

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

DECLARATION OF LEONARD G. PRESTA, Ph.D.

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List of Naturally Occurring Amino Acids¹

Amino Acid	Three-Letter Code	One-Letter Code	Charge Where Applicable
Alanine	Ala	A	
Arginine	Arg	R	Positive
Asparagine	Asn	N	
Aspartic acid	Asp	D	Negative
Cysteine	Cys	C	
Glutamic acid	Glu	E	Negative
Glutamine	Gln	Q	
Glycine	Gly	G	
Histidine	His	H	Positive
Isoleucine	Ile	I	
Leucine	Leu	L	
Lysine	Lys	K	Positive
Methionine	Met	M	
Phenylalanine	Phe	F	
Proline	Pro	P	
Serine	Ser	S	
Threonine	Thr	T	
Tryptophan	Trp	W	
Tyrosine	Tyr	Y	
Valine	Val	V	

¹ (Ex. 1007 at 8:9-10; *see also* Ex. 1001 at 13:1-17.)

I, Leonard G. Presta, Ph.D., declare as follows:

I. Introduction—U.S. Patent No. 9,358,286

1. I have been retained by Xencor, Inc. (“Petitioner”) as an independent expert consultant in this proceeding before the United States Patent and Trademark Office regarding U.S. Patent No. 9,358,286 (“the ’286 patent”) (Ex. 1001), which I understand is assigned to Merus N.V. (“Patent Owner”). I have been asked to consider whether:

(1) U.S. Publication No. US 2011/0054151 to Lazar *et al.* (“*Lazar*”) (Ex. 1004) teaches all of the limitations of claims 1, 7, 21, 22, 24, 26, 28, 30, and 32 of the ’286 patent;

(2) the combination of *Lazar* (Ex. 1004) and International Patent Application Publication No. WO 1998/050431 to Arathoon *et al.* (“*Arathoon*”) (Ex. 1006) teaches or suggests all of the limitations of claims 1-2, 7-24, 26-28, and 30-32 of the ’286 patent;

(3) International Patent Application Publication No. WO 2012/058768 to Cabrera *et al.* (“*Cabrera*”) (Ex. 1005) teaches all of the limitations of claims 1-2, 7, 21, 22, 24, 26-28, and 30-32 of the ’286 patent; and

(4) the combination of *Lazar* (Ex. 1004), *Cabrera* (Ex. 1005), and *Arathoon* (Ex. 1006) teaches or suggests all of the limitations of claims 1-2, 7-24, 26-28, and 30-32 of the ’286 patent.

2. I am being compensated at \$300 per hour, which is my normal consulting rate, for the time I spend on this matter. My compensation is in no way contingent on the nature of my findings, the presentation of my findings in testimony, or the outcome of this or any other proceeding. I have no other interest in this proceeding.

II. Qualifications

3. Below, I summarize my qualifications, as set forth in more detail in my *curriculum vitae*, which I understand is being submitted as Exhibit 1003.

4. I received a B.S. in Biology and a B.S. in Chemistry from the University of Arizona in 1976, and a Ph.D. in Biochemistry and Biophysics from Texas A&M University in 1985. The focus of my doctoral research included studying the interaction of proteins with a serine protease enzyme by computer modeling, molecular mechanics calculations, and X-ray diffraction.

5. I have spent more than 35 years in biotechnology research, primarily in the areas of antibody and protein therapeutics development. I currently work as an independent consultant in the field of biotechnology and pharmaceutical sciences.

6. Before becoming an independent consultant in 2012, I worked in the pharmaceutical industry for over 20 years, first at Genentech, Inc. (“Genentech”) and then later at Merck & Co.

7. Beginning in the 1990s, my colleagues at Genentech and I were at the forefront of developing improved methods for the production of therapeutic antibodies, including what are called bispecific antibodies (discussed in more detail in Section V).

8. The protein engineering strategies that I helped to develop at Genentech were a major advance in the field of bispecific antibody development in the late 1990s and 2000s. Relatedly, I also oversaw the engineering of antibody receptor binding domains for improving therapeutic efficacy.

9. In 2000, I became the Director of the Antibody Technology Group at Genentech. In that role, I headed Genentech's antibody therapeutic development programs. My work at Genentech led to a series of marketed therapeutic monoclonal antibodies, including Herceptin[®] (trastuzumab), Perjeta[®] (pertuzumab), Xolair[®] (omalizumab), Avastin[®] (bevacizumab), and Lucentis[®] (ranibizumab).

10. In 2001, I joined Schering-Plough Biopharma (which later became part of Merck & Co.), first as a Senior Director of Protein Engineering before later becoming a Distinguished Fellow. While there, I oversaw six groups that specialized in antibody generation (using hybridomas or phage libraries), molecular biology (specifically, plasmid and vector generation), protein expression and purification, assay development, proteomics, and protein engineering. I was also responsible for the design and engineering of therapeutic proteins, primarily

antibodies and auxiliary antibodies used for animal models, bispecific antibodies, and other new antibody formats. I left Merck & Co. in 2012 to become an independent consultant.

11. Over the course of my career, I have authored and co-authored more than 80 articles and book chapters and have been involved with the development of marketed therapeutic monoclonal antibodies and a therapeutic protein.

12. I have served as an editorial board member for the *Journal of Biological Chemistry*, *PROTEINS*, and *MABS*.

13. Additional details of my qualifications are summarized in my *curriculum vitae*, which I understand has been submitted as Exhibit 1003.

III. Materials Reviewed

14. The opinions contained in this declaration are based on the documents I reviewed, my professional judgment, as well as my education, experience, and knowledge regarding the production of monospecific and bispecific antibodies.

15. In forming my opinions expressed in this declaration, I reviewed the following documents and materials: (1) the '286 patent (Ex. 1001); (2) *Lazar* (Ex. 1004); (3) *Cabrera* (Ex. 1005); (4) *Arathoon* (Ex. 1006); and (5) any other materials I refer to in this Declaration in support of my opinions.

IV. Person of Ordinary Skill in the Art

16. Based on my review of the '286 patent, the types of problems encountered in the art, prior art solutions to those problems, the rapidity with which innovations were made, the sophistication of the technology, and the educational level of active workers in the field, I believe a person of ordinary skill in the art 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.

17. All of my opinions in this declaration are from the perspective of a person of ordinary skill in the art, as I have defined it here, at the relevant timeframe (which I have been asked to assume is April 2012). During this timeframe, I possessed at least the qualifications of a person of ordinary skill in the art, as defined above, and trained individuals who would qualify as persons of ordinary skill in the art. My opinions expressed below would not change if the level of skill were determined to be somewhat different (*e.g.*, either somewhat higher or lower).

V. Technological Overview

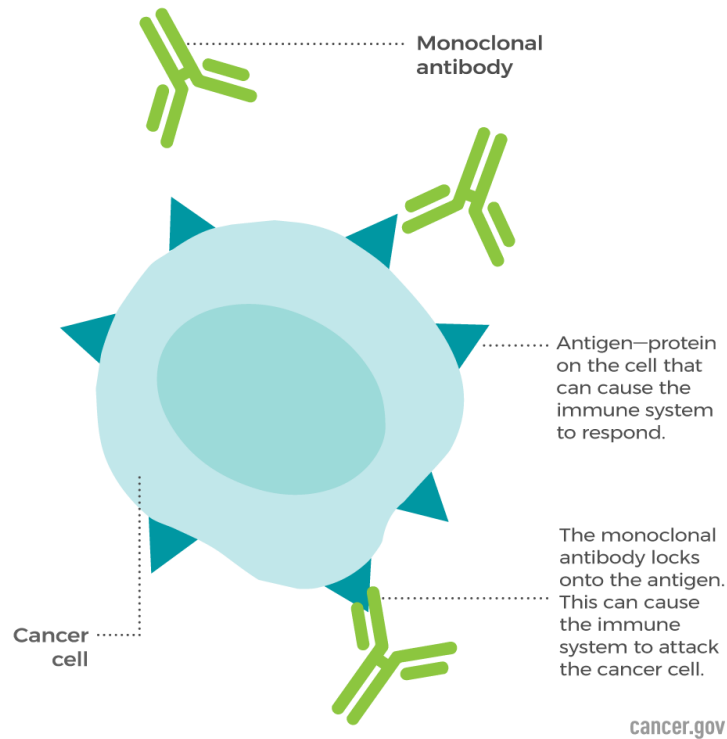
18. In this section, I present a brief overview of several technologies that were widely known before April 2012, and which relate to the issues discussed in this declaration. This section is not intended to be comprehensive, but rather is intended to provide a foundation for better understanding the '286 patent, the prior art, and certain terminology.

A. Antibodies as Therapeutics

19. In the early 20th century, Paul Ehrlich introduced the concept of the therapeutic “magic bullet,” which was the idea of selectively targeting and eliminating disease-causing agents, such as pathogens or cancer cells, while preserving healthy cells. The premise was straightforward (and enduring): maximize the benefits of a therapy while minimizing the off-target side effects.

20. This hoped-for therapy came to be realized in the 1970s through the development of monoclonal antibodies. Monoclonal antibodies are lab-made antibodies that can target specific disease-causing cells or pathways, such as cancer cells or viral cells, and ameliorate or treat the cause of disease with specificity. (*E.g.*, Ex. 1010 at 495-497.) A simplistic depiction of the function of monoclonal antibodies is shown below, from the National Cancer Institute:

Demonstrative 1: Monoclonal Antibody Function



(Ex. 1043.)

21. By 2012, monoclonal antibodies were “widely used” for the treatment of a variety of disease types, including “cancer, inflammatory and infectious diseases and other disorders.” (Ex. 1013 at 182.) In fact, by 2012, more than 20 monoclonal antibodies had been approved by the U.S. Food and Drug Administration for therapy. (Ex. 1013 at 182.)

B. Antibody Terminology and Structure

22. The monoclonal antibodies discussed above, while produced artificially, are designed to simulate (and provide the benefits of) naturally

occurring antibodies made by the body. Antibodies are proteins made by the body—often in response to an infection or upon immunization. (*E.g.*, Ex. 1011 at 111; Ex. 1042 at 1539.) These proteins have unique structures that allow them to bind specifically to a portion (often called an “epitope”) of a defined target (often called an “antigen”) in order to neutralize disease-causing pathogens or eliminate aberrant cells (like cancer cells). (*E.g.*, Ex. 1011 at 111, 120; Ex. 1042 at 1539-1540.) Human immunoglobulin G (IgG) is the most common type of antibody found in human blood.²

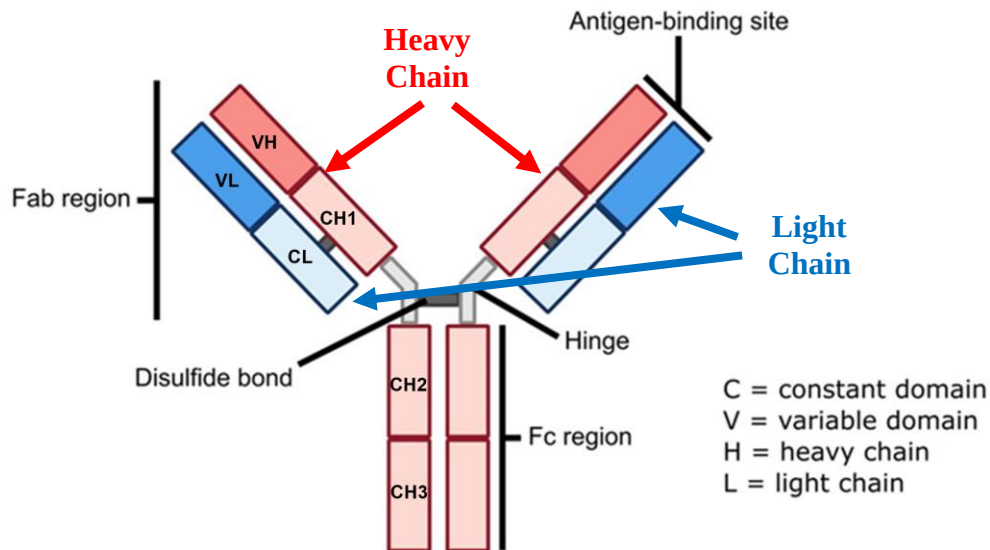
23. Like all proteins, antibodies—whether naturally occurring or lab-made—are formed from a combination of amino acids. Twenty distinct amino acids exist naturally, and the order in which those amino acids are combined dictates the identity of the protein created. I have provided a Table of Amino Acids at the beginning of this declaration, using well-known letter “codes” that are used in the field to identify each.

² Despite certain nuanced differences, the terms “antibody” and “immunoglobulin” are often used synonymously because both describe proteins with a similar structural framework. (*E.g.*, Ex. 1004 at ¶77 (“‘Antibodies’ (Abs) and ‘immunoglobulins’ (Igs) are glycoproteins (although as described herein, engineered glycoforms including aglycosylated and afucosylated forms can be made) having the same structural characteristics.”).)

24. The twenty known amino acids have distinct properties, including being positively charged, negatively charged, or neutral. Whether a given amino acid is charged—positively or negatively—or neutral turns on the properties of their side chains (also called “R groups”). The Table at the beginning of this declaration also provides the respective charge of every amino acid. As is noted in the Table, positively charged (or basic) amino acids include lysine (“Lys” or “K”), arginine (“Arg” or “R”), and histidine (“His” or “H”). Negatively charged (or acidic) amino acids include aspartic acid (“Asp” or “D”) and glutamic acid (“Glu” or “E”).

25. Once assembled from the applicable amino acid sequence, the structure of a naturally occurring antibody (like natural IgG) or a man-made monoclonal antibody may consist of two identical heavy (H) chains and two identical light (L) chains arranged in a Y-shaped configuration. (Ex. 1011 at 112-113; Ex. 1042 at 1552-1554.) This structure is depicted below, with the H chains shown in red and the L chains shown in blue.

Demonstrative 2 – Monoclonal Antibody Structure



As to the “Y” structure, the four respective chains are generated within a cell and self-assemble in the manner shown above.

26. In an antibody like the one depicted above, the respective heavy and light chains on either side of the hinge are identical (*i.e.*, the two “halves” of the “Y” mirror one another). Such an antibody is referred to as “homodimeric” or as a “homodimer” made from two (“-dimer”) of the same (“homo-”) parts. Because both sets of chains of a homodimer are identical—with two identical antigen-binding sites—they can bind to only one epitope and are thus commonly referred to as “monospecific.”

27. Additionally, Demonstrative 2 above identifies the distinct sub-parts or “regions” of the heavy and light chains. The two “arms” of the assembled “Y”

structure include antigen binding sites and are called the “Fab” (Fragment antigen-binding) regions. (Ex. 1011 at 112-114, Figure 3.3; Ex. 1007 at 1:19-22.) The Fab region consists of four immunoglobulin domains, including the light chain variable domain (VL), heavy chain variable domain (VH), light chain constant domain (CL), and the first heavy chain constant domain (CH1). (Ex. 1011 at 112-14, Figure 3.3; Ex. 1007 at 1:19-22.) It is the VL and VH domains that determine antigen specificity, and the VL and VH pair together form an “Fv” domain which binds to the specified antigen. (Ex. 1011 at 112-14, Figure 3.3; Ex. 1007 at 1:19-22.)

28. The stem of the antibody (*i.e.*, the lower portion of the Y, shown in Demonstrative 2) is referred to as the “Fc” (Fragment crystallizable) region. (Ex. 1011 at 114; Ex. 1007 at 1:21-22.) In the case of native immunoglobulin G (IgG), the Fc region contains two pairs of Constant Heavy domains: CH2 and CH3, with the CH2 domain connected to the CH1 (of the Fab) via a flexible stretch of amino acids referred to as the “hinge.” (Ex. 1011 at 114, Fig 3.1; Ex. 1007 at 1:22-25.)

29. During the antibody self-assembly process, the two heavy chains link together via disulfide bonds³ in a process commonly referred to as “dimerization”

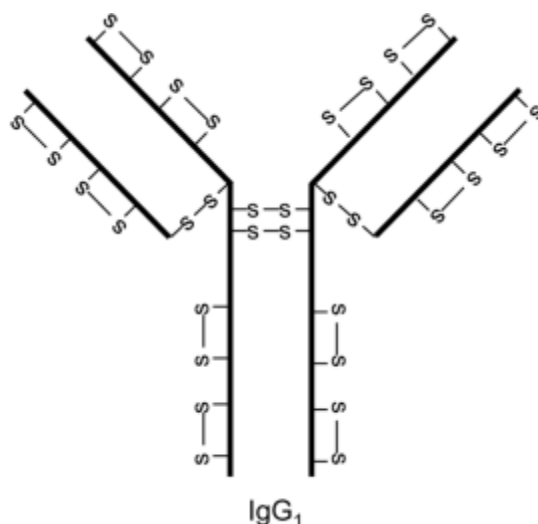
³ Disulfide bonds are covalent bonds that form between two sulfurs, present within the sulfhydryl group, of two different cysteine amino acids.

or “heavy chain dimerization.” (Ex. 1011 at 129). The Fc region—more specifically the CH3 domain of the Fc region—plays a critical role in dimerization, as interactions occurring between amino acid residues at the CH3-CH3 interface⁴ contribute to the formation and stability of the heavy chain linking. (Ex. 1015 at 617; Ex. 1007 at 1:25-4:20; Ex. 1012 at 19637-40; *see also* Ex. 1001 at 4:5-14.)

30. Moreover, each heavy chain further links to a light chain via a disulfide bond—either before or after heavy chain dimerization. (*E.g.*, Ex. 1011 at 113.) An exemplary structure depicting these disulfide bonds is shown below (with the bonds denoted by a “–” between the sulfurs (“S”) of two different cysteines):

⁴ The interface is the part of an antibody where the CH3 regions interact with each other.

Demonstrative 3 – Antibody Disulfide Bonds



(Ex. 1049 at Figure 1.)

C. The Development of Bispecific Antibodies and Their Therapeutic Advantages

31. While monospecific, homodimeric antibodies⁵ provided significant therapeutic benefits, scientists soon realized that antibodies capable of targeting multiple epitopes (whether on the same or different antigens) can enhance therapeutic efficacy. (Ex. 1013 at 182-183.) Such antibodies are commonly referred to as “bispecific” (in the case of two target epitopes) or “multispecific” (in the case of two or more target epitopes) antibodies.

⁵ As discussed above, “homodimeric antibodies” target and bind to a single epitope.

32. Bispecific antibodies are typically created by combining the variable regions from two different antibodies into a single, hybrid molecule. (Ex. 1027 at 650; Ex. 1013 at 184-185.) More detail regarding the synthesis of bispecific antibodies is discussed further below. One example of a bispecific antibody structure is shown below.

Demonstrative 4 – Bispecific Antibody Structure



(Ex. 1006 at Abstract.) Made up of two (“-dimer”) different (“hetero-”) components, bispecific antibodies are often “heterodimeric” or “heterodimers.”

33. By 2012, the field readily appreciated the advantages of such bispecific antibodies over other therapeutic options, including monospecific antibodies. For instance, bispecific antibodies can mediate more complex and targeted immune responses by linking two distinct signaling pathways or enhancing the selective targeting of disease cells. (Ex. 1013 at 183-184.) In the

treatment of cancer, for example, a bispecific antibody might be engineered to recognize both a tumor-associated antigen and a T-cell receptor, effectively redirecting the patient's immune system to target and destroy cancer cells. (Ex. 1013 at 183-188.)

34. Due to these recognized advantages, bispecific antibodies had been explored for a variety of uses by 2012. (Ex. 1013 at 183-184.) Among other applications, scientists had applied bispecific antibodies for (1) the targeting of an immune effector cell⁶ to tumor cells, where one binding site is directed against a tumor-associated antigen and the second binding site is directed against a molecule on an effector cell, and (2) dual targeting of a receptor and a ligand as a cancer therapy,⁷ wherein a cancer cell receptor is inhibited by simultaneously binding the receptor and its ligand. (Ex. 1013 at 182, 191, Tables 1-2.) A list of just some of the bispecific antibody therapies that were in development by April 2012 is shown below, excerpted from a March 2012 scientific publication:

⁶ Effector cells are cells that become activated by a stimulus, resulting in responsive action. Effector cells include B cells, T cells, natural killer (NK) cells, neutrophils, monocytes and macrophages, among others. (Ex. 1011 at 27-37, 82-103; *see also* Ex. 1004 at 6.)

⁷ Ligands are molecules that interact with (*e.g.*, are bound by) proteins. Cell surface receptors commonly bind specific ligands. (*See* Ex. 1013 at 189; Ex. 1004 at ¶¶ 152, 194.)

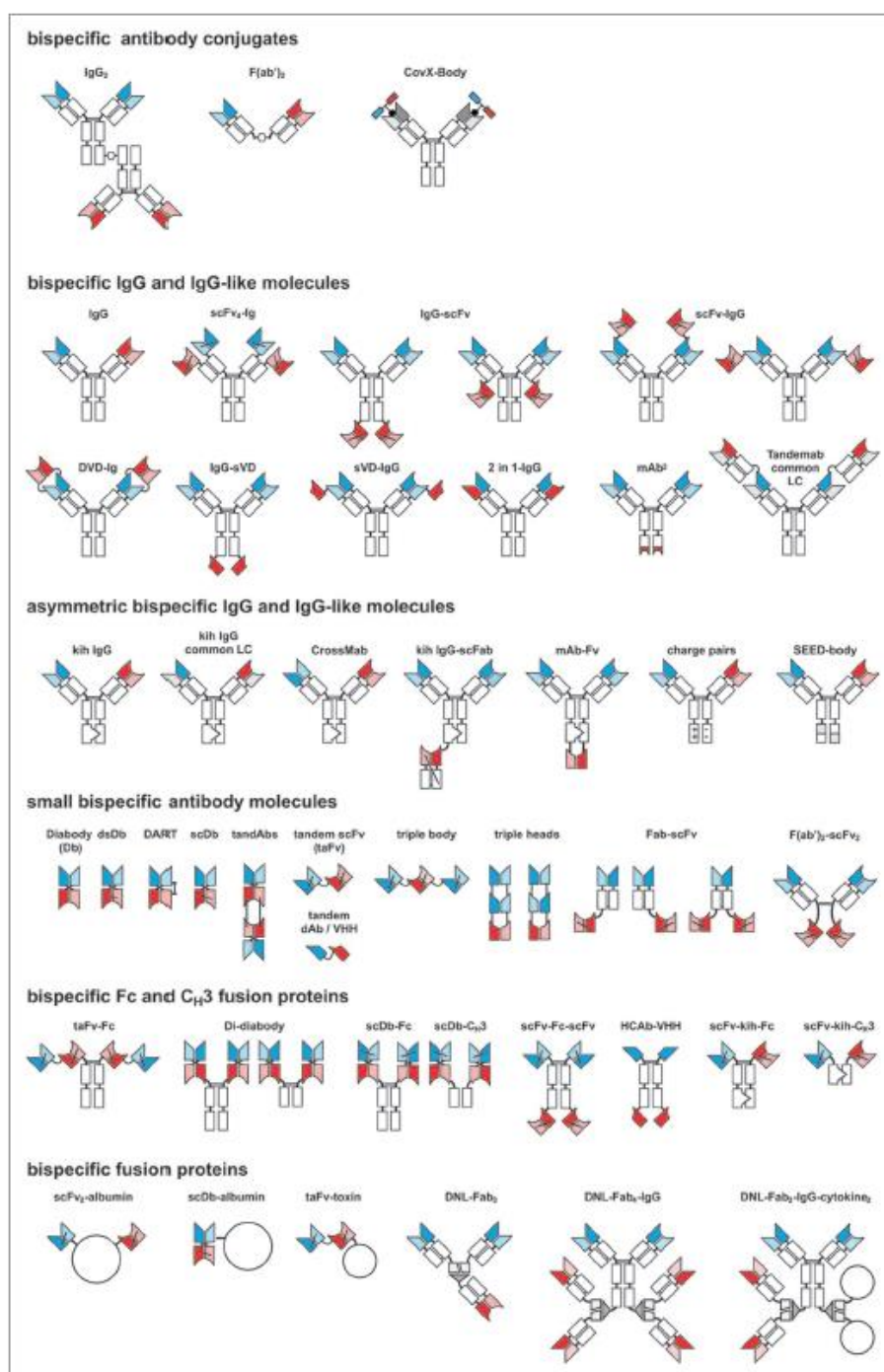
Table 1. Dual targeting approaches

Targeting	Target 1	Target 2	Format	Indication	Reference
2 receptors	TRAIL-R2	LTβR	scFv-IgG, IgG-scFv	Cancer	67
	EGFR	IGFR	Di-diabody	Cancer	51
	EGFR	IGFR	diabody	Cancer	50
	EGFR	IGFR	scFv ₂ -IgG	Cancer	49
	EGFR	IGFR	PEGylated tandem Adnectin	Cancer	52
	EGFR	IGFR	IgG-scFv	Cancer	9
	VEGFR2	VEGFR3	diabody	Cancer	61
	VEGFR2	VEGFR3	Di-diabody	Cancer	60
	VEGFR2	PDGFRα	dAb-IgG	Cancer	57
	PDGFRα	PDGFRβ	dAb-IgG	Cancer	54
	HER2	HER3	scFv-HSA-scFv	Cancer	53
	EGFR	HER2	tandem Affibody	Cancer	151
	CD20	CD22	F(ab') ₂	Cancer	65
	CD20	CD22	IgG-scFv ₂ , DNL-Fab-IgG	Cancer	62, 63
	FcεRI	CD32B	kih IgG	allergic diseases	74
	CD32B	CD79B	DART molecule	Arthritis	72
	MP65	SAP-2	tandem dAb	infectious diseases	79
1 receptor or ligand	IGFR		IgG-scFv ₂	Cancer	80
	CCR5		IgG-scFv ₂	HIV infections	24
	FcεRI		tandem DARPin	allergic diseases	81
	scorpion toxin		tandem Nanobody	envenoming	85
2 ligands	IL-17A	IL-23	taFv-Fc, scFv-Fc-scFv, IgG-scFv	inflammatory diseases	93
	IL-1α	IL-1β	DVD-Ig	inflammatory diseases	25, 92
	IL-12	IL-18	DVD-Ig	inflammatory diseases	25
	VEGF	osteopontin	DVD-Ig	Cancer	89
	VEGF	Ang-2	CrossMab	Cancer	30
	VEGF	Ang-2	CovX-Body	Cancer	20
	LukS-PV	LukF-PV	HCAb-VHH	infectious diseases	84
1 receptor and 1 ligand	PDGFRβ	VEGF	scFv-Fc-scFv	Cancer	100
	HER2	VEGF	two-in-one IgG	Cancer	26
	FcγRIII	IgE	F(ab') ₂	allergic diseases	75

(Ex. 1013 at Table 1.)

35. Further, not only had scientists explored the use of bispecific antibodies for a variety of therapeutic applications by 2012, they had also developed a significant number of bispecific antibody structures. The same March 2012 scientific article mentioned above also disclosed that, by that date, “more than 45 different [bispecific antibody] formats ha[d] been established.” (Ex. 1013,

184.) Some of the various bispecific antibody formats that had been developed are shown below:



(Ex. 1013 at Figure 2.) I note that the formats labeled as “asymmetric” in the figure above refer to heterodimeric antibodies, in which the two heavy chains are different.

**D. Bispecific Antibody Manufacturing
Basics Were Well-Understood Prior to 2012**

36. The production of bispecific antibodies begins with harnessing known methods of antibody engineering and cloning, established long before 2012.⁸ As an initial step, the DNA sequences encoding the light and heavy chains of each antibody are cloned into vectors (also referred to as plasmids). (*E.g.*, Ex. 1040 at 673-674.)

37. And once the DNA sequences are prepared, the antibodies are produced using various well-established expression systems. (Ex. 1040 at 672-675.) Mammalian cells are commonly used for therapeutic applications due to their ability to perform complex post-translational modifications, which are essential for the proper functionality of the antibodies. (Ex. 1040 at 672-676.)

⁸ Cloning refers to the process of creating genetic material or organisms through laboratory methods of genetic recombination, where DNA molecules from different sources are combined to form new genetic sequences (*i.e.*, recombinant DNA). This is typically accomplished using molecular cloning techniques, which involve inserting specific genes or gene fragments into host organisms such as bacteria, yeast, or mammalian cells. (*E.g.*, Ex. 1041 at 1393-1394, Figure 1.)

38. The DNA sequences are commonly introduced into the expression system through co-transfection, a well-known process where two or more plasmids, each encoding a different protein, are introduced into a single host cell. (*E.g.*, Ex. 1023 at 3173; Ex. 1004 at ¶¶238-239; *see also* Ex. 1001 at 43:10-14, 62:9-12.) In the case of heterodimeric antibodies, co-transfection allows the simultaneous expression of different components, such as two distinct heavy chains, within the same cell. (Ex. 1004 at ¶¶238-239; *see also* Ex. 1001 at 43:10-14, 62:9-12.) The heavy chains then self-assemble in the cell, which can be facilitated by the techniques discussed below in Section V.E. (*E.g.*, Ex. 1011 at 111-114; *see also* Ex. 1001 at 4:21-45; Ex. 1005 at 50-51; Ex. 1006 at 24:4-7; Ex. 1012 at 19640.)

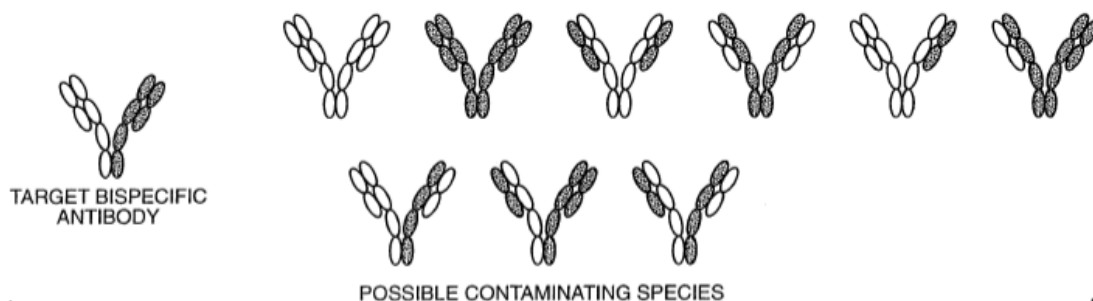
39. Once produced by the host cell, the antibodies are harvested and undergo protein purification. Harvesting refers to the collection of the expressed proteins from the host cell growth medium, which is done using long-established methods, such as centrifugation and filtration. (Ex. 1024 at 480-481; Ex. 1026 at 7, 19-20; *see also* Ex. 1001 at 17:6-9; Ex. 1005 at 92; Ex. 1012 at 19639.) After collection (*i.e.*, “harvesting”), the recovered proteins are typically purified using techniques such as ion exchange chromatography, protein A affinity chromatography, or peptide tagging. These methods, all of which were well known by 2012, ensure the isolation and enrichment of antibodies with high purity.

E. Strategies for Improved Bispecific Antibody Synthesis Were Known Before 2012

40. Not only were methods for generating bispecific antibodies known by 2012, but scientists had already spent decades developing methods that allowed for the more efficient creation of bispecific antibodies by that point in time.

41. In the early 1980s, researchers began fusing cell lines in order to create two different heavy and light chains (one pair from each of the fused cell lines) in order to make bispecific antibodies. (Ex. 1013 at 184.) But due to the random assembly of the heavy and light chains in the cell, researchers soon discovered that the chains would often mis-pair, resulting in up to ten possible heavy-light chain combinations, with only one being the desired bispecific antibody, as is illustrated in Demonstrative 5 below:

Demonstrative 5 – Coexpression Yields Ten Possible Combinations, Only One of Which is the Target Bispecific Antibody



(Ex. 1006 at Figure 1A.) This inefficiency of bispecific antibody production (only one out of 10 possible species created was the desired product) had the potential to

significantly increase the cost associated with manufacture of the contemplated antibody therapies, which is always a significant concern for drug development.

42. As a result, better methods of manufacturing bispecific antibody therapies were required. And well before 2012, scientists rose to meet this challenge, exploring and developing multiple strategies for ensuring that the correct heavy-and-light chains join to form a bispecific antibody.

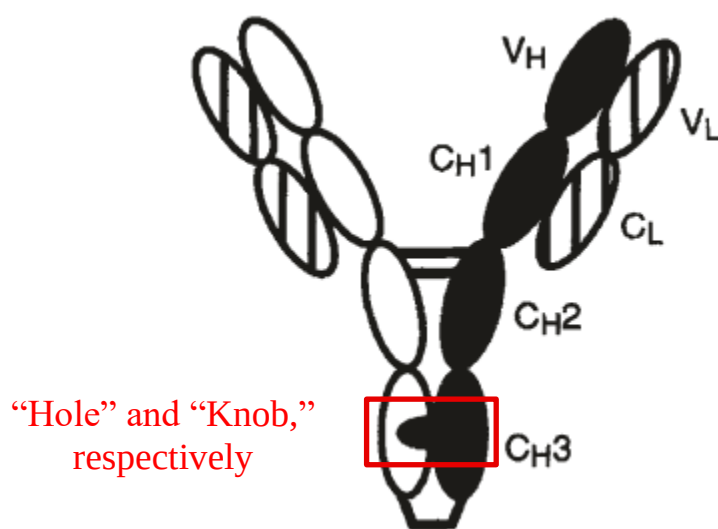
43. Moreover, while scientists pursued multiple improved synthesis methods by 2012, they typically involved a shared core tenet: manipulating interactions between amino acid residues located within the CH3 domain of the antibody heavy chain. By modifying these interactions, scientists found that they could promote the desired association of one heavy chain with a second heavy chain (yielding a heterodimeric, bispecific antibody), and discourage a heavy chain bonding with an identical heavy chain (referred to as “homodimerization” and yielding an undesired monospecific antibody).

44. Well before 2012, the field utilized various techniques for more efficient bispecific antibody production, including: (1) “knob-into-hole,” (2) common light chains, (3) inter-chain disulfide pairing, and (4) electrostatic interactions, or combinations thereof. (*E.g.*, Ex. 1013 at 184; Ex. 1017 at 677.) I describe certain such approaches below.

1. Knob-into-Hole Approach

45. One of the earliest approaches to increase heterodimer yield (*i.e.*, promoting the desired pairing of different heavy chains) was the “knob-into-hole” (“KIH”)⁹ strategy invented by my team at Genentech in the mid-1990s. (Ex. 1017 at Figure 1; *see also* Ex. 1015.) Shown below, the KIH strategy involved engineering a small “hole” into one heavy chain and a complementary protruding “knob” into the second heavy chain using amino acid substitutions:

Demonstrative 6 – “Knob-into-Hole” Approach



(Ex. 1017 at Figure 1 (annotation added).) More specifically, we created a “knob” variant by substituting the smaller amino acid threonine with the larger amino acid

⁹ The KIH approach has also been referred to by other names within the field, such as “protuberance-into-cavity.”

tyrosine at position 366 of the CH3 domain (in a CD4-Fc fusion protein), and the “hole” by replacing tyrosine with threonine at position 407 of the CH3 domain (in an anti-CD3 antibody). (Ex. 1015 at 619, Figure 1.)

46. As a result of the engineered knob and hole, the two distinct heavy chains fit together in the desired conformation, akin to a lock-and-key mechanism, during self-assembly of the chains circulating within the cell. Put differently, because of this “lock-in-key” mechanism, heterodimerization is promoted, and homodimerization (knob-to-knob or hole-to-hole) is comparatively disfavored.

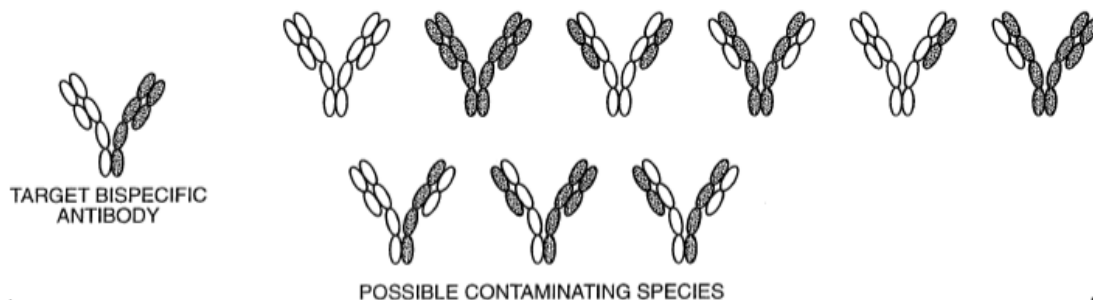
47. The KIH approach that we pioneered at Genentech provided immediate and significant benefits in bispecific antibody production. We found that the KIH-modified amino acids allowed for a 92% yield of the desired heterodimer. (Ex. 1015 at 617 (“The anti-CD3/CD4-IgG hybrid represents up to 92% of the protein A purified protein pool following co-expression of these two different heavy chains together with the anti-CD3 light chain.”).) By contrast, combination of the “unmodified” heavy chains yielded only 57% of the desired heterodimer. (Ex. 1015 at 617.)

48. The success of our KIH approach laid the groundwork for further engineering of heterodimeric antibodies through other techniques, likewise designed to capitalize on modifications to the CH3 region. (Ex. 1015 at 620; *see also* Ex. 1021 (describing KIH modifications).) And as discussed further below,

scientists (including my own group at Genentech) pursued strategies that could be used in combination, allowing for additive benefits to heterodimer synthesis efficiency.

2. Common Light Chain (CLC) Approach

49. A second method for promoting the expression of a target bispecific antibody well-established by 2012 was to use a “common light chain.” As I previously discussed, co-expression of a pair of different heavy and light chains yields ten different potential combinations during the self-assembly process in the cell, only one of which is the desired target bispecific antibody, shown again below:



(Ex. 1006 at Figure 1A.)

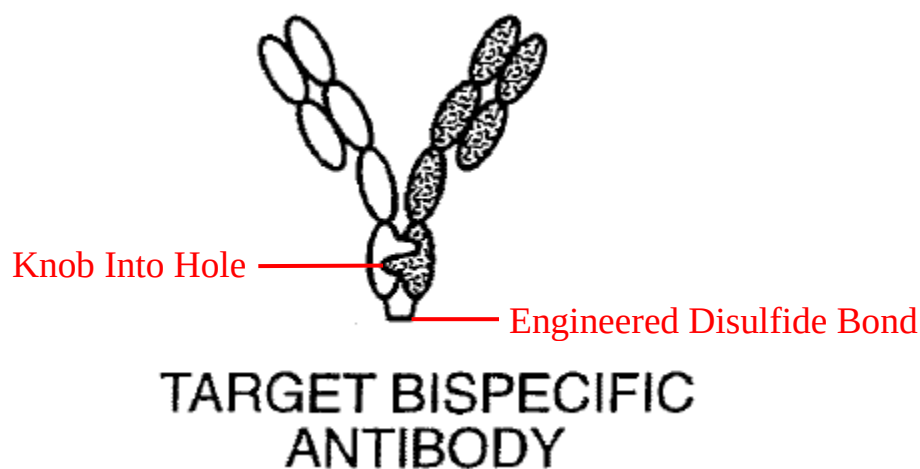
50. But we and others found that incorporating a single (or “common”) light chain—rather than two distinct light chains—reduced the number of “possible contaminating species” to use the parlance of the figure above. (Ex. 1006 at Figure 1A.) The benefits of incorporating a common light chain were well-known long before 2012. For instance, it was published 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.” (Ex. 1006 at 6:24-26.)

3. Disulfide Linkage Approach

51. A third approach developed by scientists to promote heterodimer formation involved the creation of disulfide linkages between the CH3 region of two differing heavy chains to promote heterodimer formation. As we described as early as 1998, “[n]on-naturally occurring disulfide bonds are constructed by replacing on the first polypeptide a naturally occurring amino acid with a free thiol-containing residue, such as cysteine, such that the free thiol interacts with another free thiol-containing residue on the second polypeptide such that a disulfide bond is formed between the first and second polypeptides.” (Ex. 1006 at 6:13-17.) As shown below, the insertion of disulfide linkages could be combined with other heterodimer synthesis approaches like KIH to further promote manufacturing efficiency:

Demonstrative 7 – Combination of Disulfide Linkage and KIH



(Ex. 1006 at Figure 1B (annotations in red added).)

52. Moreover, in 1998, we demonstrated that amino acids modified to promote disulfide linkages provided greater bispecific antibody manufacturing efficiency. More specifically, we reported that a modified CH3 variant (D399C/K392'C)¹⁰ designed to promote disulfide linkages between heavy chains substantially increased the yield of the heterodimer over a non-modified protein sequence (73% versus 51%, respectively). (Ex. 1006 at 44:18-45:21, Table 4.)

¹⁰ When discussing such substitutions, the first letter is the original amino acid, the number is the position of the amino acid, and the second letter is the replacing amino acid. For example, “D399C” stands for aspartic acid (D) at position 399 is substituted with a cysteine (C). The single quotation mark (prime, ') after the second number (here, “392”) denotes that this mutation is in the second (complementary) amino acid chain.

And when we combined the disulfide linkage approach with the KIH approach, we demonstrated that heterodimerization yields reached as high as “approximately 95%.” (Ex. 1006 at 44:26-45:21, Table 4.)

4. Electrostatic Steering Approach

53. As interest in making bispecific antibodies increased, a number of groups started exploring using electrostatic interactions as an additional means to increase heterodimerization and decrease homodimerization. The theory behind an electrostatic steering approach is relatively simple: By “alter[ing] charge polarity” of the CH3 region, “coexpression of electrostatically matched [(i.e., oppositely charged)] Fc chains support favorable attractive interactions [and] thereby promot[e] desired Fc heterodimer formation, whereas unfavorable repulsive charge interactions suppress unwanted Fc homodimer formation.” (Ex. 1012 at 19637.) That is, by using oppositely charged residues in the interface, heterodimerization is favored, while homodimerization is discouraged by repulsive charge interactions (positive to positive or negative to negative homodimers).

54. That simple premise dates back as early as 1998, when scientists associated with the National Institutes of Health (Drs. Ameurfina Santos and Eduardo Padlan) described the “easy production of multispecific/multivalent antibodies via heterodimer formation of electrostatically complementary Fc regions.” (Ex. 1016 (“Santos”) at 169.) To promote the desired electrostatic

interactions, *Santos* taught making amino acid substitutions to each heavy chain to be incorporated into a bispecific antibody in order to manipulate their respective charges. (Ex. 1016 at 183 (“We are making use of electrostatic complementarity for the efficient generation of heterodimeric molecules. Each molecule consists of two chains, each with one or more different antigen-binding specificities, the two chains differing from each other by the presence of oppositely charged residues at a judiciously chosen position.”).) As echoed above, the *Santos* authors explained that the “rationale behind [the described] procedure lies in the expectation that identical chains repel each other and that only heterodimers will form.” (Ex. 1016 at 183.)

55. A decade later, in 2010, researchers at Amgen likewise reported inserting complementarily charged amino acids in the CH3 domain at the Fc region interface in order to modulate electrostatic interactions using selected mutations. (Ex. 1012 (“*Gunasekaran*”) at 19637.) Consistent with *Santos*, *Gunasekaran* explained that by changing positive and/or negative charges on each CH3 domain, homodimers will have repulsive charges at the CH3 interface (*e.g.*, repulsion of positive to positive or negative to negative pairing) thus favoring heterodimerization by attraction of opposite charges (positive to negative). (Ex. 1012.) The authors summarized:

Bispecific antibodies having binding specificities for two different antigens can be produced using recombinant technologies and are projected to have broad clinical applications. However, co-expression of multiple light and heavy chains often leads to contaminants and pose purification challenges. In this work, we have modified the CH3 domain interface of the antibody Fc region with selected mutations so that the engineered Fc proteins preferentially form heterodimers. These novel mutations create altered charge polarity across the Fc dimer interface such that coexpression of electrostatically matched Fc chains support favorable attractive interactions thereby promoting desired Fc heterodimer formation, whereas unfavorable repulsive charge interactions suppress unwanted Fc homodimer formation.

(Ex. 1012 at 19637.)

56. Amgen's electrostatic steering approach did not alter amino acids at random, but instead introduced substitutions at key residues (or positions) at the CH3 domain interface. (Ex. 1012 at 19640, Supplementary Table 1.) The authors in *Gunasekaran* used a “computational scheme... to analyze the CH3 domain interface and to identify the charged residue pair that is likely to significantly impact dimer formation.” (Ex. 1012 at 19638.)

57. Scientists associated with Amgen later noted that, as a logical extension of its electrostatic engineering approach, one could also modify uncharged (neutral) residues to charged residues at the CH3 domain interface. (Ex. 1007 at 10:16-18 (“This strategy can also be extended to modifying uncharged residues to charged residues at the CH3 domain interface.”).) In addition, Amgen recognized that its electrostatic engineering strategy could be combined with

additional heterodimer-promoting techniques, including KIH mutations or a common light chain approach. (Ex. 1007 at 3:29-31; Ex. 1012 at 19645.)

58. Showing the significant interest in electrostatic steering approaches, just after the publication of *Gunasekaran*, Diaz et al. investigated the effects of introducing complementary charged amino acids in CH3 domains on heavy chain dimerization. (Ex. 1018 (“*Diaz*”) at 48-49.) Specifically, *Diaz* reported that switching neutral tyrosine (Y) to positively charged arginine (R) at position 407 and neutral threonine (T) to negatively charged glutamic acid (E) at position 366¹¹ increased the heterodimer to homodimer ratio (depicted as Y407R/T366E). (Ex. 1021 at 48, 53.)

5. CH3 Domain Interface Residues

59. As made clear in *Gunasekaran*, the heterodimer promotion methods discussed above involved making modifications at important, known residues on the CH3 domain interface. (Ex. 1012 at 19640, Supplementary Table 1; Ex. 1007 at 7:8-8:7 (Table 1); *see also* Exs. 1019, 1020.) And by 2010, the list of CH3 domain interface residues had already been cataloged and reported in the art, as shown in the table below.

¹¹ By 2012, positions 366 and 407 had already been reported to be contact residues in CH3-CH3 interface. (Ex. 1012 at Supplementary Table 1; *see also* Ex. 1007 at 7:8-8:7 (Table 1); Ex. 1001 at Table A; Ex. 1006 at 41:20-26.)

Supplementary Tables

Supplementary Table 1: List of CH3 domain interface residues in the first chain (A) and their side chain contacting residues in the second chain (B)^a

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

^aPositions involving interaction between oppositely charged residues are indicated in bold. Due to the 2-fold symmetry present in the CH3-CH3 domain interaction, each pairwise interaction is represented twice in the structure (for example, Asp A 356 --- Lys B 439' & Lys A 439 --- Asp B 356'; Figure 1). Eu numbering scheme is used here to identify residue positions.

(Ex. 1012 at Supplementary Table 1.)

VI. Overview of the '286 Patent

60. The '286 patent is titled, "Methods and Means for the Production of Ig-Like Molecules."

61. I understand from its cover that the '286 patent issued on June 7, 2016 from U.S. Application No. 14/081,848, filed November 15, 2013.

62. The '286 patent generally discusses “means and methods for producing one or more Ig-like” (*i.e.*, antibody-like) molecules within a single host cell. (Ex. 1001 at Abstract.) Specifically, the patent is directed to using electrostatic engineering—with or without other known antibody engineering strategies, like knob-into-hole—for providing improved percentages of desired heterodimeric antibodies. (Ex. 1001 at 5:55-62.)

63. However, the '286 patent recognizes that such strategies for engineering antibody heavy chains to increase heterodimer formation were already known. Specifically, the '286 patent acknowledges the prior art use of, *inter alia*, (1) knob-into-hole engineering and (2) electrostatic engineering. (Ex. 1001 at 4:29-5:52.)

64. Moreover, the '286 patent acknowledges that prior art techniques to increase heterodimerization already focused specifically on modifying residues on the CH3-CH3 interface—part of the technique claimed in the '286 patent. For instance, the '286 patent recognizes that, by April 2012, it was already “well-known that the CH3-CH3 interaction is the primary driver for Fc dimerization.” (Ex. 1001 at 4:5-6.) And it further acknowledges that it was well-known that the CH3 domains of interacting heavy chains “meet in a protein-protein interface” which is comprised of known “contact residues.” (Ex. 1001 at 4:8-12.)

65. As to the identity of these contact residues, the '286 patent recognizes that the contact residues within the CH3-CH3 interface can either be charged (either positively or negatively) amino acids or neutral amino acids. (Ex. 1001 at 13:1-3.) Again, positively charged amino acids include arginine (R), histidine (H), and lysine (K). Meanwhile, negatively charged amino acids include aspartic acid (D) and glutamic acid (E). (Ex. 1001 at 13:5-9.) The remaining amino acids are neutral, including serine (S), threonine (T), asparagine (N), glutamine (Q), cysteine (C), glycine (G), proline (P), alanine (A), valine (V), isoleucine (I), leucine (L), methionine (M), phenylalanine (F), tyrosine (Y), and tryptophan (W). (Ex. 1001 at 13:11-17.)

66. The '286 patent asserts that 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 [(i.e., replaces a neutral amino acid with a charged one)].” (Ex. 1001 at 18:7-10.) The '286 patent refers to these neutral-to-charged mutations as “an inventive alternative to” the prior art. (Ex. 1001 at 18:4-7.) But, as discussed herein, such mutations had already been disclosed in the prior art before 2012.

67. The '286 patent contains 4 independent claims, which read as follows:

1. A method for producing a heterodimeric antibody from a single cell, wherein said antibody comprises two heavy chains with CH3

- domains that are capable of forming an interface, said method comprising:
- a. providing a host cell comprising
 - (i) a first nucleic acid molecule encoding a 1st antibody heavy chain comprising at least one substitution of a neutral amino acid residue in the CH3 domain by a positively charged amino acid residue, and
 - (ii) a second nucleic acid molecule encoding a 2nd antibody heavy chain comprising at least one substitution of a neutral amino acid residue in the CH3 domain by a negatively charged amino acid residue;
 - b. culturing said host cell and allowing for expression of said two nucleic acid molecules to produce said 1st antibody heavy chain and said 2nd antibody heavy chain, wherein the at least one positively charged amino acid residue substituted in the CH3 domain of said 1st antibody heavy chain interacts with the at least one negatively charged amino acid residue substituted in the CH3 domain of said 2nd antibody heavy chain in the interface between said 1st and 2nd antibody heavy chains to produce a heterodimeric antibody; and
 - c. harvesting said heterodimeric antibody from the culture.
25. A heterodimeric antibody comprising two CH3 domains, wherein one of said two CH3 domains comprises an amino acid substitution at position 351 by an aspartic acid (D) and an amino acid substitution at position 368 by a glutamic acid (E), and wherein the other of said two CH3 domains comprises an amino acid substitution at position 366 by a lysine (K) and an amino acid substitution at position 351 by a lysine (K).
26. A recombinant host cell comprising nucleic acid sequences 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.

30. A method for making a host cell for production of a heterodimeric antibody, 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, wherein said nucleic acid sequences are introduced consecutively or concomitantly.

VII. Overview of the Prior Art

A. *Arathoon* – International Patent Application Publication WO 98/50431 (Ex. 1006)

68. *Arathoon* is titled, “A Method for Making Multispecific Antibodies Having Heteromultimeric and Common Components.” I understand that *Arathoon* was filed on April 20, 1998, as International Patent Application No. PCT/US98/08762 and published as International Patent Application Publication No. WO 98/50431 on November 12, 1998. (Ex. 1006 at Cover.)

69. I am a co-inventor on the *Arathoon* patent publication, which describes the improved heterodimer synthesis methods developed by my group at Genentech. Specifically, the reference teaches “introducing into the multispecific antibody a specific and complementary interaction at the interface of a first polypeptide and the interface of a second polypeptide, so as to promote heteromultimer formation and hinder homomultimer formation,” and further

discloses “a multispecific antibody having a common light chain associated with each heteromeric polypeptide having an antibody binding domain.” (Ex. 1006 at Abstract.)

70. *Arathoon* further instructs that by designing specific variants of the antibody’s Fc region as described in the reference, one can significantly increase the likelihood of heterodimerization, including achieving over 95% purity in the heterodimer population. (Ex. 1006 at 44:26-28.)

71. In making the disclosed modifications to the Fc region of an antibody, *Arathoon* emphasizes the importance of selecting appropriate mutations and techniques that favor the formation of heterodimers, thus optimizing the production process to reduce the presence of undesired homodimers. These techniques include combining strategies that rely on different principles to increase heterodimer purity. (Ex. 1006 at 44:18-28.)

72. For example, *Arathoon* teaches the KIH method, among others, instructing that interactions at the interface of a first and second polypeptide of a heteromultimeric antibody may be promoted by “the formation of protuberance-in-cavity complementary regions; the formation of non-naturally occurring disulfide bonds; leucine zipper; hydrophobic regions; and hydrophilic regions.” (Ex. 1006 at 6:5-7.)

73. *Arathoon* used its KIH strategy to engineer the CH3 domain of two antibody heavy chains such that the heterodimer preferentially forms. (Ex. 1006 at 40:35-42:37 (Example 1); *see also* Ex. 1015 at 617-621.) Among the residues selected included contact residues threonine at position 366 (T366) and tyrosine at position 407 (T407). (Ex. 1006 at 41:20-26.) This modification resulted in yields of up to 92%, when recovered from cells co-transfected with the two heavy chains and a common light chain. (Ex. 1006 at 41:20-42:25.) And when this KIH approach was combined with a disulfide linkage strategy, yields of approximately 95% heterodimer were obtained. (Ex. 1006 at 44:18-45:21, Table 4.)

74. *Arathoon* further included incorporating a common light chain in addition to the KIH and disulfide linkage approaches, to demonstrate the heterodimerizing technology's utility for designing complete bispecific antibodies. (Ex. 1006 at 48:23-53:34 (Example 4) (titled "Generation and assembly of heteromultimeric antibodies or antibody/immunoadhesins having common light chains").)

B. *Lazar* – U.S. Patent Application Publication US 2011/0054151 (Ex. 1004)

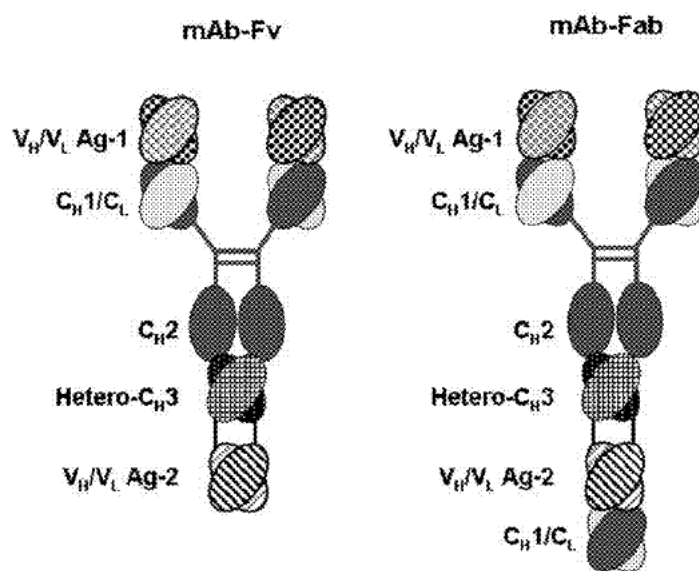
75. *Lazar* is a United States Patent Application Publication titled "Compositions and Methods for Simultaneous Bivalent and Monovalent Co-Engagement of Antigens." (Ex. 1004 at Cover.) *Lazar* was published as

US 2011/0054151 on March 3, 2011, based on a U.S. Patent Application that was filed on September 2, 2010. (Ex. 1004 at Cover.) It is my understanding that *Lazar* claims priority to a provisional application filed on September 2, 2009. (Ex. 1004 at Cover.) It is further my understanding that Drs. Gregory Lazar and Gregory Moore performed the work leading to this publication while they were employees of Xencor—the listed assignee of the *Lazar* publication. (Ex. 1004 at Cover.)

76. *Lazar* describes antibodies and antibody analogs designed to engage with at least two different antigens—*i.e.*, bispecific antibodies (or bispecific antibody analogs). (Ex. 1004 at ¶38.) Consistent with the knowledge in the field, *Lazar* explains that antibodies are immunoglobulins that bind to specific antigens, and highlights that antibodies and immunoglobulins share “the same structural characteristics.” (Ex. 1004 at ¶¶77-78.)

77. *Lazar* describes a variety of antibody formats, including full-length antibodies, antibody fragments, bispecific antibodies, antibody fusions, and antibody conjugates, among others. (Ex. 1004 at ¶99.) *Lazar* groups these various formats under the umbrella term of “antibody,” which *Lazar* defines as a protein containing one or more polypeptides, which are substantially encoded by all or part of the recognized immunoglobulin genes. (Ex. 1004 at ¶85)

78. *Lazar* identifies “mAb-Fv” and “mAb-Fab” as exemplary immunoglobulin structures for co-engaging two different antigens. (Ex. 1004 at ¶104, Figure 8.) These formats, illustrated in Figure 8, consist of three distinct immunoglobulin chains: an antibody light chain and two heavy chains. The mAb-Fv format is a bispecific antibody format in which a second antigen-binding region (“Ag-2”) consists of an antibody’s variable region (the Fv), which includes the variable domains (VH and VL) from both the light and heavy chains that bind to a specific antigen. (Ex. 1004 at ¶¶46-47, 104-106, 242.) The mAb-Fab format refers to an antibody fragment where the second antigen-binding region is composed of a Fab portion of an antibody, which includes the variable domains (VH and VL) of both the light and heavy chains, each one C-terminally fused to the appropriate constant domain CH1 or CL. (Ex. 1004 at ¶¶46-47, 104-106, 242.) These formats are illustrated below.



(Ex. 1004 at Figure 8.)

79. *Lazar* explains that mAb-Fv and mAb-Fab antibodies are heterodimeric, as the formation of the C-terminal Fv and Fab regions requires the association of two different heavy chains. (Ex. 1004 at ¶¶106-108, 242.) *Lazar* further elaborates that the mAb-Fv and mAb-Fab antibodies function as bispecific antibodies by co-engaging two distinct antigens, enhancing the clinical efficacy. (Ex. 1004 at ¶¶7, 43, 104, 242.) Further, *Lazar* demonstrates the application of bispecific mAb-Fab and mAb-Fv antibodies in Examples 3-6, showing how they can co-target antigens such as “HER2 and FcγRIIIa,” “EGFR and FcγRIIIa,” and “HM1.24 x FcγRIIIa” (Example 4); “CD19 and FcγRIIb” (Example 5, Table 3); and “HER2 and CD3,” “HM1.24 and CD3,” and “CD19 and CD3” (Example 6, Table 5). (Ex. 1004 at Examples 4-6, Tables 3-5.)

80. *Lazar* provides detailed methods for creating the heterodimeric antibodies described, highlighting how certain Fc region variants can be engineered to favor heterodimerization over homodimerization. (Ex. 1004 at ¶120.) Consistent with the knowledge in the art, *Lazar* describes how specific amino acid modifications in the CH3 domains can stabilize the Fc interface, ensuring that the heterodimeric antibody maintains its structural integrity. (Ex. 1004 at ¶¶121-25, Tables 1-2.)

81. As one manner of improving heterodimer yield, *Lazar* includes amino acid substitutions that result in replacing neutral amino acids with charged residues. (Ex. 1004 at ¶123, Tables 1-2.) For convenience, I reproduce Tables 1 and 2 from *Lazar* below and have highlighted examples of neutral amino acids that were replaced with positively charged amino acid residues (highlighted in yellow and green respectively) on one CH3 domain marked “Variant 1,” and corresponding neutral amino acids that were replaced with negatively charged amino acid residues on a second CH3 domain marked “Variant 2” (highlighted in yellow and red respectively). (Ex. 1004 at ¶123, Tables 1-2.)

“Preferred” CH3 Domain Variants from *Lazar*

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

“Most [P]referred” CH3 Domain Variants from *Lazar*

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

Many of these highlighted amino acid modifications taught by *Lazar* occur at CH3 interface positions, causing the variants to favor heterodimerization over homodimerization and thus resulting in a stable heterodimeric Fc structure (referred to as a “hetero-Fc variant”). (Ex. 1004 at ¶¶121-125, Tables 1-2.)

82. *Lazar* further explains that by utilizing the disclosed hetero-Fc variants, the proportion of heterodimers is significantly increased, while the proportion of homodimers is reduced, preferably to minimal levels (*e.g.*, to less than 5%). (Ex. 1004 at ¶¶122-123, Tables 1-2.) These variants can boost the heterodimer percentage to levels exceeding 95%, whereupon well-known purification methods can further reduce the contaminating homodimer population.

(Ex. 1004 at ¶122 (“Heterodimeric immunoglobulin species may optionally be isolated further from homodimeric species using any number of various protein purification methods well-known in the art.”).)

C. *Cabrera* – International Patent Application Publication WO 2012/058768 (Ex. 1005)

83. *Cabrera* is an international patent application publication titled “Stable Heterodimeric Antibody Design with Mutations in the Fc Domain.” (Ex. 1005 at 1.) *Cabrera* was published as WO 2012/058768 on May 10, 2012, based on an international patent application that was filed on November 4, 2011. (Ex. 1005.) It is my understanding that *Cabrera* claims priority to a U.S. patent application filed on November 5, 2010. (Ex. 1005 at Cover.) It is my understanding that the named inventors on *Cabrera* assigned this application to Zymeworks Inc. (Ex. 1005 at Cover.)

1. Summary of *Cabrera*

84. Like *Arathoon* and *Lazar*, *Cabrera* teaches strategies for designing stable heterodimeric antibodies by introducing mutations into the Fc domain of the antibody and achieving as high as 95% heterodimerization. (Ex. 1005 at 24-25, Figure 26B.) *Cabrera* emphasizes the use of engineered Fc regions that incorporate specific mutations and charge variants in order to promote heterodimer

formation, enhancing both the stability and assembly of bispecific antibodies while minimizing homodimer formation. (Ex. 1005 at 24-25.)

85. *Cabrera* outlines a structure- and computation-guided approach for designing various heterodimeric Fc variants. (Ex. 1005 at 25.) *Cabrera* also teaches that favorable interactions promoting heterodimerization can involve electrostatics, hydrogen bonding, surface complementarity, packing, and hydrophobic contact, or combinations of these heterodimer-promoting strategies. (Ex. 1005 at 25-26.)

86. *Cabrera* describes modifying at least one amino acid in one CH3 domain relative to the wild-type (*i.e.*, unmodified) CH3 domain and at least one amino acid in another CH3 relative to the wild-type CH3 domain to increase the ratio of heterodimerization to homodimerization compared to a heterodimeric antibody with a non-engineered interface. (Ex. 1005 at 26.) The amino acid modifications create favorable interactions between the CH3 domains so as to stabilize the heterodimeric Fc regions of the antibody. (Ex. 1005 at 4.) *Cabrera* further discloses that the heterodimer purity resulting from the amino acid modifications can be greater than about 99%. (Ex. 1005 at 24-25.)

87. Moreover, *Cabrera* discloses CH3 variants that include substitutions of neutral amino acids with positively charged residues in one heavy chain and neutral amino acids with negatively charged residues in another. (Ex. 1005 at

Table 1 (*e.g.*, AZ34¹².) The specific residues at which *Cabrera*'s substitutions were made, such as S400 and N390, are noted in the prior art to be CH3-domain interface residues. (Ex. 1005 at Table 1; *see also* Ex. 1012 at Supplementary Table 1; Ex. 1007 at 7:8-8:7 (Table 1).)

88. *Cabrera* teaches that heterodimers can include bispecific antibodies, which contain engineered Fc regions. (Ex. 1005 at 8, 75.) *Cabrera* discloses that bispecific antibodies can contain a common light chain. (Ex. 1005 at 10, Figure 18.) *Cabrera* also teaches that its design method can be combined with other methods, including KIH, disulfide bonds, and the Amgen electrostatic steering method. (Ex. 1005 at 19-22 (citing Ex. 1012 and Ex. 1015).)

89. Further, *Cabrera* instructs that host cells can be transfected to co-express nucleic acids encoding the individual chains of these heterodimeric proteins so that heterodimeric proteins can be expressed and recovered from the cell culture. (Ex. 1005 at 85-92.)

¹² As discussed in greater detail below, "AZ34" is a heterodimer disclosed by *Cabrera* that includes a first CH3 domain in which a neutral amino acid residue is replaced by a positively charged amino acid residue, as well as a second CH3 domain in which a corresponding neutral amino acid residue is replaced by a negatively charged amino acid residue. (See Section XII.A.4; Ex. 1005 at 39, Table 1.)

**2. Support for *Cabrera* in
U.S. Provisional Application No. 61/475,614**

90. I have also been asked to consider whether claim 76 of *Cabrera* is supported by the disclosures set forth in U.S. Provisional Patent Application No. 61/475,614 (Ex. 1009) (“the ’614 application”), and whether the ’614 application contains the same substantive disclosures as I rely on from *Cabrera* in my analysis below. I understand that the ’614 application was filed on April 14, 2011.

91. Claim 76 of *Cabrera* recites the following:

76. An isolated heteromultimer comprising a heterodimer Fc region, wherein the heterodimer Fc region comprises a first CH3 domain polypeptide comprising an amino acid modifications L351Y, F405A and Y407V and a second CH3 domain polypeptide comprises amino acid modification T394W.

(Ex. 1005 at 141.)

92. Consistent with claim 76 of *Cabrera*, the ’614 application describes “[a]n isolated heteromultimer comprising a first polypeptide and a second polypeptide which meet at an interface which has been engineered to promote heteromultimer formation, wherein at least one of said first and second polypeptide comprises a variant CH3 domain forming part of the interface.” (Ex. 1009 at ¶13.) In addition, the ’614 application describes an isolated heteromultimer having “a

first CH3 domain polypeptide comprising... amino acid modifications L351Y, F405A and Y407V.” (Ex. 1009 at ¶16; *see also* Ex. 1009 at ¶112 (Table 3 disclosing AZ33 and AZ34, both having claimed amino acid mutations).) Finally, the ’614 application describes an isolated heteromultimer having “a second CH3 domain polypeptide” comprising “amino acid modification T394W.” (Ex. 1009 at ¶16; *see also* Ex. 1009 at ¶112 (Table 3 disclosing AZ33 and AZ34, both having claimed amino acid mutations).)

93. In addition, in my analysis of *Cabrera* below, I show where corresponding disclosures of the ’614 application are contained.

VIII. Summary of Opinions

94. The claims at issue relate to methods for creating heterodimeric antibodies by replacing a neutral amino acid with a positive amino acid in the CH3 domain of a first antibody heavy chain, and replacing a neutral amino acid with a negative amino acid in the CH3 domain of a second antibody heavy chain. Both *Lazar* and *Cabrera* taught this very approach for creating heterodimeric antibodies using such neutral to charged amino acid substitutions to improve heterodimerization.

95. Additionally, a person of ordinary skill in the art as of the relevant time would have been motivated to develop methods for creating heterodimeric antibodies, which were known to target multiple pathways or receptors

simultaneously and combine different therapeutic modalities in a single molecule, thereby obviating the requirement to develop two individual antibodies and avoid substantial investment in manufacturing, clinical trials, and regulatory review. (*E.g.* Ex. 1013 at 183.)

96. A person of ordinary skill in the art would have looked to *Lazar* and *Cabrera*, which taught methods for creating heterodimeric antibodies. Indeed, a person of ordinary skill in the art would have also been motivated to combine the teachings of these references with each other, along with *Arathoon*, to arrive at the claimed invention. A person of ordinary skill in the art would have further reasonably expected to achieve the features recited in the claims because each of the steps were taught in *Lazar*, *Cabrera*, and/or *Arathoon*, and combining methods for making antibodies would have been routine for those skilled in the art as of the relevant time frame.

97. In my opinion, (1) *Lazar* (Ex. 1004) teaches all of the limitations of claims 1, 7, 21-22, 24, 26, 28, 30, and 32 of the '286 patent; (2) the combination of *Lazar* (Ex. 1004) and *Arathoon* (Ex. 1006) teaches or suggests all of the limitations of claims 1-2, 7-24, 26-28, and 30-32 of the '286 patent; (3) *Cabrera* (Ex. 1005) teaches all of the limitations of claims 1-2, 7, 21-22, 24, 26-28, and 30-32 of the '286 patent; (4) the combination of *Lazar* (Ex. 1004), *Cabrera* (Ex. 1005) and

Arathoon (Ex. 1006) teaches or suggests all of the limitations of claims 1-2, 7-24, 26-28, and 30-32 of the '286 patent.¹³

IX. Claim Construction

98. I have been informed that claims are typically given their ordinary and customary meaning in the technological field of the patent. However, when claim terms have no standard meaning in the art, I understand that the terms must be interpreted in light of the patent claims, disclosure (referred to as the “specification”), and the “prosecution history” (the record of the back-and-forth between the patent applicant and the United States Patent and Trademark Office during the process of obtaining allowance of the patent’s claims).

99. I have applied the ordinary and customary meaning to all the claim terms of the '286 patent in my analysis below. Should the PTAB adopt any other reasonable interpretation of the claim terms, I am confident that this would not alter my opinions. I further reserve the right to respond to any proposed constructions put forward by the patent owner.

¹³ Throughout this declaration, I also rely on other documents, including for background information and to show what was generally known in the field before April 2012. I am not citing any such document to show it teaches one or more features recited in the claims of the '286 patent (even though they teach one or more such features). Instead, I rely only on the teachings of *Lazar*, *Cabrera*, and *Arathoon* for the claimed features.

X. Ground 1: *Lazar* Teaches All of the Limitations of Claims 1, 7, 21-22, 24, 26, 28, 30, and 32 of the '286 Patent

100. It is my opinion that each of the limitations of claims 1, 7, 21-22, 24, 26-28, and 30-32 are taught by *Lazar* for at least the reasons explained below.

A. Claim 1

1. “A method for producing a heterodimeric antibody from a single cell,”

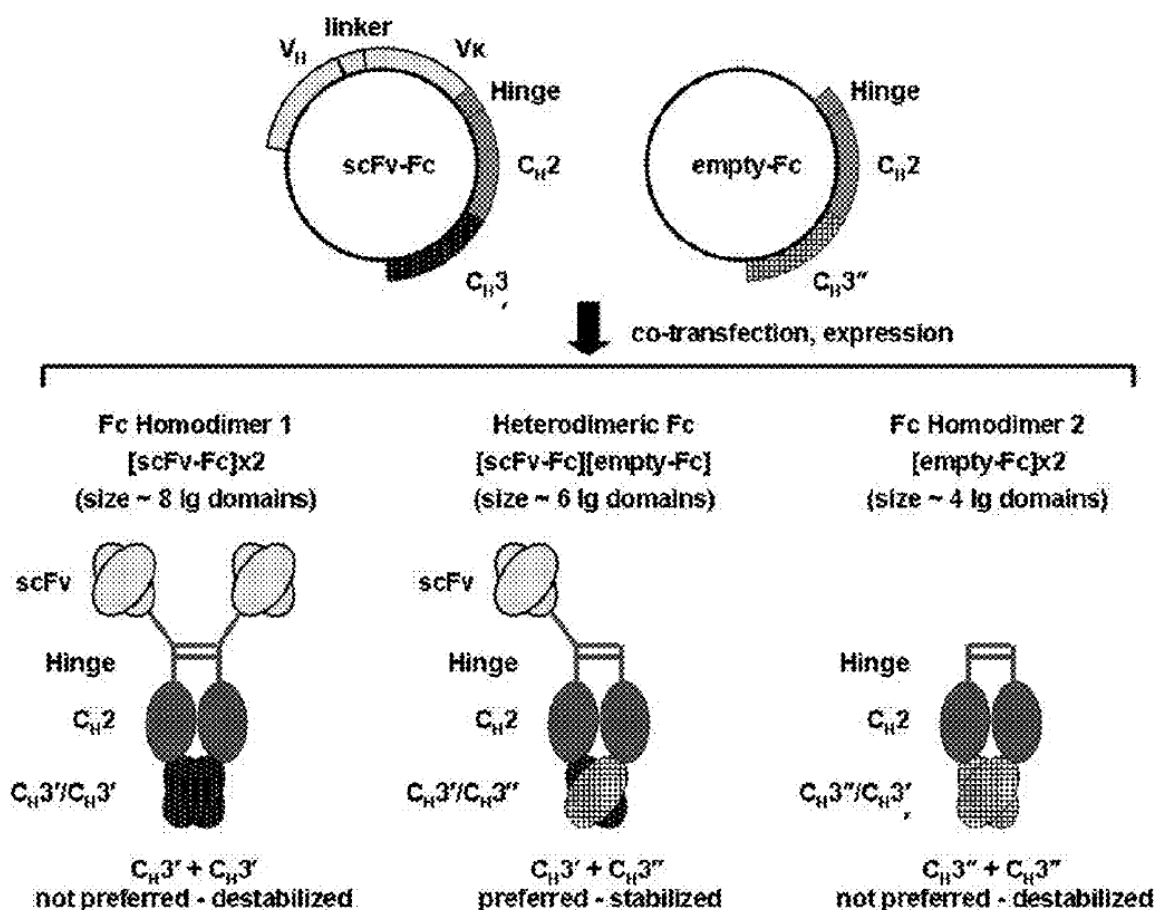
101. It is my opinion that *Lazar* discloses a method for producing a heterodimeric antibody from a single cell.

102. *Lazar* teaches methods for producing such antibodies utilizing heterodimeric Fc regions. (Ex. 1004 at Abstract, ¶¶2 (describing “antibody analogs”¹⁴ that “simultaneously co-engage antigens” and which “preferably utilize heterodimeric Fc regions”), 99-100, 120-125 (describing Fc variants that favor heterodimerization); Section V.B.)

¹⁴ The '286 patent broadly defines “antibody” as “mean[ing] a proteinaceous molecule belonging to the immunoglobulin class of proteins, containing one or more domains that bind epitope[s] on an antigen.... Antibodies are known in the art and include several isotypes, such as IgG1, IgG2, IgG3, IgG4, IgA, IgE, and IgM. An antibody according to the invention may be any of these isotypes, or a functional derivative and/or fragment of these.” (Ex. 1001 at 11:9-18.) A person of ordinary skill in the art would readily understand that *Lazar*’s “antibody analogs,” proteins that co-engage antigens, fall within this broad definition.

103. *Lazar* further describes the production of its heterodimeric antibodies from a single cell. Specifically, *Lazar* teaches the production of antibodies by cultivating host cells that have been transfected with nucleic acids, such as an expression vector (or plasmid), containing the genetic code for the polypeptide chains that form the antibody. (Ex. 1004 at ¶183.) And *Lazar* further details the co-transfection of mammalian cells with constructs designed to promote heterodimerization using CH3 domain variants. (Ex. 1004 at ¶¶182-188 (describing methods for generating nucleic acids which encode immunoglobulins and introducing them into host cells), 239-240 (describing synthesis of DNA constructs used for assessing CH3 domain variants and co-transfection into HEK293E cells), 245 (describing synthesis of DNA constructs encoding antibodies and co-transfection into HEK293E cells), 257 (same), 263 (same), Figure 1 (shown below).)

Figure 1



104. As noted above in Section V.B, co-transfection refers to the process of simultaneously introducing two or more different genetic materials (such as plasmids) into a single cell. In the context of producing a heterodimeric antibody, a person of ordinary skill in the art would have understood that co-transfection means that both heavy chains and light chain(s) of the antibody are expressed within the same cell. (Ex. 1004 at ¶¶238-239 (“Pairs of ScFv-Fc and empty-Fc constructs were cotransfected into HEK293E cells.”), Figure 1; Ex. 1023 at 3173

(“[t]ransfection is a procedure that introduces foreign nucleic acids into cells”); see also Ex. 1001 at 43:10-14 (describing “co-transfection of vectors XIII and XVI”), 62:9-12 (describing co-transfection of different constructs).)

105. The cell described above produces the different antibody chains that self-assemble into the heterodimeric structure. (Ex. 1004 at ¶¶74, 238-239, Figure 1; Ex. 1023 at 3173; see also Ex. 1001 at 43:10-14, 62:9-12.) Thus, co-transfection detailed by *Lazar* directly facilitates the production of heterodimeric antibodies by ensuring that all the components necessary for their formation are expressed in a single cell, allowing for efficient assembly and production of the desired antibody.

2. “wherein said antibody comprises two heavy chains with CH3 domains that are capable of forming an interface,”¹⁵ said method comprising:”

106. It is my opinion that *Lazar* discloses a method of producing an antibody comprising two heavy chains with CH3 domains that are capable of forming an interface.

¹⁵ As discussed above, the term “interface” refers to the physical region where two structures come into contact. (See, e.g., Ex. 1006 at 15:28-31.) An interface between the two CH3 domains therefore refers to the physical region in which the CH3 domain of two heavy chains come together and interact to form the desired heterodimeric structure. (See, e.g., Ex. 1006 at 15:28-35.)

107. To manufacture the heterodimeric antibodies described therein, *Lazar* teaches producing two heavy chains with modified CH3 domains to promote heterodimer formation and minimize homodimer formation. (Ex. 1004 at ¶¶9 (explaining “CH3 domains... can be designed to promote heterodimer formation and discourage homodimer formation”), 120-121 (same).) As *Lazar* explains:

[0120] Of particular benefit to the immunoglobulins of the invention are Fc variants that favor heterodimerization of the Fc region¹⁶ relative to homodimerization. ***That is, by modifying one or more amino acids within each heavy chain that forms the Fc region***, such that each heavy chain comprises at least one amino acid variant as compared to the other chain, binding of the different heavy chains to form heterodimeric Fc regions is favored over the individual heavy chains forming homodimers.

[0121] Such variants, referred to herein as hetero-Fc variants, comprise a pair of different variants such that one pair (referred to as variant') modifies one CH3 domain (referred to as CH3'), while the other pair (variant'') modifies another CH3 domain (CH3''). ***The variants are designed such that their interaction in a heterodimeric CH3 interface (variant'/variant'') is favorable, thus***

¹⁶ As discussed above, the Fc region contains, among other things, a CH3 domain. (Section V.B.) A person of ordinary skill in the art would have understood that the CH3 domain is a critical structural component of the Fc region, playing an essential role in dimerization—the process by which two heavy chains associate with one another, which the '286 patent itself recognizes. (See Section V.B; Ex. 1001 at 4:5-14 (describing the “CH3-CH3 interaction” and “protein-protein interface” as being “well-known”), Table A (identifying known contact residues in the CH3-CH3 interface); Ex. 1007 at 2:33-3:13 (describing methods for manipulating interactions at the CH3-CH3 interface); Ex. 1012 at 19637-19640 (describing identification of CH3-CH3 domain interface residues).)

resulting in a stable heterodimeric Fc species (comprising CH3'/CH3''). In contrast, the pairing of each variant with itself across a homodimeric CH3 interface (variant'/variant' and variant''/variant'') is unfavorable, resulting in unstable homodimeric Fc species (comprising CH3'/CH3' and CH3''/CH3'').

(Ex. 1004 at ¶¶120-121.)¹⁷

108. As *Lazar* teaches in the excerpt above, “variants are designed such that their interaction in a heterodimeric CH3 **interface**... is favorable” and interaction “across a homodimeric CH3 **interface**... is unfavorable.” (Ex. 1004 at ¶121; see Section V.B.) *Lazar*’s teaching is consistent with the knowledge, long-established by 2012, that dimerization of the two antibody heavy chains is driven by the association of CH3 domains *via* the CH3 domain interface. (See Section V.B.)

3. “providing a host cell comprising”

109. It is my opinion that *Lazar* discloses the use of a “host cell” for expressing the co-transfected nucleic acids, consistent with my discussion above. (Section X.A.1.)

110. Co-transfection, which I discuss above, involves providing a host cell because the process requires introducing genetic material (such as plasmids) into a

¹⁷ All emphases have been added unless otherwise noted.

living cell, where the expression and self-assembly of the desired antibody product can occur. (Sections V.D, X.A.1; *see also* Ex. 1004 at ¶¶238-239, Figure 1; Ex. 1041 at 1394, 1396, Figure 1; Ex. 1023 at 3174, Figure 1; Ex. 1001 at 43:10-14, 62:9-12.) Without the host cell, there would be no mechanism for the genetic material to be transcribed, translated, and assembled into functional antibodies. (See Ex. 1041 at 1396; Ex. 1023 at 3194, Figure 1.) And *Lazar* discloses, and in fact exemplifies, co-transfection of its disclosed variants into “HEK293E cells” as the specific host cell for assembly of the disclosed heterodimeric antibodies. (See, *e.g.*, Ex. 1004 at ¶239.)

4. **“(i) a first nucleic acid molecule encoding a 1st antibody heavy chain comprising at least one substitution of a neutral amino acid residue in the CH3 domain by a positively charged amino acid residue, and
(ii) a second nucleic acid molecule encoding a 2nd antibody heavy chain comprising at least one substitution of a neutral amino acid residue in the CH3 domain by a negatively charged amino acid residue;
b. culturing said host cell and allowing for expression of said two nucleic acid molecules to produce said 1st antibody heavy chain and said 2nd antibody heavy chain, wherein the at least one positively charged amino acid residue substituted in the CH3 domain of said 1st antibody heavy chain interacts with the at least one negatively charged amino acid residue substituted in the CH3 domain of said 2nd antibody heavy chain in the interface between said 1st and 2nd antibody heavy chains to produce a heterodimeric antibody; and”**

111. It is my opinion that *Lazar* discloses the above claim limitations.

112. While long, the limitations excerpted above are simple: They require substituting a neutral amino acid residue in the CH3 domain of one antibody heavy chain with a positive amino acid residue and substituting a neutral amino acid residue in the CH3 domain of a second antibody heavy chain with a negative amino acid residue. Then as a result of the positive-and-negative charges introduced, the amino acid substitutions result in favorable electrostatic interactions within the CH3 interface between the two heavy chains, to preferentially produce a heterodimeric antibody upon expression and culture in a host cell.

113. *Lazar* explicitly teaches substituting neutral amino acids in the CH3 domains of the antibody heavy chains with charged amino acids to increase heterodimerization, just as claimed.

114. Under the heading “Fc Modifications that Favor Heterodimerization,” *Lazar* explains that Fc variants were designed and screened that led to a favorable heterodimeric CH3 interface (variant'/variant") and a stable heterodimeric Fc species (comprising CH3'/CH3"). (Ex. 1004 at ¶120; *see also* Ex. 1004 at ¶¶52 (identifying amino acid modification for stabilizing a heterodimer Fc region while destabilizing a homodimeric Fc region), 121-123 (same), 236-241 (describing design and screening of Fc variants using an empty-Fc/scFv-Fc system), Tables 1-

2.) And in Tables 1 and 2, *Lazar* reports specific, preferred CH3 domain amino acid substitutions that promote more efficient heterodimerization.

115. In Tables 1 and 2, *Lazar* discloses substituting a neutral amino acid residue in the CH3 domain of one antibody heavy chain with a positive amino acid residue and substituting a neutral amino acid residue in the CH3 domain of a second antibody heavy chain with a negative amino acid residue, as claim 1 requires. I have annotated Tables 1 and 2, below, to indicate precisely where *Lazar* provides combinations of variants (Variant 1 and Variant 2) that include neutral-to-positively charged amino acid substitutions (shown in yellow and green, respectively), as well as neutral-to-negatively charged amino acids (shown in yellow and red, respectively). (See Ex. 1004 at ¶¶52 (identifying amino acid modification for stabilizing a heterodimer Fc region while destabilizing a homodimeric Fc region), 123 (same), Tables 1 and 2; see also Ex. 1007 at 10:6-14 (explaining that aspartic acid (D) and glutamic acid (E) are negatively charged, and lysine (K), arginine (R), and histidine (H) are positively charged, at neutral pH (7.0)); Ex. 1001 at 13:1-17 (same).)

116. Further, *Lazar* discloses pairs of neutral-to-charged Fc mutations which were made at residues known to reside in the interface between the two CH3 domains of separate heavy chains. (Ex. 1004 at Tables 1 and 2, Example 2 (“Screening of Variant Fc Regions for Fc Heterodimerization”); see also Ex. 1007

at 7:8-8:7 (Table 1) (illustrating known contact residues at the native CH3 interface); Ex. 1012 at Supplementary Table 1 (same); Ex. 1001 at Table A (same).) I have indicated in red boxes in the figures below where neutral-to-positive and neutral-to-negative substitutions were made at pairs of known contact residues in the native CH3 interfaces. (Ex. 1004 at ¶241 (Table 1); *see also* Ex. 1007 at 7:8-8:7 (Table 1); Ex. 1012 at Supplementary Table 1; Ex. 1001 at Table A.) These include the pairings of S364E & L368K and L351E & L351K.

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

(Ex. 1004 at ¶241 (Tables 1 and 2) (annotations added).) Each of these highlighted and boxed variants in *Lazar* therefore teaches the claim limitations excerpted above.

117. *Lazar* further teaches that additional amino acid residue substitutions may be made in conjunction with the neutral-to-negative and neutral-to-positive substitutions. For instance, *Lazar* teaches the following “[p]referred” variant:

L351E/S364D/F405A

Y349K/L351K/T394F

As claim 1 does not require that **only** a neutral-to-negative and neutral-to-positive substitution be made, such a disclosed variant with additional modifications would equally satisfy the claim limitations excerpted in the heading above.

118. Moreover, *Lazar* teaches that these amino acid substitutions were, in fact, made. *Lazar* reports that the variants of Tables 1 and 2 were actually “designed” before being subsequently made and “screened,” ultimately showing heterodimer formation (Ex. 1004 at ¶241, Figs. 3-4.)

5. “harvesting said heterodimeric antibody from the culture.”

119. It is my opinion that *Lazar* discloses harvesting a heterodimeric antibody from the culture.

120. *Lazar* provides that the disclosed heterodimeric antibodies were “purified from the supernatant using protein A affinity chromatography.” (Ex. 1004 at ¶239.) A person of ordinary skill in the art would readily understand that “purifi[cation] **from** the supernatant” refers to harvesting the disclosed heterodimeric antibodies from a culture, as recited in the claim limitation.

121. Consistent with that discussion, *Lazar* further specifies that its disclosed heterodimeric antibodies are “purified or isolated after expression... in a variety of ways known to those skilled in the art.” (Ex. 1004 at ¶189.) For instance, *Lazar* teaches that purification or isolation may be carried out by standard methods such as “chromatographic techniques... electrophoretic, isoelectric

focusing, immunological, precipitation, dialysis, and chromatofocusing techniques.” (Ex. 1004 at ¶189.)

122. And a person of ordinary skill in the art would have readily understood that, before purification or isolation steps taught by *Lazar* can be carried out, the heterodimeric antibodies must first be “harvested.” Without a first “harvesting” step, the purification or isolation steps recited in *Lazar* would be essentially non-functional, as the heterodimeric antibodies created could not be effectively purified (or isolated). (Ex. 1024 at 480 (explaining that the first step in recovering an antibody from a cell culture is to harvest the antibodies by removing cells and cell debris); Ex. 1026 at 7 (explaining that extraction, in most cases, sets free “a considerable number of contaminating molecular species” and “clarification by centrifugation” is needed before purification), 19-20 (overviewing preliminary capture methods).)

123. The '286 patent itself recognizes that harvesting represents a necessary first step to antibody purification or isolation, and that such harvesting methods were already well-known by 2012. For example, the '286 patent states, “Ig-like molecules are expressed in host cells and are **harvested** from the cells or, preferably, from the cell culture medium **by methods that are generally known to the person skilled in the art. After harvesting**, these Ig-like molecules **may be purified** by using methods known in the art.” (Ex. 1001 at 17:6-10.)

B. 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.”

124. It is my opinion that *Lazar* discloses an a method in which “the presence of contaminating homodimers is less than 5%, preferably less than 2%, more preferably less than 1%, and most preferably homodimers are essentially absent.”

125. Specifically, *Lazar* teaches Fc variants that favor heterodimerization and disfavor homodimerization. (See Sections VII.B, X.A.) For example, *Lazar* explains that in preferred embodiments, “the two heavy chains also differ from each other by the presence of amino acid substitutions in the Fc domain,” changes which 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.” (Ex. 1004 at ¶42; see also Ex. 1004 at ¶120 (“[o]f particular benefit...are Fc variants that favor heterodimerization of the Fc region relative to homodimerization”).) As a result, these “hetero-Fc variants of the invention increase the percentage population of the heterodimer while reducing the population of the homodimers.” (Ex. 1004 at ¶¶120-122.)

126. In a section describing particular “Fc Modifications that Favor Heterodimerization,” *Lazar* teaches that employing its disclosed heterodimer

manufacture techniques (including the amino acid substitutions described above with respect to claim 1), “may alter the populations such that the heterodimer populations increases to 70%, preferably 80%, more preferably 90%, and most preferably greater than 95%.” (Ex. 1004 at ¶122.)

127. As a result of increasing the population of heterodimers (or “heterodimer purity”), *Lazar* explains that undesired homodimer yield is correspondingly “reduce[d].” (Ex. 1004 at ¶122.) The engineered Fc variants of *Lazar* create a more favorable environment for the different heavy chains to pair together while reducing the likelihood of identical heavy chains pairing, thereby limiting the formation of homodimers. (Ex. 1004 at ¶¶121-122.) So, by engineering the Fc region to promote heterodimer formation, a reduction in homodimers naturally occurs based on the principle of selective pairing in the antibody assembly process. (Ex. 1004 at ¶¶79 (explaining that antibodies are comprised of two heavy chains), 123 (explaining that an increase in heterodimer population results in a decrease in homodimer population); *see also* Ex. 1012 at ¶¶6-7 (explaining use of electrostatic steering to bias formation of heterodimers); Ex. 1015 at 617 (explaining that heavy chain association is directed by interactions within the CH3, which can be engineered using KIH); Ex. 1017 at 677 (same).)

128. A person of ordinary skill would therefore readily understand that *Lazar*’s disclosure of increasing heterodimer purity to “greater than 95%,” using

the techniques disclosed therein, represents a method of reducing “contaminating homodimers” to “less than 5%,” as claimed.

C. Claim 21: “The method according claim 1, wherein said heterodimeric antibody is human IgG.”

129. It is my opinion that *Lazar* discloses a method for producing a heterodimeric antibody that is human IgG.¹⁸

130. *Lazar* expressly instructs that, “[i]n certain embodiments, the antibodies disclosed herein comprise sequences belonging to the IgG class of antibodies, including IgG1, IgG2, IgG3, or IgG4.” (Ex. 1004 at ¶90.) The “antibodies of embodiments disclosed herein” (including those that are IgG antibodies) include the engineered heterodimers described above with respect to claim 1. *Lazar* makes just this point, specifying that the disclosed Fc variants can be based on human IgG sequences, which can belong to any IgG isotype, including IgG1. (Ex. 1004 at ¶118 (“[T]he Fc variants disclosed herein are based on human

¹⁸ I note that if claim 21—or any other claim reciting a “human IgG” or “human IgG1” limitation—is understood to require an entirely human antibody sequence, a person of ordinary skill in the art would not be able to understand these claims. Each requires non-natural amino acid residue substitutions, and inserting the claimed charge amino acid charge pairs would necessarily render the variants different from the natural “human IgG” sequences. I therefore understand the claim’s requirement that the “heterodimeric antibody [be] human IgG” to mean that the amino acid substitutions recited in the claims must be applied to a human IgG sequence.

IgG sequences, and thus human IgG sequences are used as the ‘base’ sequences against which other sequences are compared”).)

131. Moreover, *Lazar*’s Example 2 expressly teaches making the “preferred” and “most preferred” neutral-to-negative and neutral-to-positive amino acid substitutions in a heterodimer based on an IgG1 backbone (*i.e.*, a human IgG). (Ex. 1004 at ¶¶238-240.)

D. Claim 22: “A heterodimeric antibody obtained by the method of claim 1.”

132. It is my opinion that *Lazar* discloses a heterodimeric antibody obtained by the method of claim 1.

133. As noted above for claim 1 in Section X.A, *Lazar* teaches that the method of claim 1 results in the production of a heterodimeric antibody which can then be isolated and purified. That is, the result of the method disclosed by *Lazar* is, a heterodimeric antibody, as claimed in claim 22.

E. Claim 24: “A heterodimeric antibody according to claim 22, wherein said antibody is human IgG.”

134. It is my opinion that *Lazar* discloses a heterodimeric antibody according to claim 22 (*i.e.*, a heterodimeric antibody obtained by the method of claim 1) that is a human IgG.

135. For the reasons discussed above with respect to claims 1 and 21, in Sections X.A and X.D, *Lazar* teaches a method for producing a heterodimeric

antibody that is a human IgG. And as explained above with respect to claim 22, *Lazar* teaches that carrying out such a method results in the production of a heterodimeric human IgG antibody, as claimed in claim 24.

F. Claim 26

1. “A recombinant host cell comprising nucleic acid sequences encoding at least a 1st and 2nd antibody heavy chain,”

136. It is my opinion that *Lazar* discloses a recombinant host cell containing nucleic acid sequences encoding at least two different antibody heavy chains, as discussed in Section X.A.

137. As noted above, *Lazar* teaches recombinant host cells (host cells that have been transfected with genetic material that has been created through a process in which DNA molecules from different sources are altered to produce new genetic sequences), containing nucleic acid sequences encoding two different antibody heavy chains. (Sections V.D, X.A.1.)

2. “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,”

138. It is my opinion that *Lazar* discloses a CH3 domain of a first antibody heavy chain having at least one substitution of a neutral amino acid residue by a positively charged amino acid residue, as discussed above in the context of claim 1 in Section X.A.4.

3. “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.”

139. It is my opinion that *Lazar* discloses a CH3 domain of a second antibody heavy chain having at least one substitution of a neutral amino acid residue by a negatively charged amino acid residue, as discussed above in the context of claim 1 in Section X.A.4.

G. Claim 28: “A pharmaceutical composition comprising a heterodimeric antibody according to claim 22 and a pharmaceutically acceptable carrier”

140. It is my opinion that *Lazar* discloses a pharmaceutical composition comprising a heterodimeric antibody according to the method of claim 22 (*i.e.*, a heterodimeric antibody obtained by the method of claim 1), as discussed in Sections X.A and X.D, and a pharmaceutically acceptable carrier.

141. *Lazar* teaches heterodimeric antibodies along with a physiologically or pharmaceutically acceptable carrier or diluent. (Ex. 1004 at ¶55.) Specifically, *Lazar* contemplates pharmaceutical compositions that include the disclosed immunoglobulins, optionally combined with one or more therapeutically active agents, and “pharmaceutically acceptable carriers, excipients or stabilizers.” (Ex. 1004 at ¶214.) *Lazar* further provides an exemplary list of acceptable carriers, excipients, and stabilizers that are nontoxic to recipients at the dosages and concentrations used. (Ex. 1004 at ¶214.)

142. The list includes buffers such as phosphate, citrate, acetate, and other organic acids; antioxidants like ascorbic acid and methionine; preservatives; low molecular weight polypeptides (less than about 10 residues); proteins such as serum albumin, gelatin, or immunoglobulins; hydrophilic polymers like polyvinylpyrrolidone; amino acids such as glycine, glutamine, asparagine, histidine, arginine, or lysine; carbohydrates including monosaccharides, disaccharides, glucose, mannose, or dextrans; sugars such as sucrose, mannitol, trehalose, or sorbitol; fillers such as microcrystalline cellulose, lactose, corn and other starches; binding agents; additives; coloring agents; salt-forming counter-ions like sodium; metal complexes (*e.g.*, Zn-protein complexes); and non-ionic surfactants like TWEEN™, PLURONICS™, or polyethylene glycol (PEG). (Ex. 1004 at ¶214.)

143. I further note that my opinion regarding *Lazar*'s disclosure is consistent with the '286 patent's own broad definition of "pharmaceutically acceptable carrier." The '286 patent states that "[a]s used herein, such 'pharmaceutically acceptable carrier' includes any and all solvents, salts, dispersion media, coatings, antibacterial and antifungal agents, isotonic and absorption delaying agents, and the like that are physiologically compatible." (Ex. 1001 at 28:18-22.) A person of ordinary skill in the art would readily understand that the carriers taught by *Lazar* fall comfortably within this broad definition.

H. Claim 30

1. “A method for making a host cell for production of a heterodimeric antibody,”

144. It is my opinion that *Lazar* discloses a method for making a host cell to produce a heterodimeric antibody, as discussed above in Section X.A.

2. “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,”

145. As discussed above with respect to claim 1 in Section X.A, it is my opinion that *Lazar* discloses a method including the step of introducing nucleic acid molecules encoding two different antibody heavy chains, which involves introducing nucleic acid molecules into a host cell (via co-transfection) where the nucleic acid molecules include a substitution on one CH3 domain of a neutral amino acid residue by a positively charged amino acid residue, and a substitution on another CH3 domain of a neutral amino acid residue by a negatively charged amino acid residue.

3. “wherein said nucleic acid sequences are introduced consecutively or concomitantly”

146. It is my opinion that *Lazar* discloses a method including introducing nucleic acid sequences consecutively or concomitantly.

147. As discussed above with respect to claim 1 in Section X.A, *Lazar* teaches the co-transfection into a host cell of two nucleic acid sequences, each encoding a different engineered CH3 domain, to promote the formation of heterodimers. (Ex. 1004 at ¶¶122-123, 194, Figure 1, Tables 1-2.) *Lazar* further explains that such co-transfection involves the introduction of two different DNAs encoding two different heavy chains. (Ex. 1004 at ¶122.) This process is specifically used to introduce Fc variants that favor heterodimerization and disfavor homodimerization. (Ex. 1004 at ¶122.) A person of ordinary skill in the art would have understood from these teachings that *Lazar*’s co-transfection process involves the simultaneous (or “concomitant”) introduction, into a host cell, of nucleic acid sequences containing the neutral-to-positive and neutral-to-negative CH3 domain modifications described above.

I. Claim 32: “The method according to claim 21 wherein antibody is human IgG1.”

148. It is my opinion that *Lazar* discloses a method for producing a heterodimeric antibody that is a human IgG, as discussed in Section X.A with respect to claim 1, Section X.C with respect to claim 21, and Section X.E with

respect to claim 24. *Lazar* teaches implementing its techniques with “any IgG isotype or IgG isotype Fc region, including but not limited to human ***IgG1***, IgG2, IgG3, and/or IgG4.” (Ex. 1004 at ¶133.) *Lazar* exemplifies creating the “preferred” and “most preferred” variants in which neutral-to-negative and neutral-to-positive amino acid substitutions were made to a heterodimer based on an IgG1 antibody (*i.e.*, a human IgG1) heavy chain. (Ex. 1004 at ¶¶ 238-241.)

* * *

149. For the reasons I discuss in Section X above, it is my opinion that a person of ordinary skill in the art would have understood *Lazar* to teach every limitation of claims 1, 7, 21-22, 24, 26, 28, and 30-32, as arranged in the claims.

XI. Ground 2: *Lazar* in view of *Arathoon* Teaches or Suggests Claims 1-2, 7-24, 26-28, and 30-32

150. In addition to my opinion that *Lazar* teaches every limitation of claims 1, 7, 21-22, 24, 26, 28, and 30-32 of the '286 patent, as discussed above in Section X, it is my opinion that a person of ordinary skill in the art would have understood that the combination of *Lazar* and *Arathoon* discloses or suggests every limitation of these same claims.

151. Additionally, a person of ordinary skill in the art would have understood that the combination of *Lazar* and *Arathoon* discloses the further limitations of claims 2, 8-20, 23, 27, and 31. These claims recite only well-known

concepts already taught by *Lazar* and *Arathoon*, including the incorporation of a common light chain (claims 2, 27, and 31), targeting of different target epitopes (claims 9, 12, 23), the location of the target epitopes (claims 13-14), and general characteristics of different target epitopes (claims 10-11, 15-20).

152. In my analysis below, I provide an overview of the teachings of *Lazar* and *Arathoon*, before explaining how the references teach or suggest every limitation of claims 1-2, 7-24, 26-28, and 30-32, which I have grouped into categories according to the nature of the claim limitations.

A. The Related Teachings of *Lazar* and *Arathoon*

153. Consistent with the significant interest in the industry for developing heterodimeric, bispecific antibodies as of 2012, both *Lazar* and *Arathoon* teach a framework for more efficiently developing heterodimeric antibodies. (Ex. 1004 at ¶¶38, 241-242; Ex. 1006 at 5:30-38.) And, as I explain below, the respective teachings of *Lazar* and *Arathoon* could have readily been combined by a person of ordinary skill in the art with a reasonable expectation of success using well-established techniques.

154. **Lazar**: As discussed above in Section X.A, *Lazar* teaches enhancing the yield of heterodimers through modifications to the CH3 domain of antibodies, resulting Fc modifications that favor heterodimerization and disfavor unwanted homodimerization. (Ex. 1004 at ¶¶120-125 (identifying amino acid modifications

within the CH3 interface, for stabilizing a heterodimer Fc region while destabilizing a homodimeric Fc region), 241 (Tables 1 & 2); Section X.A.) *Lazar* teaches amino acid modifications to the well-characterized CH3 domain, disclosing CH3 domain variants in which a pair of neutral amino acids have been substituted with a positively and negatively charged amino acids that result in beneficial electrostatic interactions. (Ex. 1004 at ¶¶121 (“[t]he variants are designed such that their interaction in a heterodimeric CH3 interface ... is favorable”), 123 (providing numerous neutral to charged substitutions in the CH3 domain), 241 (Tables 1 & 2).)

155. Furthermore, *Lazar* teaches that the disclosed Fc-modified variants—including the variants incorporating neutral-to-positive/neutral-to-negative amino acid modifications—can be made in combination with other known techniques to promote heterodimer formation. *Lazar*, in fact, specifically cites to KIH techniques and Amgen’s electrostatic steering method (discussed above in Section V.E.4). (Ex. 1004 at ¶¶124 (“[i]n some embodiments, the hetero-Fc variants are made in combinations”),¹⁹ 125 (“[o]ther Fc variants that favor heterodimerization that may find use in the creation of the antibody analogs of the invention have been

¹⁹ *Lazar*’s recognition that these “combination variants” are possible would have suggested to a person of ordinary skill that *Lazar*’s modifications for CH3 heterodimerization are compatible with *Arathoon*’s antibodies.

described,” citing Ex. 1012 (Amgen’s electrostatic steering method) and Ex. 1021 (KIH)).)

156. **Arathoon**: Like *Lazar*, *Arathoon* teaches making modifications to the CH3 domains of two heavy chains in bispecific antibody synthesis in order to promote the formation of heterodimers. (See Ex. 1006 at 5:31-6:2 (“This application describes a strategy which serves to enhance the formation of a desired heteromultimeric bispecific antibody from a mixture of monomers by engineering an interface between a first and second polypeptide.... The preferred interface between a first and second polypeptide of the heteromultimeric antibody comprises at least a part of the CH3 domain of an antibody constant domain.”).)

157. *Arathoon* teaches a variety of techniques to promote heterodimer formation and more efficiently generate bispecific antibodies, including KIH modifications, the use of non-natural disulfide bonds, and incorporation of a common light chain. (Ex. 1006 at 40:35-42:37 (Example 1) (describing use of KIH method to produce heterodimeric antibodies), 42:38-45:21 (Example 2) (describing introduction of disulfides into CH3-CH3 interface in combination with KIH), 48:23-53:34 (Example 4) (use of common light chain in combination with KIH and disulfide bonds).)

158. *Arathoon* further explains that a person of ordinary skill in the art could further increase heterodimeric yield by combining these various techniques.

For instance, *Arathoon* teaches:

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

(Ex. 1006 at 6:1-7.)

The working examples of *Arathoon* reaffirm the additive benefits of combining multiple different strategies to promote heterodimer synthesis. Example 1, for instance, states:

Disulfides combined with protuberance-into-cavity [i.e., KIH] engineering increases the yield of heterodimer to 95%. The best disulfide pair increased the percent of heterodimer to 76% and the protuberance-into-cavity strategy increased the percent of heterodimer to 87% (Table 4; see also Ridgway et al., (1996) supra). These two strategies rely on different principles to increase the probability of generating heterodimer. Therefore, we combined the two strategies, anticipating further improvement in the yield of heterodimer... . ***Yields of approximately 95% heterodimer were obtained.***

(Ex. 1006 at 44:18-28.)

159. *Arathoon* additionally instructs that its improved heterodimer production techniques are preferably applied to IgG antibodies. (*E.g.*, Ex. 1006 at

7:18-19 (“Preferably the first and second polypeptides each comprise an antibody constant domain such as the CH3 domain of a human IgG₁.”), 15:34-35 (“the preferred interface comprises the CH3 domain of an immunoglobulin which preferably is derived from an IgG antibody and most preferably a human IgG₁ antibody.”).) Echoing its preference for IgG antibodies, *Arathoon*’s working examples demonstrate applying the disclosed CH3 interface modification techniques to IgG antibodies, thus improving heterodimer yield. (Ex. 1006 at 40:36-41:1 (“The CH3 interface between the humanized anti-CD3/CD4-IgG chimera previously described by Chamow *et al*... was engineered to maximize the percentage of heteromultimers which could be recovered.”), 41:27-30 (“Phagemids encoding anti-CD3 light (L) and heavy (H) chain variants... were co-transfected into human embryonic kidney cells, 293S, together with a CD4-IgG variant encoding phagemid.”), 43:9-14 (“Disulfide bonds were modeled into the human IgG₁ Fc.... Mutations were introduced into the CH3 domain of a humanized anti-CD3 heavy chain or CD4-IgG by site-directed mutagenesis.”).)

160. Moreover, as discussed in greater detail below, a person of ordinary skill in the art would have been motivated to combine *Lazar*’s disclosed methods for heterodimer production—including the electrostatic engineering approaches that I have previously discussed with respect to Ground 1—with the heterodimer antibody structures (and methods for making the same) taught in *Arathoon*. And a

person of ordinary skill in the art would have reasonably expected success in combining the teachings of the respective references using routine, well-established techniques.

B. CH3 Domain Charge Modification Claims (Claims 1, 22, 26, 30)

161. As explained above, it is my opinion that *Lazar*, alone, discloses the claim limitations of claims 1, 22, 26, and 30. (See Sections X.A, X.D, X.F, and X.H.)

162. In addition, it is my opinion that a person of ordinary skill in the art would have understood that the combination of *Lazar* and *Arathoon* teaches or suggests every limitation of these claims.

163. Both *Lazar* and *Arathoon* describe methods for producing a heterodimeric antibody from a single, recombinant host cell, as described in Sections X.A and XI.A. And *Lazar* expressly teaches the only other limitation of claims 1, 22, 26, and 30—substituting a neutral amino acid residue in the CH3 with for a positively charged amino acid residue and corresponding substitution of a neutral amino acid residue with a negatively charged amino acid residue—as described in Sections X.A.4 and XI.A.

164. **Motivation to Combine:** A person of ordinary skill in the art would have been motivated to combine the respective teachings of *Lazar* and *Arathoon*. As an initial matter, a person of ordinary skill in the art would have appreciated

that both references are in the same field and directed to the same goal of developing more efficient means to produce bispecific antibodies.

165. And when engineering the disclosed antibodies of *Arathoon* (or *Lazar*) a person of ordinary skill in the art would have been motivated to incorporate the “neutral-to-positive” and corresponding “neutral-to-negative” amino acid residue substitutions disclosed in *Lazar* in order to increase heterodimer yield. By 2012, it was “well-known” that modifications at the CH3 domain played a critical role in promoting heterodimer synthesis—a fact that the ’286 patent admits. (Ex. 1001 at 4:5-8 (’286 patent stating that “[f]or antibodies, it is well-known that the CH3-CH3 interaction is the primary driver for Fc dimerization” and citing prior art from 1976 and 1981).) Accordingly, a person of ordinary skill in the art would have good reason to focus on modifications to the CH3 domain, including *Lazar*’s disclosed “Preferred CH3 domain variants that favor Fc heterodimerization” and “Most preferred CH3 domain variants that favor heterodimerization” in Tables 1 and 2 of Example 2, respectively. (Ex. 1004 at Tables 1, 2.) In those limited lists of “Preferred” and “Most preferred” CH3 domain variants, *Lazar* discloses the “neutral-to-negative” and corresponding “neutral-to-positive” amino acid residue substitutions that I have previously discussed. (See Section X.A.4.) Therefore, a person of ordinary skill in the art

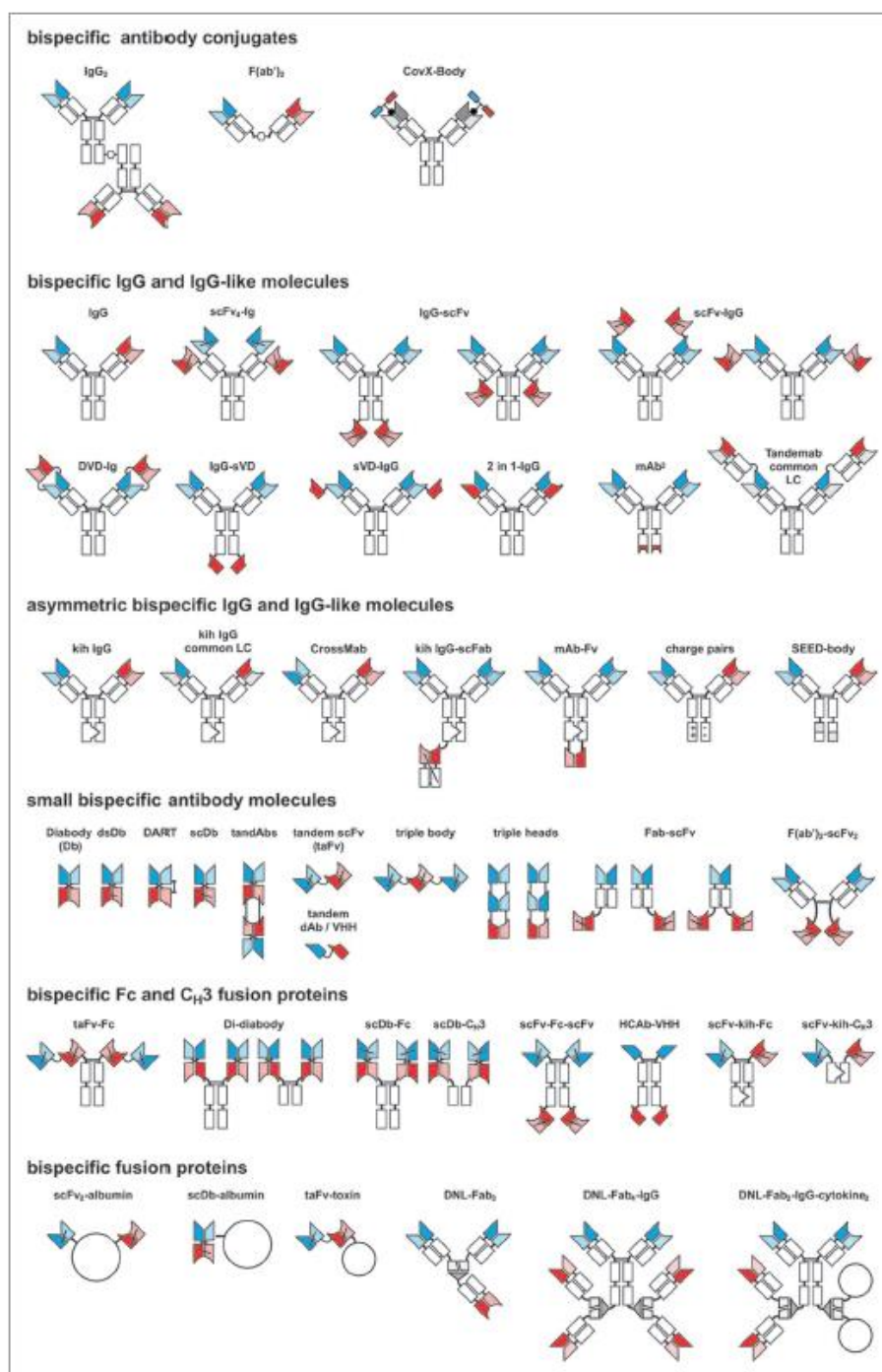
would be motivated to incorporate these modifications when following the synthesis methods disclosed in *Arathoon* (as well as *Lazar*).

166. Furthermore, a person of ordinary skill in the art would have had good reason to apply the “Preferred” and “Most preferred” heterodimer substitutions of *Lazar* as an addition to the other methods for promoting heterodimer formation disclosed in *Arathoon*. The latter expressly recognizes that “combin[ing]” multiple strategies to “increase the probability of generating heterodimer” would allow “further improvement in the yield of heterodimer.” (Ex. 1006 at 44:18-23; *see also* Ex. 1006 at 6:5-7 (describing use of various engineering methods, including KIH and disulfide bonds, to promote interactions within the CH3 domain interface), 44:18-45:21 (use of KIH and disulfide bonds to obtain high yields of heterodimers).) Therefore, a person of ordinary skill in the art would have been motivated to include *Lazar*’s disclosed CH3 modifications along with *Arathoon*’s disclosed disulfide bond or KIH approach in order to achieve even greater efficiency of heterodimer production.

167. Further, a person of ordinary skill in the art would have readily recognized that the methods and techniques taught in *Lazar* for making heterodimeric antibodies could be applied to the antibody configurations taught in *Arathoon* (or vice versa), including the preferred IgG antibody configurations of *Arathoon*. (Ex. 1006 at 15:34-35 (“[T]he preferred interface comprises the CH3

domain of an immunoglobulin which preferably is derived from an IgG antibody and most preferably a human IgG₁ antibody.”.)

168. By 2012, “more than 45 different [bispecific antibody] formats ha[d] been established.” (Ex. 1013, 184.) A prior art scientific publication from that year depicted these various bispecific antibody formats that had been developed, shown below:



(Ex. 1013, Figure 2.) And while the individual bispecific antibody structures differ, each is made up of multiple heavy chain variable domains—allowing the antibodies to engage more than one target epitope.

169. Both *Lazar* and *Arathoon* recognize that their respective techniques for increasing heterodimer yield can be applied across a range of antibody configurations that contain two different heavy chains. *Lazar* itself discusses a variety of antibody formats, and that Fc engineering could improve the heterodimer yield for each. (Ex. 1004 at ¶¶38 (explaining that the invention is “directed to a variety of antibodies”), 90 (explaining that the disclosed antibodies “may be substantially encoded by immunoglobulin genes”), 99 (describing “antibodies” as “compris[ing] a variety of structures”), 137 (describing use of mAb-Fv and mAb-Fab for antigen targeting), Figure 8 (overview of antibody and antibody analog structures).)

170. **Reasonable Expectation of Success:** A person of ordinary skill in the art would have had a reasonable expectation of success in combining *Lazar*’s and *Arathoon*’s teachings. Again, both references instruct that their respective techniques for promoting heterodimerization can be performed using a variety of antibody structures, as discussed above with respect to motivation to combine. (Ex. 1004 at ¶¶124-125; Ex. 1006 at 6:5-7, 44:18-45:21.) Moreover, such methods of carrying out the disclosed CH3 domain substitutions and the synthesis of heterodimers were well-known by 2012. (See, e.g., Ex. 1004 at ¶¶53-54, 119-125, 181-183.)

171. Further, in Example 2 of *Lazar*, the reference expressly demonstrates making the “preferred” and “most preferred” neutral-to-negative and neutral-to-positive amino acid substitutions in a heterodimer including an IgG1 antibody (*i.e.*, a human IgG). (Ex. 1004 at ¶¶238-239.) *Lazar*, in fact, demonstrates successfully synthesizing a range of heterodimeric antibodies with amino acid substitutions to a first and second amino acid chain, providing a person of ordinary skill in the art with a reasonable expectation of being able to successfully do the same.

172. Moreover, the IgG1 sequences upon which *Lazar*’s variants are based is the same type of antibody to which *Arathoon* disclosed and exemplified applying its disclosed KIH and disulfide bridge bonding techniques, further confirming that a person of ordinary skill would reasonably expect success in combining the teachings of *Lazar* and *Arathoon*. (Ex. 1006 at 7:10-14, 40:36-41:2 (“The CH3 interface between the humanized anti-CD3/CD4-IgG chimera previously described... was engineered to maximize the percentage of heteromultimers which could be recovered. Protuberance-into-cavity wild-type CH3 variants were compared in their ability to direct the formation of [heterodimers].”), 43:9-11 (“Disulfide bonds were modeled into the human IgG1 Fc”).)

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

173. Claims 2, 27, and 31 depend upon claims 1, 26, and 30, respectively, and recite only the well-known concept of incorporating a common light chain during heterodimer synthesis. As explained above, *Lazar* teaches or suggests each limitation of claims 1, 26, and 30. (Sections X.A, X.F, X.H.) And as detailed below, the combination of *Lazar* and *Arathoon* teaches or suggests the additional limitation of claims 2, 27, and 31.

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

174. It is my opinion that the combination of *Lazar* and *Arathoon* teaches or suggests the method of claim 1, further comprising providing a host cell with a nucleic acid molecule encoding a common light chain.

175. First, as discussed above in Section XI.B, the combination of *Lazar* and *Arathoon* teaches or suggests the method of claim 1.

176. Further, *Arathoon* describes using a common light chain as one technique useful for enhancing the purity of heterodimeric antibodies and minimizing mispairing of antibody chains. (Ex. 1006 at Abstract, 6:24-29.) More specifically, *Arathoon* teaches that:

[T]he 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

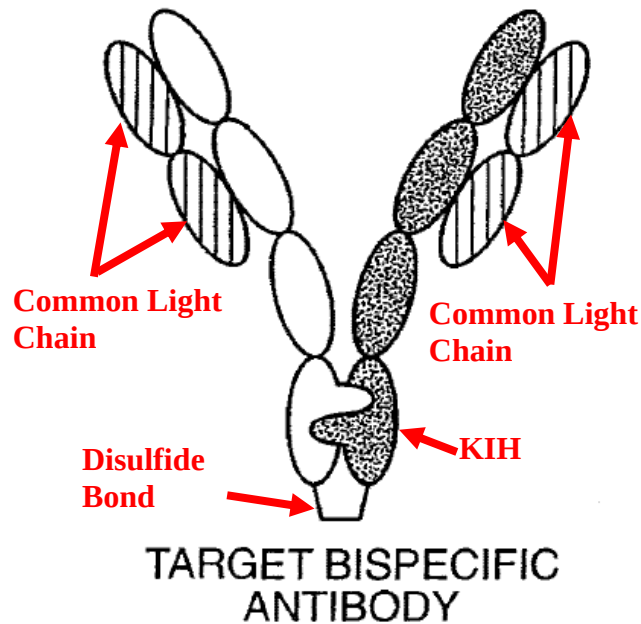
common variable light chain reduces the number of monomers that must correctly pair to form the antigen binding domains by limiting the number of light chains from two or more light chains (in a bispecific or multispecific antibody, respectively, prior to disclosure of the instant invention) to one light chain (in a multispecific antibody of the invention, see Fig. 1C).

(Ex. 1006 at 6:24-29.) *Arathoon* additionally provides an example for the generation and assembly of heteromultimeric antibodies comprising a common light chain. (Ex. 1006 at 48:23-54:36 (describing construction of Anti-Ob-R/Anti-Her3 and Anti-Mp1/Anti-Her3 bispecific antibodies which incorporate a common light chain).)

177. **Motivation to Combine:** A person of ordinary skill in the art would have been motivated to apply *Lazar*'s and *Arathoon*'s teachings of incorporating a common light chain for heterodimer antibody synthesis.

178. *Arathoon*, for instance, expressly teaches that its common light chain approach to be complementary to CH3-domain-based methods (like those disclosed in *Lazar*) for promoting heterodimerization, such as KIH and non-naturally occurring disulfide bonds (reproduced as Demonstrative 8, below):

Demonstrative 8 – Illustration of Common Light Chain from *Arathoon*

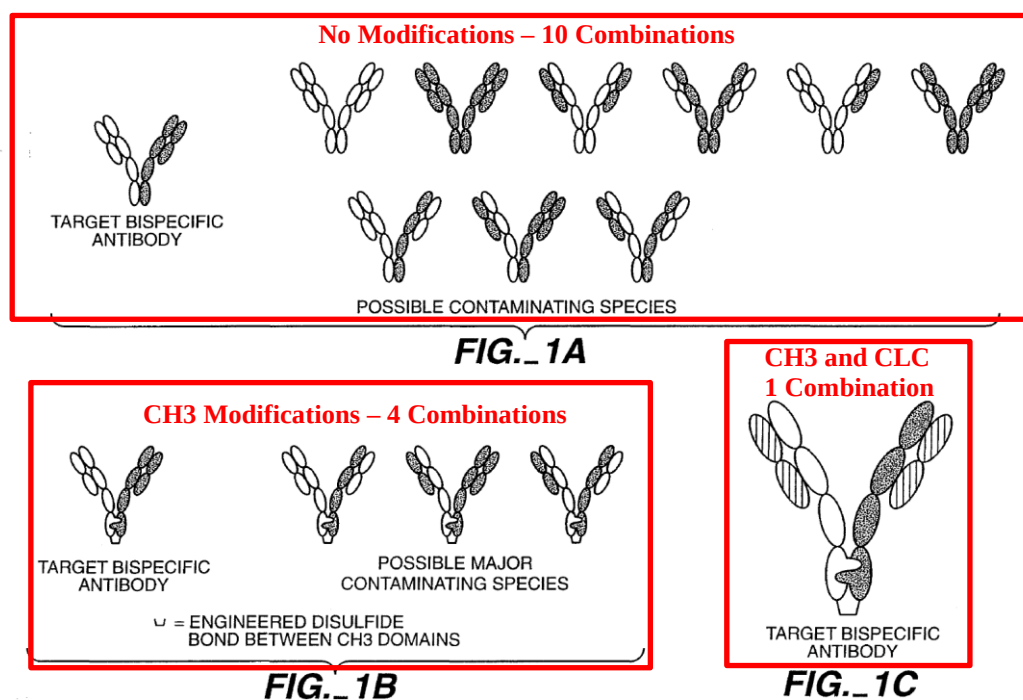


(Ex. 1006 at Figure 1C (annotations added), 40:28-34 (describing Figure 1C); *see also* Ex. 1006 at Figure 1B (explaining the bracket at the bottom of the antibody is an “engineered disulfide bond between CH3 domains”).)

179. *Arathoon*, in fact, demonstrates why a person of ordinary skill in the art would have good reason to include a common light chain approach in connection with a CH3 modification technique. Figure 1 of *Arathoon* demonstrates how the use of a common light chain reduces the total number of possible heavy-light chain combinations, as demonstrated by the transition from Figure 1A representing co-expression of two different unmodified antibodies (10 options, one of which is the target bispecific antibody and 9 of which are possible

contaminating species) to Figure 1B representing co-expression of two antibodies with CH3 modifications to drive proper heavy chain assembly (four options, one of which is the target bispecific antibody and 3 of which are possible major contaminating species), and ultimately to Figure 1C where the two antibodies share a common light chain (one option—the target bispecific antibody alone). (Ex. 1006, Figure 1.) Narrowing possible contaminants from 9 possibilities to none would have been evident and attractive to a person of ordinary skill in the art as an effective strategy for improving heterodimeric antibody production. (Ex. 1006, Figure 1.)

Demonstrative 9 – Effect of Adding Common Light Chain



(Ex. 1006, Figure 1 (annotations added).)

180. In concert with limiting the number of “possible contaminating species” through a common light chain approach, a person of ordinary skill in the art would readily appreciate that *Lazar*’s disclosed CH3 domain modifications (including its disclosed neutral-to-negative and neutral-to positive variants) could further promote heterodimer formation. Accordingly, *Arathoon*’s teachings, when combined with *Lazar*’s CH3 domain modifications, would have provided a person of ordinary skill in the art with a clear, viable, and successful strategy for enhancing the yield and purity of heterodimeric antibodies.

181. **Reasonable Expectation of Success:** A person of ordinary skill in the art would have had a reasonable expectation of success in combining *Lazar* and *Arathoon*’s teaching of using a common light chain in heterodimer synthesis with *Lazar*’s disclosure of CH3 domain variants. *Arathoon*, in fact, expressly demonstrated success in applying the common light chain approach using well-known techniques as early as 1998. (Ex. 1006 at 6:24-7:9, 25:25-36:36.) Combining a common light chain approach with other heterodimer-promoting techniques—in this case, KIH—allowed the inventors of *Arathoon* to improve heterodimer yield to approximately 95%. (Ex. 1006 at 44:18-28.)

182. Moreover, the use of a common light chain to reduce the likelihood of mispairing was a well-known solution in the art long before April 2012, and was known to be successful in combination with other heterodimerization-promoting

methods, further strengthening the person of ordinary skill in the art's reasonable expectation of success in combining these techniques. (Ex. 1006 at 6:26-29 (“[u]se of a common variable light chain reduces the number of monomers that must correctly pair to form the antigen binding domains”), Figure 1 (illustrating benefits of engineered heavy chains and common light chain for making heteromultimeric antibodies); Ex. 1017 at 677 (reporting that “[l]ight chain mispairing was circumvented by using an identical light chain”); Ex. 1005 at 19 (describing Figure 18, which illustrates incorporation of a common light chain into an asymmetric bispecific antibody), Figure 18.)

2. 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”

183. It is my opinion that the combination of *Lazar* and *Arathoon* teaches or suggests the recombinant host cell of claim 26, further comprising a nucleic acid molecule encoding a common light chain.

184. First, as discussed above in Section XI.B, the combination of *Lazar* and *Arathoon* teaches or suggests the recombinant host cell of claim 26. And for the reasons discussed above with respect to claim 2, the combination of *Lazar* and *Arathoon* further teaches or suggests incorporating a common light chain to promote heterodimer synthesis.

185. **Motivation to Combine and Reasonable Expectation of Success:**

As discussed above, a person of ordinary skill in the art would have been motivated to combine the teachings of *Lazar* and *Arathoon* to create a heterodimeric antibody utilizing *Lazar*'s CH3 domain modifications (neutral to charged) along with a common light chain, with a reasonable expectation of success. (Section XI.C.1.) By 2012, it had long been known in the art that "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" and that "[u]se of a common variable light chain reduces the number of monomers that must correctly pair to form the antigen binding domains by limiting the number of light chains from two or more light chains." (Ex. 1006 at 6:26-29.) And by 2012, a common light chain approach had already been successfully combined with CH3 domain modification strategies to promote heterodimer synthesis and yield "approximately 95% heterodimer." (Ex. 1006 at 44:18-28.)

3. **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."**

186. It is my opinion that the combination of *Lazar* and *Arathoon* teaches or suggests the method of claim 30, further comprising the step of introducing into a host cell a nucleic acid molecule encoding a common light chain.

187. First, as discussed above in Section XI.B, the combination of *Lazar* and *Arathoon* teaches or suggests the method of claim 30. And for the reasons discussed above with respect to claim 2, the combination of *Lazar* and *Arathoon* further teaches or suggests incorporating a common light chain to promote heterodimer synthesis.

188. **Motivation to Combine and Reasonable Expectation of Success:**

As discussed above, a person of ordinary skill in the art would have been motivated to combine the teachings of *Lazar* and *Arathoon* to create a heterodimeric antibody utilizing *Lazar*'s CH3 domain modifications (neutral to charged) along with a common light chain, with a reasonable expectation of success. (Section XI.C.1.) By 2012, it had long been known in the art that “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 to form the antigen binding domains by limiting the number of light chains from two or more light chains.” (Ex. 1006 at 6:24-29.) And by 2012, a common light chain approach had already been successfully combined with CH3 domain modification strategies to promote heterodimer synthesis and yield “approximately 95% heterodimer.” (Ex. 1006 at 44:18-28.)

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

189. As explained above, it is my opinion that *Lazar* alone discloses the claim limitations of claim 7. (Section X.B.)

190. As an initial matter, claim 7 of the '286 patent depends from claim 1. And for the reasons discussed above in Section XI.B, a person of ordinary skill in the art would understand that the combination of *Lazar* and *Arathoon* discloses or suggests each limitation of claim 1. It is my opinion that a person of ordinary skill in the art would additionally understand that the combination of *Lazar* and *Arathoon* likewise discloses or suggests each limitation of claim 7.

191. Both *Lazar* and *Arathoon* teach the use of CH3 domain modifications to achieve high levels of heterodimer purity, just as claimed. (Ex. 1004 at ¶¶119-125; Ex. 1006 at 5:31-7:36, 24:3-28:24 (“Generating a Protuberance and/or Cavity”), 44:18-28 (“Disulfides combined with protuberance-into-cavity”).) *Lazar* teaches that the disclosed “hetero-Fc variants may reduce the homodimer populations to 2.5% and 2.5% while increasing the heterodimer population to 95%.” (Ex. 1004 at ¶122, Figure 7.) Equally, *Arathoon* reports obtaining heterodimer yields of approximately 95% by combining multiple approaches to improve heterodimer yield (specifically, KIH and disulfide bridges). (Ex. 1006 at 44:18-45:21 (Example 2E and Table 4 reporting yields of 95 ± 2 and 95.5 ± 0.5 , respectively).) And a person of ordinary skill the art would readily understand that

achieving a heterodimer yield of 95% or greater results in less than 5% contaminating homodimers.

192. **Motivation to Combine:** Both *Lazar* and *Arathoon* provide strong motivation to optimize heterodimer yield—reducing the contaminating homodimer population to below 5%, as claimed—using multiple modification strategies. A person of ordinary skill in the art would have understood that maximizing the desired heterodimer population ensures that more of the output consists of the intended heterodimeric antibodies, which is crucial for effectiveness and therapeutic value. (Section V.D.)

193. **Reasonable Expectation of Success:** A person of ordinary skill in the art would further have had a reasonable expectation of success in combining the teachings of *Lazar* and *Arathoon* in order to synthesize heterodimer antibodies with less than 5% contaminating homodimers. *Lazar* and *Arathoon* each teach making CH3 domain modifications so as to improve heterodimer yield. (Ex. 1004 at ¶¶119-125; Ex. 1006 at 5:31-7:36, 24:3-28:24 (“Generating a Protuberance and/or Cavity”), 44:18-28 (“Disulfides combined with protuberance-into-cavity”).) Moreover, both *Lazar* and *Arathoon* teach high levels of heterodimer purity, with *Lazar* disclosing a “heterodimer population ... most preferably greater than 95%” (Ex. 1004 at ¶122). Similarly, *Arathoon* demonstrates in its working examples that combining KIH and disulfide bridge techniques resulted in heterodimer yields of

“ 95 ± 2 ” and “ 95.5 ± 0.5 ” (Ex. 1006 at 44:18-45:21 (Example 2E and Table 4).)

By incorporating another CH3 domain modification technique—like the neutral-to-negative or neutral-to-positive substitutions taught by *Lazar* to be “preferred” or “most preferred”—a person of ordinary skill in the art would reasonably expect to achieve similarly high levels of heterodimer purity.

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

194. Claims 8-20 and 23 recite general, well-known binding characteristics of bispecific antibodies, including targeting different target epitopes or antigens (claims 9, 12, 23), different antigens located on the same or different cells (claims 13-14), and certain categories of targets or specific targets (claims 10-11, 15-20). But as detailed below, the combination of *Lazar* and *Arathoon* teaches or suggests each of the additional limitations provided each of claims 8-20 and 23.

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

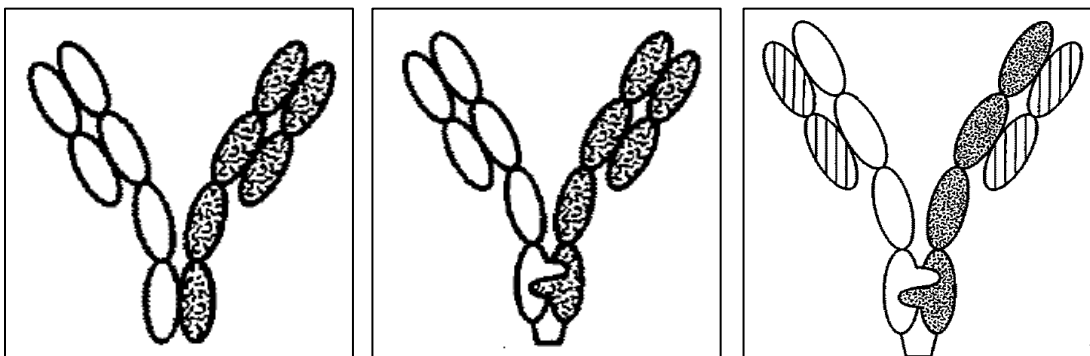
195. It is my opinion that *Lazar* and *Arathoon* together teach or suggest the method of claim 1, wherein each variable region of the 1st and 2nd antibody heavy chains recognizes a different target epitope.

196. First, as discussed above in Section XI.B, the combination of *Lazar* and *Arathoon* teaches or suggests the method of claim 1.

197. Additionally, *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.” (Ex. 1004 at ¶38, 138 (explaining that “[v]irtually any antigen may be targeted” including “epitopes belonging to the following list of antigens”).) As *Lazar* further explains, “[t]he immunoglobulins of the invention may target virtually any antigen or pair of antigens” and may more specifically “target[] distinct antigens, that is where antigen-1 and antigen-2 are different. Thus the immunoglobulins herein preferably co-engage two target antigens.” (Ex. 1004 at ¶135.) A person of ordinary skill in the art would have understood that *Lazar*’s teachings of such multi-specific antibodies discloses a heterodimeric antibody in which the variable region of the 1st and 2nd antibody heavy chains recognizes a different target epitope, as required by claim 8.

198. Similarly, *Arathoon*’s disclosure also provides multiple bispecific antibody formats in which the disclosed heterodimers recognize distinct target epitopes. (Ex. 1006, Example 4 at 48:23-53:34.) For instance, Figure 1 of *Arathoon* shows an exemplary bispecific antibody structure—incorporating CH3 domain modifications, as shown by the KIH and disulfide bond approaches depicted in the middle and right panels below—in which the heavy chain arms of the “Y” structure recognize different targets.

Demonstrative 10 – Bispecific Antibody Formats from *Arathoon*



199. **Motivation to Combine**: A person of ordinary skill would have been motivated to apply *Lazar*'s CH3 domain modifications to the bispecific antibody structure shown in *Arathoon*, for the reasons already discussed above. (Sections XI.A-B.)

200. Further, a person of ordinary skill in the art would have had good reason to combine the teachings of *Lazar* and *Arathoon* to make a bispecific antibody targeting multiple epitopes in order to target multiple pathways or receptors simultaneously. A person of ordinary skill in the art would have recognized that development of a bispecific antibody targeting multiple epitopes permits combining different therapeutic modalities and therapeutic benefits in a single molecule. This, in turn, would obviate the requirement to develop two individual antibodies, which permits a substantial reduction in costs associated with manufacturing, clinical trials, and regulatory review. (Ex. 1013 at 183 (explaining development of bispecific antibodies is "less complex because

manufacturing, preclinical and clinical testing is reduced to a single, bispecific molecule”).)

201. **Reasonable Expectation of Success:** A person of ordinary skill in the art by 2012 would have had a reasonable expectation of success in generating the claimed bispecific antibodies targeting a variety of known antigens because of the established methodologies and the increasing body of knowledge surrounding antibody engineering. (Ex. 1006 at 5:31-38, 7:37-8:28, 17:32-21:6, Example 3; Ex. 1013 at 183-185, 187, 191, Tables 1-2, Figures 1-2; Ex. 1039 at 524; Ex. 1004 at ¶3.)

202. By 2012, researchers had a good understanding of the structure-function relationships that govern antibody specificity and function, including in the context of bispecific antibodies. (Ex. 1013 at 183-185 (describing dual targeting strategies and bispecific antibody formats), Tables 1-2, Figures 1-2.) Methods of creating bispecific antibodies targeting different epitopes or antigens were also well-known. (Ex. 1013 at 183-185, 187, 191, Tables 1-2, Figures 1-2; Ex. 1039 at 524; Ex. 1004 at ¶¶3, 242 (describing ability of mAb-Fv and mAb-Fab structures to co-target antigens), 244, 256, 262, Tables 3-5 (describing bispecific mAb-Fab and mAb-Fv antibodies).) In fact, the '286 patent implicitly recognizes that implementation of various heavy chain-targeting strategies was well known by a person of ordinary skill in the art, listing various bispecific permutations and

targets without actually describing such targeting strategies in detail. (*See, e.g.*, Ex. 1001 at 25:62-26:49.)²⁰ Accordingly, a person of ordinary skill in the art would have reasonably expected to successfully produce the heterodimeric antibody of claim 1 and target multiple epitopes using the same.

2. Claim 9: “The method of claim 8, wherein the different target epitopes are located on the same target molecule.”

203. It is my opinion that *Lazar* and *Arathoon* together teach or suggest the “method of claim 8, wherein the different target epitopes are located on the same target molecule.”

204. As discussed above in Section XI.E.1, the combination of *Lazar* and *Arathoon* teaches or suggests the method of claim 8.

205. Moreover, as described above, *Lazar* teaches that the “immunoglobulins of the invention may target virtually any antigen or pair of antigens,” (Ex. 1004 at ¶135), including scenarios where “antigen-1 and antigen-2” are the same, meaning that Fv-1 and Fv-2 have specificity for the same antigen. (Ex. 1004 at ¶¶50, 137.) In fact, *Lazar* suggests that Fv-1 and Fv-2 having “specificity for the same antigen” may be beneficial in certain cases. (Ex. 1004 at

²⁰ Therefore, to the extent that the patent owner argues a person of ordinary skill in the art would not reasonably expect to design a bispecific antibody in which the “1st and 2nd antibody heavy chains recognizes a different target epitope”—or any other of the binding target claim limitations of claims 8-20 and 23—the ’286 patent would lack the disclosure to allow such a person to use the alleged invention.

¶137.) A person of ordinary skill in the art would have understood these teachings in *Lazar* to describe bispecific antibodies with different target epitopes located on the same target molecule, *i.e.*, the same antigen.

206. **Motivation to Combine and Reasonable Expectation of Success:**

As discussed above, a person of ordinary skill in the art would have been motivated to combine the teachings of *Lazar* and *Arathoon* to create a bispecific antibody utilizing *Lazar's* CH3 domain modifications (neutral to charged), with a reasonable expectation of success. (Section XI.B.) Moreover, a person of ordinary skill in the art would have been further motivated to target two epitopes located on the same target molecule, as taught in *Lazar*, due to the well-established broad applicability of bispecific antibodies. (Sections XI.B, XI.E.1.) By 2012, methods of creating bispecific antibodies targeting different epitopes or antigens were also well-known, providing a person of ordinary skill in the art with a reasonable expectation of success. (Sections XI.B, XI.E.1.)

3. Claim 10: “The method of claim 9, wherein the target molecule is a soluble molecule.”

207. It is my opinion that *Lazar* and *Arathoon* alone or together teach or suggest the “method of claim 9, wherein the target molecule is a soluble molecule.”

208. As discussed above in Section XI.E.2, the combination of *Lazar* and *Arathoon* teaches or suggests the method of claim 9.

209. In addition, *Lazar* teaches target antigens that are soluble target molecules, including: cytokines, VEGF, HGF, P1GF, IGF1, IGF2, and others. (Ex. 1004 at ¶138.)

210. **Motivation to Combine and Reasonable Expectation of Success:**

As discussed above, a person of ordinary skill in the art would have been motivated to combine the teachings of *Lazar* and *Arathoon* to create a bispecific antibody utilizing *Lazar*'s CH3 domain modifications (neutral to charged), with a reasonable expectation of success. (Section XI.B.) Moreover, a person of ordinary skill in the art would have been further motivated to target molecules, at least one of which is a soluble molecule, as taught in *Lazar*, due to the well-established broad applicability of bispecific antibodies. (Sections XI.B, XI.E.1.) For instance, *Lazar* teaches a number of therapeutic applications in which the heterodimers “co-target” at least one soluble molecule—more specifically, a cytokine. (See, e.g., Ex. 1004 at ¶¶ 145-150.) By 2012, methods of creating bispecific antibodies targeting different epitopes or antigens were also well-known, including antibodies that target soluble molecules, providing a person of ordinary skill in the art with a reasonable expectation of success. (Sections XI.B, XI.E.1.)

4. Claim 11: “The method of claim 9, wherein the target molecule is a membrane-bound molecule.”

211. It is my opinion that *Lazar* and *Arathoon* alone or together teach or suggest the “method of claim 9, wherein the target molecule is a membrane-bound molecule.”

212. As discussed above in Section XI.E.2, the combination of *Lazar* and *Arathoon* teaches or suggests the method of claim 9.

213. In addition, *Lazar* teaches target antigens that are membrane-bound target molecules, including, as one example, transmembrane receptors. (Ex. 1004 at ¶138.) Other exemplary membrane-bound molecules include cluster of differentiation (CD) proteins (e.g., CD3, CD4, CD5, CD6, CD7, CD8, etc.), Her2, Her3, Her4, and more. (Ex. 1004 at ¶138.) *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. (Ex. 1004 at ¶¶244, 256, 262, Tables 3-5.)

214. **Motivation to Combine and Reasonable Expectation of Success:**

As discussed above, a person of ordinary skill in the art would have been motivated to combine the teachings of *Lazar* and *Arathoon* to create a bispecific antibody utilizing *Lazar*'s CH3 domain modifications (neutral to charged), with a reasonable expectation of success. (Section XI.B.) Moreover, a person of ordinary

skill in the art would have been further motivated to target molecules, at least one of which is a membrane-bound molecule, as taught in *Lazar*, due to the well-established broad applicability of bispecific antibodies. (Sections XI.B, XI.E.1.) By 2012, methods of creating bispecific antibodies targeting different epitopes or antigens were also well-known, including at least one of which is a membrane-bound molecule target providing a person of ordinary skill in the art with a reasonable expectation of success. (Sections XI.B, XI.E.1.)

5. Claim 12: “The method of claim 8, wherein the different target epitopes are located on different target molecules.”

215. It is my opinion that *Lazar* and *Arathoon* alone or together teach or suggest the “method of claim 8, wherein the target molecule is a membrane-bound molecule.”

216. As discussed above in Section XI.E.1, the combination of *Lazar* and *Arathoon* teaches or suggests the method of claim 8.

217. Moreover, *Lazar* teaches that the “immunoglobulins of the invention may target virtually any antigen or pair of antigens,” (Ex. 1004 at ¶135), including where “the first and second antigens are distinct” and “Fv-1 and Fv-2 bind different antigens” (Ex. 1004 at ¶¶50, 137). A person of ordinary skill in the art would have understood that binding distinct antigens, each being its own molecule, discloses different target epitopes located on different target molecules, as claimed.

218. *Lazar* teaches several applications in which co-targets are located on different types of target molecules involved in distinct therapeutic applications—for oncology (Ex. 1004 at ¶141), autoimmune and inflammatory disorders (Ex. 1004 at ¶144), inflammatory disease (Ex. 1004 at ¶145), asthma treatment (Ex. 1004 at ¶146), rheumatoid arthritis (Ex. 1004 at ¶147), multiple sclerosis (Ex. 1004 at ¶149), and sepsis (Ex. 1004 at ¶150). *Lazar* also teaches co-targeting “Her2 and CD3” and even makes bispecific mAb-Fv antibodies which co-target the two. (Ex. 1004 at ¶¶141, 262, Table 5.) A person of ordinary skill in the art would have understood that epitopes to HER2 (a common cancer biomarker) and CD3 (a T cell co-receptor) would be located on different molecules.

219. **Motivation to Combine and Reasonable Expectation of Success:**

As discussed above, a person of ordinary skill in the art would have been motivated to combine the teachings of *Lazar* and *Arathoon* to create a bispecific antibody utilizing *Lazar*'s CH3 domain modifications (neutral to charged), with a reasonable expectation of success. (Section XI.B.) Moreover, a person of ordinary skill in the art would have been further motivated to target different epitopes on different target molecules, as taught in *Lazar*, due to the well-established broad applicability of bispecific antibodies. (Sections XI.B, XI.E.1.) By 2012, methods of creating bispecific antibodies targeting different epitopes or antigens were also well-known, including different epitopes on different target molecules providing a

person of ordinary skill in the art with a reasonable expectation of success.

(Sections XI.B, XI.E.1.)

6. Claim 13: “The method of claim 12, wherein the different target molecules are expressed on the same cells.”

220. It is my opinion that *Lazar* and *Arathoon* together teach or suggest the “method of claim 12, wherein the different target molecules are expressed on the same cells.”

221. As discussed above in Section XI.E.2, the combination of *Lazar* and *Arathoon* teaches or suggests the method of claim 9.

222. Further, *Lazar* provides an exemplary list of antigens which can be “co-targets.” (Ex. 1004 at ¶141.) A person of ordinary skill in the art would have known that some of these co-targets are expressed on the same cell, such as HER-2 and ERB3. *Lazar* also teaches target antigens that are from the TNF receptor family, chemokine receptors, and interleukin receptors, which a person of ordinary skill in the art would have understood could be co-expressed on immune cells. (Ex. 1004 at ¶¶138, 143, 146.) For example, *Lazar* teaches chemokine receptors that are commonly co-expressed on immune cells like T-cells, macrophages, and dendritic cells, including CCR1, CCR2, CCR3, CCR4, CCR5, and CCR6. (Ex. 1004 at ¶138; *see also* Ex. 1011 at 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. (Ex. 1004 at ¶138; *see also* Ex. 1011 at Appendix II.)

223. **Motivation to Combine and Reasonable Expectation of Success:**

As discussed above, a person of ordinary skill in the art would have been motivated to combine the teachings of *Lazar* and *Arathoon* to create a bispecific antibody utilizing *Lazar's* CH3 domain modifications (neutral to charged), with a reasonable expectation of success. (Section XI.B.) Moreover, a person of ordinary skill in the art would have been further motivated to target different target molecules expressed on the same cells, as taught in *Lazar*, due to the well-established broad applicability of bispecific antibodies. (Sections XI.B, XI.E.1.) By 2012, methods of creating bispecific antibodies targeting different epitopes or antigens were also well-known, including different target molecules expressed on the same cells providing a person of ordinary skill in the art with a reasonable expectation of success. (Sections XI.B, XI.E.1.)

7. **Claim 14: “The method of claim 12, wherein the different target molecules are expressed on different cells.”**

224. It is my opinion that *Lazar* and *Arathoon* alone or together teach or suggest the “method of claim 12, wherein the different target molecules are expressed on different cells.”

225. As discussed above in Section XI.E.5, the combination of *Lazar* and *Arathoon* teaches or suggests the method of claim 12.

226. *Lazar* further 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.” (Ex. 1004 at ¶6, 136.) Furthermore, *Lazar* provides specific examples in its list of target antigens that would be expressed on different types of cells because they are specific to one cell type or another or are involved in different biological processes. (Ex. 1004 at ¶141.) As an example of such an approach, *Lazar* discloses co-targeting “Her2 and CD3” and synthesizes bispecific mAb-Fv antibodies that co-target both. (Ex. 1004, ¶¶141, 262, Table 5.) A person of ordinary skill in the art would have understood that Her2 (which is a well-known cancer biomarker) and CD3 (a well-known T cell co-receptor) would be expressed on different cells.

227. **Motivation to Combine and Reasonable Expectation of Success:**

As discussed above, a person of ordinary skill in the art would have been motivated to combine the teachings of *Lazar* and *Arathoon* to create a bispecific antibody utilizing *Lazar*’s CH3 domain modifications (neutral to charged), with a reasonable expectation of success. (Section XI.B.) Moreover, a person of ordinary skill in the art would have been further motivated to target different target molecules expressed on different cells, as taught in *Lazar*, due to the well-

established broad applicability of bispecific antibodies. (Sections XI.B, XI.E.1.)

By 2012, methods of creating bispecific antibodies targeting different epitopes or antigens were also well-known, including different target molecules expressed on different cells providing a person of ordinary skill in the art with a reasonable expectation of success. (Sections XI.B, XI.E.1.)

8. Claim 15: “The method of claim 12, wherein the different target molecules are soluble molecules.”

228. It is my opinion that *Lazar* and *Arathoon* together teach or suggest the “method of claim 12, wherein the different target molecules are soluble molecules.”

229. As discussed above in Section XI.E.5, the combination of *Lazar* and *Arathoon* teaches or suggests the method of claim 12.

230. In addition, *Lazar* teaches target antigens that are soluble molecules, including, as one example, cytokines. (Ex. 1004 at ¶138.) *Lazar* further teaches a number of specific combinations of two different soluble target molecules, including HGF and VEGF, VEGF and PLGF, and IGF1 and IGF2. (Ex. 1004 at ¶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). (Ex. 1004 at ¶150.)

231. **Motivation to Combine and Reasonable Expectation of Success:**

As discussed above, a person of ordinary skill in the art would have been motivated to combine the teachings of *Lazar* and *Arathoon* to create a bispecific antibody utilizing *Lazar's* CH3 domain modifications (neutral to charged), with a reasonable expectation of success. (Section XI.B.) Moreover, a person of ordinary skill in the art would have been further motivated to target different target molecules that are soluble, as taught in *Lazar*, due to the well-established broad applicability of bispecific antibodies. (Sections XI.B, XI.E.1.) By 2012, methods of creating bispecific antibodies targeting different epitopes or antigens were also well-known, including different target molecules that are soluble providing a person of ordinary skill in the art with a reasonable expectation of success. (Sections XI.B, XI.E.1.)

9. **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.”**

232. It is my opinion that *Lazar* and *Arathoon* together teach or suggest the “method of claim 12, wherein one target molecule is a soluble molecule whereas the second target molecule is a membrane bound molecule.”

233. As discussed above in Section XI.E.5, the combination of *Lazar* and *Arathoon* teaches or suggests the method of claim 12.

234. Moreover, *Lazar* teaches target antigens that are immune receptors, which are “activated upon immune complexation,” which *Lazar* describes as “cross-linking, achieved typically by antibody/antigen immune complexes.” (Ex. 1004 at ¶136.) In such cases, an antibody would bind both an immune cell and another target. *Lazar* teaches that the target antigen on the immune cell could be membrane-bound, while the second target could be soluble. More specifically, *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 c-MET and HGF, IGR1R and VEGF, Her2 and VEGF. (Ex. 1004 at ¶141.) *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). (Ex. 1004at ¶150.)

235. **Motivation to Combine and Reasonable Expectation of Success:**

As discussed above, a person of ordinary skill in the art would have been motivated to combine the teachings of *Lazar* and *Arathoon* to create a bispecific antibody utilizing *Lazar*’s CH3 domain modifications (neutral to charged), with a reasonable expectation of success. (Section XI.B.) Moreover, a person of ordinary skill in the art would have been further motivated to target different target molecules that are membrane-bound, as taught in *Lazar*, due to the well-established broad applicability of bispecific antibodies. (Sections XI.B, XI.E.1.)

By 2012, methods of creating bispecific antibodies targeting different epitopes or antigens were also well-known, including different target molecules that are membrane-bound providing a person of ordinary skill in the art with a reasonable expectation of success. (Sections XI.B, XI.E.1.)

10. Claim 17: “The method of claim 8, wherein at least one of said target epitopes is located on a tumor cell.”

236. It is my opinion that *Lazar* and *Arathoon* alone or together teach or suggest the “method of claim 8, wherein at least one of said target epitopes is located on a tumor cell.”

237. As discussed above in Section XI.E.1, the combination of *Lazar* and *Arathoon* teaches or suggests the method of claim 8.

238. In addition, *Lazar* teaches “an immunoglobulin of the present invention that is intended as an anti-cancer therapeutic,” and lists several potential cancers to be targeted. (Ex. 1004 at ¶196; *see also* Ex. 1004 at ¶¶203, 206-207.). More particularly, *Lazar* teaches the “immunoglobulins herein” are useful 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.” (Ex. 1004 at ¶¶206-207.) A person of ordinary skill in the art would have understood from this disclosure that *Lazar* is teaching that one of the target epitopes for its heterodimeric antibodies would be located on a tumor cell (such as a T or NK cell).

Additionally, *Lazar* expressly teaches targeting of Her2+ SK-BR-3 breast carcinoma cells using bispecific antibody constructs designed to co-target Her2 and FcγRIIIa. (Ex. 1004 at ¶¶244, 254, Table 3.)

239. **Motivation to Combine and Reasonable Expectation of Success:**

As discussed above, a person of ordinary skill in the art would have been motivated to combine the teachings of *Lazar* and *Arathoon* to create a bispecific antibody utilizing *Lazar*'s CH3 domain modifications (neutral to charged), with a reasonable expectation of success. (Section XI.B.) Moreover, a person of ordinary skill in the art would have been further motivated to target different an epitope on a tumor cell, as taught in *Lazar*, particularly given the known use of “antibody-based therapeutics... to treat a variety of diseases, including cancer and autoimmune/inflammatory disorders,” and *Lazar*'s disclosure of cancer-treatment applications. (See Ex. 1004 at ¶¶3, 203, 206; see also Sections XI.B, XI.E.1.) By 2012, methods of creating bispecific antibodies targeting different epitopes or antigens were also well-known, including an epitope on a tumor cell, providing a person of ordinary skill in the art with a reasonable expectation of success. (Sections XI.B, XI.E.1.)

11. Claim 18: “The method of claim 8, wherein at least one of said target epitopes is located on an effector cell.”

240. It is my opinion that *Lazar* and *Arathoon* together teach or suggest “the method of claim 8, wherein at least one of said target epitopes is located on an effector cell.”

241. As discussed above in Section XI.E.1, the combination of *Lazar* and *Arathoon* teaches or suggests the method of claim 8.

242. *Lazar* further teaches target antigens that are immune receptors, which are “activated upon immune complexation,” which *Lazar* describes as “cross-linking, typically achieved by antibody/antigen immune complexes.” (Ex. 1004 at ¶136.) In such cases, *Lazar*’s heterodimeric antibody must bind both an immune cell and another target. A person of ordinary skill in the art would have understood that immune receptors are located on immune cells, which are a type of effector cell. Types of immune system cells that would have been recognized as effector cells include T-cells, B-cells, macrophages. *Lazar* teaches target antigens that would be located on such effector cells, including those located on T cells (CD3, CD4, CD8, CD28, and OX40); 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). (Ex. 1004 at ¶¶138, 142, ¶¶243-244, 255-256, 261-262, Tables 3-5.) *Lazar* further specifically describes bispecific constructs that monovalently target

CD16 (FcγRIIIa), an activating receptor located on NK cells. (Ex. 1004 at Example 4, Table 3, ¶¶243-254.)

243. **Motivation to Combine and Reasonable Expectation of Success:**

As discussed above, a person of ordinary skill in the art would have been motivated to combine the teachings of *Lazar* and *Arathoon* to create a bispecific antibody utilizing *Lazar*'s CH3 domain modifications (neutral to charged), with a reasonable expectation of success. (Section XI.B.) Moreover, a person of ordinary skill in the art would have been further motivated to target different an epitope on an effector cell, as taught in *Lazar*, due to the well-established broad applicability of bispecific antibodies. (Sections XI.B, XI.E.1.) By 2012, methods of creating bispecific antibodies targeting different epitopes or antigens were also well-known, including an epitope on an effector cell, providing a person of ordinary skill in the art with a reasonable expectation of success. (Sections XI.B, XI.E.1.)

12. 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.”

244. It is my opinion that *Lazar* and *Arathoon* alone or together teach or suggest “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.”

245. As discussed above in Section XI.E.11, the combination of *Lazar* and *Arathoon* teaches or suggests the method of claim 18.

246. Additionally, *Lazar* discloses that the heterodimeric antibodies of its invention are useful as an anti-cancer therapeutic. (Ex. 1004 at ¶¶196, 203, 206-207.) As described above, *Lazar* teaches the “immunoglobulins herein” are useful for treating a wide range of cancers. (Ex. 1004 at ¶¶206-207.) *Lazar* also teaches specific activating antigens typically found on NK cells (CD16 and NKG2D), T-cells (CD3, CD4, CD8, CD28, and OX40), B-cells (BAFF-R and TACI), monocytes (IL-2R, TLR-2, TLR-4, and CCR2), macrophages (TLR-2, TLR-4, TNF Receptors, IL4R), dendritic cells (TLRs, CCR7), and neutrophilic granulocytes (TNFRs, TLR-2, TLR-4, TLR-9). (Ex. 1004 at ¶¶138-139, 141-143, 146, 243-244, 255-256, 261-262, Tables 3-5; Ex. 1011 at Appendix II.)

247. **Motivation to Combine and Reasonable Expectation of Success:**

As discussed above (Section XI.A), a person of ordinary skill in the art would have been motivated to combine the teachings of *Lazar* and *Arathoon* to make a bispecific antibody utilizing the CH3 domain modifications of *Lazar* (neutral to charged) with a reasonable expectation of success. A person of ordinary skill in the art would have been further motivated—for such bispecific antibodies—to target epitopes on effector cells, wherein the target 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. (Section XI.A.)

13. 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.”

248. It is my opinion that *Lazar* and *Arathoon* alone or together teach or suggest “the method of claim 18, wherein said target epitope is located on a CD3, CD16, CD25, CD28, CD64, CD89, NKG2D or a NKp46 molecule.”

249. As discussed above in Section XI.E.11, the combination of *Lazar* and *Arathoon* teaches or suggests the method of claim 18.

250. Moreover, *Lazar* teaches target antigens that are located on effector cells, and specifically lists: CD3, CD16, CD25, CD28, CD64, CD89, (Ex. 1004 at ¶138) and NKG2D (Ex. 1004 at ¶142). *Lazar* further teaches bispecific mAb-Fab and mAb-Fv antibodies which target CD3 and CD16 (FcγRIIIa). (Ex. 1004 at ¶¶244, 262, Tables 3, 5.)

251. Motivation to Combine and Reasonable Expectation of Success:

As discussed above (Section XI.A), a person of ordinary skill in the art would have been motivated to combine the teachings of *Lazar* and *Arathoon* to make a bispecific antibody utilizing the CH3 domain modifications of *Lazar* (neutral to charged) with a reasonable expectation of success. A person of ordinary skill in the art would have been 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. (Section XI.A.)

14. 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.”

252. It is my opinion that *Lazar* and *Arathoon* alone or together teach or suggest “the method of claim 22, wherein said heterodimeric antibody binds to different epitopes on the same antigen or to different epitopes on different antigens.”

253. As discussed above in Section XI.B, the combination of *Lazar* and *Arathoon* teaches or suggests the heterodimeric antibody according to claim 22.

254. *Lazar* further teaches a heterodimeric antibody capable of binding to different epitopes on the same antigen or to different epitopes on different antigens as discussed above. (*E.g.*, Section XI.E.1.)

255. Motivation to Combine and Reasonable Expectation of Success:

As discussed above, a person of ordinary skill in the art would have been motivated to combine the teachings of *Lazar* and *Arathoon* to create a bispecific antibody utilizing *Lazar*’s CH3 domain modifications (neutral to charged), with a reasonable expectation of success. (Section XI.B.) Moreover, a person of ordinary skill in the art would have been further motivated to target different epitopes on the

same antigen or to different epitopes on different antigens, as taught in *Lazar*, due to the well-established broad applicability of bispecific antibodies. (Sections XI.B, XI.E.1.) By 2012, methods of creating bispecific antibodies targeting different epitopes or antigens were also well-known, including different epitopes on the same antigen or to different epitopes on different antigens, providing a person of ordinary skill in the art with a reasonable expectation of success. (Sections XI.B, XI.E.1.)

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

256. As explained above, it is my opinion that *Lazar*, alone, discloses the claim limitations of claims 21, 24, and 32. (See Sections X.C, X.E, and X.I.)

257. In addition, it is my opinion that a person of ordinary skill in the art would have understood that *Lazar* and *Arathoon*, alone, or the combination of *Lazar* and *Arathoon* in combination teaches or suggests every limitation of these claims.

258. Both *Lazar* and *Arathoon* teach that the heterodimeric antibodies described therein may be made up from sequences encoding for human IgG—more specifically, human IgG1. *Lazar* expressly instructs that, “[i]n certain embodiments, the antibodies disclosed herein comprise sequences belonging to the IgG class of antibodies, including IgG1, IgG2, IgG3, or IgG4.” (Ex. 1004 at ¶90; see also Ex. 1004 at ¶118 (“[T]he Fc variants disclosed herein are based on human

IgG sequences, and thus human IgG sequences are used as the ‘base’ sequences against which other sequences are compared”).) Equally, *Arathoon* states that, in its disclosed heterodimers, “[p]referably the first and second polypeptides each comprise an antibody constant domain such as the CH3 domain of a human IgG₁.” (Ex. 1006 at 7:18-19; *see also* Ex. 1006 at 23:10-12 (“In a preferred embodiment, the immunoglobulin sequences used in the construction of the immunoadhesins of the present invention are from an IgG immunoglobulin heavy chain constant domain. For human immunoadhesins, the use of human IgG₁ and IgG₃ immunoglobulin sequences is preferred.”).)

259. The examples of *Lazar* and *Arathoon* reaffirm its written disclosures directed to heterodimeric antibodies based upon the sequences for human IgG (human IgG1, more specifically). *Lazar*’s Example 2 describes making the “preferred” and “most preferred” neutral-to-negative and neutral-to-positive amino acid substitutions in heterodimeric sequences encoding for an IgG1 antibody chain. (Ex. 1004 at ¶¶ 238-241.) *Arathoon* includes similar examples that apply the disclosed CH3 interface modifications to human IgG1 antibody sequences so as to improve heterodimer production. (Ex. 1006 at 43:9-14 (“Disulfide bonds were modeled into the human IgG₁.... Mutations were introduced into the CH3 domain of a humanized anti-CD3 heavy chain or CD4-IgG by site-directed mutagenesis.”).)

260. **Motivation to Combine and Reasonable Expectation of Success:**

Both *Lazar* and *Arathoon* provide strong motivation to apply the disclosed heterodimeric enhancement techniques to human IgG sequences, including human IgG1. Again, both exemplify doing just that, providing a person of ordinary skill in the art with good reason to follow their teachings. Further, a person of ordinary skill in the art would have had a reasonable expectation of success in combining *Lazar's* and *Arathoon's* teachings. Both references instruct that their respective techniques for promoting heterodimerization can be performed using a variety of antibody structures, and expressly exemplify their disclosed techniques to human IgG1 sequences. (Ex. 1004 at ¶¶124-125, 238-239; Ex. 1006 at 6:1-23, 43:31-45:21.)

G. Pharmaceutical Composition (Claim 28)

261. As explained above, it is my opinion that *Lazar*, alone, discloses a “pharmaceutical composition comprising a heterodimeric antibody according to claim 22 and a pharmaceutically acceptable carrier.” (See Section X.G.)

262. In addition, it is my opinion that a person of ordinary skill in the art would have understood that the combination of *Lazar* and *Arathoon* teaches or suggests every limitation of this claim.

263. *Lazar* teaches heterodimeric antibodies formulated with a physiologically or pharmaceutically acceptable carrier or diluent. (Ex. 1004 at

¶55.) *Lazar* further discloses an exemplary list of acceptable carriers, excipients, and stabilizers that are nontoxic to recipients at the dosages and concentrations used, which may be used for the delivery of the disclosed heterodimeric antibodies. (Ex. 1004 at ¶214.) Equally, *Arathoon* instructs that “[t]he heteromultimeric multispecific antibody may be provided in the form of a composition further comprising a pharmaceutically acceptable carrier.” (Ex. 1006, 7:28-30.)

264. **Motivation to Combine and Reasonable Expectation of Success:**

A person of skill in the art would have been motivated to follow the teachings of *Lazar* and *Arathoon* and formulate the disclosed heterodimeric antibodies in a pharmaceutical composition. Like all therapeutics, engineered antibodies are formulated in pharmaceutical carriers for delivery to subjects. And a person of ordinary skill in the art would reasonably expect to use routine techniques to carry out the disclosures of *Lazar* and *Arathoon*.

XII. Ground 3: *Cabrera* Teaches All of the Limitations of Claims 1-2, 7, 21-22, 24, 26-28, and 30-32 of the '286 Patent

265. It is my opinion that each of the limitations of claims 1-2, 7, 21-22, 24, 26-28, and 30-32 are taught by *Cabrera* for at least the reasons explained below.

A. Claim 1

1. “A method for producing a heterodimeric antibody from a single cell,”

266. It is my opinion that *Cabrera* discloses a method for producing a heterodimeric antibody from a single cell.

267. *Cabrera* discloses a “novel method for designing Fc heterodimers that results in both stable and highly specific heterodimer formation.” (Ex. 1005 at 22; see also Ex. 1009 at ¶¶12 (describing a “purified stable heterodimeric Fc”), 13.)

268. A person of ordinary skill in the art would have understood the terms “Fc heterodimer,” “Fc variant heterodimers,” and “Fc variant” in *Cabrera* to refer to heterodimeric antibodies. (*E.g.*, Ex. 1005 at Cover (Title: “Stable Heterodimeric Antibody Design with Mutations in the Fc Domain”), 1 (“the present invention relates to ... antibodies comprising a heterodimeric Fc domain”), 17 (“Fc regions comprising a modified CH3 domain ... are referred to herein as ‘Fc variants’, ‘heterodimer’ or ‘heteromultimers’”), 92 (“Fc variant (e.g., antibody, or a fusion protein)”), see also Ex. 1009 at ¶¶9 (“a heterodimeric Fc scaffold is provided”), 13 (describing a “heteromultimer” as having “an interface which has been engineered to promote heteromultimer formation” which “comprises a variant CH3 domain”).) *Cabrera* explicitly references “antibody or fusion protein[s]” in parentheses when discussing “Fc variant[s],” leaving no doubt that the Fc variants

discussed therein refer to antibodies or antibody fusion proteins, rather than Fc modifications unrelated to the CH3 domain interface. (Ex. 1005 at 93.)

269. *Cabrera* further teaches the production of heterodimeric antibodies from a single cell. The reference makes clear that conventional techniques, such as co-transfection, may be used for expression of the disclosed antibodies. (Ex. 1005 at 85-86 (describing methods for constructed expression vectors and transfecting cells), 108-109 (Example 1, describing transfection of HEK293 cells with nucleic acids encoding antibody heavy and light chains); *see also* Ex. 1009 at ¶36, Claims 54-59 (claiming a host cell comprising nucleic acids encoding the heteromultimer and a method for culturing the host cell); Section V.B.) Antibody expression commonly involves introducing nucleic acids, such as an expression vector (or plasmid), containing the genetic code for the antibody (including sequences for “both the heavy and light chains”) so that they “may be co-expressed in the host cell for expression of the entire immunoglobulin molecule.” (Ex. 1005 at 85-86, 108-111 (Example 1); *see also* Ex. 1009 at ¶36, Claims 54-59.)

2. “wherein said antibody comprises two heavy chains with CH3 domains that are capable of forming an interface, said method comprising”

270. It is my opinion that *Cabrera* discloses an antibody comprising two heavy chains with CH3 domains that are capable of forming an interface.

271. *Cabrera* states that the “present invention provides modified CH3 domains comprising specific amino acid modifications to promote heterodimer formation.” (Ex. 1005 at 16-17, 18; *see also* Ex. 1009, ¶¶13 (describing CH3 domains as forming an interface), 65 (same), 80 (explaining that the CH3 domains of two heavy chains interact via protein-protein contacts).) *Cabrera* discloses heterodimeric Fc regions consisting of two heavy chains, each containing a variant CH3 domain. (Ex. 1005 at 4 (describing a heteromultimer “comprising a heterodimer Fc region, wherein the heterodimer Fc region comprises a variant CH3 domain”), Table 1 (“CH3 domain amino acid modifications for the generation of Fc variant heterodimers.”); *see also* Ex. 1009 at ¶¶13, 65.) The variant CH3 domains of the two antibody heavy chains form an “interface” that enables self-assembly of the heterodimers. (See Ex. 1005 at 18 (describing “interface” as “compris[ing] the CH3 domain of an Fc region”); *see also* Ex. 1009 at ¶80 (explaining that the CH3 domains of two heavy chains interact via protein-protein contacts).)

3. “providing a host cell comprising”

272. It is my opinion that *Cabrera* discloses a method of making an antibody using a host cell.

273. As discussed above, *Cabrera* teaches the process of co-transfection, which involves introducing an expression vector (or plasmid), containing the

genetic code for the antibody into a host cell. (Ex. 1005 at 85-86; *see also* Ex.

1009 at ¶36, Claims 54-59, Section XI.A.1.)

4. **“(i) a first nucleic acid molecule encoding a 1st antibody heavy chain comprising at least one substitution of a neutral amino acid residue in the CH3 domain by a positively charged amino acid residue, and
(ii) a second nucleic acid molecule encoding a 2nd antibody heavy chain comprising at least one substitution of a neutral amino acid residue in the CH3 domain by a negatively charged amino acid residue;
b. culturing said host cell and allowing for expression of said two nucleic acid molecules to produce said 1st antibody heavy chain and said 2nd antibody heavy chain, wherein the at least one positively charged amino acid residue substituted in the CH3 domain of said 1st antibody heavy chain interacts with the at least one negatively charged amino acid residue substituted in the CH3 domain of said 2nd antibody heavy chain in the interface between said 1st and 2nd antibody heavy chains to produce a heterodimeric antibody; and”**

274. It is my opinion that *Cabrera* discloses the above claim limitations.

275. *Cabrera*, like *Lazar*, discloses modifying neutrally charged amino acids in CH3 domains of an Fc by substituting a positively charged amino acid on one chain and a negatively charged amino acid on the other. For example, *Cabrera* includes an example modifying an asparagine (N) (yellow) to a positively charged arginine (R) (green) at position 390 in one chain (chain “B”), and modifying a neutral serine (S) (yellow) to a negatively charged glutamic acid (E)

(red) at position 400 in a separate chain (chain “A”). (See Ex. 1005 at 39 (describing “AZ34” in Table 1); *see also* Ex. 1009 at Table 3.)

276. Below I have included an excerpt of Table 1, which provides the variant AZ34, where a neutral amino acid residue in the CH3 domain is substituted with a positively charged amino acid residue (green highlighting) in Chain B. (Ex. 1005 at 39, Table 1; *see also* Ex. 1009 at ¶112, Table 3.) As discussed above, contact residues at the CH3 interface had been described in the prior art. S400 and N390 are among those identified as interacting residues. (Ex. 1007 at 7:8-8:7 (Table 1) (illustrating known contact residues at the native CH3 interface); Ex. 1012 at Supplementary Table 1 (same); *see also* Ex. 1001 at Table A.)

TABLE 1-continued

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	—	—	—	

277. *Cabrera* further discloses culturing a host cell to express the nucleic acid molecules encoding for the antibody heavy chains. As discussed above in Section XII.A.3, *Cabrera* teaches transfecting a host cell with an expression vector, which contains the nucleic acid that encodes for an Fc variant (*e.g.*,

antibody.) (Ex. 1005 at 85-86; *see also* Ex. 1009 at ¶36, Claims 54-59.) *Cabrera* also teaches that the host cell (containing the expression vector) is “cultured by conventional techniques” and that the Fc variant (*e.g.*, antibody) is “produced by recombinant expression.” (Ex. 1005 at 86, 92; *see also* Ex. 1009 at Claims 57-59.)

5. “harvesting said heterodimeric antibody from the culture.”

278. *Cabrera* teaches harvesting the heterodimeric antibody from the culture. *Cabrera* explains that heterodimeric antibodies produced are “recovered from the [cell] culture medium” or cell lysate. (Ex. 1005 at 92; Ex. 1009 at ¶¶36, 129, Claim 57.) A person of ordinary skill in the art would readily understand that “recover[ing]” an antibody is synonymous with “harvesting” the antibody.

279. In addition, *Cabrera* teaches that the recovered antibodies are purified by known methods, including chromatography (*e.g.*, ion exchange, affinity (including protein A, and sizing column chromatography), centrifugation, and differential solubility, among others). (Ex. 1005 at 12 (describing Figure 26B as “Protein A purified heterodimer variants” including AZ34), 92 (explaining that the Fc variant is “generally recovered from the culture” and providing exemplary purification methods), Figure 26B; *see also* Ex. 1009 at ¶¶36, 129, Claim 57 (“recovering the heteromultimer from the cell culture”), Table 3; *see also* Section V.D.) As discussed above in Section X.A.5, a person of ordinary skill in the art

would understand that harvesting the expressed antibody occurs prior to such purification steps.

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

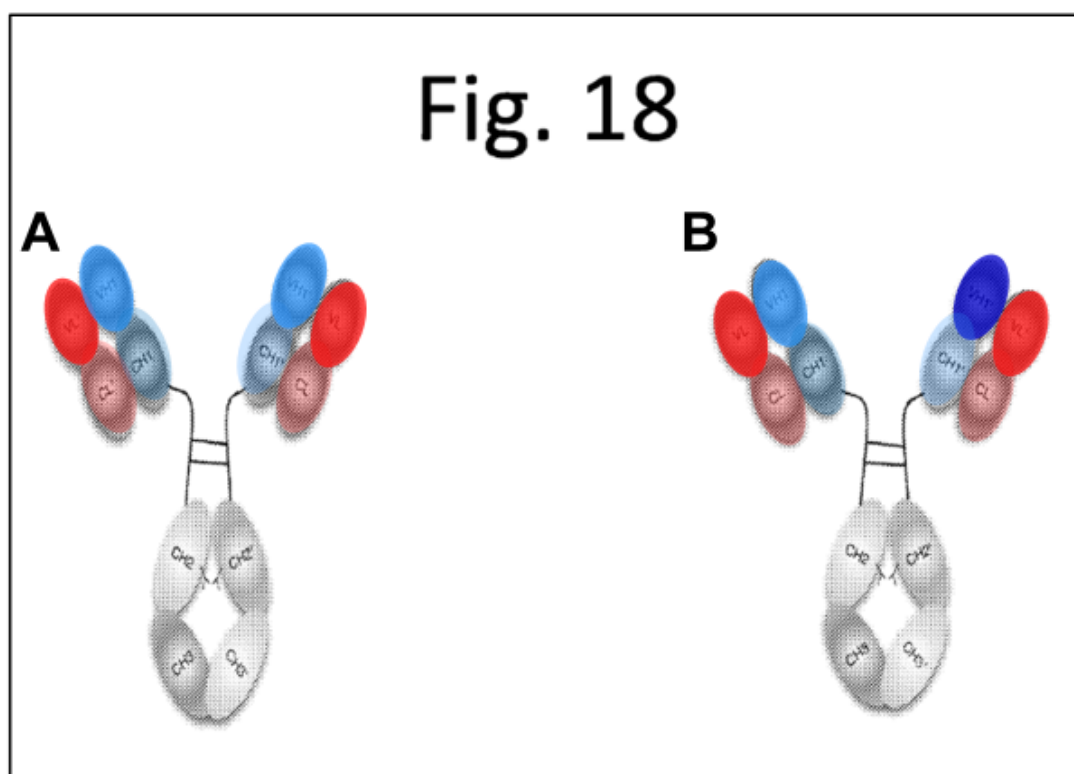
280. It is my opinion that *Cabrera* discloses the use of a host cell containing a nucleic acid molecule encoding a common light chain.

281. Figure 18 of *Cabrera*, for example, teaches “multifunctional molecules based on the asymmetric Fc scaffold,”²¹ including “Asymmetric Fc-Monospecific IgG arms and Asymmetric Fc-Bispecific IgG Arms (Common Light Chain).”²² Below, I reproduce a modified version Figure 18 below to demonstrate how it would be interpreted by a person of ordinary skill in the art at the relevant time.

²¹ A person of ordinary skill in the art would have understood that the “asymmetric Fc scaffold” *Cabrera* is describing is the modified CH3 domains that it discloses, including AZ34, which “promote heterodimer formation,” and “improve[] stability and purity.” (Ex. 1005 at 24, 35, 39 (Table 1, variant AZ34); see also Ex. 1009 at ¶¶113, 112 (Table 3).)

²² *Cabrera* explains that “asymmetric amino acid modification” is used to mean “any modification wherein an amino acid at a specific position on one polypeptide (e.g., ‘Chain A’) is different from the amino acid on the second polypeptide (e.g., ‘Chain B’) at the same position of the heterodimer or Fc variant.” (Ex. 1005 at 17-18; see also Ex. 1009 at ¶¶112, 136, Table 3.)

Demonstrative 11 – Antibody Structures Illustrated in *Cabrera*



282. Panel A of modified Figure 18 of *Cabrera* illustrates an antibody with Asymmetric Fc-Monospecific IgG arms, featuring a heterodimeric Fc region with monospecific binding (designed to bind a single antigen) and identical light chains on both arms. The VH and CH regions are shown in medium and light blue, respectively, across both chains, signifying their identical nature. Similarly, the VL and CL chains are depicted in dark and light red, again showing their commonality across both arms.

283. Panel B of modified Figure 18 of *Cabrera* depicts an antibody with Asymmetric Fc-Bispecific IgG arms and a common light chain. This design features a heterodimeric Fc region and bispecific binding (designed to bind two different antigens). In this panel, the VH and CH regions on the left side are again shown in medium and light blue, while the VH and CH regions on the right side are shown in dark and light blue, signifying that the VH (dark blue) on the right differs from the VH (medium blue) on the left, reflecting the bispecific nature. I have ensured that the VL and CL chains remain consistent in color, reinforcing their commonality across both arms.

284. A person of ordinary skill in the art would therefore recognize the structure disclosed in *Cabrera* as representing a common light chain because an identical light chain interacts with both heavy chains.

285. Given the structures shown in Figure 18, a person of ordinary skill in the art would have understood the term “asymmetric Fc scaffold” to encompass both the Asymmetric Fc-Monospecific IgG Arms antibodies shown in panel A and the Asymmetric Fc-Bispecific IgG Arms antibodies in panel B.

286. And *Cabrera* specifically mentions asymmetric modifications in the context of variant AZ34—a variant which incorporates the neutral-to-negative and neutral-to-positive amino acid residue substitutions, discussed above—noting that acid modifications are introduced “in an asymmetric fashion.” (Ex. 1005 at 17-18

(“The present Fc variants comprise a CH3 domain that has been asymmetrically modified...”), Table 1; *see also* Ex. 1009 at ¶¶6, 136, Table 3 (“CH3 domain mutations for the creation of asymmetric Fc scaffold.”).) Therefore, a person of ordinary skill in the art would have understood that Figure 18 encompasses variant AZ34 and related antibody structures. (Ex. 1005 at 17-18, Table 1; *see also* Ex. 1009 at ¶136, Table 3.) Therefore, it is my opinion that a person of ordinary skill in the art would have understood *Cabrera*’s figure and its disclosures about asymmetric amino acid modifications to indicate that the heterodimeric antibodies in *Cabrera* may include a common light chain.

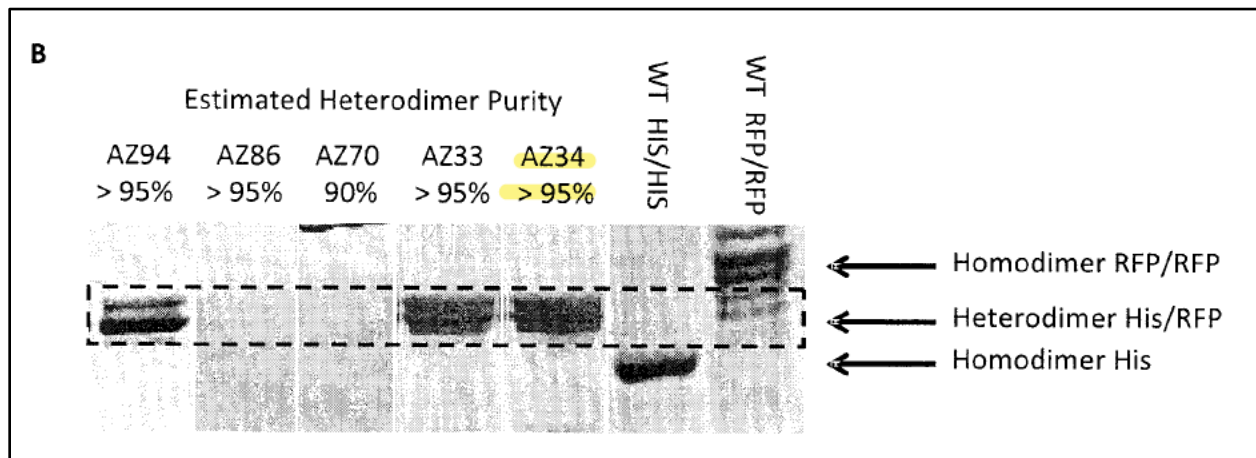
C. Claim 7: “The method according to claim 1, wherein the presence of contaminating homodimers is less than 5%, preferably less than 2%, more preferably less than 1%, and most preferably contaminating homodimers are essentially absent.”

287. It is my opinion that *Cabrera* discloses an antibody in which “the presence of contaminating homodimers is less than 5%, preferably less than 2%, more preferably less than 1%, and most preferably homodimers are essentially absent.”

288. *Cabrera* explains that the Fc heterodimer regions disclosed are specifically designed to promote heterodimer formation while enhancing both stability and purity. (Ex. 1005 at 4, 23; *see also* Ex. 1009 at ¶¶12 (describing a “purified stable heterodimeric Fc”), 13.) *Cabrera* further teaches that the

mutations described result in heterodimer yield ranging from 90% to 100% (with a corresponding level of homodimer yield of between 0% to 10%). (Ex. 1005 at 24-25; *see also* Ex. 1009 at Table 3 (disclosing variant AZ34).)

289. Moreover, *Cabrera* expressly teaches that AZ34, the variant incorporating the neutral-to-negative and neutral-to-positive amino acid residue substitutions discussed with respect to claim 1, results in greater than 95% heterodimer formation. Figure 26B, reproduced below for convenience, demonstrates that making the AZ34 variant yields a composition consisting of more than 95% heterodimer, with less than 5% homodimer contamination. (Ex. 1005 at Figure 26B; *see also* Ex. 1009 at Table 3.)



A person of ordinary skill in the art would therefore readily understand that *Cabrera* teaches the additional limitation of claim 7.

D. Claim 21: “The method according claim 1, wherein said heterodimeric antibody is human IgG.”

290. It is my opinion that *Cabrera* discloses a method for producing a heterodimeric antibody that is a human IgG isotype.

291. *Cabrera* discloses that the Fc regions of the two heavy chains that form *Cabrera*’s heterodimeric antibodies are “preferably ... derived from an IgG antibody and most preferably a human IgG₁ antibody.” (Ex. 1005 at 18 (explaining that the interface “preferably is derived from an IgG antibody and most preferably a human IgG₁ antibody), 35 (“the Fc region is a human IgG Fc region” which in some embodiments is “a human IgG₁”), Table 1; *see also* Ex. 1009 at ¶133.) *Cabrera* further teaches that its methods of producing heterodimeric antibodies “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.” (Ex. 1005 at 35; *see also* Ex. 1009 at ¶133.)

E. Claim 22: “A heterodimeric antibody obtained by the method of claim 1.”

292. It is my opinion that *Cabrera* discloses a method for producing a heterodimeric antibody according to the method of claim 1. As noted above for claim 1 in Section XII.A, *Cabrera* teaches that the method of claim 1 results in the production of a heterodimeric antibody which can then be isolated or purified.

F. Claim 24: “A heterodimeric antibody according to claim 22, wherein said antibody is human IgG.”

293. It is my opinion that *Cabrera* discloses a heterodimeric antibody according to claim 22 (*i.e.*, a heterodimeric antibody obtained by the method of claim 1). (Section XII.A and Section XII.E.)

G. Claim 26

1. “A recombinant host cell comprising nucleic acid sequences encoding at least a 1st and 2nd antibody heavy chain,”

294. It is my opinion that *Cabrera* discloses recombinant host cells containing nucleic acid sequences encoding at least two different antibody heavy chains, as discussed above in Section XII.A.

2. “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.”

295. It is my opinion that *Cabrera* discloses the example AZ34 having a substitution on one CH3 domain of a neutral amino acid residue by a positively charged amino acid residue (N390R), and a substitution on another CH3 domain of a neutral amino acid residue by a negatively charged amino acid residue (S400E), as discussed above in Section XII.A.4.

H. 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”

296. It is my opinion that *Cabrera* discloses a recombinant host cell that contains a nucleic acid sequence encoding a common light chain. (Section XII.A and Section XII.B.)

I. Claim 28: “A pharmaceutical composition comprising a heterodimeric antibody according to claim 22 and a pharmaceutically acceptable carrier”

297. It is my opinion that *Cabrera* discloses a pharmaceutical composition comprising a heterodimeric antibody according to the method of claim 22 (*i.e.*, a heterodimeric antibody obtained by the method of claim 1). *Cabrera* further teaches heterodimers formulated in “a composition comprising... a pharmaceutically acceptable carrier.” (Ex. 1005 at 8; *see also* Ex. 1009 at ¶35.)

J. Claim 30

1. “A method for making a host cell for production of a heterodimeric antibody,”

298. It is my opinion that *Cabrera* discloses a method for making a host cell to produce a heterodimeric antibody, as discussed above in Section XII.A.1.

2. **“the method comprising the step of introducing into said host cell nucleic acid molecules encoding at least a 1st and 2nd antibody heavy chain,” / [30.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 and” / [30.c]: “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,”**

299. It is my opinion that *Cabrera* discloses a method including the step of introducing nucleic acid molecules encoding two different antibody heavy chains wherein the CH3 domains comprise at least one substitution of a neutral amino acid residue by a positively charged amino acid residue and at least one substitution of a neutral amino acid residue by a negatively charged amino acid residue, as discussed above in Section XII.A.4.

300. More specifically, *Cabrera* teaches example AZ34 with a substitution on one CH3 domain of a neutral amino acid residue by a positively charged amino acid residue (N390R), and a substitution on another CH3 domain of a neutral amino acid residue by a negatively charged amino acid residue (S400E). (Section XII.A.4.)

3. “wherein said nucleic acid sequences are introduced consecutively or concomitantly”

301. It is my opinion that *Cabrera* discloses a method including introducing nucleic acid sequences consecutively or concomitantly, as discussed above in Section XII.A.1.

302. Specifically, *Cabrera* teaches that expression vectors can be transferred to a host cell and the host cells cultured in order to produce antibodies. (Ex. 1005 at 85-86; *see also* Ex. 1009 at ¶36.) Further, *Cabrera* teaches that the host cell may be “co-transfected” with two expression vectors. (Ex. 1005 at 94; *see also* Ex. 1009 at ¶36, Claims 54-59.) A person of ordinary skill in the art would have understood “co-transfect[ion]” in *Cabrera* to teach nucleic acid sequences being introduced into the host cell “concomitantly,” as claimed.

K. 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.”

303. It is my opinion that *Cabrera* discloses a method for making a host cell for production of a heterodimeric antibody, as discussed above in Section XII.A. Further, as discussed in Section XII.B, this method includes the step of introducing into the host cell a nucleic acid sequence encoding a common light chain.

L. Claim 32: “The method according to claim 21 wherein antibody is human IgG1.”

304. It is my opinion that *Cabrera* discloses a method for producing a heterodimeric antibody, as discussed in Section XII.A. Further, as discussed in Section XII.D that includes a method wherein the antibody is human IgG1.

* * *

305. For the reasons I discuss in Section XII above, it is my opinion that a person of ordinary skill in the art would have understood *Cabrera* to disclose every limitation of claims 1-2, 7, 21, 22, 24, 26-28, and 30-32 as arranged in the claims.

XIII. Ground 4: *Lazar* in view of *Arathoon* and *Cabrera* Teaches or Suggests Claims 1-2, 7-24, 26-28, and 30-32

306. In addition to understanding that *Lazar* and *Cabrera* both teach every limitation of claims 1-2, 7, 21-22, 24, 26-28, and 30-32 of the '286 patent, as discussed above in Sections X and XII, a person of ordinary skill in the art would have understood that the combination of *Lazar*, *Arathoon*, and *Cabrera* discloses the further limitations of claims 8-20 and 23.

307. These claims recite only well-known concepts already taught by *Lazar*, *Arathoon*, and *Cabrera*, including the targeting of different target epitopes (claims 9, 12, 23), the location of the target epitopes (claims 13-14), and general characteristics of different target epitopes (claims 10-11, 15-20).

A. The Related Teachings of *Lazar*, *Arathoon*, and *Cabrera*

308. I have previously summarized the disclosures of *Lazar* and *Arathoon*, which are directed to techniques for enhancing the yield of heterodimeric antibodies, which I incorporate here. (Sections VII, X-XI.) The same is true of *Cabrera*. (Ex. 1005 at 2-3, 19-22; *see also* Ex. 1009 at ¶¶101-02.) Moreover, each of these references teaches a framework for more efficiently developing heterodimeric antibodies for numerous applications. (Section VII.A-C.)

309. Like with *Lazar* and *Arathoon*, *Cabrera* teaches techniques for boosting heterodimer yield through CH3 domain modifications, (Section VII.C), envisions combination modifications (Ex. 1005 at 19-22, 36-47 (Table 1); *see also* Ex. 1009 at ¶13), and applies its modifications to a variety of structures (Ex. 1005 at 10-11, Figs. 17-21 (showing “alternative multifunctional molecules based on the asymmetric Fc scaffold”); *see also* Ex. 1009 at ¶63, Figure 21).

310. Given the interest in heterodimeric antibodies and the focus on increasing their yield during production, a person of ordinary skill in the art would have also looked to *Cabrera* when considering *Lazar* and *Arathoon*. (Section V.D.)

311. A person of ordinary skill in the art would have known that the methods and techniques taught in *Lazar* and *Arathoon* for making heterodimeric antibodies could be applied to the antibody configurations taught in *Cabrera*.

Cabrera expressly teaches that its design method can be combined with other methods, including KIH, disulfide bonds, and electrostatic steering. (Ex. 1005 at 19-22 (citing Ex. 1012 and Ex. 1015); *see also* Ex. 1009 at ¶¶102, 112.) A person of ordinary skill in the art would therefore have been motivated and would have had a reasonable expectation of success in combining *Cabrera* with *Lazar* and *Arathoon*, because these references utilize the very strategies *Cabrera* contemplated combining into a single embodiment, *i.e.*, KIH, disulfide bonds, and electrostatic steering. (Ex. 1004 at ¶168 (disulfide bonds), ¶¶124-25 (KIH and electrostatic steering), Tables 1 and 2 (same); Ex. 1006 at 6:5-7 (disulfide bonds and KIH).) And in fact, as noted above (Section XII.A), *Cabrera* is not the only reference disclosing that the KIH, disulfide bonds, and electrostatic steering methods may be combined. For example, *Lazar* also disclosed that combining these methods is desirable. (Ex. 1004 at ¶¶124-25.)

312. In view of these considerations, the teachings from *Cabrera* that I discuss above in Section XII with regard to the limitations of claims 1-2, 7, 21, 22, 24, 26-28, and 30-32, would have also applied to the combination of *Lazar*, *Arathoon*, and *Cabrera*. Indeed, *Cabrera*'s teachings would have supplemented the combination of *Lazar* and *Arathoon* that I discuss above in Sections X and XI. For instance, while I discuss above in Section XI how *Lazar* and *Arathoon*'s techniques for increasing heterodimer yield and purity could be combined,

Cabrera provides additional teachings and motivation for increasing heterodimer yield and purity. Similarly, in the same way that *Arathoon*'s teachings for promoting heterodimer formation could have been applied to *Lazar*, a person of ordinary skill in the art would have recognized based on the teachings of *Lazar*, *Arathoon*, and *Cabrera*, that *Arathoon*'s techniques also could have been applied to *Cabrera*'s process for making a heterodimeric antibody, for the reasons I discuss above.

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

313. As discussed above in Section XI.E, claims 8-20 and 23 include additional limitations generally directed to bispecific antibodies and recite various well-known types of bispecific targeting. These include targeting the same or different target molecules/antigens, different antigens located on the same or different cells, and certain categories of targets or specific targets.

314. *Cabrera* explains, with regard to bispecific antibodies, 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[.]” (Ex. 1005 at 4; *see also* Ex. 1009 at ¶¶11, 13, 40, 65.) For instance, as shown in Figure 18 (reproduced above as Demonstrative 11), *Cabrera* teaches “Bispecific IgG Arms” built “on the asymmetric Fc scaffold.” (Ex. 1005 at 10, Figure 18; *see also* Ex.

1005 at 17-18 (explaining the “present Fc variants comprise a CH3 domain that has been asymmetrically modified to generate heterodimer Fc variants or regions.”); *see also* Ex. 1009 at ¶60, Figure 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.” (Ex. 1005 at 76-77; *see also* Ex. 1009 at ¶¶34 (“the heteromultimer is a bispecific antibody”), 73 (same), claims 41-42, 49.)

315. Based on these disclosures, it is my opinion that a person of ordinary skill in the art would have understood the CH3 modifications taught in *Cabrera* to apply to bispecific antibodies. Specifically, a person of ordinary skill in the art would have understood *Cabrera*’s disclosure of “Bispecific IgG Arms” built “on the asymmetric Fc scaffold” (Ex. 1005 at 10, Figure 18; *see also* Ex. 1009 at ¶60, Figure 18) and that “[a]ntibodies of the invention may be... bispecific” (Ex. 1005 at 76-77; *see also* Ex. 1009 at ¶¶32, 34) to refer to bispecific antibodies having the CH3 modifications taught therein. That is, a person of ordinary skill in the art would understand that the “asymmetric Fc scaffold” and “antibodies of the invention” to refer to antibodies having the CH3 modifications taught in *Cabrera*.

316. In addition to the analysis provided above in Section X regarding the combination of *Lazar* and *Arathoon*, it is my opinion that *Cabrera*'s additional teachings (set forth below) further demonstrate that the limitations recited in claims 8-20 and 23 were known in the art and would have been combined by a person of ordinary skill in the art to arrive at the claims.

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

317. It is my opinion that *Lazar*, *Arathoon*, and *Cabrera* together teach or suggest the “method of claim 1, wherein each variable region of the 1st and 2nd antibody heavy chains recognizes a different target epitope.”

318. As discussed above in Section XI.E.1, the combination of *Lazar* and *Arathoon* teaches or suggests the method of claim 8.

319. In addition, *Cabrera* teaches that “[a]ntibodies of the invention may be monospecific, bispecific, trispecific or have greater multispecificity.” (Ex. 1005 at 76; *see also* Ex. 1009 at ¶¶34 (“the heteromultimer is a bispecific antibody”), 73 (same), claims 41-42, 49.) A person of ordinary skill in the art would have understood from this disclosure that multispecific antibodies necessarily recognize different target epitopes.

320. *Cabrera* also teaches that “[m]ultispecific antibodies may specifically bind to different epitopes of [a] desired target molecule” or “have binding

specificities for at least two different antigens,” which confirms that the antibodies taught in *Cabrera* recognize different target epitopes. (Ex. 1005 at 76; *see also* Ex. 1005 at 10, Figure 18; Ex. 1009 at ¶¶34, 60, 73, 125 (“Bispecific molecules that interact with two different receptor molecules can be useful...”), claims 41-42, 49.)

321. **Motivation to Combine and Reasonable Expectation of Success:**

As noted above (Section XI.A), a person of ordinary skill in the art 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* and vice versa. A person of ordinary skill in the art would have been motivated and had a reasonable expectation of success in combining *Lazar*’s and *Arathoon*’s teachings, recognizing that the methods and techniques taught in *Lazar* for making heterodimeric antibodies are compatible with those *Arathoon*, in particular given both references suggest making antibodies with a combination of modification types (*e.g.*, KIH, disulfide bonds, and/or electrostatic steering). Similarly, *Cabrera* teaches methods and techniques for making heterodimeric antibodies, and also suggests utilizing a combination of modification types. (Ex. 1005 at 19-22 (citing Ex. 1012 and Ex. 1015); *see also* Ex. 1009 at ¶102, Section XII.A.) *Cabrera*, like *Lazar* and *Arathoon*, further teaches that its methods and techniques for making heterodimeric antibodies can be applied to bispecific antibodies (Sections XI.E, XII.B). A person of ordinary skill in the art would

therefore have been motivated to create bispecific antibodies using the combined teachings of *Lazar*, *Cabrera*, and *Arathoon*.

322. With regard to claim 8, a person of ordinary skill in the art would have been further motivated to target different epitopes on the same target molecule, as taught in *Lazar* and *Cabrera*, due to the well-established broad applicability of bispecific antibodies. By 2012, methods of creating bispecific antibodies targeting different epitopes or antigens were also well-known, providing a person of ordinary skill in the art with a reasonable expectation of success in targeting different epitopes on the same target molecule. (Ex. 1013 at 183-184 (dual targeting strategies), Table 1 (dual targeting approaches), Table 2 (dual retargeting approaches), Figure 1 (dual targeting strategies using bispecific antibodies); Ex. 1004 at ¶¶3 (“considerable diversity of the antibody variable region (Fv) makes it possible to produce an Fv that recognizes virtually any molecule”), 167 (describing process of affinity maturation in order to modify the variable region of an antibody, in order to “enhance binding” and “improve selectivity” for a target antigen).)

2. Claim 9: “The method of claim 8, wherein the different target epitopes are located on the same target molecule.”

323. It is my opinion that *Lazar*, *Arathoon*, and *Cabrera* together teach or suggest the “method of claim 8, wherein the different target epitopes are located on the same target molecule.”

324. As discussed above in Section XI.E.2, the combination of *Lazar* and *Arathoon* teaches or suggests the method of claim 9.

325. *Cabrera* additionally teaches that its bispecific antibodies can simultaneously bind “different epitopes of the same antigen.” (Ex. 1005 at 1, 76 (“[m]ultispecific antibodies may specifically bind to different epitopes of [a] desired target molecule”); see also Ex. 1009 at ¶¶121-122.) A person of ordinary skill in the art would have understood that when antibodies simultaneously bind “different epitopes of the same antigen,” the target epitopes would be located on the same target molecule.

326. Motivation to Combine and Reasonable Expectation of Success:

As noted above (Section XI.A), a person of ordinary skill in the art 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* and vice versa. A person of ordinary skill in the art would have been motivated and had a reasonable expectation of success in combining *Lazar*’s and

Arathoon's teachings, recognizing that the methods and techniques taught in *Lazar* for making heterodimeric antibodies are compatible with those in *Arathoon*, in particular given both references suggest making antibodies with a combination of modification types (*e.g.*, KIH, disulfide bonds, and/or electrostatic steering). Similarly, *Cabrera* teaches methods and techniques for making heterodimeric antibodies, and also suggests utilizing a combination of modification types. (Ex. 1005 at 19-22 (citing Ex. 1012 and Ex. 1015); *see also* Ex. 1009 at ¶102, Section XII.A.) *Cabrera*, like *Lazar* and *Arathoon*, further teaches that its methods and techniques for making heterodimeric antibodies can be applied to bispecific antibodies (Sections XI.E, XII.B). A person of ordinary skill in the art would therefore have been motivated to create bispecific antibodies using the combined teachings of *Lazar*, *Cabrera*, and *Arathoon*.

327. With regard to claim 9, a person of ordinary skill in the art would have been further motivated to target different epitopes on the same target molecule, as taught in *Lazar* and *Cabrera*, due to the well-established broad applicability of bispecific antibodies. By 2012, methods of creating bispecific antibodies targeting different epitopes or antigens were also well-known, providing a person of ordinary skill in the art with a reasonable expectation of success in targeting different epitopes on the same target molecule.

3. Claim 10: “The method of claim 9, wherein the target molecule is a soluble molecule.”

328. It is my opinion that *Lazar*, *Arathoon*, and *Cabrera* together teach or suggest the “method of claim 9, wherein the target molecule is a soluble molecule.”

329. As discussed above in Section XI.E.3, the combination of *Lazar* and *Arathoon* teaches or suggests the method of claim 10.

330. *Cabrera* further teaches a list of exemplary antigens that can be “targeted by and/or incorporated into a variant Fc heterodimer protein.” (Ex. 1005 at 78.) A person of ordinary skill in the art would have recognized that certain of the listed antigens in *Cabrera* included soluble molecules (*e.g.* TNF alpha) and various cytokines (*e.g.*, IL-12 and IL-5), which are also soluble molecules. (Ex. 1005 at 79; *see also* Ex. 1009 at ¶37.)

331. Motivation to Combine and Reasonable Expectation of Success:

As noted above (Section XI.A), a person of ordinary skill in the art 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* and vice versa. A person of ordinary skill in the art would have been motivated and had a reasonable expectation of success in combining *Lazar*’s and *Arathoon*’s teachings, recognizing that the methods and techniques taught in *Lazar*

for making heterodimeric antibodies are compatible with those *Arathoon*, in particular given both references suggest making antibodies with a combination of modification types (*e.g.*, KIH, disulfide bonds, and/or electrostatic steering). Similarly, *Cabrera* teaches methods and techniques for making heterodimeric antibodies, and also suggests utilizing a combination of modification types. (Ex. 1005 at 19-22 (citing Ex. 1012 and Ex. 1015); *see also* Ex. 1009 at ¶102, Section XII.A.) *Cabrera*, like *Lazar* and *Arathoon*, further teaches that its methods and techniques for making heterodimeric antibodies can be applied to bispecific antibodies (Sections XI.E, XII.B). A person of ordinary skill in the art would therefore have been motivated to create bispecific antibodies using the combined teachings of *Lazar*, *Cabrera*, and *Arathoon*.

332. With regard to claim 10, a person of ordinary skill in the art would have been further motivated to target soluble molecules, as taught in *Lazar* and *Cabrera*, due to the well-established broad applicability of bispecific antibodies. By 2012, methods of creating bispecific antibodies targeting different epitopes or antigens were also well-known, providing a person of ordinary skill in the art with a reasonable expectation of success in targeting a soluble molecule.

4. Claim 11: “The method of claim 9, wherein the target molecule is a membrane-bound molecule.”

333. It is my opinion that *Lazar*, *Arathoon*, and *Cabrera* together teach or suggest the “method of claim 9, wherein the target molecule is a membrane-bound molecule.”

334. As discussed above in Section XI.E.4, the combination of *Lazar* and *Arathoon* teaches or suggests the method of claim 11.

335. *Cabrera* additionally teaches targeting membrane-bound molecules. Specifically, a person of ordinary skill in the art would have recognized that certain of the listed target molecules in *Cabrera* included membrane-bound molecules such as CD11a, CD20, CD3, IL-6 receptor, etc. (Ex. 1005 at 79; *see also* Ex. 1009 at ¶¶37, 125 (describing bispecific antibodies that interact with receptor molecules).)

336. Motivation to Combine and Reasonable Expectation of Success:

As noted above (Section XI.A), a person of ordinary skill in the art 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* and vice versa. A person of ordinary skill in the art would have been motivated and had a reasonable expectation of success in combining *Lazar*’s and *Arathoon*’s teachings, recognizing that the methods and techniques taught in *Lazar*

for making heterodimeric antibodies are compatible with those in *Arathoon*, in particular given both references suggest making antibodies with a combination of modification types (*e.g.*, KIH, disulfide bonds, and/or electrostatic steering). Similarly, *Cabrera* teaches methods and techniques for making heterodimeric antibodies, and also suggests utilizing a combination of modification types. (Ex. 1005 at 19-22 (citing Ex. 1012 and Ex. 1015); *see also* Ex. 1009 at ¶102, Section XII.A.) *Cabrera*, like *Lazar* and *Arathoon*, further teaches that its methods and techniques for making heterodimeric antibodies can be applied to bispecific antibodies (Sections XI.E, XII.B). A person of ordinary skill in the art would therefore have been motivated to create bispecific antibodies using the combined teachings of *Lazar*, *Cabrera*, and *Arathoon*.

337. With regard to claim 11, a person of ordinary skill in the art would have been further motivated to target membrane-bound molecules, as taught in *Lazar* and *Cabrera*, due to the well-established broad applicability of bispecific antibodies. By 2012, methods of creating bispecific antibodies targeting different epitopes or antigens were also well-known, providing a person of ordinary skill in the art with a reasonable expectation of success in targeting a membrane-bound molecule.

5. Claim 12: “The method of claim 8, wherein the different target epitopes are located on different target molecules.”

338. It is my opinion that *Lazar*, *Arathoon*, and *Cabrera* together teach or suggest the “method of claim 8, wherein the different target epitopes are located on different target molecules.”

339. As discussed above in Section XI.E.5, the combination of *Lazar* and *Arathoon* teaches or suggests the method of claim 12.

340. Furthermore, *Cabrera* teaches targeting different molecules, including using bispecific antibodies designed to mediate interactions between a target and a variety of effector cells. (Ex. 1005 at 1, 96; *see also* Ex. 1009 at ¶¶37, 99 (“Bispecific antibodies ... are designed to mediate interactions between the target and a variety of effector cells”), 125 (describing bispecific antibodies that interact with two different receptor molecules).) *Cabrera* further explains that bispecific antibodies can be designed such that one arm binds an antigen on a tumor cell, while the second binds an antigen expressed on an effector cell. (Ex. 1005 at 1.) A person of ordinary skill in the art would have recognized that when this type of targeting occurs, the antibody is targeting epitopes located on different target molecules.

341. Motivation to Combine and Reasonable Expectation of Success:

As noted above (Section XI.A), a person of ordinary skill in the art 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* and vice versa. A person of ordinary skill in the art would have been motivated and had a reasonable expectation of success in combining *Lazar*'s and *Arathoon*'s teachings, recognizing that the methods and techniques taught in *Lazar* for making heterodimeric antibodies are compatible with those in *Arathoon*, in particular given both references suggest making antibodies with a combination of modification types (*e.g.*, KIH, disulfide bonds, and/or electrostatic steering). Similarly, *Cabrera* teaches methods and techniques for making heterodimeric antibodies, and also suggests utilizing a combination of modification types. (Ex. 1005 at 19-22 (citing Ex. 1012 and Ex. 1015); *see also* Ex. 1009 at ¶102, Section XII.A.) *Cabrera*, like *Lazar* and *Arathoon*, further teaches that its methods and techniques for making heterodimeric antibodies can be applied to bispecific antibodies (Sections XI.E, XII.B). A person of ordinary skill in the art would therefore have been motivated to create bispecific antibodies using the combined teachings of *Lazar*, *Cabrera*, and *Arathoon*.

342. With regard to claim 12, a person of ordinary skill in the art would have been further motivated to target different epitopes on different target molecules, as taught in *Lazar* and *Cabrera*, due to the well-established broad applicability of bispecific antibodies. By 2012, methods of creating bispecific

antibodies targeting different epitopes or antigens were also well-known, providing a person of ordinary skill in the art with a reasonable expectation of success in targeting different epitopes on different target molecules.

6. Claim 13: “The method of claim 12, wherein the different target molecules are expressed on the same cells.”

343. It is my opinion that *Lazar*, *Arathoon*, and *Cabrera* together teach or suggest the “method of claim 12, wherein the different target molecules are expressed on the same cells.”

344. As discussed above in Section XI.E.6, the combination of *Lazar* and *Arathoon* teaches or suggests the method of claim 13.

345. In addition, *Cabrera* teaches co-targeting targets that are expressed on the same cell. This includes targets such as CD20 and CD22, and HER2 and EGFR, which a person of ordinary skill in the art would have recognized are expressed on the same cells. (Ex. 1005 at 79; *see also* Ex. 1009 at ¶37.)

346. Motivation to Combine and Reasonable Expectation of Success:

As noted above (Section XI.A), a person of ordinary skill in the art 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* and vice versa. A person of ordinary skill in the art would have been motivated and had a reasonable expectation of success in combining *Lazar*’s and

Arathoon's teachings, recognizing that the methods and techniques taught in *Lazar* for making heterodimeric antibodies are compatible with those in *Arathoon*, in particular given both references suggest making antibodies with a combination of modification types (*e.g.*, KIH, disulfide bonds, and/or electrostatic steering). Similarly, *Cabrera* teaches methods and techniques for making heterodimeric antibodies, and also suggests utilizing a combination of modification types. (Ex. 1005 at 19-22 (citing Ex. 1012 and Ex. 1015); *see also* Ex. 1009 at ¶102, Section XII.A.) *Cabrera*, like *Lazar* and *Arathoon*, further teaches that its methods and techniques for making heterodimeric antibodies can be applied to bispecific antibodies (Sections XI.E, XII.B). A person of ordinary skill in the art would therefore have been motivated to create bispecific antibodies using the combined teachings of *Lazar*, *Cabrera*, and *Arathoon*.

347. With regard to claim 13, a person of ordinary skill in the art would have been further motivated to target different epitopes on different target molecules in such bispecific antibodies, as taught in *Lazar* and *Cabrera*, due to the well-established broad applicability of bispecific antibodies. By 2012, methods of creating bispecific antibodies targeting different epitopes or antigens were also well-known, providing a person of ordinary skill in the art with a reasonable expectation of success in targeting different epitopes on different target molecules.

7. Claim 14: “The method of claim 12, wherein the different target molecules are expressed on different cells.”

348. It is my opinion that *Lazar*, *Arathoon*, and *Cabrera* together teach or suggest the “method of claim 12, wherein the different target molecules are expressed on different cells.”

349. As discussed above in Section XI.E.7, the combination of *Lazar* and *Arathoon* teaches or suggests the method of claim 14.

350. Further, *Cabrera* teaches co-targeting targets that are expressed on different cells. This includes antibodies co-targeting a tumor cell and effector cells, as described above. (Ex. 1005 at 1, 96; *see also* Ex. 1009 at ¶¶37, 99, Section XII.B.5.)

351. Motivation to Combine and Reasonable Expectation of Success:

As noted above (Section XI.A), a person of ordinary skill in the art 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* and vice versa. A person of ordinary skill in the art would have been motivated and had a reasonable expectation of success in combining *Lazar*’s and *Arathoon*’s teachings, recognizing that the methods and techniques taught in *Lazar* for making heterodimeric antibodies are compatible with those in *Arathoon*, in particular given both references suggest making antibodies with a combination of

modification types (*e.g.*, KIH, disulfide bonds, and/or electrostatic steering).

Similarly, *Cabrera* teaches methods and techniques for making heterodimeric antibodies, and also suggests utilizing a combination of modification types. (Ex. 1005 at 19-22 (citing Ex. 1012 and Ex. 1015); *see also* Ex. 1009 at ¶102, Section XII.A.) *Cabrera*, like *Lazar* and *Arathoon*, further teaches that its methods and techniques for making heterodimeric antibodies can be applied to bispecific antibodies (Sections XI.E, XII.B). A person of ordinary skill in the art would therefore have been motivated to create bispecific antibodies using the combined teachings of *Lazar*, *Cabrera*, and *Arathoon*.

352. With regard to claim 14, a person of ordinary skill in the art would have been further motivated to target different target molecules on different target cells in such bispecific antibodies, as taught in *Lazar* and *Cabrera*, due to the well-established broad applicability of bispecific antibodies. By 2012, methods of creating bispecific antibodies targeting different epitopes or antigens were also well-known, providing a person of ordinary skill in the art with a reasonable expectation of success in targeting different target molecules on different cells.

8. Claim 15: “The method of claim 12, wherein the different target molecules are soluble molecules.”

353. It is my opinion that *Lazar*, *Arathoon*, and *Cabrera* together teach or suggest the “method of claim 12, wherein the different target molecules are soluble molecules.”

354. As discussed above in Section XI.E.8, the combination of *Lazar* and *Arathoon* teaches or suggests the method of claim 15.

355. Additionally, *Cabrera* teaches a list of exemplary antigens that can be “targeted by and/or incorporated into a variant Fc heterodimer protein.” (Ex. 1005 at 78.) A person of ordinary skill in the art would have recognized that certain of the listed antigens in *Cabrera* included soluble molecules (*e.g.* TNF alpha) and various cytokines (*e.g.*, IL-12 and IL-5), which are also soluble molecules. (Ex. 1005 at 79; *see also* Ex. 1009 at ¶37.) A person of ordinary skill in the art would have further recognized that these soluble molecules can be co-targeted by a single antibody.

356. **Motivation to Combine and Reasonable Expectation of Success:**

As noted above (Section XI.A), a person of ordinary skill in the art 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* and vice versa. A person of ordinary skill in the art would have been

motivated and had a reasonable expectation of success in combining *Lazar*'s and *Arathoon*'s teachings, recognizing that the methods and techniques taught in *Lazar* for making heterodimeric antibodies are compatible with those *Arathoon*, in particular given both references suggest making antibodies with a combination of modification types (*e.g.*, KIH, disulfide bonds, and/or electrostatic steering). Similarly, *Cabrera* teaches methods and techniques for making heterodimeric antibodies, and also suggests utilizing a combination of modification types. (Ex. 1005 at 19-22 (citing Ex. 1012 and Ex. 1015); *see also* Ex. 1009 at ¶102, Section XII.A.) *Cabrera*, like *Lazar* and *Arathoon*, further teaches that its methods and techniques for making heterodimeric antibodies can be applied to bispecific antibodies (Sections XI.E, XII.B.) A person of ordinary skill in the art would therefore have been motivated to create bispecific antibodies using the combined teachings of *Lazar*, *Cabrera*, and *Arathoon*.

357. With regard to claim 15, a person of ordinary skill in the art would have been further motivated to target different soluble molecules, as taught in *Lazar* and *Cabrera*, due to the well-established broad applicability of bispecific antibodies. By 2012, methods of creating bispecific antibodies targeting different epitopes or antigens were also well-known, providing a person of ordinary skill in the art with a reasonable expectation of success in targeting different soluble molecules.

9. 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.”

358. It is my opinion that *Lazar*, *Arathoon*, and *Cabrera* together teach or suggest the “method of claim 12, wherein one target molecule is a soluble molecule whereas the second target molecule is a membrane bound molecule.”

359. As discussed above in Section XI.E.9, the combination of *Lazar* and *Arathoon* teaches or suggests the method of claim 16.

360. *Cabrera* further teaches targets that are soluble molecules and targets that are membrane-bound molecules, as set forth above. (Sections XII.B.3-4.)

361. Motivation to Combine and Reasonable Expectation of Success:

As noted above (Section XI.A), a person of ordinary skill in the art 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* and vice versa. A person of ordinary skill in the art would have been motivated and had a reasonable expectation of success in combining *Lazar*’s and *Arathoon*’s teachings, recognizing that the methods and techniques taught in *Lazar* for making heterodimeric antibodies are compatible with those in *Arathoon*, in particular given both references suggest making antibodies with a combination of modification types (*e.g.*, KIH, disulfide bonds, and/or electrostatic steering). Similarly, *Cabrera* teaches methods and techniques for making heterodimeric

antibodies, and also suggests utilizing a combination of modification types. (Ex. 1005 at 19-22 (citing Ex. 1012 and Ex. 1015); *see also* Ex. 1009 at ¶102, Section XII.A.) *Cabrera*, like *Lazar* and *Arathoon*, further teaches that its methods and techniques for making heterodimeric antibodies can be applied to bispecific antibodies (Sections XI.E, XII.B). A person of ordinary skill in the art would therefore have been motivated to create bispecific antibodies using the combined teachings of *Lazar*, *Cabrera*, and *Arathoon*.

362. With regard to claim 16, a person of ordinary skill in the art would have been further motivated to target a soluble molecule and a membrane-bound molecule, as taught in *Lazar* and *Cabrera*, due to the well-established broad applicability of bispecific antibodies. By 2012, methods of creating bispecific antibodies targeting different epitopes or antigens were also well-known, providing a person of ordinary skill in the art with a reasonable expectation of success in targeting a soluble molecule and a membrane-bound molecule.

10. Claim 17: “The method of claim 8, wherein at least one of said target epitopes is located on a tumor cell.”

363. It is my opinion that *Lazar*, *Arathoon*, and *Cabrera* together teach or suggest the “method of claim 8, wherein at least one of said target epitopes is located on a tumor cell.”

364. As discussed above in Section XI.E.10, the combination of *Lazar* and *Arathoon* teaches or suggests the method of claim 17.

365. Moreover, *Cabrera* teaches targeting epitopes located on tumor cells. Specifically, *Cabrera* teaches the “antibodies of the invention ... specifically bind cancer antigens,” including many exemplary cancer antigens, including HER2 and EGFR. (Ex. 1005 at 1, 80-81; *see also* Ex. 1009 at ¶¶37, 38 (describing the treatment of cancer using a heteromultimer).) A person of ordinary skill in the art would have known that HER2 and EGFR were tumor target molecules. *Cabrera* also teaches one use of bispecific antibodies is for “cross-linking tumor and effector cells.” (Ex. 1005 at 1; *see also* Ex. 1009 at ¶99 (“Bispecific antibodies ... are designed to mediate interactions between the target and a variety of effector cells”).)

366. **Motivation to Combine and Reasonable Expectation of Success:**

As noted above (Section XI.A), a person of ordinary skill in the art 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* and vice versa. A person of ordinary skill in the art would have been motivated and had a reasonable expectation of success in combining *Lazar*’s and *Arathoon*’s teachings, recognizing that the methods and techniques taught in *Lazar* for making heterodimeric antibodies are compatible with those in *Arathoon*, in

particular given both references suggest making antibodies with a combination of modification types (*e.g.*, KIH, disulfide bonds, and/or electrostatic steering).

Similarly, *Cabrera* teaches methods and techniques for making heterodimeric antibodies, and also suggests utilizing a combination of modification types. (Ex. 1005 at 19-22 (citing Ex. 1012 and Ex. 1015); *see also* Ex. 1009 at ¶102, Section XII.A.) *Cabrera*, like *Lazar* and *Arathoon*, further teaches that its methods and techniques for making heterodimeric antibodies can be applied to bispecific antibodies (Sections XI.E, XII.B). A person of ordinary skill in the art would therefore have been motivated to create bispecific antibodies using the combined teachings of *Lazar*, *Cabrera*, and *Arathoon*.

367. With regard to claim 17, a person of ordinary skill in the art would have been further motivated to target epitopes on a cancer cell, as taught in *Lazar* and *Cabrera*, due to the well-established broad applicability of bispecific antibodies. By 2012, methods of creating bispecific antibodies targeting different epitopes or antigens were also well-known, providing a person of ordinary skill in the art with a reasonable expectation of success in targeting epitopes on a cancer cell.

11. Claim 18: “The method of claim 8, wherein at least one of said target epitopes is located on an effector cell.”

368. It is my opinion that *Lazar*, *Arathoon*, and *Cabrera* together teach or suggest the “method of claim 8, wherein at least one of said target epitopes is located on an effector cell.”

369. As discussed above in Section XI.E.11, the combination of *Lazar* and *Arathoon* teaches or suggests the method of claim 18.

370. And in addition, *Cabrera* teaches targeting epitopes on effector cells. Specifically, *Cabrera* teaches bispecific antibodies designed to mediate interactions between the target and a variety of effector cells, such as “cross-linking tumor and effector cells.” (Ex. 1005 at 1, 79; *see also* Ex. 1009 at ¶¶37-38, 99.) *Cabrera* specifically names CD3 as a potential target, which is widely known as an activating effector cell target. (Ex. 1005 at 79.) A person of ordinary skill in the art would have known that cross-linking tumor and effector cells would necessarily require targeting an epitope on an effector cell.

371. **Motivation to Combine and Reasonable Expectation of Success:**

As noted above (Section XI.A), a person of ordinary skill in the art 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* and vice versa. A person of ordinary skill in the art would have been

motivated and had a reasonable expectation of success in combining *Lazar*'s and *Arathoon*'s teachings, recognizing that the methods and techniques taught in *Lazar* for making heterodimeric antibodies are compatible with those in *Arathoon*, in particular given both references suggest making antibodies with a combination of modification types (*e.g.*, KIH, disulfide bonds, and/or electrostatic steering). Similarly, *Cabrera* teaches methods and techniques for making heterodimeric antibodies, and also suggests utilizing a combination of modification types. (Ex. 1005 at 19-22 (citing Ex. 1012 and Ex. 1015); *see also* Ex. 1009 at ¶102, Section XII.A.) *Cabrera*, like *Lazar* and *Arathoon*, further teaches that its methods and techniques for making heterodimeric antibodies can be applied to bispecific antibodies (Sections XI.E, XII.B). A person of ordinary skill in the art would therefore have been motivated to create bispecific antibodies using the combined teachings of *Lazar*, *Cabrera*, and *Arathoon*.

372. With regard to claim 18, a person of ordinary skill in the art would have been further motivated to target epitopes on effector cells, as taught in *Lazar* and *Cabrera*, due to the well-established broad applicability of bispecific antibodies. By 2012, methods of creating bispecific antibodies targeting different epitopes or antigens were also well-known, providing a person of ordinary skill in the art with a reasonable expectation of success in targeting epitopes on effector cells.

12. 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.”

373. It is my opinion that *Lazar*, *Arathoon*, and *Cabrera* together teach or suggest 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.”

374. As discussed above in Section XI.E.12, the combination of *Lazar* and *Arathoon* teaches or suggests the method of claim 19.

375. Further, *Cabrera* teaches targeting the claimed effector cells. Specifically, *Cabrera* teaches targets such as CD3 and CD4 and CD20, among others. (Ex. 1005 at 79; *see also* Ex. 1009 at ¶¶37-38, 99.) A person of ordinary skill in the art would have known that CD3 and CD4 are located on T cells, and CD20 is located on B cells.

376. Motivation to Combine and Reasonable Expectation of Success:

As noted above (Section XI.A), a person of ordinary skill in the art 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* and vice versa. A person of ordinary skill in the art would have been motivated and had a reasonable expectation of success in combining *Lazar*’s and *Arathoon*’s teachings, recognizing that the methods and techniques taught in *Lazar* for making heterodimeric antibodies are compatible with those in *Arathoon*, in

particular given both references suggest making antibodies with a combination of modification types (*e.g.*, KIH, disulfide bonds, and/or electrostatic steering).

Similarly, *Cabrera* teaches methods and techniques for making heterodimeric antibodies, and also suggests utilizing a combination of modification types. (Ex. 1005 at 19-22 (citing Ex. 1012 and Ex. 1015); *see also* Ex. 1009 at ¶102, Section XII.A.) *Cabrera*, like *Lazar* and *Arathoon*, further teaches that its methods and techniques for making heterodimeric antibodies can be applied to bispecific antibodies (Sections XI.E, XII.B). A person of ordinary skill in the art would therefore have been motivated to create bispecific antibodies using the combined teachings of *Lazar*, *Cabrera*, and *Arathoon*.

377. With regard to claim 19, a person of ordinary skill in the art would have been further motivated 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* and *Cabrera*, due to the well-established broad applicability of bispecific antibodies. By 2012, methods of creating bispecific antibodies targeting different epitopes or antigens were also well-known, providing a person of ordinary skill in the art with a reasonable expectation of success in targeting the claimed epitopes.

13. 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.”

378. It is my opinion that *Lazar*, *Arathoon*, and *Cabrera* together teach or suggest the “method of claim 18, wherein said target epitope is located on a CD3, CD16, CD25, CD28, CD64, CD89, NKG2D or a NKp46 molecule.”

379. As discussed above in Section XI.E.13, the combination of *Lazar* and *Arathoon* teaches or suggests the method of claim 20.

380. Additionally, *Cabrera* teaches targeting these epitopes, including CD3, CD25, CD64. (Ex. 1005 at 79; *see also* Ex. 1009 at ¶37.)

381. Motivation to Combine and Reasonable Expectation of Success:

As noted above (Section XI.A), a person of ordinary skill in the art 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* and vice versa. A person of ordinary skill in the art would have been motivated and had a reasonable expectation of success in combining *Lazar*’s and *Arathoon*’s teachings, recognizing that the methods and techniques taught in *Lazar* for making heterodimeric antibodies are compatible with those in *Arathoon*, in particular given both references suggest making antibodies with a combination of modification types (*e.g.*, KIH, disulfide bonds, and/or electrostatic steering). Similarly, *Cabrera* teaches methods and techniques for making heterodimeric

antibodies, and also suggests utilizing a combination of modification types. (Ex. 1005 at 19-22 (citing Ex. 1012 and Ex. 1015); *see also* Ex. 1009 at ¶102, Section XII.A.) *Cabrera*, like *Lazar* and *Arathoon*, further teaches that its methods and techniques for making heterodimeric antibodies can be applied to bispecific antibodies (Sections XI.E, XII.B). A person of ordinary skill in the art would therefore have been motivated to create bispecific antibodies using the combined teachings of *Lazar*, *Cabrera*, and *Arathoon*.

382. With regard to claim 20, a person of ordinary skill in the art would have been further motivated to target epitopes located on a CD3, CD16, CD25, CD28, CD64, CD89, NKG2D or a NKp46 molecule, as taught in *Lazar* and *Cabrera*, due to the well-established broad applicability of bispecific antibodies. By 2012, methods of creating bispecific antibodies targeting different epitopes or antigens were also well-known, providing a person of ordinary skill in the art with a reasonable expectation of success in targeting epitopes on the claimed molecules.

14. 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.”

383. It is my opinion that *Lazar*, *Arathoon*, and *Cabrera* together teach or suggest 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.”

384. As discussed above in Section XI.E.14, the combination of *Lazar* and *Arathoon* teaches or suggests the heterodimeric antibody of claim 23.

385. Furthermore, *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. (Sections XIII.B.1-2.)

386. **Motivation to Combine and Reasonable Expectation of Success:**

As noted above (Section XI.A), a person of ordinary skill in the art 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* and vice versa. A person of ordinary skill in the art would have been motivated and had a reasonable expectation of success in combining *Lazar*’s and *Arathoon*’s teachings, recognizing that the methods and techniques taught in *Lazar* for making heterodimeric antibodies are compatible with those in *Arathoon*, in particular given both references suggest making antibodies with a combination of modification types (*e.g.*, KIH, disulfide bonds, and/or electrostatic steering). Similarly, *Cabrera* teaches methods and techniques for making heterodimeric antibodies, and also suggests utilizing a combination of modification types. (Ex. 1005 at 19-22 (citing Ex. 1012 and Ex. 1015); *see also* Ex. 1009 at ¶102, Section

XII.A.) *Cabrera*, like *Lazar* and *Arathoon*, further teaches that its methods and techniques for making heterodimeric antibodies can be applied to bispecific antibodies (Sections XI.E, XII.B). A person of ordinary skill in the art would therefore have been motivated to create bispecific antibodies using the combined teachings of *Lazar*, *Cabrera*, and *Arathoon*.

387. With regard to claim 23, a person of ordinary skill in the art would have been further motivated to target different epitopes on the same antigen or different epitopes on different antigens, as taught in *Lazar* and *Cabrera*, due to the well-established broad applicability of bispecific antibodies. By 2012, methods of creating bispecific antibodies targeting different epitopes or antigens were also well-known, providing a person of ordinary skill in the art with a reasonable expectation of success in targeting different epitopes on the same antigen or different epitopes on different antigens.

* * *

388. Because both *Lazar* and *Cabrera* taught that the CH3 domain modifications they were testing would have been applicable to their bispecific antibodies, creating bispecific antibodies with the claimed CH3 domain modifications, as described in both *Lazar* and *Cabrera*, a person of ordinary skill in the art would have been motivated to apply their teachings together with *Arathoon* and would have had a reasonable expectation of success in doing so.

XIV. Conclusion

389. I declare that all statements made herein to my knowledge are true, that all statements made on information and belief are believed to be true, and that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code.

* * *

Declaration of Leonard G. Presta, Ph.D.
U.S. Patent No. 9,358,286

Executed on: *Feb 11, 2025*

By: *Leonard G Presta*

Leonard G. Presta, Ph.D.