TrialPracticeGuideConsolidated. Familiarity with the Trial Practice Guide is expected.

D. PETITIONER’S ASSERTED PRIOR ART

We review and summarize the relevant portions of Petitioner’s asserted prior art references below. There is currently no dispute that each asserted reference constitutes prior art.

1. Lazar (Ex. 1004)

Petitioner asserts that Lazar is prior art under 35 U.S.C. §§ (AIA) 102(a)(1) and 102 (a)(2) or (pre-AIA) §§ 102(a), (b), and (e). Pet. 4 n.2, 17–18.

Lazar, titled “COMPOSITIONS AND METHODS FOR SIMULTANEOUS BIVALENT AND MONOVALENT CO-ENGAGEMENT OF ANTIGENS,” is the March 3, 2011, publication of U.S. Application 12/875,015, which was filed on September 2, 2010, and indicates priority to U.S. Provisional Application 61/239,316, filed on September 2, 2009. Ex. 1004, codes (12), (21), (22), (43), (54), (60). It is notable that the assignee identified on the face of Lazar is “Xencor, Inc.” *Id.* at code (73).

Lazar discloses: “Immunoglobulin compositions that simultaneously co-engage antigens, where one of the antigens is bound bivalently and the other antigen is bound monovalently. The novel immunoglobulins described preferably utilize heterodimeric Fc regions.” *Id.* at Abstract. Lazar discloses “a variety of antibodies (generally referred to herein as ‘antibody analogs’ . . .) that co-engage at least two different antigens in different ways,” e.g., using three antigen binding domains or two antigen binding domains. *Id.* ¶ 38. Lazar states that, “by changing amino acids in each heavy chain, different heavy chains are more likely to associate to form the

antibody analog structure than to form homodimers with the same Fc amino acid sequences.” *Id.* ¶ 42; *see also id.* ¶¶ 114–118.

Lazar teaches modifying the Fc region of an IgG antibody by, *inter alia*, substituting amino acids in the CH3 domain of each heavy chain (which Lazar respectively refers to as CH3’ and CH3”) “such that their interaction in a heterodimeric CH3 interface (variant’/variant”) is favorable, thus resulting in a stable heterodimeric Fc species (comprising CH3’/CH3”).” *Id.* ¶¶ 114–121. Lazar teaches that its methods can produce a population of “greater than 95%” of such heterodimeric antibodies relative to homodimeric variants. *Id.* ¶ 122.

As for the disclosed amino acid substitutions, Lazar states:

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, 401K, 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.

Id. ¶ 123 (identifying the domain sites and substitute amino acids).

Moreover, in relation to screening of variant Fc regions for Fc heterodimerization, Lazar teaches “[a] number of designed variants increased the content of heterodimer relative to that of the native parent Fc

region. Preferred and most preferred variants from this screen are listed in Tables 1 and 2 respectively.” *Id.* at 238–241 (Example 1). Tables 1 and 2 are reproduced side-by-side below:

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

Id. Lazar teaches that the two columns of these tables show respective, paired heavy chain modifications at residues in two heavy chains, i.e., “Variant 1” and “Variant 2,” and what original amino acid is swapped for what new amino acid. *Id.* ¶ 123–124. Lazar states that using these variants in IgG1 antibody Fc regions “favor[s] heterodimerization when applied to CH3’ and CH3”.” *Id.* ¶ 241; see also *id.* at claims 1, 7, 12, 13, 16, 17 (claiming such amino acid substitutions in an antibody’s two heavy chains’ respective CH3 domains). According to the Petition, several of these

disclosed modifications are substitutions of a neutral amino acid for a charged amino acid, for example, S364E and L368K. Pet. 24–28; Ex. 1002 ¶¶ 115–118 (discussing the disclosed substitutions, identifying 364 and 368 as known interacting, contact residues, citing Kannan, 7:8–8:7).¹³

2. Arathoon (Ex. 1006)

Petitioner asserts that Arathoon is prior art under 35 U.S.C. §§ (AIA) 102(a)(1) and 102 (a)(2) or (pre-AIA) §§ 102(a), (b), and (e). Pet. 4 n.2, 16.

Arathoon, titled “A METHOD FOR MAKING MULTISPECIFIC ANTIBODIES HAVING HETEROMULTIMERIC AND COMMON COMPONENTS,” is the November 12, 1998, publication of International Application PCT/US98/08762, which was filed on April 30, 1998, and indicates priority as early as June 24, 1997, whereon U.S. Provisional Application 60/050,661 was filed. Ex. 1006, codes (21), (22), (30), (43), (54). Of note, Arathoon lists Leonard G. Presta as an inventor. *Id.* at code (72).

Regarding its invention, Arathoon states:

The invention relates to a method of preparing heteromultimeric polypeptides such as bispecific antibodies, bispecific immunoadhesins and antibody-immunoadhesin chimeras. The invention also relates to the heteromultimers

¹³ Exhibit 1007 (G. Kannan et al., WO 2009/089004 A1, pub. July 16, 2009) (“Kannan”) discloses its “invention relates to methods of making Fc-heterodimeric proteins or polypeptides,” for example, bispecific IgG antibodies, by altering the CH3 domains by replacing residues that make up the CH3-CH3 interface with charged amino acids. Ex. 1007, Abstract, 1, 2–3. Kannan discloses identifying residues involved in the CH3-CH3 domain interaction and Table 1 listing 24 interface residues contacting one another in the CH3-CH3 interface. *Id.* at 6–8. Kannan states, “[t]his strategy can also be extended to modifying uncharged residues to charged residues at the CH3 domain interface.” *Id.* at 10.

prepared using the method. Generally, the method provides a multispecific antibody having a common light chain associated with each heteromeric polypeptide having an antibody binding domain. Additionally the method further involves introducing into the multispecific antibody a specific and complementary interaction at the interface of a first polypeptide and the interface of a second polypeptide, so as to promote heteromultimer formation and hinder homomultimer formation; and/or a free thiol-containing residue at the interface of a first polypeptide and a corresponding free thiol-containing residue in the interface of a second polypeptide, such that a non-naturally occurring disulfide bond is formed between the first and second polypeptide. The method allows for the enhanced formation of the desired heteromultimer relative to undesired heteromultimers and homomultimers.

Id. at Abstract.

Arathoon discloses that there are a variety of therapeutic uses for bispecific antibodies (BsAbs) that have binding specificities for at least two different antigens, including: enzyme immunoassays, cancer treatment, directed cytotoxicity (useful for cancer treatment), and vaccine adjuvants.

Id. at 1:1–2:27. And, although Arathoon discloses that bispecific antibody fragments can be made, it further discloses that full length bispecific antibodies are preferred for clinical applications because of longer half-life and possible effector functions. *Id.* at 3:31–34.

Arathoon states,

[a]ntibody heavy chains have previously been engineered to drive heterodimerization by introducing sterically complementary mutations in multimerization domains at the CH3 domain interface (Ridgway et al. Protein Eng. 9:617-621 (1996)) and optimization by phage display as described herein. Chains containing the modified C_H3 domains yield up to

approximately 90% heterodimer as judged by formation of an antibody/immunoadhesin hybrid (Ab/Ia).

Id. at 5:24–29. Arathoon then discloses its invention includes

a strategy which serves to enhance the formation of a desired heteromultimeric bispecific antibody from a mixture of monomers by engineering an interface between a first and second polypeptide for hetero-oligomerization and by providing a common variable light chain to interact with each of the heteromeric variable heavy chain regions of the bispecific antibody.

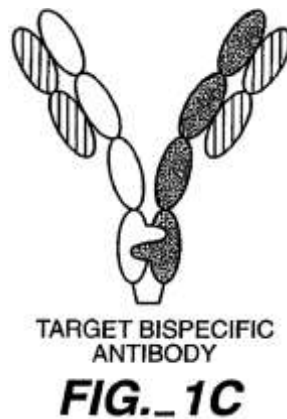
Id. at 5:31–34.

Arathoon states:

The preferred interface between a first and second polypeptide of the heteromultimeric antibody comprises at least a part of the CH3 domain of an antibody constant domain. The domain of each of the first and second polypeptides that interacts at the interface is called the multimerization domain. Preferably, the multimerization domain promotes interaction between a specific first polypeptide and a second polypeptide, thereby increasing the yield of desired heteromultimer (Fig. 1B). Interaction may be promoted at the interface by the formation of protuberance-into-cavity complementary regions; the formation of non-naturally occurring disulfide bonds; leucine zipper; hydrophobic regions; and hydrophilic regions.

Id. at 6:1–7 (missing spaces added for readability). Arathoon discloses obtaining such an antibody by culturing a host cell comprising nucleic acids encoding the polypeptides, which are expressed, and recovering the antibody from the host cell culture. *Id.* at 7:4–6.

Arathoon shows a heteromultimeric, bispecific antibody in Fig. 1C, reproduced below:



Arathoon states that “Fig. 1C is a diagram showing pairing that occurs when antibodies are chosen which share the same light (L) chain to circumvent the problem of light chains pairing with non-cognate heavy chains.” *Id.* at 8:33–35. Fig. 1C shows an illustration of an antibody having two different heavy chains of four domains (the white and darker speckled-fill ovals) and common light chains (the lined ovals).

Arathoon discloses that an interacting interface between an antibody’s heavy chains can occur, for example, at residue T366 on one chain’s CH3 domain and Y407 on the other chain’s CH3 domain. *Id.* at 41:3–21.

Arathoon’s examples disclose mutations at these residues, substituting one amino acid for another, to enhance heterodimer formation and stability. *Id.* at 40–47.

3. Cabrera (Ex. 1005)

Petitioner asserts that Cabrera is prior art under 35 U.S.C. § (AIA) 102(a)(2) or (pre-AIA) § 102(e). Pet. 4 n.2, 19 n.6.

Cabrera, titled “STABLE HETERODIMERIC ANTIBODY DESIGN WITH MUTATIONS IN THE FC DOMAIN,” is the May 10, 2012, published version of International Application PCT/CA2011/001238, which was filed on November 4, 2011, and indicates priority as early as November 5, 2010, based on the filing of U.S. Provisional Application 61/410,746. Ex. 1005, codes (21), (22), (30), (43), (54).

Regarding its invention, Cabrera states:

The provided scaffolds have heavy chains that are asymmetric in the various domains (e.g. CH2 and CH3) to accomplish selectivity between the various Fc receptors involved in modulating effector function, beyond those achievable with a natural homodimeric (symmetric) Fc molecule, and increased stability and purity of the resulting variant Fc heterodimers. These novel molecules comprise complexes of heterogeneous components designed to alter the natural way antibodies behave and that find use in therapeutics.

Id. at Abstract. Cabrera explains that “[b]ispecific antibodies are antibody-based molecules that can simultaneously bind two separate and distinct antigens (or different epitopes of the same antigen),” and identifies that they are therapeutically useful for cancer treatment (killing tumor cells). *Id.* at 1–2.

Cabrera discloses that “[t]raditional production of full-length bispecific antibodies is based on the co-expression of two immunoglobulin heavy chain-light chain pairs, where the two chains have different specificities,” but that there were challenges due to the potential of producing “up to 10 different IgG molecules consisting of various combinations of heavy and light chains, of which only one has the correct bispecific structure.” *Id.* at 2. Cabrera teaches mitigating this problem by producing variant CH3 domains (and CH2 domains) with amino acid

mutations (insertions, deletions, substitutions, or rearrangements) promoting heterodimer formation and stability (measured as the melting temperature (T_m)). *Id.* at 4, 16–17.

Cabrera teaches its antibodies have “two heavy chain constant domain polypeptides – Chain A and Chain B,” respectively, where “amino acid modifications are introduced into the CH3 in an asymmetric fashion resulting in a heterodimer when two modified CH3 domains form an Fc variant (See, e.g., Table 1).” *Id.* at 17–18. Cabrera explains that “[t]he first and second polypeptide meet at an ‘interface’” and

[t]he “interface” comprises those “contact” amino acid residues in the first polypeptide that interact with one or more “contact” amino acid residues in the interface of the second polypeptide. As used herein, the interface comprises the CH3 domain of an Fc region that preferably is derived from an IgG antibody and most preferably a human IgG1 antibody.

Id. at 18. Cabrera explains that its production of Fc heterodimers by mutating the IgG1 CH3 domain “us[es] only standard cell culture conditions” and achieve “more than 90% purity,” and up to “greater than about 99%” of the produce being the desired heterodimer antibody. *Id.* at 22, 25.

As noted above, Cabrera includes Table 1, which lists CH3 amino acid modifications for generating Fc variant heterodimers based on IgG1 antibodies. *See id.* 36–47. We reproduce a portion of Table 1 below:

Table 1: CH3 domain amino acid modifications for the generation of Fc variant heterodimers.

Wild-Type IgG1	Variant	Chains	Fc Mutations							
		A	-	-	-	-	-	-	-	-
		B	-	-	-	-	-	-	-	-
	AZ34	A	L351Y	S400E	F405A	Y407V	-	-	-	-
		B	T366I	N390R	K392M	T394W	-	-	-	-

Id. at 36, 39. According to the Petition (at 61–62), Cabrera’s variant AZ34 includes the replacement of neutral amino acid serine (S) with negatively charged amino acid glutamic acid (E) at the 400 residue position of the CH3 domain of one heavy chain (A), and the replacement of neutral amino acid asparagine (N) with positively charged amino acid arginine (R) at the 390 residue position of the CH3 domain of a second heavy chain (B). Ex. 1005, 39; *see also* Ex. 1002 ¶¶ 276–278 (discussing these modifications, identifying 400 and 390 as known interacting, contact residues, citing Kannan, 7:8–8:7). Such antibodies are disclosed as having common light chains. Ex. 1005, 10, Fig. 18.

To produce such antibodies, Cabrera discloses, as well known in the art, transfecting host cells with recombinant DNA encoding the Fc variants, culturing those cells to express the antibody proteins, and harvesting and purifying the antibody. *Id.* at 85–92. Using such a process, Cabrera discloses producing bivalent monospecific antibodies with heterodimer Fc domains (Example 1, including AZ34 listed in Table 1). *Id.* at 108–111.

E. GROUND 1—ASSERTED ANTICIPATION BY LAZAR

Under Ground 1, Petitioner asserts that claims 1, 7, 22, 24, 26, 28, 30, and 32 are anticipated by Lazar. Pet. 21–33 (citing, *inter alia*, Ex. 1001, 13:1–17, 17:67–18:3, 19:5–12; Ex. 1002 ¶¶ 100–150; Ex. 1004 ¶¶ 2, 9, 38,

30, 42, 55, 66–67, 77–79, 85, 90, 120–123, 133, 182–183, 189, 214, 238–241 (Tables 1, 2), 245, Fig. 1; Ex. 1007, 7:19–20 (Table 1), 8:9–10; Ex. 1008, 244–46).

Patent Owner contests Petitioner’s assertions, arguing Lazar does not disclose all of the elements of the challenged claims and, for this reason, trial should not be instituted. Prelim. Resp. 12–20 (citing, *inter alia*, Ex. 1001, 3:27–31, 11:58–63; Ex. 1002 ¶¶ 112, 115; Ex. 1004 ¶¶ 46, 48, 121, 238, 240–241, Figs. 1, 8; Ex. 2008 ¶¶ 44, 48–49, 51–52, 55–58, 60–63; Ex. 2020, 51:22–41).

We review and analyze the parties’ positions on Ground 1 below and make the following preliminary determinations, none of which constitutes a final determination of any fact or the issue of patentability.

1. Petitioner’s Positions

Petitioner asserts that Lazar discloses the claimed invention and maps each element of claims 1, 7, 22, 24, 26, 28, 30, and 32 to Lazar. Pet. 21–33. Focusing on independent claim 1, beginning with its preamble (“A method for producing a heterodimeric antibody from a single cell” and “wherein said antibody comprises two heavy chains with CH3 domains that are capable of forming an interface”), Petitioner asserts that Lazar teaches transfecting host cells with vectors having nucleic acids encoding heterodimeric immunoglobulins (antibodies) with CH3 domain amino acid substitutions engineered so the two CH3 domains interact/interface. *Id.* at 21–22 (citing Ex. 1002 ¶¶ 100–108; Ex. 1004 ¶¶ 2, 9, 38, 39, 85, 103–105, 121, 182–183, 239–240, 245).

Regarding the next limitation of claim 1 (“a. providing a host cell comprising”), Petitioner asserts Lazar discloses using a host cell to express

co-transfected nucleic acids (to make the antibody). *Id.* at 22 (citing, *inter alia*, Ex. 1002 ¶¶ 109–110).

The next few clauses of claim 1 relate to the polypeptides encoded by the transfected nucleic acid molecules and produced by the host cell, and to how the engineered modifications function; they recite:

- (i) a first nucleic acid molecule encoding a 1st antibody heavy chain comprising at least one substitution of a neutral amino acid residue in the CH3 domain by a positively charged amino acid residue, and
- (ii) a second nucleic acid molecule encoding a 2nd antibody heavy chain comprising at least one substitution of a neutral amino acid residue in the CH3 domain by a negatively charged amino acid residue;

b. culturing said host cell and allowing for expression of said two nucleic acid molecules to produce said 1st antibody heavy chain and said 2nd antibody heavy chain, wherein the at least one positively charged amino acid residue substituted in the CH3 domain of said 1st antibody heavy chain interacts with the at least one negatively charged amino acid residue substituted in the CH3 domain of said 2nd antibody heavy chain in the interface between said 1st and 2nd antibody heavy chains to produce a heterodimeric antibody.

In brief summary, these limitations require one CH3 heavy chain to have a positive amino acid substituted in place of a neutral one, the other CH3 heavy chain to have a negative amino acid substituted in place of a neutral one, and that when the heavy chains are expressed by culturing the host cell these positive and negative amino acids interact and the antibody produced is a heterodimeric antibody.

Petitioner asserts that Lazar expressly teaches engineering two CH3 domains so that, when expressed, they interact and form a heterodimeric CH3 interface by making neutral-to-positive and neutral-to-negative amino

acid substitutions at known interacting residues on each CH3 domain, e.g., S364E (changing neutral serine to negative glutamic acid at residue 364) on one CH3 domain, and L368K (changing neutral leucine to positive lysine at residue 368) on the other CH3 domain; or T366D (swapping neutral threonine for negative aspartic acid at residue 366) on one CH3 domain and L351K (swapping neutral leucine for positive lysine at residue 351) on the other CH3 domain; that these residues were known in the art to be respective interfacing contact residues; that these modifications favor Fc heterodimerization; and that they result in a heterodimeric antibody (proof-of-concept shown by synthesizing and screening). Pet. 23–28 (citing Ex. 1001, 13:1–17, 17:67–18:3, 19:5–12; Ex. 1002 ¶¶ 111–119; Ex. 1004 ¶¶ 121, 183, 241 (Tables 1, 2); Ex. 1007, 8:9–10, 17:19–20 (Table 1); Ex. 1008, 244–36).

As for the final limitation of claim 1 (“c. harvesting said heterodimeric antibody from the culture”), Petitioner asserts that Lazar discloses producing, purifying, and isolating heterodimeric antibodies as known to those skilled in the art, i.e., recovering the product of the host cells expressing the polypeptides. Pet. 28 (citing Ex. 1002 ¶¶ 120–124; Ex. 1004 ¶ 189).

Petitioner has accounted for Lazar disclosing each element of claim 1. At this stage of the proceeding, we will not review Petitioner’s specific assertions as to the remaining challenged claims. However, they will be addressed in any final decision.

2. Patent Owner's Positions
"heavy chains"

In opposing Petitioner's positions on unpatentability, Patent Owner argues that Lazar fails to disclose the "heavy chains" required by the claims, as that term is allegedly defined by the Specification. Prelim. Resp. 13–17.

This argument primarily relies on our adopting Patent Owner's position that the '286 patent's written description expressly defines "heavy chains," which, at this point, we do not. *See supra* Section II.C.

Patent Owner's argument further relies on the position that Lazar also fails to disclose antibody heavy chains having the typical IgG structure of VH, CH1, CH2, and CH3 domains (in particular, lacking a CH1 domain), and also having different specificity (for different targets/antigens), because this is how the Specification describes the invention's heavy chains. Prelim. Resp. 13–14 (citing Ex. 1001, 3:27–31, 11:58–63). Patent Owner also argues that Lazar discloses scFV-Fc/empty-Fc (and some alternative) formats that do not have full heavy chains or different antigen specificities because there is only one binding site. *Id.* at 15–17 (citing Ex. 1004 ¶¶ 46, 48, 238, 240–241, Fig. 1; Ex. 2008 ¶¶ 48–49, 51–52, 55–57).

We are not persuaded by these arguments.

The '286 patent's Specification does not limit the scope of the claims as to any unrecited elements; in particular, it does not limit the claimed *antibody* to any specific antibody or the claimed *heavy chains* to any specific form of antibody heavy chain. For example, the '286 patent explicitly states that, when referring to "Ig-like molecule," i.e., an immunoglobulin-like molecule, it "means a proteinaceous molecule that possesses at least one immunoglobulin (Ig) domain . . . [with] at least an immunoglobulin CH3

domain.” Ex. 1001, 10:42–47. The ’286 patent also expressly states that when it refers to “[t]he term ‘antibody’ . . . [it] means a proteinaceous molecule belonging to the immunoglobulin class of proteins, containing one or more domains that bind epitope on an antigen . . . such as IgG1, IgG2, IgG3, IgG4, IgA, IgE, and IgM” and “[a]n antibody according to the invention may be any of these isotypes or a functional derivative and/or fragment of these.” *Id.* at 11:5–21. IgG type antibodies have heavy chains with the VH, CH1, CH2, and CH3 domains that Patent Owner argues must be present to meet the claims, but IgE and IgM antibodies have an additional CH4 domain and antibody fragments may have any subset of antibody component polypeptides, for example, only sub-parts of full chains. Thus, we disagree with Patent Owner’s position.

In any event, Lazar discloses heterodimeric, bivalent (modified) IgG antibodies, which would have VH, CH1, CH2, and CH3 domains, which can bind at least two, but possibly three, antigens. *See* Ex. 1004, Abstract, ¶¶ 2, 16, 38–44, 50, 66–67, 77–80, 85, 90, 97, 99, 106, 118, 129, Fig. 8. Even if Lazar discloses scFv-Fc/empty-Fc formats (as examples used for proof-of-concept and to screen proposed Fc variants), Lazar also uses “traditional” antibody structures (two heavy chains associated with two light chains), explicitly states that it is directed to “antibodies,” which would include all the component domains of normal antibodies, states that its antibodies are encoded by all of the recognized immunoglobulin genes (e.g., for IgG), and discloses modifying human IgG1 antibodies to favor heterodimerization. *See* Ex. 1004 ¶¶ 2, 38–44, 66–67, 77–80, 85, 97–100, 104, 106, 118, 133. As Patent Owner identifies, Lazar discloses testing scFv-Fc/empty-Fc fragment structures, but the reference states that it did so as a “proof-of-

concept” and to screen for Fc variants that favor heterodimerization — in and of antibodies. *See id.* ¶¶ 9, 10, 235–241. Tables 1 and 2 of Lazar, which list “Preferred” and “Most Preferred” CH3 domain variants that favor Fc heterodimerization, were developed from this testing. *See id.* Again, Lazar states that its

invention provides antibody analogs. By “antibody” herein is meant a protein consisting of one or more polypeptides substantially encoded by all or part of the recognized immunoglobulin genes . . . which encode the IgM, IgD, IgG (IgG1, IgG2, IgG3, and IgG4), IgE, and IgA (IgA1 and IgA2) isotypes respectively. Antibody herein is meant to include full length antibodies and antibody fragments, and may refer to a natural antibody from any organism, an engineered antibody, or an antibody generated recombinantly for experimental, therapeutic, or other purposes.

Id. ¶¶ 85, 99–100. Lazar even claims antibody analogs with two heavy chains. *See id.* at claim 1. Thus, the fragments Lazar teaches as produced to identify useful amino acid substitutions at certain residue locations was for the purpose of providing entire antibodies, at least in some embodiments, and does not limit Lazar’s disclosure.

“interacting”

Patent Owner argues that Lazar fails to disclose the “interacting” element of claim 1, i.e., the interaction of substituted residues. Prelim. Resp. 17–20 (citing Ex. 2008 ¶¶ 60–61). Patent Owner asserts that Lazar only discloses general CH3-CH3 interaction, not specific residue interactions. *Id.*

The “interacting” claim element recites

wherein the at least one positively charged amino acid residue substituted in the CH3 domain of said 1st antibody heavy chain ***interacts*** with the at least one negatively charged amino acid residue substituted in the CH3 domain of said 2nd antibody

heavy chain in the interface between said 1st and 2nd antibody heavy chains to produce a heterodimeric antibody.

Ex. 1001, 71:55–61 (emphasis added).

This clause recites an intended result of engineering and producing the two CH3 domains of the antibody otherwise recited elsewhere in the claim.

A “whereby [or wherein] clause in a method claim is not given weight when it simply expresses the intended result of a process step positively recited.” *See Hoffer v. Microsoft Corp.*, 405 F.3d 1326, 1329 (Fed. Cir. 2005) (quoting *Minton v. Nat’l Ass’n of Securities Dealers, Inc.*, 336 F.3d 1373, 1381 (Fed. Cir. 2003)). The determination of whether a “wherein” clause imposes a limitation in a claim must be determined on a case-by-case basis. *See, e.g., Griffin v. Bertina*, 285 F.3d 1029, 1033–34 (Fed. Cir. 2002) (finding that a “wherein” clause limited a claim where the clause gave “meaning and purpose to the manipulative steps” of the claim); *Tex. Instruments Inc. v. ITC*, 988 F.2d 1165, 1172 (Fed. Cir. 1993) (holding that “[a] ‘whereby’ clause that merely states the result of the limitations in the claim adds nothing to the patentability or substance of the claim.” (citation omitted)).”

At this stage of the proceeding, neither party has provided an argument or evidence addressing whether this wherein clause, i.e., the “interacting” claim element, should be given patentable weight and, if so, why; although much of Patent Owner’s preliminary arguments depend on it being given patentable weight. Because of the lack of briefing at this stage in the proceeding and the fact that Petitioner accounts in the Petition for the claimed interactions between modified residues, we are not inclined to consider denying institution based on this argument.

Moreover, even if this clause reciting a resultant interaction between modified residues should be accorded patentable weight as a limitation, at this point we find that Petitioner's evidence supports that the antibody residues at which Lazar teaches to substitute a charged amino acid for a neutral one were known sites of CH3 interactions. *See* Ex. 1004 ¶ 241 (Tables 1 and 2); Ex. 1007, 7 (Table 1); *see also* Ex. 1005, 36–47 (Table 1); Ex. 1018, 50 (identifying the T366/Y407 interaction). Some are the same residue cites identified in the '286 patent itself, e.g., L351 and T366. *See* Ex. 1001, 12:40–65 (Table A), claims 3–5; Ex. 1004 ¶ 241 (Tables 1 and 2). This fact is further supported by the disclosure of Kannan,¹⁴ which identifies known interaction between a first CH3 residue 351 and a second CH3 residue 366. Ex. 1007, 7 (Table 1).

Therefore, whether the recited interaction between modified residues is a limitation or not, we find that the record at this point supports that Lazar discloses it, for example, in disclosing substitutions made to “favor heterodimerization” because of “their interaction in a heterodimeric CH3 interface.” Ex. 1004 ¶¶ 119–123, 241 (Tables 1, 2).

3. Summary

We have considered Petitioner's assertions, Patent Owner's arguments, and the evidence of record at this stage of the proceeding, and find that, on the current record, Petitioner has sufficiently mapped the limitations/steps of at least claim 1 to the disclosure of Lazar. Based on the

¹⁴ In fact, WO2009/089004, which is Kannan (Ex. 1007), is cited by the '286 patent as background on CH3-CH3 amino acid replacements (to swap charge) in forming a heterodimeric antibody and it also discloses several of the residue positions where the two heavy chain domains interact. Ex. 1001, 5:17–32.

evidence presented at this stage of the proceeding, Petitioner has shown under Ground 1 that there is a reasonable likelihood that at least one of the '286 patent's claims is anticipated by Lazar.

We have addressed only independent claim 1 above, but our institution is to all grounds and all claims, which should all be addressed at trial and will all be addressed in any final written decision. *See* 37 C.F.R. § 42.108(a).

F. GROUND 3—ASSERTED ANTICIPATION BY CABRERA

Because we find sufficient reason to institute on Petitioner's Ground 1, we need not address the merits of Ground 3, but for the sake of completeness we do so below.

Petitioner's Ground 3 asserts that claims 1, 2, 7, 21, 22, 24, 26–28, and 30–32 are anticipated by Cabrera. Pet. 59–69 (citing, *inter alia*, Ex. 1002 ¶¶ 266–306; Ex. 1005, 1, 10, 12, 16–18, 22, 24–25, 29, 35–47 (Table 1), 85–86, 92, 94, 108–111 (Example 1), Figs. 18, 26B; Ex. 1007 ¶ 277; Ex. 1008, 244–46).

Patent Owner opposes Petitioner's positions under Ground 3. Prelim. Resp. 11, 28–33 (citing, *inter alia*, Ex. 1002 ¶ 276; Ex. 1005, 17, 24, 41 (Table 1), Tables 3–4, 169, 185–239, Tables 6–7, Figs. 1–4, 6–7, 9, 11, 13, 16, 29–34; Ex. 2008 ¶¶ 79–89).

We review and analyze the parties' positions on Ground 3 below and make the following preliminary determinations, none of which constitutes a final determination of any fact or the issue of patentability.

1. Petitioner's Positions

Similar to the assertions under Ground 1 regarding Lazar, under Ground 3 Petitioner asserts Cabrera discloses the claimed invention and

maps each element of claims 1, 2, 7, 21, 22, 24, 26–28, and 30–32 to Cabrera. Pet. 59–69. Focusing on independent claim 1, beginning with its preamble (“A method for producing a heterodimeric antibody from a single cell” and “wherein said antibody comprises two heavy chains with CH3 domains that are capable of forming an interface”), Petitioner asserts Cabrera discloses designing Fc heterodimers, i.e., heterodimeric antibodies, producing them by recombinant expression from a single cell that includes vectors for polynucleotide sequences encoding the heavy and light chains of an entire immunoglobulin molecule, where the engineered modifications to the antibody are to its CH3 domains so that they form an interface to promote heterodimer formation. *Id.* at 59–60 (citing Ex. 1002 ¶¶ 266–272; Ex. 1005, 1, 16–18, 29, 92, 85–86 108–111).

Turning to the first clause of claim 1 (“providing a host cell comprising”), Petitioner asserts Cabrera discloses using a host cell, transfected with nucleic acids that express the antibody polypeptides. *Id.* at 60 (citing Ex. 1002 ¶¶ 273–274).

Regarding the next few clauses of claim 1 that relate to the polypeptides produced by the host cell and how the engineered modifications function; which, again, require one CH3 heavy chain to have a positive amino acid substituted in place of a neutral one, the other CH3 heavy chain to have a negative amino acid substituted in place of a neutral one, and when the heavy chains are expressed by culturing the host cell the new positive and negative amino acids interact and the antibody produced is a heterodimeric antibody, Petitioner asserts that this is all disclosed by Cabrera. *Id.* at 61–62. Petitioner asserts that Cabrera’s Example AZ34 discloses modifications to the two respective CH3 domains of an antibody,

including S400E (swapping the neutral serine amino acid with negatively charged glutamic acid at residue 400 on a first CH3 domain) and N390R (swapping the neutral asparagine amino acid with positive arginine at residue 390 on the second CH3 domain). *Id.* (citing Ex. 1002 ¶¶ 275–278; Ex. 1005, 36–47 (Table 1), 86, 92; Ex. 1007, Table 1 (evidencing known contact residues in CH3 domains)). Petitioner asserts that residues 400 and 390 were known positions of CH3 interaction and that by modifying the charges there, the interaction promotes the formation of heterodimer antibodies. *Id.* (citing Ex. 1002 ¶¶ 275–278).

As for the final clause of claim 1 (“c. harvesting said heterodimeric antibody from the culture”), Petitioner asserts Cabrera discloses recovering, i.e., harvesting, and purifying heterodimeric antibodies, including the AZ34 example, produced from cultured cell lysate. *Id.* at 63 (citing Ex. 1002 ¶¶ 279–280; Ex. 1005, 12, 92, Fig. 26B).

Petitioner has accounted for Cabrera disclosing each element of claim 1. At this stage of the proceeding, we do not review Petitioner’s specific assertions as to the remaining challenged claims. However, they will be addressed in any final decision.

2. Patent Owner’s Positions

“interacting”

Similar to Patent Owner’s arguments over Ground 1 and Lazar, Patent Owner also argues that Cabrera fails to disclose the modified residues of its CH3 domains interact to promote heterodimerization. Prelim. Resp. 28. Patent Owner argues that “Cabrera does not contain a single example that shows an interaction.” *Id.* at 29.

On the present record, we are not persuaded by this argument.

If, indeed, the *interacting* clause is a limitation, Cabrera discloses that its objective in mutating Fc regions of antibody CH3 regions is so the CH3 regions will interface and interact at their contact residues to produce stable, bispecific, heterodimeric antibodies. See Ex. 1005, 1, 4–5, 16–20, 27.

Cabrera states:

The “first polypeptide” is any polypeptide that is to be associated with a second polypeptide, also referred to herein as “Chain A”. The first and second polypeptide meet at an “interface”. The “second polypeptide” is any polypeptide that is to be associated with the first polypeptide via an “interface”, also referred to herein as “Chain B”. The “interface” comprises those “contact” amino acid residues in the first polypeptide that interact with one or more “contact” amino acid residues in the interface of the second polypeptide.

Id. at 18. Furthermore, Cabrera states:

The present Fc variants comprise a CH3 domain that has been asymmetrically modified to generate heterodimer Fc variants or regions. The Fc region is comprised of two heavy chain constant domain polypeptides - Chain A and Chain B, which can be used interchangeably provided that each Fc region comprises one Chain A and one Chain B polypeptide. The amino acid modifications are introduced into the CH3 in an asymmetric fashion resulting in a heterodimer when two modified CH3 domains form an Fc variant (See, e.g., Table 1). As used herein, asymmetric amino acid modifications are any modification wherein an amino acid at a specific position on one polypeptide (e.g., “Chain A”) is different from the amino acid on the second polypeptide (e.g., “Chain B”) at the same position of the heterodimer or Fc variant. This can be a result of modification of only one of the two amino acids or modification of both amino acids to two different amino acids from Chain A and Chain B of the Fc variant. It is understood

that the variant CH3 domains comprise one or more asymmetric amino acid modifications.

Id. at 17–18. In other parts, Cabrera calls these “critical protein-protein interactions between chain A and B in the Fc regions . . . at the interface of the CH3 domains.” *Id.* at 27.

Thus, the purpose of Cabrera’s disclosed amino acid substitutions on paired CH3 domains of an antibody is so that the modifications cause interactions between the CH3 domains resulting in heterodimer formation. So, for example, in Cabrera’s Example AZ34, where heavy Chain A’s CH3 region is modified S400E (substituting negatively charged glutamic acid for neutral serine) and heavy Chain B’s CH3 region is modified N390R (substituting positively charged arginine for neutral asparagine), these two associated modifications to respective CH3 domains are made so they interact to cause the heterodimer to form. *Id.* at 39. According to evidence of record, i.e., the ’286 patent and Kannan, the S400 and N390 CH3 (neutral) residues were known “interface residues” that contact one another for interdomain interactions. Ex. 1001, 12:40–65 (Table A); Ex. 1007, 7–8 (Table 1).

Patent Owner also argues that the Cabrera Example AZ34 cited by Petitioner as disclosing the claimed CH3 modifications and interactions actually makes the antibody less stable, as evidenced by the measured melting temperature (T_m), which is indicative of stability. Prelim. Resp. 30–31 (citing Ex. 2008 ¶¶ 84–85; Ex. 1005, 17:4–6). Patent Owner compares the measured melting temperature of Example AZ33 to that of Example AZ34, because each Example has the same CH3 modifications other than the S400E and N390R substitutions of AZ34 — the T_m s are, respectively, 74°C and 73.5°C for AZ33 and AZ34. *Id.* at 31–32 (citing

Ex. 2008 ¶85). Patent Owner argues that this means that, in the AZ34 example, the new E400 and R390 residues do not interact because there is no longer a hydrogen bond there. *Id.* at 32 (citing Ex. 2008 ¶ 87).

At this point, we are not persuaded by this argument.

Cabrera discloses that its engineered heterodimers have a T_m of about 70°C or greater (without an added disulfide bond); a temperature indicating greater stability. *See* Ex. 1005, 4–5, 22–24. It is possible that Cabrera’s AZ34 is marginally less stable than AZ33 because its T_m is disclosed to be 0.5°C lower; however, both examples have T_ms higher than the 70°C stability threshold Cabrera sets for its heterodimeric antibodies. More than once, Cabrera points out the S400E and N390R modifications as preferred. *See* Ex. 1005, 5, 16–18 (pointing to the variants of Table 1 to increase T_m and heterodimer stability), 29–30. The possibility that a hydrogen bond interaction at the 400-390 residue interface may have been replaced by a positive-negative charge interaction is not a persuasive point on this record. Cabrera discloses that, in selecting the amino acid modifications of its invention, including in Example AZ34, extensive modeling and simulation were conducted to achieve “novel structural and physico-chemical insights about the potential role of individual amino acids and their cooperative action,” i.e., their interaction. *Id.* at 26–29.

3. Summary

We have considered Petitioner’s assertions, Patent Owner’s arguments, and the evidence of record at this stage of the proceeding, and find that, on the current record, Petitioner has sufficiently mapped the limitations/steps of at least claim 1 to the disclosure of Cabrera. Based on the evidence presented at this stage of the proceeding, Petitioner has shown

under Ground 3 that there is reasonable likelihood that at least one of the '286 patent's claims is anticipated by Cabrera.

We have addressed only independent claim 1 above, but our institution is to all grounds and all claims, which should all be addressed at trial and will all be addressed in any final written decision. *See* 37 C.F.R. § 42.108(a).

G. GROUND 2 AND 4—ASSERTED OBVIOUSNESS

Under Ground 2, Petitioner asserts that claims 1, 2, 7–24, 26–28, and 30–32 would have been obvious over Lazar and Arathoon and are unpatentable under 35 U.S.C. § 103. Pet. 34–59. Under Ground 4, Petitioner asserts that claims 1, 2, 7–24, 26–28, and 30–32 would have been obvious over Lazar, Arathoon, and Cabrera and are unpatentable under § 103. *Id.* at 70–74. Patent Owner opposes each of these grounds. Prelim. Resp. 20–28, 33–37.

We have addressed Grounds 1 and 3 above and determined that, on this record, Petitioner has demonstrated a reasonable likelihood of showing at trial that claim 1 is unpatentable over each of Lazar and Cabrera as anticipated. At this stage in the proceeding, we do not address the merits of Grounds 2 and 4, but our institution is to all grounds and all claims, which should all be addressed at trial and will all be addressed in any final written decision. *See* 37 C.F.R. § 42.108(a).

III. CONCLUSION

On the record before us at this stage in the proceeding, Petitioner has demonstrated a reasonable likelihood of showing at trial that at least one challenged claim of the '286 patent is unpatentable under at least one ground. Accordingly, we institute an *inter partes* review of the challenged

claims of the '286 patent on all grounds alleged by Petitioner. Our findings at this stage of the proceeding are preliminary. This decision does not reflect a final determination on the patentability of the claims.

ORDER

Accordingly, it is hereby:

ORDERED that, pursuant to 35 U.S.C. § 314, an *inter partes* review of claims 1, 2, 7–24, 26–28, and 30–32 of the '286 patent, in accordance with each ground of challenge in the Petition, is hereby *instituted*; and

FURTHER ORDERED that, pursuant to 35 U.S.C. § 314(c) and 37 C.F.R. § 42.4(b), *inter partes* review of the '286 patent will commence on the entry date of this Decision, and notice is hereby given of the institution of a trial.

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