UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

XENCOR, INC.,
Petitioner

v.

MERUS N.V.,
Patent Owner

Patent No. 9,358,286

PETITION FOR *INTER PARTES* REVIEW OF U.S. PATENT NO. 9,358,286

TABLE OF CONTENTS

TABLE OF AUTHORITIES

Page(s)

Cases

Statutes

LIST OF EXHIBITS[1]

List of Exhibits

Exhibit	Document
EX1001	U.S. Patent No. 9,358,286 to De Kruif, *et al.* ("the '286 patent")
EX1002	Declaration of Leonard G. Presta, Ph.D.
EX1003	Curriculum Vitae of Leonard G. Presta, Ph.D.
EX1004	U.S. Patent Application Publication No. US 2011/0054151 A1 to Lazar *et al.* ("*Lazar*")
EX1005	International Patent Application Publication No. WO 2012/058768 A1 to Cabrera *et al.* ("*Cabrera*")
EX1006	International Patent Application Publication No. WO 1998/050431 A2 to Arathoon *et al.* ("*Arathoon*")
EX1007	International Patent Application Publication No. WO 2009/089004 A1 to Kannan *et al.* ("Kannan")
EX1008	File History for U.S. Patent No. 9,358,286
EX1009	U.S. Provisional Patent Application 61/475,614
EX1010	Georges Köhler & César Milstein, *Continuous culture of fused cells secreting antibody of predefined specificity*, NATURE, Aug. 7, 1975, 256(5517), at 495-497
EX1011	*Excerpts from* Kenneth Murphy *et al.*, *Janeway's Immunobiology* (7th ed. 2008)

[1] Citations to non-patent publications are to the original page numbers of the publication, and citations to patent publications are to the column:line number or paragraph number, as applicable.

Exhibit	Document
EX1012	Gunasekaran Kannan *et al.*, *Enhancing Antibody Fc Heterodimer Formation through Electrostatic Steering Effects*, J. BIOLOGICAL CHEM., 285(25), 19637-19646 (2010) (“Gunasekaran”)
EX1013	Roland Kontermann, *Dual targeting strategies with bispecific antibodies*, MABS, 4(2), 182-197 (2012)
EX1014	*Reserved*
EX1015	John Ridgway *et al.*, *“Knobs-into-holes” engineering of antibody CH3 domains for heavy chain heterodimerization*, PROTEIN ENGINEERING, 9(7), 617-621 (1996)
EX1016	Ameurfina Santos & Eduardo Padlan, *Development of More Efficacious Antibodies for Medical Therapy and Diagnosis*, PROGRESS IN NUCLEIC ACID RESEARCH AND MOLECULAR BIOLOGY, 1998:60, 169-194 (1998)
EX1017	A. Margaret Merchant *et al.*, *An efficient route to human bispecific IgG*, NATURE BIOTECH., 167(7), 677-81 (1998)
EX1018	Maria A. Angela *et al.*, *Effects of engineering charged amino acids in the CH3 domains on antibody heavy chain dimerization*, PHILIPPINE SCI. LETTERS, 4(1), 48-55 (2011) (“Diaz”)
EX1019	U.S. Provisional Patent Application No. 61/019,569
EX1020	U.S. Provisional Patent Application No. 61/120,305
EX1021	U.S. Patent No. 5,731,168 to Carter *et al.*
EX1022	*Reserved*
EX1023	Tae Kyung Kim & James Eberwine, *Mammalian cell transfection: the present and the future*, ANALYTICAL AND BIOANALYTICAL CHEM., 397(8), 3173-3178 (2010)
EX1024	Hui F. Liu *et al.*, *Recovery and purification process development for monoclonal antibody production*, MABS, 2(5), 480-499 (2010)

Exhibit	Document
EX1025	*Reserved*
EX1026	*Excerpts from* Jan-Christer Janson & Lars Rydén, *Protein Purification* (2nd ed. 1998)
EX1027	Jonathan Marvin & Zhenping Zhu, *Recombinant approaches to IgG-like bispecific antibodies*, ACTA PHARMACOLOGICA SINICA, 26(6), 649-658 (2005)
EX1028	*Reserved*
EX1029	*Reserved*
EX1030	*Reserved*
EX1031	*Reserved*
EX1032	*Reserved*
EX1033	*Reserved*
EX1034	*Reserved*
EX1035	*Reserved*
EX1036	*Reserved*
EX1037	*Reserved*
EX1038	*Reserved*
EX1039	Patrick Dufner et al., *Harnessing phage and ribosome display for antibody optimization*, TRENDS IN BIOTECH., 24(11), 523-529 (2006)
EX1040	John R. Birch & Andrew J. Racher, *Antibody production*, ADVANCED DRUG DELIVERY REVIEWS, 58(5-6), 671-685 (2006)

Exhibit	Document
EX1041	Florian M. Wurm, *Production of recombinant protein therapeutics in cultivated mammalian cells*, NATURE BIOTECH., 22(11), 1393-1398 (2004)
EX1042	*Excerpts from* Bruce Alberts *et al.*, *Molecular Biology of the Cell* (5th ed 2008)
EX1043	*Monoclonal Antibody*, National Cancer Institute, https://www.cancer.gov/sites/g/files/xnrzdm211/files/styles/cgov_enlarged/public/cgov_image/media_image/2019-12/Monoclonal-antibodies-illustration.gif (last visited Feb. 7, 2025)
EX1044	Bibliographic Data, U.S. Patent Application No. 14/081,848, Patent Center, USPTO
EX1045	Prosecution History for U.S. Patent Application No. 13/866,747 – Application Data Sheet Dated Apr. 19, 2013.
EX1046	*United States District Courts – National Judicial Caseload File*, https://www.uscourts.gov/sites/default/files/2024-12/fcms_na_distprofile0930.2024.pdf (last visited Feb. 7, 2025)
EX1047	*Interim Procedure for Discretionary Denials in AIA Post-Grant Proceedings With Parallel District Court Litigation*, https://www.uspto.gov/sites/default/files/documents/interim_proc_discretionary_denials_aia_parallel_district_court_litigation_memo_20220621_.pdf (last visited Feb. 7, 2025)
EX1048	Docket Sheet, *Merus N.V. v. Xencor, Inc.*, Civil Action No. 24-913-CFC (D. Del.)
EX1049	Hongcheng Liu & Kimberly May, *Disulfide bond structures of IgG molecules*, MABS, 4(1), 17-23 (2012)
EX1050	*Reserved*

I. INTRODUCTION

Petitioner Xencor, Inc. requests *inter partes* review of claims 1-2, 7-24, 26-28, and 30-32 of U.S. Patent No. 9,358,286 ("the '286 patent"). According to PTO records, the '286 patent is assigned to Merus N.V. ("Patent Owner" or "Merus"). The '286 patent is generally directed to heterodimeric antibodies—antibodies made from two ("-dimeric") different ("hetero-") parts. The '286 patent claims a heterodimeric antibody with modifications to amino acid residues that result in a positive-negative charge interaction at a known interface within the antibody (the "CH3 domain interface").

Merus stressed these modifications as a point of novelty over the prior art during prosecution of the '286 patent, but the prior art (including *Lazar* and *Cabrera*) expressly teaches the claimed modifications. And the remaining limitations of the independent claims recite only commonplace techniques used for decades in antibody production, which are likewise disclosed in *Lazar* and *Cabrera*. As a result, *Lazar* and *Cabrera* each anticipate the challenged independent claims of the '286 patent—claims 1, 26, and 30. Because the challenged dependent claims similarly recite only commonplace features taught by the prior art, they are also anticipated by *Lazar* and/or *Cabrera*. Every challenged claim is further rendered obvious by the combinations of *Lazar* and *Arathoon* or

Lazar, *Arathoon*, and *Cabrera*. (EX1002, ¶¶94-97.) Xencor therefore requests that the Board institute trial and find all challenged claims unpatentable.

II. MANDATORY NOTICES

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

Related Matters: Pursuant to 37 C.F.R. § 42.8(b)(2), Petitioner states that the '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.

Counsel and Service Information: Lead counsel is Naveen Modi (Reg. No. 46,224). Backup counsel are Eric W. Dittmann (Reg. No. 51,188), Isaac S. Ashkenazi (Reg. No. 53,957), Ashley N. Mays-Williams (Reg. No. 69,874), Daniel Zeilberger (Reg. No. 65,349), Michael A. Wolfe (Reg. No. 71,922), Ryan Meuth (*pro hac vice* to be filed), and Amanda K. Taylor (*pro hac vice* to be filed). Service information is shown below. Petitioner consents to electronic service.

Paul Hastings LLP
2050 M Street NW
Washington, D.C. 20036
Tel.: 202.551.1700
Fax: 202.551.1705
Email: PH-Xencor-Merus-IPR@paulhastings.com

III. PAYMENT OF FEES

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

IV. GROUNDS FOR STANDING

Petitioner certifies that the ’286 patent is available for review and that Petitioner is not barred or estopped from requesting review on the grounds identified herein.

V. PRECISE RELIEF REQUESTED AND GROUNDS RAISED

Petitioner respectfully requests review of claims 1-2, 7-24, 26-28, and 30-32 of the ’286 patent on the following grounds:

Ground 1: Claims 1, 7, 21, 22, 24, 26, 28, 30, and 32 are unpatentable as anticipated by *Lazar* (EX1004).

Ground 2: Claims 1-2, 7-24, 26-28, and 30-32 are unpatentable as obvious over *Lazar* in view of *Arathoon* (EX1006).

Ground 3: Claims 1-2, 7, 21, 22, 24, 26-28, and 30-32 are unpatentable as anticipated by *Cabrera* (EX1005).

Ground 4: Claims 1-2, 7-24, 26-28, and 30-32 are unpatentable as obvious based on *Lazar* in view of *Arathoon* and *Cabrera*.

Lazar, *Arathoon*, and *Cabrera* qualify as prior art under at least 35 U.S.C. §§ 102(a)(1) and 102(a)(2). (Sections VIII.A, VII.B, VIII.C.)[2]

VI. BACKGROUND

A. Technology Overview

1. Antibodies and Their Structure

Antibodies are proteins made by the body, including in response to infection. (EX1002, ¶¶19-22.) Their role in the immune system is to seek out and bind to particular portions ("epitopes") of particular targets ("antigens"), thereby neutralizing disease-causing agents ("pathogens"). (EX1002, ¶22.) Antibodies

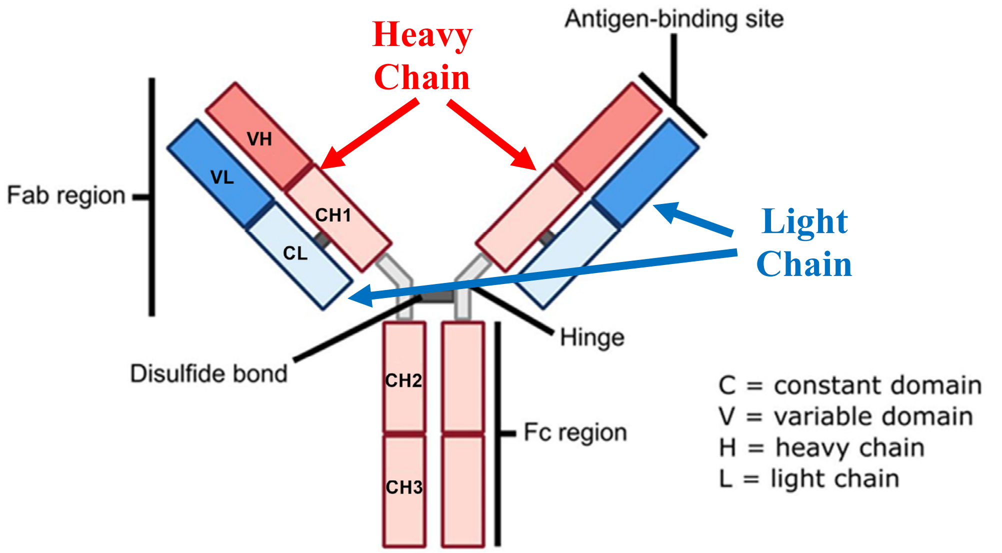
---

[2] According to PTO records, the '286 patent is an AIA patent. (EX1044.) Merus acknowledged this during prosecution of the parent application for the '286 patent by noting it included claims not entitled to a pre-AIA priority date. (EX1045, 4.) Even if the '286 patent were a pre-AIA patent, however, *Lazar* and *Arathoon* would qualify as prior art under at least pre-AIA §§ 102(a), (b), and (e) and *Cabrera* would qualify under at least pre-AIA § 102(e). Therefore, the challenged claims of the '286 patent are unpatentable and should be cancelled, regardless of whether considered under the governing AIA or pre-AIA statutory provisions.

typically bind very specifically to the target, meaning they do not indiscriminately bind other molecules. (EX1002, ¶¶19-22.)

Based upon these beneficial pathogen-neutralizing and binding-specificity characteristics, antibody-based therapeutics have been in development for decades. (*E.g.*, EX1004, ¶¶3-4; EX1002, ¶¶19-35.) By the 2012 timeframe (*i.e.*, the earliest alleged priority date of the ’286 patent), antibody engineering and production had progressed significantly, such that antibody therapeutics had already become widely utilized to treat a variety of diseases, including cancers and other disorders. (EX1001, 1:28-42; EX1002, ¶¶19-39.)

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



(EX1013, 112-13; EX1002, ¶¶23-30.) These four amino acid chains are generated within a cell and self-assemble to form the antibody. (EX1002, ¶¶29-30.) The top two arms of the "Y" include antigen binding sites, which is why those portions are called the "Fab" (**F**ragment **a**ntigen-**b**inding) region. (EX1013, 112-15, Fig. 3.3; EX1002, ¶¶25-28.) The lower portion of the "Y" is the "Fc" (**F**ragment **c**rystallizable) region. (EX1002, ¶¶25-28.) As shown above, this Fc portion in natural IgG is comprised of two pairs of **C**onstant **H**eavy domains—CH2 and CH3. (EX1002, ¶¶25-28.) The CH3 domains, specifically, play a critical role in the pairing of the two heavy chains, called "dimerization". (EX1002, ¶29.) The pairing of the light chains to the heavy chains can occur before or after this heavy chain dimerization. (EX1002, ¶30.)

Because the two halves of the common antibody structure shown above (one heavy chain & one light chain) are identical, this is known as a "homodimeric" antibody. (EX1002, ¶26.) Furthermore, because the two Fab regions and antigen binding sites are identical, this is a "monospecific" antibody—meaning it binds to only one target. (*Id.*) At the relevant time, the industry had also built other antibody constructs from this basic structure to improve antibody therapeutics and develop new uses thereof. (EX1002, ¶¶31-35; EX1013, Figure 2.) One of those improvements was bispecific antibodies.

2. Bispecific Antibodies

Bispecific antibodies were also well known in the art by 2012. As their name suggests, these antibodies are capable of simultaneously engaging two targets. (EX1004, ¶38; EX1006, 1, 10; EX1013, 183; EX1002, ¶31.) The targets of a bispecific antibody can be different epitopes on the same antigen or epitopes located on different antigens. (EX1004, ¶50; EX1013, 182-83; EX1002, ¶¶31-32.) In one example of a bispecific antibody structure, the antigen binding regions at the end of each tip at the top of the "Y" are different. (EX1002, ¶32.) One way this can be accomplished is by including one heavy and light chain pair from one antibody with specificity for a particular antigen with a heavy and light chain pair from a different antibody with specificity for a different antigen, as depicted below:

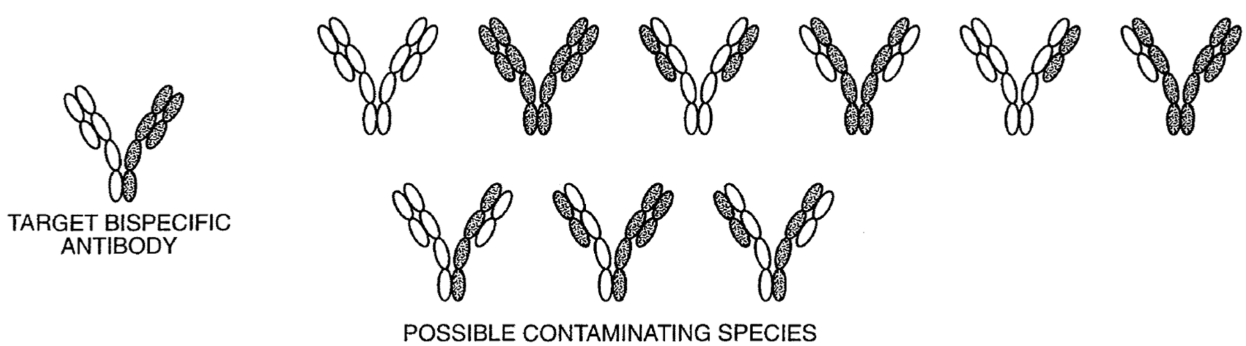
(EX1006, Fig. 1A.)

The capability of bispecific antibodies to simultaneously bind different targets allowed for new therapeutic mechanisms and provided an attractive area for research and development in the 2012 timeframe. (EX1002, ¶¶33-35; EX1013, 184-185, Table 1 (describing a variety of bispecific antibody therapies in development by March 2012), Figure 2 (instructing that "more than 45 different [bispecific antibody] formats ha[d] been established" by this timeframe).) For instance, bispecific antibodies were known to bind multiple different targets (allowing for neutralization of both a receptor and its target molecule, for example) and to bind multiple epitopes on the same target (allowing for more effective neutralization of a single receptor or molecule). (EX1002, ¶¶33-34.) Such binding mechanisms were useful for a variety of therapies, including the treatment of cancer, autoimmune/inflammatory diseases, and infectious diseases. (EX1013, 182-84; EX1004, ¶¶3, 6; EX1006, 1-2.)

Given these known binding mechanisms and promising therapeutic applications, persons of ordinary skill in the art ("POSAs") interested in developing antibody-based therapeutics at the relevant time were motivated to develop bispecific antibodies. (EX1002, ¶¶31-35.)

3. Bispecific Production Concerns and Prior Art Solutions

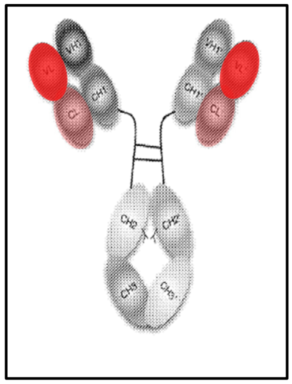
One area of particular focus was achieving sufficiently high yields for bispecific antibody production, which was limited primarily by undesired interactions between heavy chains and light chains. (EX1002, ¶¶36-59.) As illustrated in the graphic below, two main undesired interactions can occur: (1) mismatching of the heavy chains; and (2) mismatching of the light chains to the heavy chains.

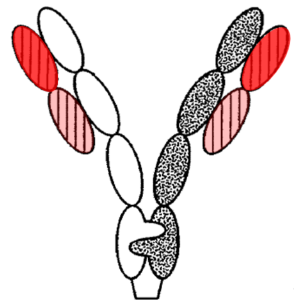


(EX1006, Fig. 1A.)

By 2012, there were several strategies known in the art to mitigate these mismatch problems. (EX1002, ¶¶40-59.) To address heavy chain mismatching, one set of techniques involved modifying the CH3 domains in the Fc region of the heavy chains to favor mixed-chain pairing (heterodimerization) and/or disfavor same-chain pairing (homodimerization). (EX1002, ¶¶43-44; EX1013, 184; EX1017, 677.) Early efforts included a "knob-into-hole" (KIH) strategy, which involved introducing a protuberance (knob) in one CH3 domain and a corresponding cavity (hole) in the complementary CH3 domain of the second heavy chain to achieve a lock-in-key mechanism. (EX1001, 4:49-5:2; EX1007, 2:5-21; EX1002, ¶¶45-48.) As research progressed, scientists also introduced electrostatic interactions, which involved replacing residues within the two different CH3 regions with oppositely charged amino acid residues, such that mixed-chain pairing was electrostatically favored and same-chain pairing disfavored (also referred to herein as "electrostatic engineering"). (EX1016, 188-190; EX1007, 2:33-3:7; EX1012, 19637; EX1002, ¶¶53-59.) As discussed below, *Lazar*, *Cabrera*, and the '286 patent all disclose such CH3-domain modification techniques. (EX1002, ¶¶60-93.)

To reduce the incidence of mismatched light chains, one well-known technique as of the relevant timeframe was to reduce the total number of possible pairings by using the same light chain on both arms of the Y—a "common light chain." (EX1002, ¶¶49-50.)





(EX1005, Fig. 18; EX1006, Fig. 1C (annotations added).)

POSAs understood that these techniques could be used together in complementary fashion to additively improve the yield of desired heterodimeric, bispecific antibodies and reduce the production of undesired mismatches. (*E.g.*, EX1002, ¶57; EX1006, 42-44 (Example 2 combining KIH and non-natural disulfide linkages), 48-55 (same for Example 4); EX1017, 678 (Fig. 1 showing same, described as "Generic route to bispecific IgG").)

4. Recombinant Antibody Production Using Host Cells

Heterodimeric, bispecific antibodies can be produced in different ways. (EX1002, ¶¶36-39.) The most common way is by recombinant expression in a host cell. (*Id.*; *see* EX1004, ¶¶180-89 (*Lazar* describing "Production of Immunoglobulins"); EX1005, 85-86 (*Cabrera* describing "[r]ecombinant expression"); EX1006, 28-36 (similar for *Arathoon*).) The '286 patent itself admits that "[e]xpression of antibodies in recombinant host cells has been extensively described in the art." (EX1001, 15:54-57, 16:48-51.) In this well-known method for antibody production, a nucleotide sequence is designed that, when expressed, will produce a protein chain (*e.g.*, a heavy or light chain of an antibody). (EX1002, ¶¶36-37.) Nucleotide sequences for each desired chain in the antibody are then inserted into a cell ("co-transfected"), which is then cultured so the cell expresses the desired protein chains. (*Id.*, ¶38.) Those chains then self-assemble within the cell to form antibodies (the step at which mismatches can occur, as explained above). (*Id.*) Those antibodies must then be "harvested" or recovered from the cells, after which they are generally further purified for future use. (*Id.*, ¶39.)

B. '286 Patent Overview

The '286 patent, titled "Methods and Means for the Production of Ig-Like Molecules," issued on June 7, 2016 from the '848 application, which was filed on November 15, 2013. (EX1001, Cover.) The '286 patent claims priority to Application No. 13/866,747, filed on April 19, 2013, which claims priority to a provisional application filed on April 20, 2012.[3] Generally speaking, the '286

---

[3] As noted above, Merus recognized during prosecution of the '747 application that the '747 application included claims not supported by the provisional application, and hence the '286 patent is an AIA patent. Petitioner does not necessarily agree

patent concerns "Ig-like molecules" and "antibod[ies]," which it defines broadly as not only including the native antibody structures, but also "functional derivative[s] and/or fragment[s]" of any of the Ig isotypes known in the art (such as IgG1). (*Id.*, 11:9-21; *see* EX1002, ¶¶60-67.)

The Background section of the '286 patent acknowledges that "it is well-known that the CH3-CH3 interaction is the primary driver for Fc dimerization." (EX1001, 4:5-6.) According to the '286 patent, it was also "well-known" that the CH3 domains of interacting heavy chains "meet in a protein-protein interface which comprises 'contact' residues." (*Id.*, 4:8-12.) Those contact residues are described as "known," having "been identified" previously in the prior art, with the '286 patent listing those contact residues in Table A. (*Id.*, 12:8-13:17.)

The '286 patent also recites known strategies for increasing heterodimer formation through engineering CH3 domains, including knob-into-hole engineering and electrostatic engineering, among others. (*Id.*, 4:29-5:52.) These various methods, according to the '286 patent, could be combined to "achieve said further improved percentages of desired (bispecific) antibodies." (*Id.*, 5:58-62.)

---

that the '286 patent is entitled to priority as claimed, but the challenged claims are unpatentable even applying an April 2012 priority date.

The ’286 patent is directed to a method for producing antibodies using electrostatic engineering. (*Id.*) Although the ’286 patent admits that “electrostatic engineering” was known in the prior art, it attempts to distinguish prior art techniques as supposedly being limited to a “charge reversal strategy” (*i.e.*, modifying an already-charged amino acid residue to the opposite charge). (*Id.*, 5:17-32, 17:67-18:4.) According to the ’286 patent, the “present invention . . . does not exchange charged contact amino acids by amino acids of opposite charge[,] but substitutes non-charged CH3 amino acids for charged ones.” (*Id.*, 18:7-10.) The ’286 patent contends these neutral-to-charged mutations to be “an inventive alternative to” the prior art. (*Id.*, 18:4-7.) They were not.

C. ’286 Patent Prosecution History

The ’286 patent’s prosecution evidences a consistent focus on the neutral-to-charged concept as the purported novel aspect of the claims. During prosecution, the Examiner issued only one office action, rejecting the claims as anticipated over two different prior art references. (EX1008, 217-20.) To overcome both of these references, Merus argued that the prior art “does <u>*not*</u> disclose a heterodimeric antibody in which the CH3 domain of the first heavy chain contains a substitution of a neutral amino acid with a positively charged amino acid, and the CH3 domain of the second heavy chain contains a substitution of a neutral amino acid with a negatively charged amino acid.” (EX1008, 244-46 (emphasis original).) The

Examiner accepted this rationale in allowing the claims, finding "the prior art does not teach or suggest replacing a neutral amino acid . . . with a positively charged amino acid in the CH3 domain." (EX1008, 274-75.) In other words, Merus successfully convinced the Examiner that the neutral-to-positive and neutral-to-negative limitations were a point of novelty over the prior art.

But as explained below, the independent claim limitations are expressly disclosed in both *Lazar* and *Cabrera*.[4]

VII. LEVEL OF ORDINARY SKILL

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.)

[4] Cabrera was not considered by the Examiner, and, although the PCT publication of *Lazar* and *Arathoon* were listed as considered by the Examiner (EX1008, 284, 286), they were never discussed in any office action.

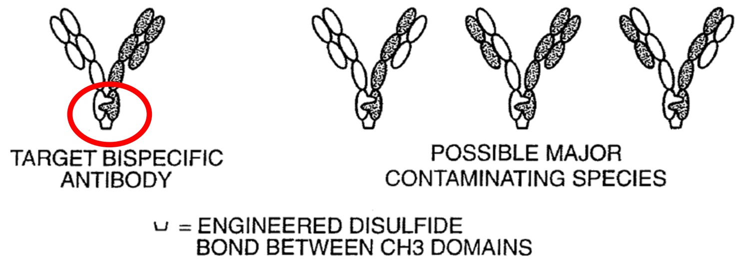
VIII. PRIOR ART OVERVIEW

A. *Arathoon* (EX1006)

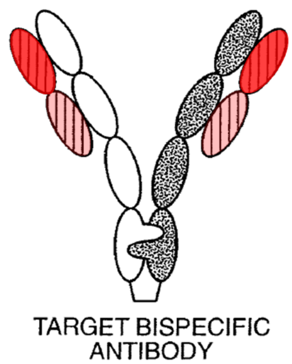
Arathoon is a publication of an international patent application titled "A Method for Making Multispecific Antibodies Having Heteromultimeric and Common Components." (EX1006, 1.) *Arathoon* was filed by Genentech on April 20, 1998, and published on November 12, 1998, listing Xencor's expert in this proceeding, Dr. Leonard Presta, as an inventor. (EX1006, 1.) *Arathoon* is thus prior art to the '286 patent under at least 35 U.S.C. §§ 102(a)(1) and 102(a)(2).

Arathoon teaches methods of producing bispecific, heterodimeric antibodies. (EX1006, Abstract; EX1002, ¶¶68-74.) *Arathoon* provides an overview of bispecific antibodies, explains the mismatch problems in producing bispecific antibodies, and discloses various solutions to those problems (while explaining that those solutions are complementary and can be used together to further improve heterodimer yield). (EX1006, 1-3, 5-8, 42-4.) *Arathoon* teaches that the number of contaminating species (*see* Section VI.A.3; EX1006, Fig. 1A) can be reduced by making CH3 domain modifications that promote heterodimer formation for the two heavy chains—such as KIH modifications, engineered disulfide bonds[5], or both:

[5] The sulfur atoms in cysteines added to each of the CH3 regions form a disulfide bond.



(EX1006, Fig. 1B (annotation added).) *Arathoon* also teaches the use of a common light chain to further improve the purity of the target bispecific antibody:



(EX1006, Fig. 1C (annotations added); EX1002, ¶74.) *Arathoon* teaches that, by combining these methods, one can significantly increase heterodimerization, including achieving more than 95% purity. (EX1006, 44-45; EX1002, ¶73.)

B. *Lazar* (EX1004)

Lazar is a publication of a patent application filed by Petitioner Xencor on September 10, 2010, titled "Compositions and Methods for Simultaneous Bivalent and Monovalent Co-engagement of Antigens." (EX1004, Cover.) *Lazar* published on March 3, 2011. (*Id.*) *Lazar* thus is prior art to the '286 patent under at least 35

U.S.C. §§ 102(a)(1) and 102(a)(2). *Lazar*, like *Arathoon*, teaches methods for producing bispecific, heterodimeric antibodies. (EX1004, Abstract.)

To promote synthesis of the desired heterodimeric antibodies, *Lazar* describes "Fc Modifications," which involve amino acid substitutions at certain locations on the Fc region of the heavy chains—and specifically on the CH3 domain. (EX1004, ¶¶114-25; EX1002, ¶¶75-82.) *Lazar* teaches that, by using these Fc modifications, the heterodimer population can be increased significantly, as high as "greater than 95%." (EX1004, ¶122; EX1002, ¶82.) *Lazar* discloses specific positions at which amino acid substitutions were made, further experimentally testing particular substitutions. (EX1004, ¶123, Figs. 5-7; EX1002, ¶¶80-81.) Based on these modifications and testing, *Lazar* provides a list of "Preferred" and "Most preferred" "CH3 domain variants that favor heterodimerization." (EX1004, ¶241 (Tables 1 & 2).) Many of these preferred modification pairs include neutral-to-charged modifications, and several include both neutral-to-positive and neutral-to-negative modifications at locations that were known to be on the CH3 domain interface. (*Id.*; EX1002, ¶81; Section X.A.1.iv.)

Lazar also discloses particular uses for its bispecific, heterodimeric antibodies, based upon a variety of potential targets or co-targets, several therapeutic applications, and pharmaceutical compositions containing these antibodies. (EX1004, ¶¶56, 134-52, 202-32.) Finally, *Lazar* also discloses details regarding the production of such antibodies, including using "host cell[s] transformed with nucleic acid," a well-known procedure at the relevant time. (EX1004, ¶¶180-89.)

C. *Cabrera* (EX1005)

Cabrera is the publication of an international patent application titled "Stable Heterodimeric Antibody Design with Mutations in the Fc Domain," which was filed on November 4, 2011. (EX1005, 1.) *Cabrera* is thus prior art to the '286 patent under at least 35 U.S.C. § 102(a)(2).[6]

Like *Lazar* and *Arathoon*, *Cabrera* discloses methods for forming heterodimeric, bispecific antibodies. (EX1005, 1; EX1002, ¶¶83-89.) *Cabrera* notes that "[a] major obstacle in the general development of bispecific antibodies

---

[6] To the extent that the '286 patent is considered under the pre-AIA 35 U.S.C. §§ 102 and 103, which it should not be, *Cabrera* remains prior art to the '286 patent based on its international filing date. In fact, *Cabrera* claims priority to several provisional applications, including at least one filed on April 14, 2011 (EX1009), that substantively recites the same disclosures as relied on in this petition. (EX1002, ¶¶90-93.) Accordingly, to the extent needed under pre-AIA 35 U.S.C. § 102(e), *Cabrera*'s priority date stretches back to April 14, 2011.

has been the difficulty of producing materials of sufficient quality and quantity for both preclinical and clinical studies." (EX1005, 2.) To address this problem, *Cabrera* teaches antibodies with "a heterodimer Fc region, wherein the heterodimer Fc region comprises a variant CH3 domain comprising amino acid mutations to promote heterodimer formation." (EX1005, 4; EX1002, ¶¶86-88.)

Employing the disclosed strategy, Example AZ34 in *Cabrera* teaches a neutral-to-positive and neutral-to-negative pair of modifications at amino acid locations known to be on the CH3 domain interface—"S400E" and "N390R."[7] (EX1005, 39; EX1002, ¶87.) *Cabrera* discloses that the "Estimated Heterodimer Purity" of this AZ34 embodiment was ">95%." (EX1005, 172 (Fig. 26B).) This finding comports with *Cabrera*'s other teachings that its Fc modifications result in purities between 90-100%, including purities "greater than about 95%." (EX1005, 24-25.) Cabrera further teaches that the heterodimers described therein, including AZ34, can be applied to make a broad array of bispecific antibodies. (EX1005, 10, 16-17, 50, 75, Fig. 18.)

---

[7] In the nomenclature used by POSAs, this indicates that serine (S, neutral) at position 400 is replaced with a glutamine (E, negatively charged) on one heavy chain and asparagine (N, neutral) at position 390 is replaced with an arginine (R, positively charged) on the other heavy chain.

IX. CLAIM CONSTRUCTION

Claim terms need only be construed "to the extent necessary to resolve the controversy." *Vivid Techs., Inc. v. Am. Sci. & Eng'g, Inc.*, 200 F.3d 795, 803 (Fed. Cir. 1999). Petitioner submits that no terms of the '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.)

X. DETAILED EXPLANATION OF GROUNDS

A. Ground 1: *Lazar* Anticipates Claims 1, 7, 21, 22, 24, 26, 28, 30, and 32

1. Claim 1

i) [1.pre] "A method for producing a heterodimeric antibody from a single cell,"

Regardless of whether the preamble is limiting, *Lazar* discloses a "method for producing a heterodimeric antibody from a single cell." (EX1004, ¶¶2, 38, 39, 85; EX1002, ¶¶100-05.) *Lazar* further explains that the disclosed heterodimeric antibodies may be produced from a single cell "by culturing a host cell transformed with nucleic acid, *e.g.*, an expression vector, containing nucleic acid encoding the immunoglobulins, under the appropriate conditions to induce or cause expression of the protein." (EX1004, ¶183; EX1002, ¶¶103-05.) As one specific example, *Lazar* teaches "co-transfect[ing]" HEK293E cells for the purpose of producing heterodimeric antibodies using nucleotide sequences with the disclosed CH3 domain amino acid substitutions. (EX1004, ¶¶239, 245.) The process of co-transfection involves the introduction ("transfection") into a single cell of separate nucleotide sequences needed for producing the antibodies of interest. (EX1004, ¶¶182-83, 239-40, 245; EX1002, ¶¶104-05.)

ii) [1.pre.ii] "wherein said antibody comprises two heavy chains with CH3 domains that are capable of forming an interface, said method comprising:"

Regardless of whether the preamble is limiting, *Lazar* discloses synthesizing an antibody having two different heavy chains with modified CH3 domains that are capable of forming an interface to promote heterodimer formation. (EX1004, ¶9; EX1002, ¶¶106-08.) *Lazar* teaches that the "variants are designed such that their interaction in a heterodimeric CH3 ***interface*** . . . is favorable" and interaction "across a homodimeric CH3 ***interface*** . . . is unfavorable." (EX1004, ¶121.)[8]

iii) [1.a] "a. providing a host cell comprising"

As explained above, *Lazar* discloses the use of a "host cell" for expressing the co-transfected nucleic acids. (Section X.A.1.ii).) (EX1002, ¶¶109-10.)

---

[8] All emphases and annotations to figures have been added unless otherwise noted.

iv) **[1.b] "(i) a <u>first nucleic acid</u> molecule encoding a 1st antibody heavy chain comprising at least one substitution of a <u>neutral</u> amino acid residue in the CH3 domain by a <u>positively</u> charged amino acid residue, and**
(ii) a <u>second nucleic acid</u> molecule encoding a 2nd antibody heavy chain comprising at least one substitution of a <u>neutral</u> amino acid residue in the CH3 domain by a <u>negatively</u> 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 <u>interacts</u> 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"

These claim limitations, although lengthy, are interrelated and are therefore addressed together. These limitations require nucleic acids encoding two antibody heavy chains, each with one or more amino acid residue substitutions in the CH3 domain. (EX1002, ¶¶111-19.) One chain substitutes a neutral-for-positive amino acid residue, and the other substitutes a neutral-for-negative amino acid residue. (EX1002, ¶112.) The substituted amino acids "interact" in the interface between the two antibody heavy chains to produce a heterodimeric antibody after being cultured and expressed in the host cell. (*Id.*; EX1001, 17:67-18:3 (describing substitution locations as those that "were known to be involved in CH3-CH3 pairing"), 19:5-12 (describing positions 366 and 351 as "interacting" and "hav[ing] been reported to be a pair of contact residues in the CH3-CH3 interface").)

Although Patent Owner argued during prosecution that these limitations were a key point of novelty over the prior art (EX1008, 244-46), *Lazar* expressly teaches the claimed substitutions in the CH3 domain for several pairings of positions. (EX1004, ¶241 (Tables 1 & 2); EX1002, ¶¶113-18.) *Lazar* explains that the "hetero-Fc variants" made from these disclosed substitutions "are designed such that their ***interaction*** in a heterodimeric CH3 interface . . . is favorable, thus resulting in a stable heterodimeric Fc species[.]" (EX1004, ¶121.)

Below, Tables 1 and 2 of *Lazar* have been annotated to show substitutions where neutral amino acids (in yellow—lysine (L), serine (S), threonine (T), or tyrosine (Y)) are replaced on a first chain by either positively charged amino acids (in green—lysine (K) or histidine (H)) or negatively charged amino acids (in red—aspartic acid (D) or glutamic acid (E)), and the complementary negative/positive substitution on a second heavy chain.[9] (*See* EX1002, ¶¶115-17; *see also* EX1007, 8:9-10; EX1001, 13:1-17 (listing amino acid charges).) Furthermore, *Lazar* discloses making such neutral-to-positive and neutral-to-negative substitutions at

[9] For instance, in the first red box below, "Variant 1" teaches substituting a serine (S) residue at position 364 with a glutamic acid (E) residue—shown as "S364E."

previously disclosed contact residues on the known interface in the native CH3 domains, as shown in the red boxes in the annotated Tables 1 and 2 of *Lazar*, below.[10] (EX1004, ¶241 (Tables 1, 2); EX1007, 7:19-20 (Table 1 listing known "CH3 domain interface residues"); EX1002, ¶¶115-17.)

[10] Even if a POSA would not have known the charges of the amino acids that *Lazar* teaches substituting (but they would have), "[i]nsufficient prior understanding of the inherent properties of a known composition does not defeat a finding of anticipation." *Atlas Powder Co. v. IRECO Inc.*, 190 F.3d 1342, 1349 (Fed. Cir. 1999).

TABLE 1

Preferred CH3 domain variants that favor Fc heterodimerization.

Variant 1	Variant 2
F405A	T394F
S364D	Y349K
S364E	L368K
S364E	Y349K
S364F	K370G
S364H	Y349K
S364H	Y349T
S364Y	K370G
T411K	K370E
V397S/F405A	T394F
K370R/T411K	K370E/T411E
L351E/S364D	Y349K/L351K
L351E/S364E	Y349K/L351K
L351E/T366D	L351K/T366K
P395T/V397S/F405A	T394F
S364D/K370G	S364Y/K370R
S364D/T394F	Y349K/F405A
S364E/F405A	Y349K/T394F
S364E/F405S	Y349K/T394Y
S364E/T411E	Y349K/D401K
S364H/D401K	Y349T/T411E
S364H/F405A	Y349T/T394F
S364H/T394F	Y349T/F405A
Y349C/S364E	Y349K/S354C
L351E/S364D/F405A	Y349K/L351K/T394F
L351K/S364H/D401K	Y349T/L351E/T411E
S364E/T411E/F405A	Y349K/T394F/D401K
S364H/D401K/F405A	Y349T/T394F/T411E
S364H/F405A/T411E	Y349T/T394F/D401K

TABLE 2

Most preferred CH3 domain variants that favor Fc heterodimerization.	
Variant 1	Variant 2
F405A	T394F
S364D	Y349K
S364E	Y349K
S364H	Y349T
L351K	L351E
D401K	T411E
S364D/T394F	Y349K/F405A
S364E/F405A	Y349K/T394F
S364H/D401K	Y349T/T411E
S364H/F405A	Y349T/T394F
S364H/T394F	Y349T/F405A
L351K/S364H/D401K	Y349T/L351E/T411E
S364H/D401K/F405A	Y349T/T394F/T411E
S364H/F405A/T411E	Y349T/T394F/D401K

(EX1004, ¶241 (Tables 1, 2); EX1002, ¶¶115-17.) Each of the highlighted *and* boxed pairs of "domain variants" thus teaches claim limitation 1.b.

Not only does *Lazar* teach that such amino acid residue substitutions could be made—*Lazar* expressly exemplifies making heterodimeric antibodies in which neutral-to-positive and neutral-to-negative substitutions were made on the known interface of the CH3 domain. *Lazar* reports that the variants of Tables 1 and 2 were "designed," synthesized, and subsequently "screened." (EX1004, ¶241.)

Furthermore, *Lazar* teaches "culturing said host cell and allowing for expression of said two nucleic acid molecules" to produce the two heavy chains in addition to the rest of the antibody (*e.g.*, EX1004, ¶183)—a well-known procedure in the art before 2012. (EX1002, ¶119).

v) [1.c] "c. harvesting said heterodimeric antibody from the culture."

Lazar teaches that the heterodimeric antibodies are "purified or isolated after expression . . . in a variety of ways known to those skilled in the art." (EX1004, ¶189.) A POSA would have understood *Lazar*'s teaching of "isolat[ing]" to disclose "harvesting" as claimed. (EX1002, ¶¶120-24.) Moreover, a POSA would have understood that "harvesting" would have been a necessary step in the recovery of the antibodies before they are purified, as taught by *Lazar*. (EX1002, ¶¶123-24.)

2. Claim 7: "The method according to claim 1, wherein the presence of contaminating homodimers is less than 5%, preferably less than 2%, more preferably less than 1%, and most preferably contaminating homodimers are essentially absent."

Lazar teaches that, in "preferred" embodiments, "the two heavy chains . . . differ from each other by the presence of amino acid substitutions in the Fc domain," changes that make the "different heavy chains . . . more likely to associate to form the antibody analog structure than to form homodimers with the same Fc amino acid sequences." (EX1004, ¶¶42, 120.) In other words, the "hetero-Fc variants of the invention increase the percentage population of the heterodimer while reducing the population of the homodimers." (*Id.*, ¶122; EX1002, ¶¶127-28.)

Describing the disclosed "Fc Modifications that Favor Heterodimerization," *Lazar* specifies different levels of achievable heterodimer purities, such as "70%, preferably 80%, more preferably 90%, and most preferably greater than 95%." (EX1004, ¶122.) *Lazar* explains that the heterodimer purity is increased by "reduc[ing] the homodimer populations" using *Lazar*'s "hetero-Fc variants." (*Id.*) Because *Lazar* discloses heterodimer purity of "greater than 95%," a POSA would have understood *Lazar* to teach the "presence of contaminating homodimers is less than 5%," as claimed. (EX1002, ¶¶125-29.)

3. Claim 21: "The method according claim 1, wherein said heterodimeric antibody is human IgG."

Lazar teaches that "[t]he antibodies of embodiments disclosed herein may be substantially encoded by immunoglobulin genes belonging to any of the antibody classes," including "the IgG class of antibodies."[11] (EX1004, ¶90; *see also id.*,

[11] To the extent claims 21/24's "antibody is human IgG" limitation or claim 32's "antibody is human IgG1" limitation requires entirely human residues—*i.e.*, an antibody with an unaltered human IgG sequence—the claims would be indefinite because the claims ***do*** require non-natural modifications. (EX1002, ¶130 n.18.)

¶¶66-67, 77-79; EX1002, ¶¶130-32.) And Example 2 of *Lazar* expressly describes applying the "[p]referred" and "[m]ost preferred" neutral-to-positive and neutral-to-negative amino acid substitutions on a heterodimer based upon an IgG1 antibody (*i.e.*, a human IgG) heavy chain sequence. (EX1004, ¶¶238-39; *see also id.*, ¶133.)

4. Claim 22: "A heterodimeric antibody obtained by the method of claim 1."

Lazar teaches that the method of claim 1 results in the production of a heterodimeric antibody, which can then be "obtained" by isolation and/or purification. (*See* Section X.A.1.v; EX1002, ¶¶133-34.)

5. Claim 24: "A heterodimeric antibody according to claim 22, wherein said antibody is human IgG."

Lazar teaches a heterodimeric antibody obtained by the method of claim 1 that is based upon a human IgG sequence. (Sections X.A.1, X.A.3-4; EX1002, ¶¶135-36.)

6. Claim 26

i) [26.pre]: "A recombinant host cell comprising"

[26.a]: "nucleic acid sequences encoding at least a 1st and 2nd antibody heavy chain,"

Regardless of whether the preamble is limiting, *Lazar* teaches these limitations. As noted above, *Lazar* teaches host cells containing nucleic acid sequences encoding two different antibody heavy chains. (Section X.A.1.ii;

EX1002, ¶¶137-38.) A POSA would have understood these host cells to be "recombinant" because they include the exogenous recombinant nucleic acids. (EX1002, ¶138; *see also* EX1004, ¶85.)

ii) [26.b]: "wherein the CH3 domain of said 1st antibody heavy chain comprises at least one substitution of a neutral amino acid residue by a positively charged amino acid residue," / [26.b]: "and wherein the CH3 domain of said 2nd antibody heavy chain comprises at least one substitution of a neutral amino acid residue by a negatively charged amino acid residue."

As described above, *Lazar* teaches neutral-to-positive and neutral-to-negative substitutions on the CH3 domain interface. (Section X.A.1.iv; EX1002, ¶139-40.)

7. Claim 28: "A pharmaceutical composition comprising a heterodimeric antibody according to claim 22 and a pharmaceutically acceptable carrier."

Lazar teaches the "present invention provides compositions comprising antibody analog polypeptides described herein, and a physiologically or pharmaceutically acceptable carrier or diluent." (EX1004, ¶55.) Specifically, *Lazar* teaches "[p]harmaceutical compositions" comprising the "immunoglobulins disclosed herein" together with "optional pharmaceutically acceptable carriers." (*Id.*, ¶214; EX1002, ¶¶141-44.)

8. Claim 30:

i) [30.pre]: "A method for making a host cell for production of a heterodimeric antibody,"

Regardless of whether the preamble is limiting, *Lazar* discloses a method for co-transfecting host cells for producing heterodimeric antibodies. (Section X.A.1; EX1002, ¶145.)

ii) [30.a]: "the method comprising the step of introducing into said host cell nucleic acid molecules encoding at least a 1st and 2nd antibody heavy chain, wherein the CH3 domain of said 1st antibody heavy chain comprises at least one substitution of a neutral amino acid residue by a positively charged amino acid residue and wherein the CH3 domain of said 2nd antibody heavy chain comprises at least one substitution of a neutral amino acid residue by a negatively charged amino acid residue,"

Lazar teaches introducing into a host cell (via co-transfection) nucleic acid molecules with a neutral-to-positive substitution on one CH3 domain and a neutral-to-negative substitution on another CH3 domain. (Section X.A.1.iv; EX1002, ¶146.)

iii) [30.b]: "wherein said nucleic acid sequences are introduced consecutively or concomitantly."

Lazar teaches the co-transfection into a host cell and expression of two nucleic acid sequences, each containing a different engineered CH3 domain, to promote the formation of heterodimers. (EX1004, ¶122-23, 194, Fig. 1, Tables 1-2.) *Lazar* teaches that co-transfection involves "transfection of two different

DNAs encoding two different heavy chains." (*Id.*, ¶122.) A POSA would have understood from these teachings that *Lazar*'s co-transfection discloses "concomitantly" introducing, into a host cell, nucleic acid sequences with the neutral-to-positive and neutral-to-negative modifications discussed above. (EX1002, ¶¶147-48; Section X.A.1.)

9. Claim 32: "The method according to claim 21 wherein antibody is human IgG1."

Lazar teaches a method for producing a heterodimeric antibody (Section X.A.1), that is based upon a human IgG1 sequence (Section X.A.3). *Lazar* describes that the "antibodies of embodiments disclosed herein may be substantially encoded by immunoglobulin genes belonging to any of the antibody classes"—expressly referencing "the IgG class of antibodies." (EX1004, ¶90; *see also id.*, ¶¶66-67, 77-79; EX1002, ¶¶149-50.) Further, Example 2 of *Lazar* expressly discloses applying the "[p]referred" and "[m]ost preferred" neutral-to-positive and neutral-to-negative amino acid substitutions on a heterodimer that incorporates an IgG1 antibody (*i.e.*, a human IgG1) heavy chain sequence. (EX1004, ¶¶238-39; *see also id.*, ¶133.)

B. Ground 2: *Lazar* in View of *Arathoon* Renders Obvious Claims 1-2, 7-24, 26-28, and 30-32[12]

1. Similarity and Compatibility of *Lazar* and *Arathoon*, Reasons to Combine, and Reasonable Expectation of Success

Lazar and *Arathoon* each teach a framework for more efficiently developing heterodimeric antibodies for numerous applications.[13] (EX1004, ¶¶38, 241-242; EX1006, 5.) And given the interest in heterodimeric antibodies and the focus on increasing their yield during production, POSAs at the relevant time would have

---

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

[13] Similar to *Lazar*, *Arathoon* discloses producing heterodimeric antibodies using customary methods such as co-transfection of nucleotide sequences into a host cell, expression of those sequences, and isolation and purification of the antibody. (EX1005, 7, 28-37; EX1002, ¶¶73, 160.)

had good reason to look to both *Lazar* and *Arathoon* to increase heterodimer yield. (Sections VI.A.2-3; EX1002, ¶¶154-61.)

As described above, *Lazar* teaches techniques for boosting heterodimer yield through "Fc Modifications that Favor Heterodimerization," disclosing several "[p]referred CH3 domain variants" that teach neutral-to-positive and neutral-to-negative substitutions, as recited in the challenged claims. (EX1004, ¶¶119-125, 241 (Tables 1 & 2); Section X.A.1.) Similarly, *Arathoon* teaches modifying amino acids at the CH3 domain interface to promote heterodimerization, such as KIH modifications and non-natural disulfide bonds. (EX1006, Examples 1, 2, 4, 12; EX1002, ¶¶157-59.)

In addition, both *Lazar* and *Arathoon* specifically teach combining heterodimer-promoting techniques to achieve even greater heterodimer yield. (EX1002, ¶¶155-59.) For example, *Lazar* builds upon the described individual "Fc variants that favor heterodimerization," explaining that "combination variants" are envisioned. (EX1004, ¶124 ("[i]n some embodiments, the hetero-Fc variants are made in combinations").) Together with the amino acid substitutions described, *Lazar* teaches (in the very next paragraph) that other prior art "Fc variants that favor heterodimerization that may find use in the creation of the antibody analogs of the invention," including KIH modifications (which are also taught in *Arathoon*). (*Id.*, ¶125 (citing EX1015 and EX1021); EX1006, Fig. 1C.)

Similarly, *Arathoon* contemplates combining techniques for promoting heterodimer formation. (EX1002, ¶¶157-61.) For instance, *Arathoon* teaches several types of modifications for promoting interaction at the CH3 interface, including "formation of protuberance-into-cavity [(*i.e.*, KIH)] complementary regions; the formation of non-naturally occurring disulfide bonds; leucine zipper; hydrophobic regions; and hydrophilic regions." (EX1006, 6.) *Arathoon* then teaches that these techniques can be used "in conjunction" with each other (*id.*, 40), providing a specific example of "[d]isulfides combined with protuberance-into-cavity" that "increases the yield of heterodimer to 95%" (*id.*, 44).

A POSA would have had good reason for combining the teachings of *Lazar* and *Arathoon* and a reasonable expectation of success in combining their techniques. (EX1002, ¶161.) For instance, a POSA would have recognized that the methods and techniques taught in *Lazar* for making heterodimeric antibodies could be applied to the antibody configurations taught in *Arathoon*, or conversely the methods taught in *Arathoon* for making heterodimeric antibodies could be combined with the antibody configurations taught in *Lazar*. (*Id.*; *see* EX1004, ¶¶124-25; EX1006, 6, 44-45.) Moreover, *Lazar* and *Arathoon* both teach that their techniques for increasing heterodimer purity can be applied to a variety of different antibody structures. (EX1004, ¶¶38, 90, 99, 137, Fig. 8; EX1006, 10:33-36.)

2. CH3 Charge Modifications (Claims 1, 22, 26, 30)

As discussed above in Ground 1, *Lazar* anticipates claims 1, 22, 26, and 30. (Sections X.A.1, X.A.4, X.A.6, X.A.8.) *Lazar*'s teachings discussed above also render these claims unpatentable as obvious over *Lazar* in view of *Arathoon*, given that *Arathoon*'s disclosures are compatible with *Lazar* and further promote heterodimer formation. (EX1002, ¶¶162-73.) A POSA would have recognized that the methods and techniques taught in *Lazar* for making heterodimeric antibodies could be applied to the IgG antibody configurations taught in *Arathoon* (and vice-versa). (EX1002, ¶¶165-73.)

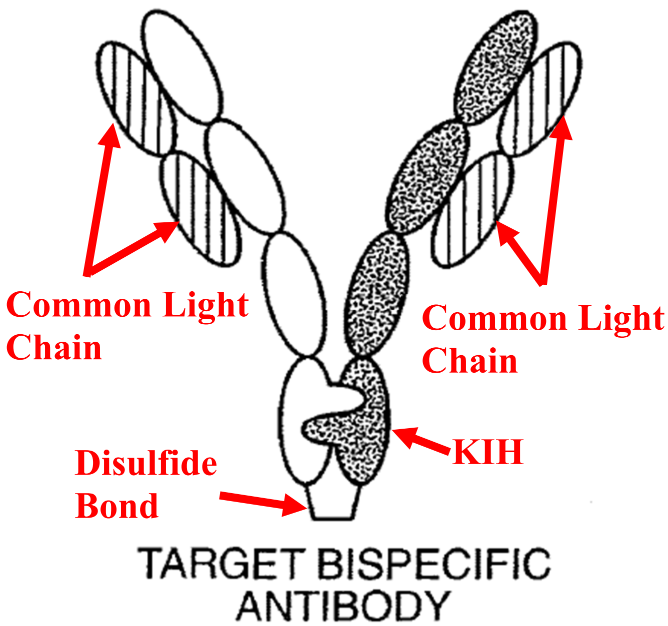
The obviousness of the remaining challenged dependent claims is discussed below.

3. Common Light Chain (Claims 2, 27, 31)

Claims 2, 27, and 31 are directed to heterodimeric antibodies having a "common light chain." Well before April 2012, it was known that incorporating a common light chain during the production of heterodimeric antibodies promoted heterodimerization by reducing the number of potential heavy/light-chain mismatches. (EX1002, ¶174.) For instance, *Arathoon* taught as early as 1998 "that the preparation of a desired heteromultimeric multispecific antibody is enhanced when a common light chain is provided to pair with each of the variable heavy chains of the multispecific antibody. Use of a common variable light chain reduces the number of monomers that must correctly pair." (EX1006, 6.)

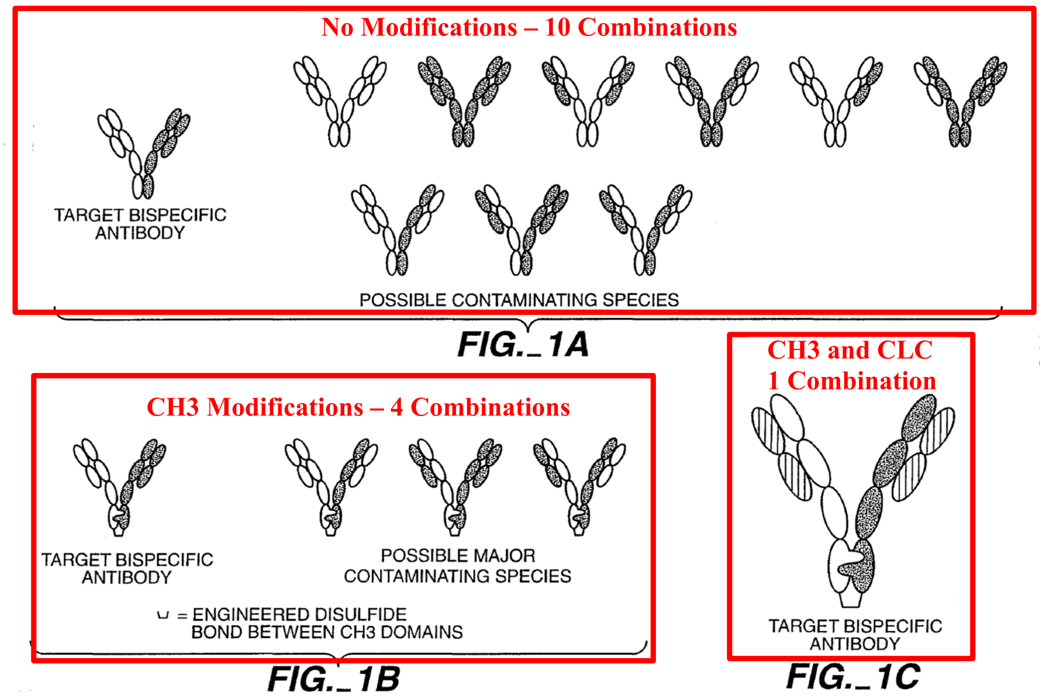
i) Claim 2: "The method of claim 1, further comprising providing said host cell with a nucleic acid molecule encoding a common light chain."

Arathoon discloses incorporating a "common light chain" as a technique for increasing the purity of heterodimeric antibody production. (EX1006, Abstract, 6; EX1002, ¶¶175-77.) *Arathoon* explains that this "common light chain is provided to pair with each of the variable heavy chains" such that it "reduces the number of monomers that must correctly pair." (*Id.* (citing "Fig. 1C").) Figure 1C illustrates the common light chain in *Arathoon*, and it also shows *Arathoon*'s understanding of this technique as complementary with other CH3 domain-based techniques for promoting heterodimerization, such as KIH and non-naturally occurring disulfide bonds:



(EX1006, Fig. 1C (annotations added), 40 (describing Fig. 1C).)

A POSA would have been motivated to combine the teachings of *Lazar* and *Arathoon* because both references teach constructing heterodimeric antibodies by making amino acid modifications to the CH3 domains to promote heterodimer formation. (*See* Section X.B.1.) A POSA would have further looked to combine the complementary techniques of using *Lazar*'s CH3 domain modifications with the common light chain taught in *Arathoon* because a POSA would have been motivated to increase heterodimer purity in the same way as *Arathoon*—to "circumvent[] the problem of light chain mispairing." (EX1006, 40; EX1002, ¶¶178-81.) *Arathoon*'s Figure 1 teaches the complementary nature of these techniques for reducing the total number of possible heavy-light chain combinations, showing a reduction from Fig. 1A to 1B from ten to four combinations by CH3 modifications, and then from Fig. 1B to 1C down to one combination by adding a common light chain:



(EX1006, Fig. 1 (annotations added).)

Arathoon's teachings would have also given a POSA a reasonable expectation of success in using *Arathoon*'s light chain teachings with the CH3 modifications taught in *Lazar*. (EX1002, ¶¶182-83.) *Arathoon*, itself, successfully combines a common light chain approach with amino acid substitutions at the CH3 domain—just as required in the Fc variants disclosed by *Lazar*. (EX1002, ¶182.) A POSA would have further understood that using a common light chain to reduce potential mismatches was a well-known solution that could have been applied with a reasonable expectation of success. (EX1002, ¶183; *see* EX1013, 184; EX1012, 19645; EX1017, Abstract; EX1005, 19, Figure 18.)

Accordingly, claim 2—reciting a method for producing a heterodimeric antibody with the recited CH3 domain amino acid substitutions and a common light chain—is unpatentable as obvious over *Lazar* in view of *Arathoon.* (EX1002, ¶¶175-83.)

ii) Claim 27: "A recombinant host cell according to claim 26, wherein said host cell further comprises a nucleic acid sequence encoding a common light chain."

Lazar teaches a recombinant host cell that contains the antibody nucleic acid sequences according to claim 26. (Section X.A.6.) Further, the combination of *Lazar* and *Arathoon* teaches incorporating a common light chain in the production of a heterodimeric antibody, like the one recited in claim 26, for the reasons discussed for claim 2. (Section X.B.3.i; EX1002, ¶¶184-86.)

iii) Claim 31: "A method according to claim 30, further comprising the step of introducing into said host cell a nucleic acid sequence encoding a common light chain."

Lazar teaches the method of making a heterodimeric antibody according to claim 30. (Section X.A.8.) Further, the combination of *Lazar* and *Arathoon* teaches incorporating a common light chain in the production of a heterodimeric antibody, like the method recited in claim 30, for the reasons discussed for claim 2. (Section X.B.3.i; EX1002, ¶¶187-89.)

4. Less Than 5% Contaminating Homodimers (Claim 7)

Lazar in view of *Arathoon* renders obvious the claimed heterodimer antibody production with contaminating homodimers being less than 5%. (EX1002, ¶¶190-94.)

Lazar teaches the desirability for high heterodimer purity. (EX1004, ¶¶42, 52, 119-25; EX1002, ¶192; *see also* EX1012, 19637 (explaining that authors explored adding electrostatic steering methods to further reduce homodimer populations above KIH techniques).) *Arathoon* expresses a similar desire, explaining that its invention "allows for the enhanced formation of the desired heteromultimer relative to undesired heteromultimers and homomultimers." (EX1006, Abstract; EX1002, ¶192.) Both references teach making CH3 domain modifications to improve heterodimer purity. (EX1004, ¶¶119-125; EX1006, 5-7, 24-28 ("Generating a Protuberance and/or Cavity"), 44 ("Disulfides combined with protuberance-into-cavity").) And both references disclose high levels of heterodimer purity, with *Lazar* disclosing a "heterodimer population . . . most preferably greater than 95%" (EX1004, ¶122) and *Arathoon* disclosing "[y]ields of approximately 95% heterodimer were obtained" in its combination embodiment, including reported yields of "95 ± 2" and "95.5 ± 0.5" (EX1006, 44-45 (Example

2.E and Table 4)). Given these disclosures of motivation to optimize heterodimer purity, including using multiple types of modifications, and disclosures of purities in excess of 95%, including techniques to achieve such purities, a POSA would have reasonably expected to be able to achieve "contaminating homodimers [of] less than 5%," as claimed. (EX1002, ¶¶193-94.)

5. Binding Targets (Claims 8-20, 23)

Claims 8-20 and 23 are directed to bispecific antibodies. At the relevant time, the antibody therapeutic industry was interested in producing bispecific antibodies due to their ability to bind distinct targets, which allowed for novel and more efficient therapeutic applications. (Sections VI.A.2-3; EX1002, ¶¶31-35.) Both *Lazar* and *Arathoon* are directed to such bispecific antibodies. (EX1004, Abstract, ¶¶3, 99; EX1006, 1.)

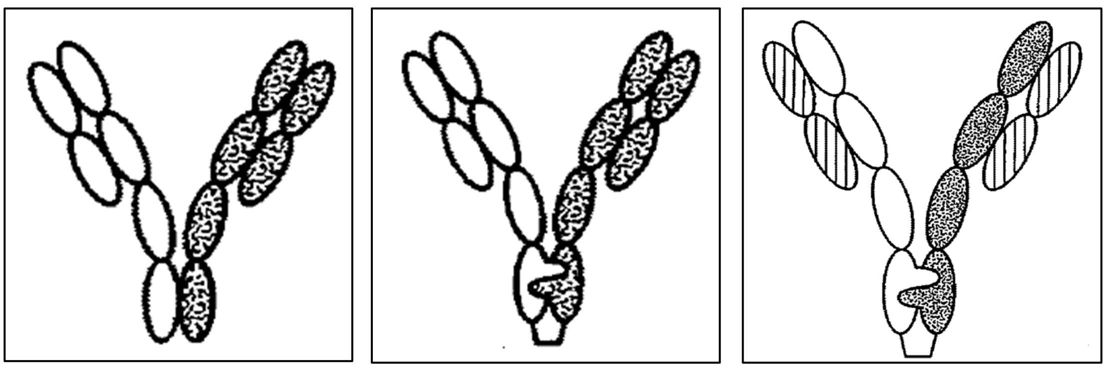
Dependent claims 8-20 and 23 recite various well-known types of bispecific targeting, such as targeting the same or different target molecules/antigens (claims 9, 12, and 22), different antigens located on the same or different cells (claims 13-14), and certain categories of targets or specific targets (claims 10-11 and 15-20). (EX1001, 73:1-38.) As discussed below in the individual sections addressing claims 8-20 and 23, *Lazar* expressly teaches each of these claimed binding targets. (Sections X.B.5.i-xiv.)

Lazar also teaches bispecific antibody characteristics and some of the features that make them attractive as therapeutic agents. (EX1004, ¶¶3-7, 38-56, 242.) *Lazar* describes multiple improvements, two of which are (1) novel variations to Fc regions to promote purity during heterodimeric antibody production and (2) a "novel antibody format referred to as mAb-Fv or mAb-Fab." (EX1004, Figs. 5-8, ¶¶46, 52.) *Lazar* teaches its novel, Fc-region mutations are broadly applicable to "antibody analogs," which are not limited to the mAb-Fv and mAb-Fab constructs, and instead include "bispecific antibodies." (EX1004, ¶¶98-113; *see also id.*, 38, 46, 52, 85 (broadly defining "antibody" and "antibody analogs" in the context of the "present invention"), 90, 97; 114-25 (discussing "Fc Modifications").)

Because *Lazar* teaches all of the claimed targets and target pairs, and that its Fc modifications apply to a bispecific antibody structure, *Lazar* alone anticipates and renders obvious claims 8-20 and 23. *See Realtime Data, LLC v. Iancu*, 912 F.3d 1368, 1373 (Fed. Cir. 2019) ("[A] disclosure that anticipates under § 102 also renders the claim invalid under § 103, for anticipation is the epitome of obviousness." (cleaned up)).

Moreover, a POSA would have found claims 8-20 and 23 obvious based on the combined teachings of *Lazar* and *Arathoon*. For example, a POSA would have found it obvious to apply the CH3 modifications taught in *Lazar* (including

Lazar's neutral-to-positive / neutral-to-negative substitutions) to the heterodimeric, antibody configurations taught by *Arathoon*. *Arathoon* expressly discloses such a well-known bispecific structure, and also describes particular CH3 domain modifications made for the same purpose described in *Lazar*—promoting heterodimer purity.



(EX1006, Fig. 1 (showing three varieties of bispecific antibody structures wherein the two arms of the "Y" recognize different targets).)

Lazar's and *Arathoon*'s disclosure of the individual limitations in claims 8-20 and 23 is described below.

i) Claim 8: "The method of claim 1, wherein each variable region of the 1st and 2nd antibody heavy chains recognizes a different target epitope."

Lazar teaches that the "present invention is directed to a variety of antibodies" (which *Lazar* also refers to as "antibody analogs") that "co-engage at least two different antigens in novel ways." (EX1004, ¶¶38, 138; EX1002, ¶¶195-203.) Binding to two different targets is the essence of a bispecific antibody.

Thus, as described above, *Lazar* teaches engineering of antibodies in: (1) their Fc regions to promote heterodimer formation—*e.g.*, using the modifications taught as preferable in Tables 1 and 2 (EX1004, ¶241); and (2) their antigen binding regions to have "two different antigen binding domains" with the ability to "preferably co-engage two target antigens," in which "the first and second antigens are distinct." (*Id*., ¶¶43, 50, 135, 137.) Furthermore, *Lazar* teaches several applications, such as cancer treatment, in which it is "beneficial to co-target two antigens," listing exemplary co-targets. (EX1004, ¶¶141, 144-50.) A POSA would have understood *Lazar*'s teaching of a heterodimeric antibody structure that can target (and co-engage) distinct antigens discloses "the variable region of the 1st and 2nd antibody heavy chains recognizes a different target epitope." (EX1002, ¶198.)

Further, *Lazar* in view of *Arathoon* would have rendered claim 8 obvious. (EX1002, ¶¶196-203.) As described above, *Arathoon* discloses an antibody structure in which the different variable regions above the hinge recognize two different epitopes on the same or different antigens. (Sections VII.A, X.B.1; EX1002, ¶199.) A POSA would have been motivated to apply *Lazar*'s CH3 domain modifications to the heterodimeric antibody structure as shown in *Arathoon* to create a bispecific antibody that has high purity of heterodimer formation during production, as discussed above. (EX1002, ¶¶200-01.) A POSA would have reasonably expected success with this combination because *Arathoon* already incorporates CH3 modifications for increasing heterodimer purity in a bispecific antibody structure and recognizes the ability and benefit of using additional CH3 modifications for promoting heterodimerization. (EX1002, ¶¶202-03.)

ii) Claim 9: "The method of claim 8, wherein the different target epitopes are located on the same target molecule."

As described above, *Lazar* teaches that the "immunoglobulins of the invention may target virtually any ***antigen*** or pair of antigens" (EX1004, ¶135), including where "antigen-1 and antigen-2" are "the same, i.e. Fv-1 and Fv-2 have specificity for the same antigen" (*id.*, ¶¶50, 137). In fact, *Lazar* teaches that Fv-1 and Fv-2 having "specificity for the same antigen" may be beneficial in some cases. (*Id.*, ¶137.) A POSA would have understood these teachings to disclose heterodimeric antibodies with different target epitopes that "are located on the same target molecule"—*i.e.*, the same antigen. (EX1002, ¶¶204-06.)

In addition to the teachings regarding bispecific antibodies discussed above with respect to claim 8 (Section X.B.5.i), a POSA would have been further motivated—for such bispecific antibodies—to target different epitopes on the same target molecule as taught in *Lazar* with a reasonable expectation of success given the accepted broad applicability of bispecific antibodies and the prior art's successful demonstration of synthesizing bispecific antibodies that bind to distinct epitopes. (EX1002, ¶207.)

iii) Claim 10: "The method of claim 9, wherein the target molecule is a soluble molecule."

Lazar teaches target antigens that are soluble target molecules, including, as one example, cytokines. (EX1004, ¶138; EX1002, ¶¶208-10.) Many other soluble molecules are listed as exemplary targets in *Lazar*, including: VEGF, HGF, P1GF, IGF1, IGF2, and others. (*Id*.; EX1002, ¶210.)

In addition to the teachings regarding bispecific antibodies discussed above with respect to claim 8 (Section X.B.5.i), a POSA would have been further motivated—for such bispecific antibodies—to target soluble molecules as taught in *Lazar* with a reasonable expectation of success given the accepted broad applicability of bispecific antibodies and the prior art's successful demonstration of synthesizing bispecific antibodies that bind to distinct epitopes. (EX1002, ¶211.)

iv) Claim 11: "The method of claim 9, wherein the target molecule is a membrane-bound molecule."

Lazar teaches target antigens that are membrane-bound molecules, including, as one example, transmembrane receptors. (EX1004, ¶138; EX1002, ¶¶212-14.) Many other membrane-bound molecules are listed as exemplary targets in *Lazar*, including cluster of differentiation (CD) proteins (*e.g.*, CD3, CD4, CD5, CD6, CD7, CD8, etc.), Her2, Her3, Her4, and others. (EX1004, ¶138; EX1002,

¶214.) *Lazar* further teaches bispecific mAb-Fab and mAb-Fv antibodies which target membrane-bound molecules, including CD3, CD19, Her2, EGFR, FcγRIIb, FcγRIIIa, and HM1.24. (EX1004, ¶¶244, 256, 262, Tables 3-5.)

In addition to the teachings regarding bispecific antibodies discussed above for claim 8 (Section X.B.5.i), a POSA would have been further motivated—for such bispecific antibodies—to target membrane-bound molecules as taught in *Lazar* with a reasonable expectation of success given the accepted broad applicability of bispecific antibodies and the prior art's successful demonstration of synthesizing bispecific antibodies that bind to distinct epitopes. (EX1002, ¶215.)

v) Claim 12: "The method of claim 8, wherein the different target epitopes are located on different target molecules."

As described above, *Lazar* teaches that the "immunoglobulins of the invention may target virtually any antigen or ***pair of antigens***" (EX1004, ¶135), including where "the first and second antigens are distinct" and "Fv-1 and Fv-2 bind different antigens" (*id.*, ¶¶50, 137). (EX1002, ¶¶216-19.) A POSA would have understood binding distinct antigens—which each are their own molecule—discloses different target epitopes "located on different target molecules," as claimed. (EX1002, ¶¶218.) As an example, *Lazar* teaches co-targeting "Her2 and CD3" and makes bispecific antibodies that co-target the two. (EX1004, ¶¶141, 262, Table 5.) A POSA would have understood that Her2 (a common cancer biomarker) and CD3 (a T cell co-receptor) would be located on different molecules. (EX1002, ¶219.)

In addition to the teachings regarding bispecific antibodies discussed above for claim 8 (Section X.B.5.i), a POSA would have been further motivated—for such bispecific antibodies—to target different epitopes on different target molecules as taught in *Lazar* with a reasonable expectation of success given the accepted broad applicability of bispecific antibodies and the prior art's successful demonstration of synthesizing bispecific antibodies that bind to distinct epitopes. (EX1002, ¶¶220.)

vi) Claim 13: "The method of claim 12, wherein the different target molecules are expressed on the same cells."

Lazar teaches "co-targets" that a POSA would have understood are expressed on the same cell, such as "HER-2 and ERB3." (EX1004, ¶141; EX1002, ¶¶221-23.) For example, *Lazar* teaches target antigens from chemokine receptors that are commonly co-expressed on immune cells like T-cells, macrophages, and dendritic cells, including CCR1-CCR6. (EX1004, ¶138; *see also* EX1011, Appendix II.) Lazar also identifies common T-cell surface markers, such as CD28 and CD3, which are co-expressed with T-cell specific markers, including CD4, CD8 and CD40L. (EX1004, ¶138; *see also* EX1011, Appendix II; EX1002, ¶223.)

In addition to the teachings regarding bispecific antibodies discussed above for claim 8 (Section X.B.5.i), a POSA would have been further motivated—for such bispecific antibodies—to target different target molecules expressed on the same cells as taught in *Lazar* with a reasonable expectation of success given the accepted broad applicability of bispecific antibodies and the prior art's successful demonstration of synthesizing bispecific antibodies that bind to distinct epitopes. (EX1002, ¶224.)

vii) Claim 14: "The method of claim 12, wherein the different target molecules are expressed on different cells."

Lazar explains that "many antigens that are attractive as co-targets" utilize mechanisms that rely on cell-to-cell contact, such as "effector cell to target cell engagement." (EX1004, ¶¶6, 136; EX1002, ¶¶225-27.) A POSA would have understood that *Lazar*'s teaching of heterodimeric antibodies that co-target different antigens in a way that causes "cell to . . . cell engagement" discloses different target molecules that are "expressed on different cells," as claimed. (EX1002, ¶227.) As an example, *Lazar* teaches co-targeting "Her2 and CD3" and makes bispecific antibodies that co-target the two. (EX1004, ¶¶141, 262, Table 5.) A POSA would have understood that Her2 (a common cancer biomarker) and CD3 (a T cell co-receptor) would be expressed on different cells. (EX1002, ¶227.)

In addition to the teachings regarding bispecific antibodies discussed above for claim 8 (Section X.B.5.i), a POSA would have been further motivated—for such bispecific antibodies—to target different target molecules expressed on different cells as taught in *Lazar* with a reasonable expectation of success given the accepted broad applicability of bispecific antibodies and the prior art's successful demonstration of synthesizing bispecific antibodies that bind to distinct epitopes. (EX1002, ¶228.)

viii) Claim 15: "The method of claim 12, wherein the different target molecules are soluble molecules."

Lazar teaches target antigens that are soluble molecules, including, as one example, cytokines. (EX1004, ¶138; EX1002, ¶¶229-31.) Additionally, *Lazar* teaches a number of specific combinations of two different soluble target molecules, including "HGF and VEGF," "VEGF and PLGF[,]" and "IGF1 and IGF2." (EX1004, ¶141.) *Lazar* also teaches binding one or more targets involved in sepsis, which includes a number of soluble molecules (*e.g.,* TNF, IL-1, IL-6, and IL-8). (*Id.*, ¶150.)

In addition to the teachings regarding bispecific antibodies discussed above for claim 8 (Section X.B.5.i), a POSA would be further motivated—for such bispecific antibodies—to target soluble molecules as taught in *Lazar* with a reasonable expectation of success given the accepted broad applicability of bispecific antibodies and the prior art's successful demonstration of synthesizing bispecific antibodies that bind to distinct epitopes. (EX1002, ¶232.)

ix) Claim 16: "The method of claim 12, wherein one target molecule is a soluble molecule whereas the second target molecule is a membrane bound molecule."

Lazar identifies pairs of target molecules, which a person of ordinary skill in the art would have understood as combinations of soluble and membrane-bound targets, for example "HGF and c-MET[,]" "IGF1R and VEGF[,]" and "Her2 and VEGF." (EX1004, ¶141; EX1002, ¶¶233-35.) *Lazar* also teaches binding one or more targets involved in sepsis, which includes both soluble molecules (*e.g.*, "TNF, IL-1 . . . IL-6, [and] IL-8") and membrane bound molecules (*e.g.*, Toll-like receptors). (EX1004, ¶150; EX1002, ¶235.)

In addition to the teachings regarding bispecific antibodies discussed above for claim 8 (Section X.B.5.i), a POSA would have been further motivated—for such bispecific antibodies—to target soluble molecules and membrane bound molecules as taught in *Lazar* with a reasonable expectation of success given the accepted broad applicability of bispecific antibodies and the prior art's successful demonstration of synthesizing bispecific antibodies that bind to distinct epitopes. (EX1002, ¶236.)

x) Claim 17: "The method of claim 8, wherein at least one of said target epitopes is located on a tumor cell."

Lazar teaches "an immunoglobulin of the present invention that is intended as an anti-cancer therapeutic," and lists several potential cancers to be targeted. (EX1004, ¶196; *see also id*., ¶¶203, 206-207; EX1002, ¶¶237-39.) For instance, *Lazar* teaches targeting of Her2$^+$ SK-BR-3 breast carcinoma cells using bispecific antibody constructs designed to co-target Her2 and FcγRIIIa, which a POSA would understand includes one target epitope located on a tumor cell. (EX1004, ¶¶244, 254, Table 3.)

In addition to the teachings regarding bispecific antibodies discussed above for claim 8 (Section X.B.5.i), a POSA would have been further motivated—for such bispecific antibodies—to target epitopes on a tumor cell as taught in *Lazar* with a reasonable expectation of success given the accepted broad applicability of bispecific antibodies and the prior art's successful demonstration of synthesizing bispecific antibodies that bind to distinct epitopes. (EX1002, ¶240.)

xi) Claim 18: "The method of claim 8, wherein at least one of said target epitopes is located on an effector cell."

Lazar teaches target antigens that are located on effector cells, including those located on T cells (CD3, CD4, CD8, CD28); located on B cells (CD19 and CD20); or located on any of B cells, T cells or macrophages (LFA-1, CD40, CD44, CD45, Mac-1, and VLA-4) (EX1004, ¶¶138, 142, 243-244, 255-256, 261-262, Tables 3-5; EX1002, ¶¶241-43.) A POSA would have readily understood that such immune cells are types of effector cells. (EX1002, ¶243.)

In addition to the teachings regarding bispecific antibodies discussed above for claim 8 (Section X.B.5.i), a POSA would have been further motivated—for such bispecific antibodies—to target epitopes on an effector cell as taught in *Lazar* with a reasonable expectation of success given the accepted broad applicability of bispecific antibodies and the prior art's successful demonstration of synthesizing bispecific antibodies that bind to distinct epitopes. (EX1002, ¶244.)

xii) Claim 19: "The method of claim 18, wherein said effector cell is an NK cell, a T cell, a B cell, a monocyte, a macrophage, a dendritic cell or a neutrophilic granulocyte."

As described above, *Lazar* teaches that the heterodimeric antibodies of its invention are useful as anti-cancer therapeutics, including for treating cancers such as "tumors of the mature T and NK cells, including peripheral T-cell leukemias, adult T-cell leukemia/T-cell lymphomas." (EX1004, ¶¶196, 203, 206-07; Section X.B.5.xi; EX1002, ¶¶245-47.) *Lazar* also teaches specific antigens typically found on such NK cells (CD16 and CD56), T-cells (CD3, CD4, CD8, and CD28), and B-cells (CD19 and CD20). (EX1004, ¶¶138-139, 243-244, 255-256, 261-262, Tables 3-5; EX1011, Appendix II; EX1002, ¶247.)

In addition to the teachings regarding bispecific antibodies discussed above for claim 8 (Section X.B.5.i), a POSA would have been further motivated—for such bispecific antibodies—to target epitopes on effector cells, wherein the effector cell is an NK cell, a T cell, a B cell, a monocyte, a macrophage, a dendritic cell or a neutrophilic granulocyte as taught in *Lazar* with a reasonable expectation of success given the accepted broad applicability of bispecific antibodies. (EX1002, ¶248.)

xiii) Claim 20: "The method of claim 18, wherein said target epitope is located on a CD3, CD16, CD25, CD28, CD64, CD89, NKG2D or a NKp46 molecule."

As described above, *Lazar* teaches target antigens that are located on effector cells, such as: CD3, CD16, CD25, CD28, CD64, CD89 (EX1004, ¶138) and NKG2D (*id*., ¶142). (EX1002, ¶¶249-51.) *Lazar* further teaches bispecific mAb-Fab and mAb-Fv antibodies which target CD3 and CD16 (FcγRIIIa). (EX1004, ¶¶244, 262, Tables 3, 5.)

In addition to the teachings regarding bispecific antibodies discussed above for claim 8 (Section X.B.5.i), a POSA would be further motivated—for such bispecific antibodies—to target epitopes on effector cells, wherein the target epitope is on a CD3, CD16, CD25, CD28, CD64, CD89, NKG2D or a NKp46 molecule as taught in *Lazar* with a reasonable expectation of success given the accepted broad applicability of bispecific antibodies. (EX1002, ¶252.)

xiv) Claim 23: "A heterodimeric antibody according to claim 22, wherein said heterodimeric antibody binds to different epitopes on the same antigen or to different epitopes on different antigens."

Lazar teaches a heterodimeric antibody capable of binding to different epitopes on the same antigen or to different epitopes on different antigens as discussed above. (Sections X.B.5.i-ii, X.B.5.v; EX1002, ¶¶253-55.)

In addition to the teachings regarding bispecific antibodies discussed above for claim 8 (Section X.B.5.i), a POSA would have been further motivated—for such bispecific antibodies—to target different epitopes on the same antigen or to different epitopes on different antigens as taught in *Lazar* with a reasonable expectation of success given the accepted broad applicability of bispecific antibodies. (EX1002, ¶256.)

6. Human IgG/IgG1 (Claims 21, 24, 32)

As discussed above, *Lazar* discloses that its heterodimeric antibodies comprise sequences belonging to human IgG/IgG1. (Sections X.A.3, X.A.5, X.A.9.) Example 2 of *Lazar*, for instance, teaches making the "[p]referred" and "most preferred" neutral-to-positive and neutral-to-negative amino acid substitutions in a heterodimer including an IgG1 antibody (*i.e.*, a human IgG). (EX1004, ¶¶238-39, 241.) A POSA would have also recognized that *Lazar*'s exemplary methods and techniques could be applied to human IgG/IgG1 sequences to make heterodimeric antibodies in view of *Arathoon*'s teachings. (EX1006, 10;

EX1002, ¶¶257-60.) *Arathoon* likewise demonstrates applying the CH3 interface modification techniques to human IgG1 antibody sequences, thus improving heterodimer yield. (EX1006, 43 ("Disulfide bonds were modeled into the human IgG_1 Fc . . . . Mutations were introduced into the CH3 domain of a humanized anti-CD3 heavy chain or CD4-IgG by site-directed mutagenesis.").)

A POSA would have recognized that the methods and techniques taught in *Lazar* for making heterodimeric antibodies could be applied to the antibody configurations taught in *Arathoon*, or conversely the methods taught in *Arathoon* for making heterodimeric antibodies could be combined with the antibody configurations taught in *Lazar*. (EX1002, ¶261; *see also* EX1004, ¶¶124-25; EX1006, 6, 44-45.) And in addition to having a good reason for combining the teachings of *Lazar* and *Arathoon*, a POSA would have also had a reasonable expectation of success in creating the heterodimeric antibodies taught in *Lazar* and *Arathoon* based on human IgG/IgG1 sequences. (EX1002, ¶261.)

7. Pharmaceutical Composition (Claim 28)

In addition to the teachings of *Lazar* discussed above (Section X.A.7), a POSA would have understood that the heterodimeric antibodies taught in *Lazar* and *Arathoon* would be formulated into pharmaceutical compositions with a pharmaceutically acceptable carrier for use as a therapeutic treatment. (EX1002, ¶¶262-64.) Similar to *Lazar*, *Arathoon* discloses "[t]he heteromultimeric multispecific antibody may be provided in the form of a composition further comprising a pharmaceutically acceptable carrier." (EX1006, 7.) A POSA also would have had a reasonable expectation of success in creating heterodimeric antibodies taught in *Lazar* and *Arathoon* formulated into pharmaceutical compositions with a pharmaceutically acceptable carrier for use as a therapeutic treatment. (EX1002, ¶265.)

C. Ground 3: *Cabrera* Anticipates Claims 1-2, 7, 21, 22, 24, 26-28, and 30-32

1. Claim 1

i) [1.pre.i] "A method for producing a heterodimeric antibody from a single cell,"

Regardless of whether the preamble is limiting, *Cabrera* discloses "a method for producing a heterodimeric antibody from a single cell." (EX1002, ¶¶266-70.) *Cabrera* teaches "a novel method for designing Fc heterodimers that results in both stable and highly specific heterodimer formation." (EX1005, 22.) A POSA would understand the "Fc heterodimer," "Fc variant heterodimers," and "Fc variant" teachings in *Cabrera* to refer to a heterodimeric antibody. (*E.g.*, EX1005, 1, 29, 92 (Title: "Stable Heterodimeric Antibody Design with Mutations in the Fc Domain"); EX1002, ¶269.)

Cabrera further teaches producing such heterodimeric antibodies from a single cell. (EX1002, ¶270.) Specifically, *Cabrera* teaches "conventional techniques" for recombinant expression of antibodies by construction of expression vectors containing polynucleotide sequences that "encode[] both the heavy and light chains" such that they both "may be co-expressed in the host cell for expression of the entire immunoglobulin molecule." (EX1005, 85-86, 108-11 (Example 1).)

ii) [1.pre.ii] "wherein said antibody comprises two heavy chains with CH3 domains that are capable of forming an interface, said method comprising:"

Cabrera discloses that the "present invention provides modified CH3 domains comprising specific amino acid modifications to promote heterodimer formation." (EX1005, 16-17; *see also id.*, 18; EX1002, ¶¶271-72.) *Cabrera* further teaches heterodimeric antibodies having two heavy chains where the CH3 domains form an interface. (*See* EX1005, 17, 18 (explaining that two polypeptide chains meet at an "interface" between the CH3 heavy chain domains), 51; EX1002, ¶272.) Accordingly, regardless of whether the preamble is limiting, *Cabrera* teaches heterodimeric antibodies comprised of two heavy chains with CH3 domains capable of forming an interface.

iii) [1.a] "providing a host cell comprising"

As explained above, *Cabrera* discloses the use of a "host cell" for expressing the transfected nucleic acids. (Section X.C.1.i; EX1002, ¶¶273-74.)

iv) [1.b] "(i) a <u>first nucleic acid</u> molecule encoding a 1st antibody heavy chain comprising at least one substitution of a <u>neutral</u> amino acid residue in the CH3 domain by a <u>positively</u> charged amino acid residue, and
(ii) a <u>second nucleic acid</u> molecule encoding a 2nd antibody heavy chain comprising at least one substitution of a <u>neutral</u> amino acid residue in the CH3 domain by a <u>negatively</u> 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 <u>interacts</u> 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"

As discussed above, these limitations require a neutral-to-positive and a neutral-to-negative amino acid residue substitution in two respective CH3 domains, wherein the substituted residues "interact" after being cultured and expressed in the host cell. (Section X.A.1.iv; EX1002, ¶¶275-78.) Again, despite Patent Owner's prosecution arguments declaring this to be a point of novelty, (EX1008, 244-46), *Cabrera* expressly teaches these limitations.

Cabrera, like *Lazar*, teaches various examples of pairs of CH3 domain mutations to promote the formation of heterodimers. (EX1005, 36-47 (Table 1).) Example AZ34 describes nucleic acids encoding two antibody heavy chains, in which both chains have an amino acid substitution wherein a neutral amino acid is switched to a charged amino acid. (*See* EX1005, 39; *see also* EX1002, ¶¶276-78 (List of Naturally Occurring Amino Acids).) Specifically, as shown below, AZ34 teaches modifying a neutral (yellow) asparagine (N) to a positively charged (green) arginine (R) at position 390, and a neutral serine (S) to a negatively charged (red) glutamic acid (E) at position 400.

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

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

(EX1005, 39.) These mutations were made at positions forming the interface between the two CH3 domains within the heavy chains. (EX1007, Table 1 (illustrating known contact residues at the native CH3 interface); EX1002, ¶277.)

Cabrera also teaches the claimed "culturing said host cell and allowing for expression of said two nucleic acid molecules" to produce the two heavy chains, a well-known procedure in the art for obtaining heterodimeric antibodies. (EX1005, 86 ("transfected cells are then cultured by conventional techniques"), 92 (describing antibody "produc[tion] by recombinant expression"); EX1002, ¶278.)

v) [1.c] "c. harvesting said heterodimeric antibody from the culture."

Cabrera teaches the heterodimeric antibodies produced are "recovered from the culture medium as a secreted polypeptide" or "from host cell lysate." (EX1005, 92.) Further, *Cabrera* teaches the recovery of heterodimers, including AZ34, following Protein A purification. (EX1005, 12, Figure 26B.) A POSA would have understood that, to perform a purification of heterodimers as taught in *Cabrera*, one must first "harvest" them. (EX1002, ¶¶279-80.)

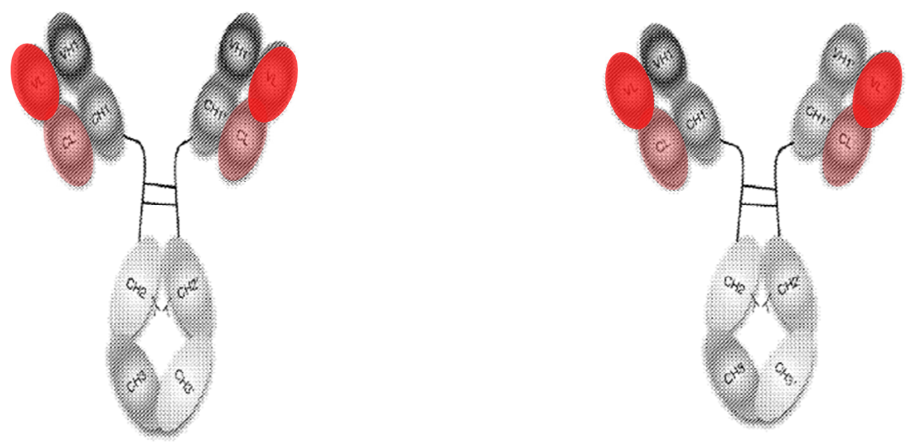
2. Claim 2: "The method of claim 1, further comprising providing said host cell with a nucleic acid molecule encoding a common light chain."

Cabrera discloses heterodimeric antibodies that utilize a "Common Light Chain" in combination with two heavy chains. (EX1005, 10 (describing Fig. 18); EX1002, ¶¶281-87.) Figure 18 of *Cabrera* (reproduced below), for instance, shows "multifunctional molecules based on the asymmetric Fc scaffold,"[14] including "Asymmetric Fc-Monospecific IgG arms and Asymmetric Fc-Bispecific IgG Arms ('Common Light Chain')."

---

[14] A POSA would understand that *Cabrera*'s "asymmetric Fc scaffold" refers to the modified CH3 domains that "promote heterodimer formation," and "improve[] stability and purity," which include AZ34. (EX1005, 24, 35, 39; EX1002, ¶¶286-87.)

Fig. 18

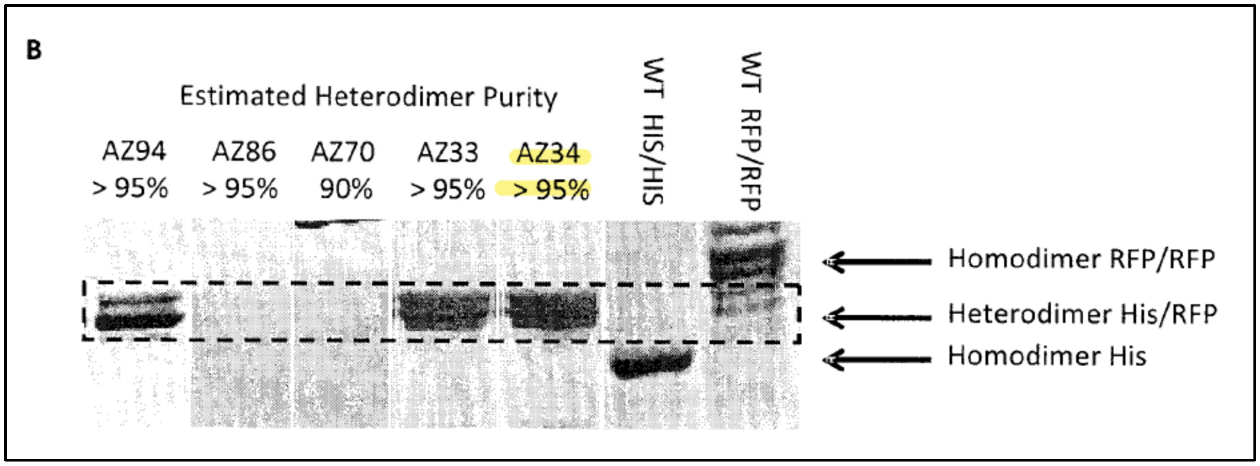


(EX1005, Fig. 18 (annotations added).)

3. Claim 7: "The method according to claim 1, wherein the presence of contaminating homodimers is less than 5%, preferably less than 2%, more preferably less than 1%, and most preferably contaminating homodimers are essentially absent."

Cabrera explains that its CH3 domain amino acid mutations are designed to "promote heterodimer formation" and "improve[] stability and purity." (EX1005, 24, 35; EX1002, ¶¶288-90.) *Cabrera* explains that the mutations disclosed therein result in Fc variant heterodimers that can have "purity" ranges between 90% to 100%. (EX1005, 24-25.) This teaching includes purities "greater than about 95%." (*Id.*)

Synthesis of *Cabrera*'s exemplary AZ34 heterodimer, which includes a neutral-to-positive and neutral-to-negative amino acid residue substitution at a known CH3 interface (discussed above with respect to claim 1), results in a heterodimer yield that is ">95%" pure:



(*Id*., Fig. 26B (annotation added).)

Because the heterodimer purity percentage in *Cabrera* is greater than 95%, the presence of contaminating homodimers would have been necessarily less than 5%, as recited in claim 7. (EX1002, ¶¶288-90.)

4. Claim 21: "The method according claim 1, wherein said heterodimeric antibody is human IgG."

Cabrera discloses that the Fc regions of the two heavy chains that form *Cabrera*'s heterodimeric antibody are "preferably . . . derived from an IgG antibody and most preferably a human IgG_1 antibody." (EX1005, 18; EX1002, ¶¶291-92.) *Cabrera* used Fc domains from human IgG1 in its heterodimeric antibodies, as described in Example 1, for instance. (EX1005, 108-11.) *Cabrera* further teaches that "this new method of designing Fc variant heterodimers with improved stability and purity can be applied to other classes and isotypes of Fc regions," expressly listing "a human IgG Fc region" and "IgG1." (EX1005, 35.)

5. Claim 22: "A heterodimeric antibody obtained by the method of claim 1."

Cabrera teaches that the method of claim 1 results in the production of a heterodimeric antibody that can then be isolated or purified. (Section X.C.1.v; EX1002, ¶293.)

6. Claim 24: "A heterodimeric antibody according to claim 22, wherein said antibody is human IgG."

Cabrera teaches a heterodimeric antibody obtained by the method of claim 1 that is based upon a human IgG sequence. (Sections X.C.1, X.C.4, X.C.5, X.C.6; EX1002, ¶294.)

7. Claim 26

i) [26.pre]: "A recombinant host cell comprising"

[26.a]: "nucleic acid sequences encoding at least a 1st and 2nd antibody heavy chain,"

Regardless of whether the preamble is limiting, *Cabrera* teaches recombinant host cells containing nucleic acid sequences encoding at least two different antibody heavy chains. (Section X.C.1; EX1002, ¶295.) These host cells are "recombinant" because they include the exogenous recombinant nucleic acids. (EX1002, ¶295.)

ii) [26.b]: "wherein the CH3 domain of said 1st antibody heavy chain comprises at least one substitution of a neutral amino acid residue by a positively charged amino acid residue," / [26.b]: "and wherein the CH3 domain of said 2nd antibody heavy chain comprises at least one substitution of a neutral amino acid residue by a negatively charged amino acid residue."

As described above, *Cabrera* teaches example AZ34 with a neutral-to-positive substitution (N390R) and a neutral-to-negative substitution (S400E) in the CH3 domain. (Section X.C.1; EX1002, ¶296.)

8. Claim 27: "A recombinant host cell according to claim 26, wherein said host cell further comprises a nucleic acid sequence encoding a common light chain."

Cabrera teaches a recombinant host cell (Section X.C.7) that contains a nucleic acid sequence encoding a common light chain (Section X.C.2). (EX1002, ¶297.)

9. Claim 28: "A pharmaceutical composition comprising a heterodimeric antibody according to claim 22 and a pharmaceutically acceptable carrier."

Cabrera teaches the "heteromultimer of the invention" is "provided a composition comprising . . . a pharmaceutically acceptable carrier." (EX1005, 8; EX1002, ¶298.)

10. Claim 30:

i) [30.pre]: "A method for making a host cell for production of a heterodimeric antibody,"

Regardless of whether the preamble is limiting, *Cabrera* discloses a method for making host cells for producing heterodimeric antibodies. (EX1005, 86 ("The expression vector is transferred to a host cell by conventional techniques and the transfected cells are then cultured by conventional techniques to produce an Fc variant of the invention."); Section X.C.1; EX1002, ¶299.)

ii) [30.a]: "the method comprising the step of introducing into said host cell nucleic acid molecules encoding at least a 1st and 2nd antibody heavy chain, wherein the CH3 domain of said 1st antibody heavy chain comprises at least one substitution of a neutral amino acid residue by a positively charged amino acid residue and wherein the CH3 domain of said 2nd antibody heavy chain comprises at least one substitution of a neutral amino acid residue by a negatively charged amino acid residue,"

As described above, *Cabrera* teaches example AZ34 with a neutral-to-positive substitution (N390R) and a neutral-to-negative substitution (S400E) in the CH3 domain. (Section X.C.1; EX1002, ¶¶300-01.)

iii) [30.b]: "wherein said nucleic acid sequences are introduced consecutively or concomitantly."

Cabrera teaches that expression vectors containing the polynucleotide sequences for its heterodimeric antibodies are transferred to a host cell and the host cells are cultured to produce antibodies. (EX1005, 85-86; EX1002, ¶¶302-03.)

Additionally, *Cabrera* teaches that "[t]he host cell may be co-transfected with two expression vectors of the invention." (EX1005, 94.) A POSA would have understood "co-transfection" in *Cabrera* to teach nucleic acid sequences being introduced into the host cell "concomitantly" (or "simultaneously"), as claimed. (EX1002, ¶¶302-03.)

11. Claim 31: "A method according to claim 30, further comprising the step of introducing into said host cell a nucleic acid sequence encoding a common light chain."

Cabrera teaches a method for making a host cell for production of a heterodimeric antibody (Section X.C.10), including the step of introducing into the host cell a nucleic acid sequence encoding a common light chain (Section X.C.2). (EX1002, ¶304.)

12. Claim 32: "The method according to claim 21 wherein antibody is human IgG1."

Cabrera teaches a method for producing a heterodimeric antibody (Section X.C.1) that is based upon a human IgG1 sequence (Section X.C.4). (EX1002, ¶¶305-06.)

D. Ground 4: *Lazar* in View of *Arathoon* and *Cabrera* Renders Obvious Claims 1-2, 7-24, 26-28, and 30-32

1. Similarity and Compatibility of *Lazar*, *Arathoon*, and *Cabrera*, Reasons to Combine, and Reasonable Expectation of Success

As discussed above, *Lazar* and *Arathoon*, are both directed to techniques for improving heterodimeric antibody yield, and both teach a framework for more efficiently developing heterodimeric antibodies for numerous applications. (Section X.B.1.) The same is true of *Cabrera*. (EX1002, ¶¶307-13.) Furthermore, as with *Lazar* and *Arathoon*, *Cabrera* teaches techniques for boosting heterodimer yield through CH3 domain modifications (Section X.B.1), envisions combination modifications (EX1005, 19-22, 36-47 (Table 1)), and applies its modifications to a variety of antibody structures (EX1005, 10-11; Figs. 17-21 (showing "alternative multifunctional molecules based on the asymmetric Fc scaffold")). (EX1002, ¶310.) Given the interest in heterodimeric antibodies, including increasing their production yield, a POSA would have also looked to *Cabrera* when considering *Lazar* and *Arathoon*. (Section X.B.1; EX1002, ¶¶311-12.)

Cabrera's teachings disclosing the limitations of claims 1-2, 7, 21, 22, 24, 26-28, and 30-32, discussed above (Section X.C), would have also rendered these claims obvious over the combination of *Lazar*, *Arathoon*, and *Cabrera* given that *Cabrera*'s teachings are compatible with both *Lazar* and *Arathoon* (the combination of which is discussed above, Section X.B), and would have further promoted heterodimer formation. (EX1002, ¶¶312-13.)

The obviousness of the remaining challenged dependent claims, claims 8-20 and 23, is discussed below.

2. Binding Targets (Claims 8-20 and 23)

As discussed above in Section X.B.5, claims 8-20 and 23 are directed to bispecific antibodies and recite various well-known types of bispecific targeting. In addition to the analysis provided above in Section X.B.5 regarding the combination of *Lazar* and *Arathoon*, *Cabrera*'s additional teachings would have further rendered these claims obvious.

A POSA would have understood the CH3 modifications taught in *Cabrera* apply to bispecific antibodies. (EX1002, ¶¶314-17.) *Cabrera* explains that "one aspect of the invention" is "an isolated heteromultimer comprising a heterodimer Fc region, wherein the heterodimer Fc region comprises a variant CH3 domain comprising amino acid mutations to promote heterodimer formation[.]" (EX1005, 4.) For instance, as shown in Figure 18, *Cabrera* teaches "Bispecific IgG Arms" built "on the asymmetric Fc scaffold." (EX1005, 10, Fig. 18; *see also id.*, 17-18.) Furthermore, *Cabrera* explains that "[a]ntibodies of the invention may be monospecific, bispecific, trispecific, or have greater multispecificity," and that "[a]ntibodies with more than two valencies [such as trispecific antibodies] incorporating variant CH3 domains and resulting Fc heterodimers of the invention are contemplated." (EX1005, 76-77.) *Cabrera* also discloses the specific limitations of each of claims 8-20 and 23, as described below.

Claim 8: *Cabrera*'s bispecific antibodies "may specifically bind to different epitopes of [a] desired target molecule" and "have binding specificities for at least two different antigens." (EX1005, 76; *see also id.*, 10, Fig. 18; EX1002, ¶¶318-23.)

Claim 9: *Cabrera*'s bispecific antibodies can simultaneously bind "different epitopes of the same antigen." (EX1005, 1, 76 ("Multispecific antibodies may specifically bind to different epitopes of [a] desired target molecule"); EX1002, ¶¶324-28.)

Claim 10: *Cabrera* teaches a list of exemplary antigens that can "be targeted by and/or incorporated into a variant Fc heterodimer protein," including soluble molecules, such as TNF alpha, VEGF, and various cytokines (*e.g.*, IL-5, IL-12), among others. (EX1005, 78-79; EX1002, ¶¶329-33.)

Claim 11: *Cabrera* teaches targeting membrane-bound molecules, such as CD11a, CD20, CD3, and IL-6 receptors. (EX1005, 79; EX1002, ¶¶334-38.)

Claim 12: *Cabrera* teaches targeting different molecules. (EX1002, ¶¶339-43.) For example, *Cabrera* teaches bispecific antibodies designed to mediate interactions between a target and a variety of effector cells. (EX1005, 1, 96; EX1002, ¶341.) *Cabrera* also teaches bispecific antibodies that bind a tumor cell antigen with one arm, while the second arm binds an effector cell antigen. (EX1005, 1, 96.)

Claim 13: *Cabrera* teaches targets that a POSA would have understood to be expressed on the same cell, such as CD20 and CD22, and HER2 and EGFR. (EX1005, 79-80; EX1002, ¶¶344-48.)

Claim 14: *Cabrera* teaches targets that a POSA would have understood to be expressed on different cells, such as a tumor cell and an effector cell, as described above. (EX1005, 1, 96; EX1002, ¶¶349-53.)

Claim 15: *Cabrera* teaches soluble molecule targets for the reasons described above for claim 10. (EX1005, 78-80; EX1002, ¶¶354-58.)

Claim 16: *Cabrera* teaches both soluble molecule and membrane-bound molecule targets, as described above for claims 10 and 11. (EX1002, ¶¶359-63.)

Claim 17: *Cabrera* teaches targets that a POSA would have understood to be located on tumor cells, as described above for claim 14. *Cabrera* also teaches the "antibodies of the invention . . . specifically bind cancer antigens," including many exemplary cancer antigens, such as HER2 and EGFR—which are known tumor target molecules. (EX1005, 1, 80-81; EX1002, ¶¶364-68.)

Claim 18: *Cabrera* teaches effector cell targets, as described above for claim 14. (EX1005, 1, 79; EX1002, ¶¶369-73.)

Claim 19: *Cabrera* teaches targets on the claimed effector cells, such as CD3 and CD4 (on T cells) and CD20 (on B cells), among others. (EX1005, 78-80; EX1002, ¶¶374-78.)

Claim 20: *Cabrera* teaches the claimed targets, including CD3, CD25, and CD64. (EX1005, 78-80; EX1002, ¶¶379-83.)

Claim 23: *Cabrera* teaches a heterodimeric antibody capable of binding to different epitopes on the same antigen or to different epitopes on different antigens as discussed above for claims 9 and 12. (EX1005, 1, 76, 96; EX1002, ¶¶384-88.)

* * *

The bispecific antibodies recited in claims 8-20 and 23 are unpatentable as obvious over *Lazar* in view of *Arathoon* because (1) *Lazar* taught bispecific antibodies with the independent claims' CH3 domain modifications and all of the claimed targets, and (2) *Arathoon* taught a bispecific antibody structure and the fundamental concept that CH3 domain modifications can be successfully used in combinations. (Section X.B.5.) These bispecific claims are only further rendered obvious by the addition of *Cabrera*, which also discloses bispecific antibodies with the required CH3 domain modifications and lists the claimed targets. (EX1002, ¶¶389-90.)

XI. DISCRETIONARY DENIAL IS NOT APPROPRIATE

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

The Board should not exercise its discretion under 35 U.S.C. § 325(d) to deny this Petition. Regarding part one of the *Advanced Bionics* framework, *Cabrera* was not considered during the prosecution of the ’286 patent or any related patent (EX1001, Cover); and while *Arathoon* and the PCT publication of *Lazar* were considered by the Examiner, they were never discussed in any office action. *See TCL Corp. v. Lexington Luminance LLC*, IPR2017-01780, Paper 8 (Jan. 2, 2018) (describing *Fox Factory, Inc. v. SRAM, LLC*, IPR2016-01876, Paper 8 (Apr. 3, 2017), as "declining to exercise discretion based on § 325(d) where the prior art was merely 'cited on an IDS [and] there is no evidence that it was considered by the Examiner'"). The only substantive rejections were based on other prior art references, which according to the Examiner did not disclose the claimed amino acid substitutions. Indeed, it is clear from the Notice of Allowance that the Examiner was under the mistaken impression that "the prior art does not teach or suggest replacing a neutral amino acid (considered to be any amino acid other than R, K, H, E or D) with a positively charged amino acid in the CH3 domain." (EX1008, 274.) This confirms that the Examiner was not aware of *Lazar*'s disclosure of CH3 domain variants having neutral-to-positive and neutral-to-negative amino acid substitutions. (Section X.A.1.iv.)

Regarding part two of the *Advanced Bionics* framework, even if the Board determines part one of the framework is satisfied—which it is not—the Office did not have the benefit of the teachings, arguments, obviousness combinations, and evidence presented in this Petition. For example, during the prosecution history of the ’848 application, the Examiner did not consider any of the clear teachings in the art, such as those provided by *Lazar* and *Cabrera*, both individually disclosing heterodimeric antibodies using the claimed neutral-to-positive and neutral-to-negative mutations on the CH3 domain. The Office also erred by not considering any combination of the references relied on by Petitioner.

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

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

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

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

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

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

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

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

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

XII. CONCLUSION

Petitioner requests institution of IPR for claims 1-2, 7-24, 26-28, and 30-32 of the ’286 patent based on the grounds specified in this Petition.

Respectfully submitted,

Dated: February 11, 2025

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

CERTIFICATE OF COMPLIANCE

Pursuant to 37 C.F.R. § 42.24(d), the undersigned certifies that the foregoing Petition for *Inter Partes* Review of U.S. Patent No. 9,358,286 contains, as measured by the word-processing system used to prepare this paper, 13,948 words. This word count does not include the items excluded by 37 C.F.R. § 42.24 as not counting towards the word limit.

Respectfully submitted,

Dated: February 11, 2025

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

CERTIFICATE OF SERVICE

I hereby certify that on February 11, 2025, I caused a true and correct copy of the foregoing Petition for *Inter Partes* Review of U.S. Patent No. 9,358,286 and supporting exhibits to be served via express mail on the Patent Owner at the following correspondence address of record as listed on Patent Center:

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

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

Peter J. Armenio
Colleen Tracy James
Jessica M. Stookey
Camille H. Mangiaratti
CAHILL GORDON & REINDEL LLP
parmenio@cahill.com
ctracyjames@cahill.com
jstookey@cahill.com
cmangiaratti@cahill.com

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