

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

Xencor, Inc.,
Petitioner

v.

Merus N.V.,
Patent Owner

Patent No. 11,926,859

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 13:35-49.)

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

I. Introduction—U.S. Patent No. 11,926,859

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. 11,926,859 (“the ’859 patent”) (Ex. 1001), which I understand is assigned to Merus N.V. (“Patent Owner”). I have been asked to consider whether:

(1) a person of ordinary skill in the art would have understood the named inventors of the ’859 patent to be in possession of the subject matter recited in claims 1-7 of the ’859 patent based upon the disclosures of the provisional and non-provisional patent applications identified on the face of the ’859 patent;

(2) U.S. Patent No. 10,472,427 to Desjarlais *et al.* (“*Desjarlais*”) (Ex. 1036) teaches all of the limitations of claims 1-7 of the ’859 patent;

(3) *A robust heterodimeric Fc platform engineered for efficient development of bispecific antibodies of multiple formats* by Gregory Moore *et al.* (“*Moore*”) (Ex. 1038) teaches all of the limitations of claims 1-7 of the ’859 patent; and

(4) U.S. Patent Application Publication No. US 2011/0054151 to Lazar *et al.* (“*Lazar*”) (Ex. 1004) alone or in combination with International Patent Application Publication No. WO2009/089004 to Kannan *et al.* (“*Kannan*”) (Ex. 1007) teaches or suggests all of the limitations of claims 1-7 of the ’859 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. My full qualifications, including a list of publications that I have authored and patents for which I have been named an inventor, are summarized in my *curriculum vitae*, referenced above.

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 '859 patent (Ex. 1001); (2) *Desjarlais* (Ex. 1036); (3) *Moore* (Ex. 1038); (4) *Lazar* (Ex. 1004); (5) *Kannan* (Ex. 1007); and (6) 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 '859 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 time of alleged invention. As discussed below, I have been asked to assume the following dates of the alleged invention:

- **Grounds 1 and 2:** With respect to my discussion of *Desjarlais* and *Moore*, I have been asked to assume that the date of alleged invention of the '859 patent is May 16, 2023, which I understand is the filing date of U.S. Patent Application No. 18/318,507 (“the '507 application”)—the patent application that issued as the '859 patent.

- **Ground 3:** With respect to my discussion of *Lazar* and *Kannan*, I have been asked to assume that the date of alleged invention of the '859 patent is April 20, 2012, which I understand is the filing date of the earliest provisional application identified on the face of the '859 patent.

18. Regardless of which timeframe applies, 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

19. In this section, I present a brief overview of several technologies that were widely known before April 2012—let alone before May 2023—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 '859 patent, the prior art, and certain terminology.

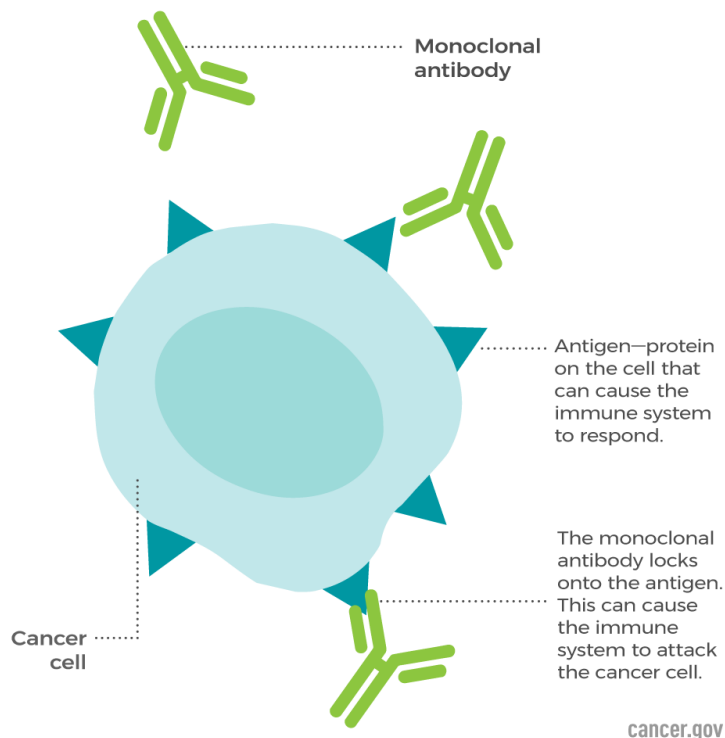
A. Antibodies as Therapeutics

20. 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.

21. 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.)

22. By 2012—let alone by 2023—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, as early as 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

23. 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 Additionally, many antibody therapeutics are based on human IgG1 sequences.

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

24. 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.

25. 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”).

26. Once assembled from the applicable amino acid sequence, the structure of a naturally occurring antibody (like natural IgG) or a man-made

‘immunoglobulins’ (Igs) are glycoproteins (although as described herein, engineered glycoforms including aglycosylated and afucosylated forms can be made) having the same structural characteristics.”.)

binding sites—they can bind to only one epitope and are thus commonly referred to as “monospecific.”

28. 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 1:19-21.) 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.)

29. 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.)

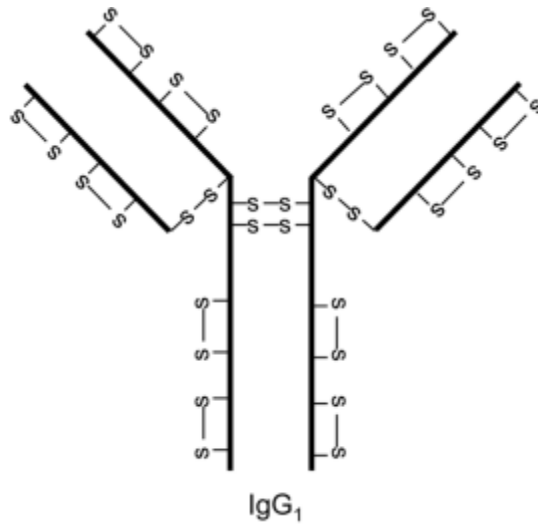
30. During the antibody self-assembly process, the two heavy chains link together via disulfide bonds³ in a process commonly referred to as “dimerization” or “heavy chain dimerization.” The Fc region—more specifically the CH3 domain of the Fc region—plays a critical role in dimerization, as interactions 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 19637-19640; *see also* Ex. 1001 at 4:21-45.)

31. 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):

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

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

32. 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.

33. 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.”

34. By 2012—let alone by 2023—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.)

35. Due to these recognized advantages, bispecific antibodies had been explored for a variety of uses by 2012, and even more so by 2023. (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 182-184, 191, Tables 1-2.) A list of just some of the bispecific antibody therapies that were in

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.)

development by April 2012 is shown below, excerpted from a March 2012

scientific publication:

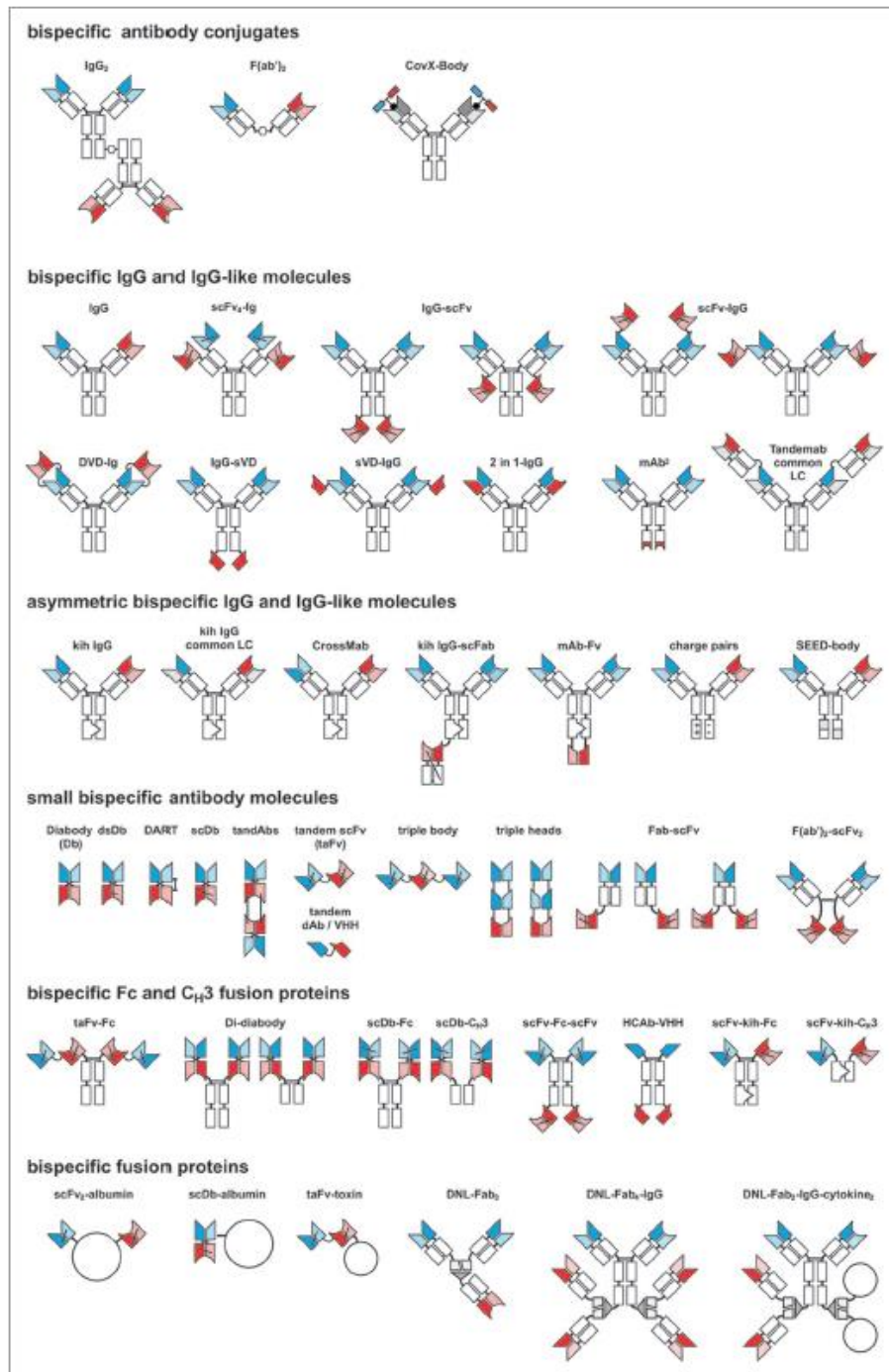
Table 1. Dual targeting approaches

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.)

36. Further, not only had scientists explored the use of bispecific antibodies for a variety of therapeutic applications by 2012 (and even more so by 2023), they had also developed a significant number of bispecific antibody structures. The same March 2012 scientific publication 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**

37. The production of bispecific antibodies begins with harnessing known methods of antibody engineering and cloning,⁸ established long before 2012 (let alone by 2023). 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.)

38. 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.)

39. 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 44:39-44, 63:55-58.) 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 44:39-44, 63:55-58.) 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.)

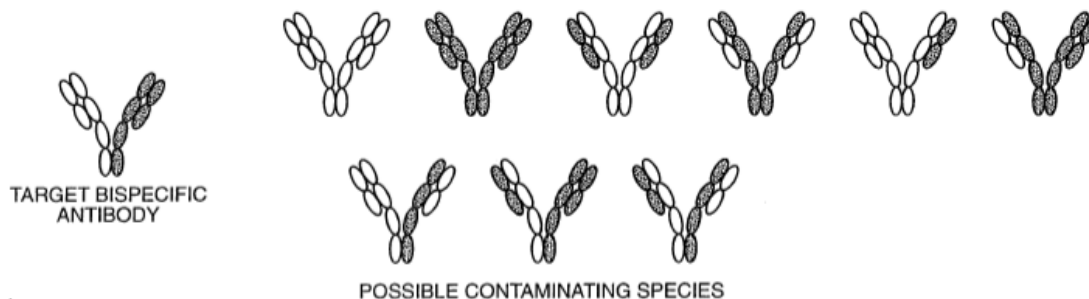
40. Once produced by the host cell, the antibodies are harvested and undergo protein purification. Harvesting refers to the collection of the expressed proteins from the host cell growth medium, which is done using long-established methods, such as centrifugation and filtration. (Ex. 1024 at 480-481; Ex. 1026 at 6-8, 19-20; *see also* Ex. 1001 at 17:39-42; 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

41. Not only were methods for generating bispecific antibodies known by 2012 (and long before by 2023), but scientists had already spent decades developing methods that allowed for the more efficient creation of bispecific antibodies by that point in time.

42. 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.

43. 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.

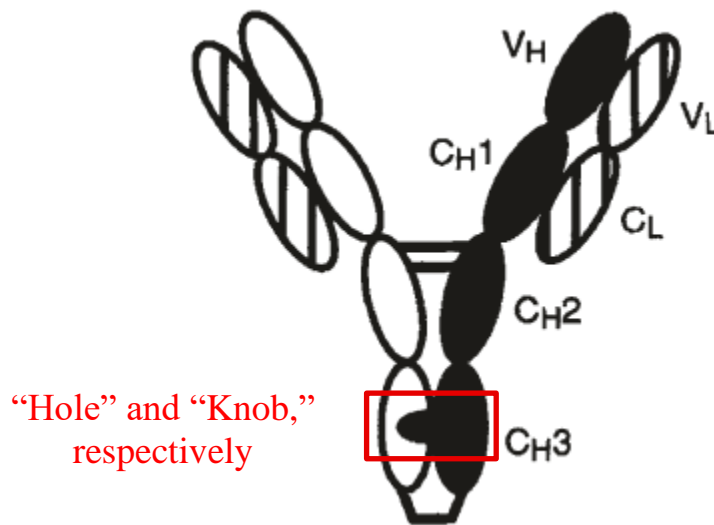
44. Moreover, while scientists pursued multiple improved synthesis methods before 2012, they typically involved a shared core tenet: manipulating interactions between amino acid residues located within the CH3 domain of the antibody heavy chain. By modifying these interactions, scientists found that 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).

45. By 2012 (let alone by 2023), 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

46. 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.)

47. 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) comparatively disfavored.

48. 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.)

49. 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,

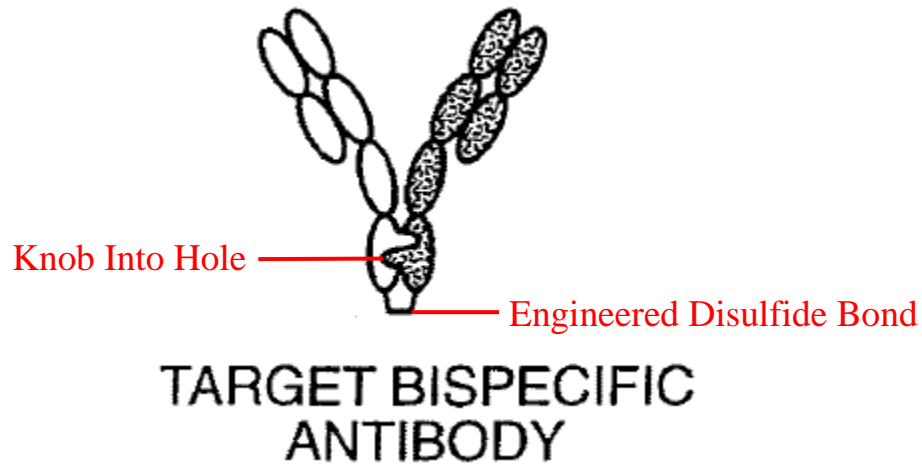
scientists (including my own group at Genentech) pursued strategies that could be used in combination, allowing for additive benefits to heterodimer synthesis efficiency.

2. Disulfide Linkage Approach

50. A second approach developed by scientists to promote heterodimer formation involved the creation of disulfide linkages¹⁰ 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:

¹⁰ As I mentioned above, disulfide linkages refers to the forming of covalent bonds between two sulfur atoms, present within the sulfhydryl “R” or side group of two different cysteine amino acids.

Demonstrative 7 – Combination of Disulfide Linkage and KIH



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

51. 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)¹¹ designed to promote disulfide linkages between heavy chains substantially increased the yield of the heterodimer over a non-modified protein sequence (76% versus 52%, respectively). (Ex. 1006 at 44:18-45:21, Table 4.)

¹¹ 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 being 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 44:26-28, Table 4.)

3. Electrostatic Steering Approach

52. 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).

53. That simple premise dates back as early as 1998, when scientists associated with the National Institutes of Health (Drs. Ameurfinia 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.”).) More specifically, the *Santos* authors replaced a neutral tyrosine (at position 407) on the first chain and a neutral phenylalanine (at position 506) on the second chain with amino acids of complementary charge. (Ex. 1016 at 186-187.) And as echoed above, the *Santos* authors explained that the “rationale behind [the neutral-to-charged amino acid mutations] lies in the expectation that identical chains repel each other and that only heterodimers will form.” (Ex. 1016 at 183.)

54. 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.)

55. 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.)

56. 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 to make charge pairs. (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. (Ex. 1007 at 3:20-24; Ex. 1012 at 19645.)

57. 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 on a first CH3 domain and neutral threonine (T) to negatively charged glutamic acid (E) at position 366 on a second CH3 domain¹² increased the heterodimer to homodimer ratio (depicted as Y407R/T366E). (Ex. 1021 at 48, 53.)

4. CH3 Domain Interface Residues

58. 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

¹² 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.)

domain interface residues had already been cataloged and reported in the art, as shown in the table below.

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'
<i>ARG A 355</i>	THR B 350'
ASP A 356	TYR B 349' LYS B 439'
GLU A 357	TYR B 349' LYS B 370'
<i>LYS A 360</i>	GLN B 347' TYR B 349'
SER A 364	LEU B 368' LYS B 370'
THR A 366	LEU B 351' TYR B 407'
LEU A 368	SER B 364' LYS B 409'
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.)

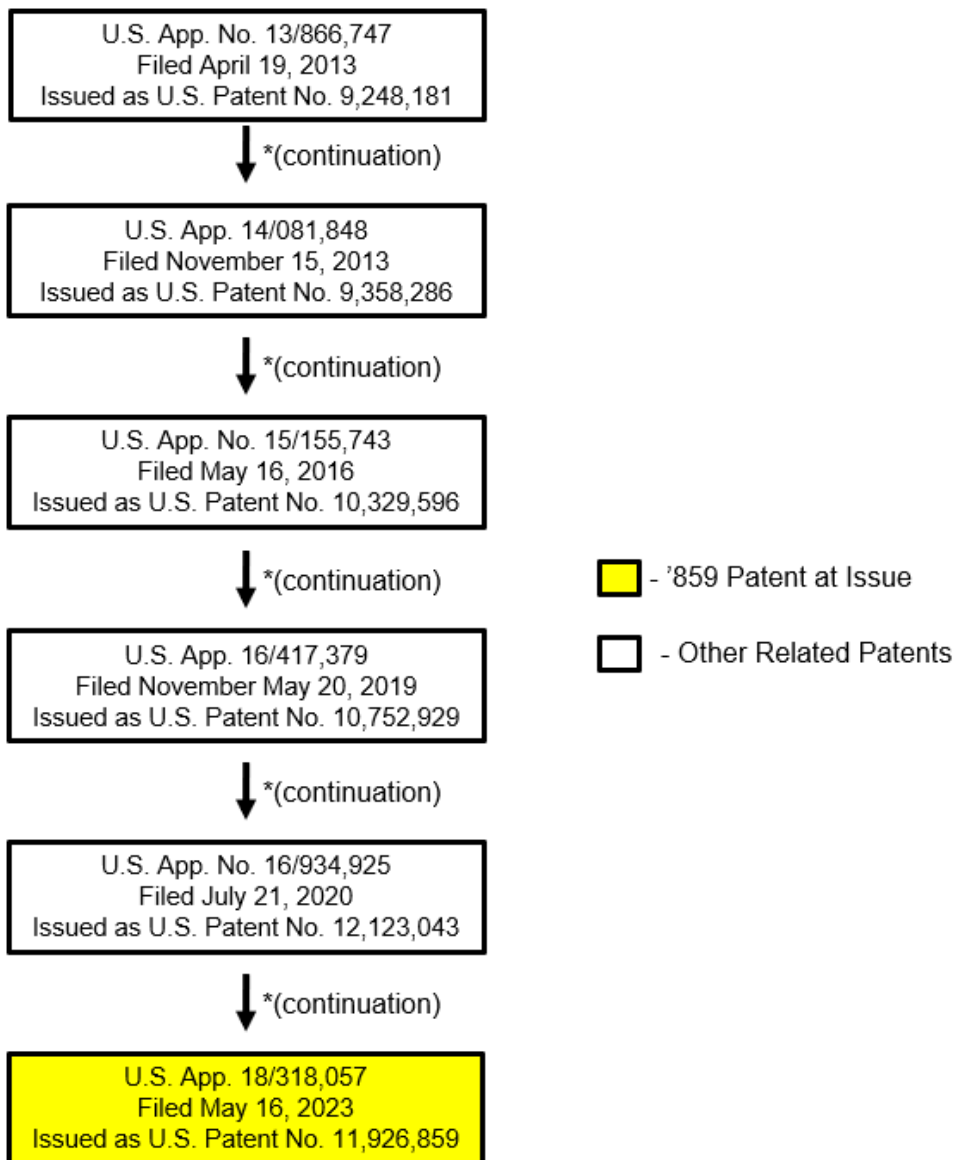
VI. Overview of the '859 Patent

59. The '859 patent is titled, "Methods and Means for the Production of Ig-Like Molecules."

60. I understand from its cover that the '859 patent issued on March 12, 2024 from the '507 application, filed May 16, 2023.

61. The '507 application was filed as the last of a series of continuation applications, which I have depicted in the chart below:

Demonstrative 9 – Continuation Applications Leading to the '859 Patent



(Ex. 1001 at Cover.)

62. The '859 patent further identifies on its face U.S. Provisional Application No. 61/635,935, filed on April 20, 2012. (Ex. 1001 at Cover.)

63. The '859 patent generally discusses “means and methods” for producing 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—optionally combined with other known antibody engineering strategies, like knob-into-hole—for providing improved percentages of desired heterodimeric antibodies. (Ex. 1001 at 6:4-14.)

64. However, the '859 patent recognizes that such additional strategies for engineering antibody heavy chains to increase heterodimer formation were already known. Specifically, the '859 patent acknowledges the prior art use of, *inter alia*, (1) knob-into-hole engineering and (2) electrostatic engineering. (Ex. 1001 at 4:46-5:49.)

65. Moreover, the '859 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 '859 patent. For instance, the '859 patent recognizes that, as by April 2012, it was already “well-known that the CH3-CH3 interaction is the primary driver for Fc dimerization.” (Ex. 1001 at 4:21-24.) 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 4:21-28.)

66. As to the identity of these contact residues, the '859 patent recognizes that the contact residues within the CH3-CH3 interface can either be neutral amino acids or charged amino acids (either positively or negatively). (Ex. 1001 at 13:33-35.) 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 13:37-41.) The remaining twenty 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 13:41-49.)

67. The '859 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 18:42-45.) The '859 patent refers to these neutral-to-charged mutations as “an inventive alternative to” the prior art. (Ex. 1001 at 18:39-42.) But, as discussed herein, such mutations had already been disclosed in the prior art before 2012—let alone by 2023. Likewise, neutral-to-negative and neutral-to-positive amino acid mutations at the specific positions

recited in claims 1-7 of the '859 patent had previously been disclosed by those dates.

68. The '859 patent contains a single independent claim, which reads as follows:

1. A heterodimeric antibody comprising a first human CH3 domain comprising a positively charged amino acid residue at position 364 according to the EU numbering system, and a second human CH3 domain comprising a negatively charged amino acid residue at position 368 according to the EU numbering system.

69. The '859 patent further contains six dependent claims, all of which depend from claim 1. They read as follows:

2. The heterodimeric antibody of claim 1, wherein said positively charged amino acid residue at position 364 comprises a lysine (K) or an arginine (R) residue, and wherein said negatively charged residue at position 368 comprises an aspartic acid (D) or glutamic acid (E) residue.
3. The heterodimeric antibody of claim 2, wherein said positively charged amino acid residue, wherein said positively charged amino acid residue at position 364 comprises a lysine (K) residue, and wherein said negatively charged amino acid residue at position 368 comprises an aspartic acid (D).
4. The heterodimeric antibody of claim 1, wherein said heterodimeric antibody is a bispecific antibody.
5. The heterodimeric antibody of claim 1, wherein said heterodimeric antibody is human IgG.
6. The heterodimeric antibody of claim 1, wherein said heterodimeric antibody is human IgG1.

7. A pharmaceutical composition comprising the heterodimeric antibody according to claim 1, and a pharmaceutically acceptable carrier.

70. However, as discussed below in Section X, it is my opinion that a person of ordinary skill in the art would not have understood the provisional or non-provisional applications identified on the cover of the '859 patent to describe the specific antibody claimed in claims 1-7 of the '859 patent, which recites a pair of amino acid substitutions on two distinct CH3 domains. (Section X.)

VII. Overview of the Prior Art

A. *Desjarlais* – U.S. Patent No. 10,472,427 (Ex. 1036)

71. *Desjarlais* is a United States Patent titled “Heterodimeric Proteins.” (Ex. 1036 at Cover.) The application that issued as *Desjarlais* was filed on June 26, 2017 as United States Application No. 15/633,629. (Ex. 1036 at Cover.) *Desjarlais* then subsequently issued on November 12, 2019. (Ex. 1036 at Cover.) It is my understanding that *Desjarlais* claims priority to a provisional application filed on January 14, 2013.

72. The assignee listed on the face of *Desjarlais* is Xencor, Inc. Further, the named inventors on *Desjarlais* are: John Desjarlais, Gregory Moore, Rumana Rashid, and Matthew Bennett.

73. Under the heading, “Summary of the Invention,” *Desjarlais* states that “the invention provides heterodimeric antibodies comprising a first heavy chain

comprising a first Fc domain and a single chain Fv region that binds a first antigen. The heterodimeric antibodies also comprise a second heavy chain and a first variable light chain, wherein the first and second Fc domains are different.” (Ex. 1036 at 3:24-30.) Additionally, *Desjarlais* teaches making amino acid mutations so as to promote heterodimer formation, stating, “The present invention is generally directed to the creation of heterodimeric proteins such as antibodies that can co-engage antigens in several ways, relying on amino acid variants in the constant regions that are different on each chain to promote heterodimeric formation and/or allow for ease of purification of heterodimers over the homodimers.” (Ex. 1036 at 8:28-33.)

74. As one manner of “promot[ing] heterodimer[] formation,” *Desjarlais* expressly teaches the use of “electrostatic steering.” (*E.g.*, Ex. 1036 at 21:52-67.) In fact, *Desjarlais* recognizes that such electrostatic steering techniques were established in the art well before its filing, stating:

An additional mechanism that finds use in the generation of heterodimers is sometimes referred to as “electrostatic steering” as described in Gunasekaran et al., *J. Biol. Chem.* 285(25):19637 (2010)¹³, hereby incorporated by reference in its entirety. This is sometimes referred to as “charge pairs.” In this embodiment, electrostatics are used to skew the formation towards heterodimerization.

¹³ The lead author of this article, Dr. Gunasekaran Kannan, is the first named inventor of the *Kannan* reference discussed below.

(Ex. 1036 at 9:12-18.)

75. Employing its disclosed techniques, *Desjarlais* teaches “heterodimerization variants” and “novel steric variants” that “find particular use in the present invention.” (Ex. 1036 at 4:55-62.) Figure 4 of *Desjarlais*, for instance, instructs making precise amino acid mutations so as to create “[p]referred steric variants that favor Fc heterodimerization.” (Ex. 1036 at Figure 4A.) The disclosed list of variants is reproduced below:

Preferred steric variants that favor Fc heterodimerization.

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

(Ex. 1036 at Figure 4A.)

76. *Desjarlais* goes on to describe “[s]pecifically preferred steric variants that favor Fc heterodimerization” in Figure 4B, reproduced below:

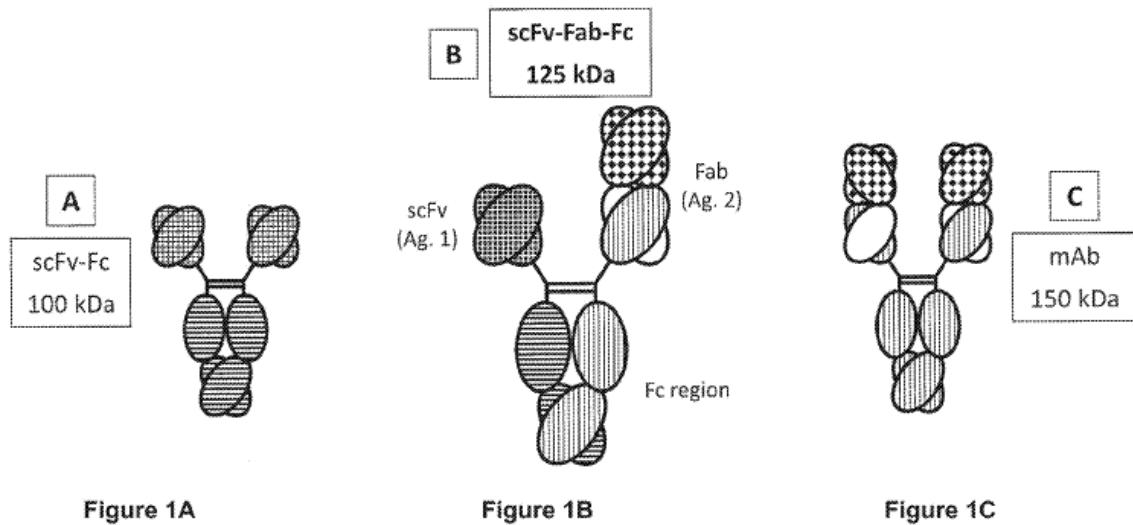
Specifically preferred steric variants that favor Fc heterodimerization.

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

(Ex. 1036 at Figure 4B.)

77. *Desjarlais* teaches that the amino acid mutations of the disclosed steric variants are defined by the “EU” numbering index. It reads, “For all positions discussed in the present invention that relate to antibodies, unless otherwise noted, amino acid position numbering is according to the EU index. The EU index or EU index as in Kabat or EU numbering scheme refers to the numbering of the EU antibody.” (Ex. 1036 at 12:64-13:2.)

78. *Desjarlais* also notes that its disclosed techniques can be applied to a wide variety of bispecific antibody formats. (Ex. 1036 at 15:41-56.) For instance, *Desjarlais* identifies the following heterodimeric antibody structures as examples of those to which its heterodimer-promotion techniques can be applied:



(Ex. 1036 at Figures 1A-C; *see also* Ex. 1036 at Figures 2-3 (illustrating additional antibody formats).)

B. *Moore – A robust heterodimeric Fc platform engineered for efficient development of bispecific antibodies of multiple formats (Ex. 1038)*

79. *Moore* is a peer-reviewed scientific article published in the journal *Methods*, and made available online on October 23, 2018. The lead author of *Moore* is Gregory Moore, who I understand was (and continues to be) a scientist at

Xencor. Several other scientists at Xencor are further identified as co-authors, including various named inventors on the *Desjarlais* and *Lazar* references.

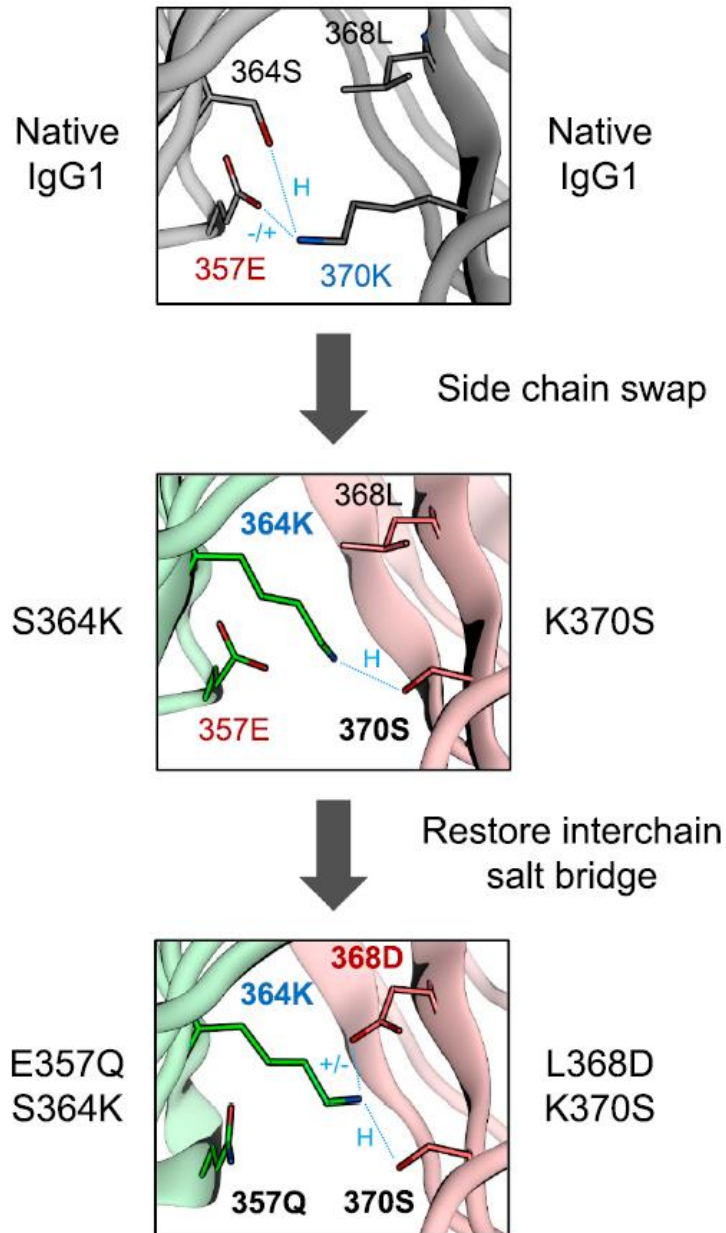
80. In its Abstract, *Moore* explains that “[b]ispecific [antibody] formats containing a heterodimeric Fc region are of particular interest, as a heterodimeric Fc empowers both bispecificity and altered valencies while retaining the developability and druggability of a monoclonal antibody.” (Ex. 1038 at 38.)¹⁴ To meet this interest in bispecific antibody production, *Moore* “present[s] a heterodimeric Fc platform, called the XmAb[®] bispecific platform, engineered for efficient development of bispecific antibodies and Fc fusions of multiple platforms,” which incorporates amino acid substitutions “capable of achieving heterodimer yields over 95% with little change in thermostability.” (Ex. 1038 at 38.)

81. *Moore* teaches specific amino acid substitutions that result in beneficial electrostatic interactions. On one chain, (1) the positively charged lysine (K)¹⁵ replaces the neutral serine (S) at position 364, and (2) the neutral glutamine

¹⁴ Throughout this declaration, I cite to the native pagination of a document unless otherwise noted.

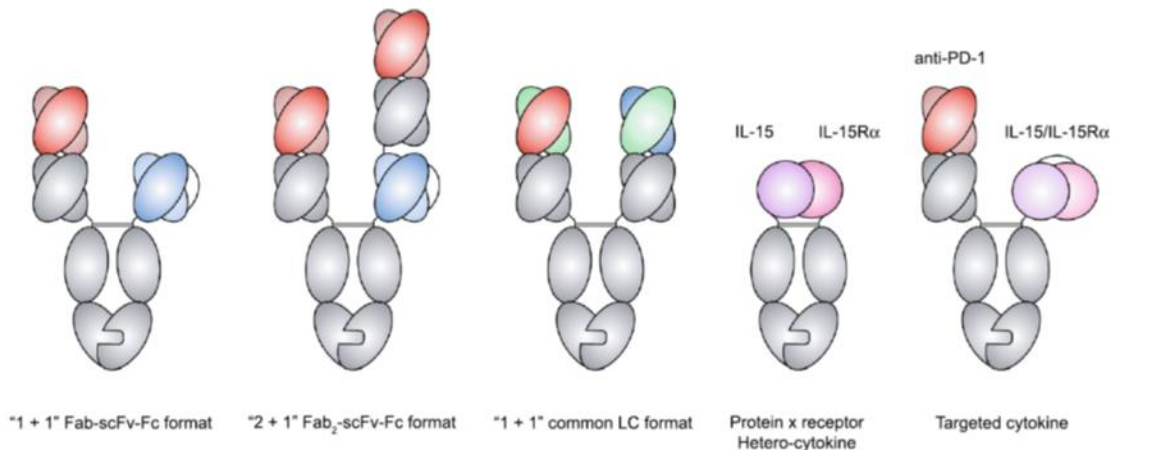
¹⁵ At certain places throughout this declaration, I have marked positively charged amino acids in green highlighting and negatively charged amino acids in red highlighting for ease of reference.

(Q) replaces the negatively charged glutamic acid (E) at position 357. (Ex. 1038 at 42.) On the second chain, (3) the negatively charged aspartic acid (D) replaces the neutral leucine (L) at position 368, and (4) the neutral serine (S) replaces the positively charged lysine (K) at position 370. (Ex. 1038 at 42.) *Moore* refers to this engineered construct as the “E357Q/S364K [on CH3 domain 1]-L368D/K370S [on CH3 domain 2] heterodimer.” (Ex. 1038 at 42.) And in Figure 5—titled, “Structural models confirming feasibility of heterodimeric Fc design rationale”—*Moore* depicts the referenced amino acid substitutions and illustrates their promotion of heterodimerization:



(Ex. 1038 at Figure 5.) Further, as indicated in the figure above, *Moore* states that the disclosed substitutions were introduced into a native human heavy chain IgG1 sequence. (Ex. 1038 at Figure 5, 39.)

82. *Moore* also teaches that its XmAb[®] bispecific platform can be used in a variety of formats, as detailed in Figure 1, which is reproduced below:



(Ex. 1038 at Figure 1, 45.)

83. Finally, *Moore* discloses that its XmAb[®] platform was used in the generation of several heterodimeric, bispecific antibodies then actively in clinical testing, writing, "Our Fc heterodimer technology has proven to be an efficient component to rapidly enable multiple clinical bispecific candidates." (Ex. 1038 at 49.)

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

84. *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

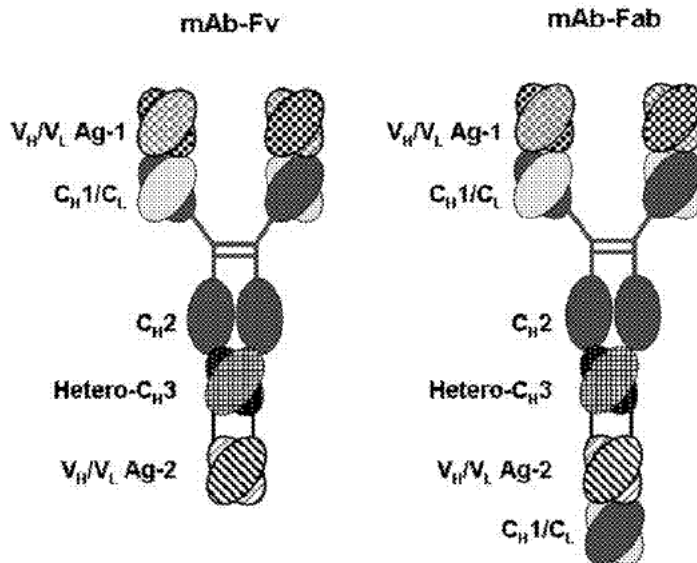
filed on September 2, 2010. (Ex. 1004 at Cover.) It is my understanding that *Lazar* claims priority to a provisional application filed on September 2, 2009. (Ex. 1004 at Cover.) It is further my understanding that Drs. Gregory Lazar and Gregory Moore performed the work leading to this publication while they were employees of Xencor—the listed assignee of the *Lazar* publication. (Ex. 1004 at Cover.)

85. *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 at the relevant time, *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.)

86. *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)

87. *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: two copies of one antibody light chain (one on each arm) 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 format where the second antigen-binding region is composed of a Fab portion of an antibody, which also 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.)

88. *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. (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.)

89. *Lazar* provides detailed methods for creating the described heterodimeric antibodies, 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 at the relevant time, *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.)

90. As one manner of improving heterodimer yield, *Lazar* includes amino acid substitutions that replace 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

(Ex. 1004 at Table 1.)

91. *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.”).)

D. *Kannan* – International Patent Publication WO2009/089004 (Ex. 1007)

92. *Kannan* is an International Patent Publication titled “Method for Making Antibody Fc-Heterodimeric Molecules Using Electrostatic Steering Effects.” (Ex. 1007 at Cover.) *Kannan* was published as WO2009/089004 on July 16, 2009, based on an international patent application filed on January 6, 2009. (Ex. 1007 at Cover.) Gunasekaran Kannan is listed as the first named inventor on the *Kannan* publication, who I understand was then a scientist at Amgen.

93. *Kannan* reports that its disclosure “relates to methods of making Fc-heterodimeric proteins or polypeptides.” (Ex. 1007 at Abstract.) More specifically, *Kannan* describes “a strategy for altering a pair of CH3 domains to reduce the ability of each domain to interact with itself but to increase the ability of the domains to interact with each other, i.e., form heterodimers.” (Ex. 1007 at 2:33-35.) As to the mechanism by which *Kannan* achieves that goal, the

reference teaches “replacing one or more residues that make up the CH3-CH3 interface in both CH3 domains with a charged amino acid such that homodimer formation is electrostatically unfavorable but heterodimerization is electrostatically favorable.” (Ex. 1007 at 2:35-3:7.)

94. *Kannan* first identifies a list of CH3 domain interface residues at Table 1—the sites at which *Kannan* instructs applying the disclosed electrostatic steering techniques. Table 1, captioned “List of CH3 domain interface residues in the first chain (A) and their contacting residues in the second chain (B),” is reproduced below:

Table 1: List of CH3 domain interface residues in the first chain (A) and their 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' PRO B 352' PRO B 353' SER B 354' THR B 366'
SER A 354	TYR B 349' THR B 350' LEU B 351'
<i>ARG A 355^b</i>	THR B 350'
ASP A 356	TYR B 349' LYS B 439'
GLU A 357	TYR B 349' LYS B 370'
<i>LYS A 360^b</i>	GLN B 347' TYR B 349'
SER A 364	LEU B 368' LYS B 370'
THR A 366	LEU B 351' TYR B 407'
LEU A 368	SER B 364' LYS B 409'
LYS A 370	GLU B 357' SER B 364'
ASN A 390	SER B 400'
LYS A 392	LEU B 398' 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 393' 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' SER B 408' 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 pair-wise interaction is represented twice in the structure (for example, Asp A 356 --- Lys B 439' & Lys A 439 --- Asp B 356'; Figure 5)

(Ex. 1007 at 7:19-8:7 (Table 1).)

95. From that broader list, *Kannan* identifies specific amino acid mutations to promote heterodimerization. At Table 2, *Kannan* identifies “possible mutations involving charge change,” and teaches that the “mutations can be combined to enhance the electrostatic effects.” (Ex. 1007 at 9:15-17.) Table 2a,

titled “List of some possible pair-wise charge residue mutations to enhance heterodimer formation” is reproduced below:

Table 2a: List of some possible pair-wise charge residue mutations to enhance heterodimer formation^a

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

^aCombinations of the above pair-wise charge residue mutations could also be used. For example Lys409 --- Asp399' interaction pair mutations could be combined with Lys439 --- Asp356' pair mutations.

(Ex. 1007 at 9:18-19 (Table 2a).)

96. In Table 2a, *Kannan* teaches that, where a negative charge is being introduced, either aspartic acid (“Asp” or “**D**”) or glutamic acid (“Glu” or “**E**”) may be substituted in. Similarly, where a positive charge is being introduced, either of lysine (“Lys” or “**K**”) or arginine (“Arg” or “**R**”) may be substituted in.

(Ex. 1007 at 9:18-19 (Table 2a); *see also* Ex. 1007 at 10:6-7 (“Each positively charged residue (Lys and Arg) can be mutated to two negatively charged residues (Asp or Glu) and *vice versa*”) (emphasis added).)

97. Additionally, *Kannan* teaches that its electrostatic steering approach can be applied by swapping “uncharged” (*i.e.*, neutral) amino acid residues for corresponding positively or negatively charged amino acids so as to promote

heterodimerization. (Ex. 1007 at 10:16-18 (“This strategy can also be extended to modifying uncharged residues to charged residues at the CH3 domain interface.”).)

VIII. Summary of Opinions

98. The claims at issue relate to a heterodimeric antibody made by substituting a neutral amino acid with a positive amino acid at a specific position in the CH3 domain of a first antibody heavy chain, and substituting a neutral amino acid with a negative amino acid at a specific position in the CH3 domain of a second antibody heavy chain.

99. However, the provisional and non-provisional applications identified on the face of the '859 patent do not demonstrate that the inventors named on the '859 patent were in possession of the subject matter claimed as of their respective filing dates. Specifically, the identified provisional and non-provisional applications do not describe substituting a positively charged amino acid residue at position 364 in one CH3 domain sequence together with substituting a negatively charged amino acid residue at position 368 in a second CH3 domain sequence, as recited in each of claims 1-7 in the '859 patent—let alone the specific substitutions required in claims 2 and 3.

100. By contrast, *Desjarlais* and *Moore* did disclose the claimed subject matter well before May 2023, which I understand to be the filing date of the application that led to the '859 patent.

101. Equally, *Lazar* alone or in combination with *Kannan* disclosed or suggested the heterodimeric antibodies and pharmaceutical composition recited in claims 1-7 of the '859 patent by April 2012. A person of ordinary skill in the art as of the relevant time would have been motivated to develop heterodimeric antibodies. And a person of ordinary skill in the art would have looked to *Lazar* and *Kannan*. Both taught methods for creating heterodimeric antibodies, including making electrostatic interactions at known CH3 interface residues in order to promote heterodimer yield. In fact, *Lazar* expressly identifies *Kannan* as describing “Fc variants that favor heterodimerization.” (Ex. 1004 at ¶125 (referencing “PCT/US2009/000071,” *i.e.*, the application that published as *Kannan*)). A person of ordinary skill in the art would have further reasonably expected to achieve the features recited in the claims using methods already taught in the prior art, including in *Lazar* and *Kannan*.

102. In my opinion, (1) *Desjarlais* (Ex. 1036) teaches all of the limitations of claims 1-7 of the '859 patent; (2) *Moore* (Ex. 1038) teaches all of the limitations of claims 1-7 of the '859 patent; and (3) *Lazar* (Ex. 1004) alone or in combination

with *Kannan* (Ex. 1007) teaches or suggests all of the limitations of claims 1-7 of the '859 patent.¹⁶

IX. Claim Construction

103. 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).

104. I have applied the ordinary and customary meaning to all the claim terms of the '859 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.

¹⁶ 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 (and well before May 2023). I am not citing any such document to show it teaches one or more features recited in the claims of the '859 patent (even though it may teach one or more such features). Instead, I rely only on the teachings of *Desjarlais*, *Moore*, *Lazar*, and *Kannan* for the claimed features.

X. Lack of Disclosure of Certain Claim Limitations

105. It is my opinion that a person of ordinary skill in the art would not have understood the provisional or non-provisional applications identified on the cover of the '859 patent to describe a heterodimeric antibody in which a positively charged amino acid residue is substituted in at position 364 in one CH3 domain sequence, and in which a negatively charged amino acid residue is substituted in at position 368 in a second CH3 domain sequence, as claimed in the '859 patent. Therefore, it is my opinion that a person of ordinary skill in the art would not have understood the inventors of the '859 patent to be in possession of the antibody claimed in claims 1-7, based on the disclosures of the specifications of the provisional and non-provisional applications identified on the cover of the '859 patent.

A. Antibody Claimed in the '859 Patent

106. As I discuss above in Section VI, the claims of the '859 recite a “heterodimeric antibody” with a **pair** of **two** very specific amino acid substitutions. Claim 1 requires insertion of a positively charged amino acid residue at position 364 in one CH3 domain sequence **and** insertion of a negatively charged amino acid residue at position 368 in a second CH3 domain sequence. Claims 4, 5, 6, and 7 require the same. (Ex. 1001 at claims 1, 4-7.)

107. Claims 2 and 3 then further require the insertion of specific amino acids—as the respective positively and negatively charged amino acids—at the identified position in each CH3 domain sequence. Claim 2 specifies that lysine (K) or arginine (R) are inserted as the “positively charged amino acid residue at position 364” in the first CH3 domain sequence, and that aspartic acid (D) or glutamic acid (E) are inserted as the “negatively charged residue at position 368” in the second CH3 domain sequence. (Ex. 1001 at claim 2.) Claim 3 goes one step further, requiring that lysine (K) is inserted as the “positively charged amino acid residue at position 364” in the first CH3 domain sequence, and that aspartic acid (D) is inserted as the “negatively charged amino acid residue at position 368” in the second CH3 domain sequence. (Ex. 1001 at claim 3.)

108. But, as I discuss in more detail below, the provisional and non-provisional applications identified on the cover of the '859 patent do not describe the specific pair of amino acid substitutions required in the claims of the '859 patent. That is, the identified applications do not describe inserting a positively charged amino acid residue at position 364 in one CH3 domain sequence together with inserting a negatively charged amino acid residue at position 368 in a second CH3 domain sequence—let alone the specific substitutions required in claims 2 and 3.

B. Provisional Application No. 61/635,935 Does Not Describe the Claimed Antibody

109. Provisional Application No. 61/635,935 (“the ’935 application”) (Ex. 1030) was filed on April 20, 2012. (Ex. 1001 at Cover.) And while the ’935 application is listed on the face of the ’859 patent, it does not describe a heterodimeric antibody with the specific pair of amino acid insertions on a first and second CH3 domain at positions 364 and 368, respectively, recited in the claims of the issued ’859 patent.

110. I have been informed that, during prosecution of the ’859 patent, the patent owner contended that Example 13 and Table 7 of the ’935 application describe the heterodimeric antibody recited in claims 1-7 of the ’859 patent. I disagree.

111. Example 13 can be broken down into essentially two experiments, which I will address separately. Example 13 is titled, “[I]dentification of novel charge pair mutants.” (Ex. 1030 at 51.) Example 13 reads, “[M]any interface contact residues in the IgG CH3 domain were scanned one by one or in groups for substitutions that would result in repulsion of *identical heavy chains* – i.e., reduced homodimer formation – via electrostatic interaction.” (Ex. 1030 at 51 (emphasis added).)

112. As Example 13 makes clear, the “first step” (or first experiment in Example 13) involved amino acid substitutions on “*identical heavy chains*”—and not a modification to a “first human CH3 domain” and a second modification to a “second human CH3 domain,” as recited in the issued claims of the ’859 patent. (See Ex. 1030 at 51; Ex. 1001 at claim 1.) Example 13 specifies that “In a follow up, the identified substitutions will be used to generate bispecific antibodies ... by engineering matched pairs of CH3 residues in one or more IgG heavy chains – CH3 regions.” (Ex. 1030 at 51.) This clarifies that this first experiment of Example 13 did *not* utilize pairs of substitutions to generate bispecific antibodies, but that such pairs of substitutions would be tested in the second experiment, which I address below. That is, this experiment of Example 13 did not involve the creation of heterodimers because “identical” heavy chains were used—heterodimers necessarily require distinct heavy chains.

113. Table 7 provides the “list of amino acid substitutions” tested in the “first step” described in Example 13. I have reproduced Table 7 below:

Declaration of Leonard G. Presta, Ph.D.
 U.S. Patent No. 11,926,859

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

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

Y407D		
Y349D, S364K, S400K, T407D	47	+
D399K	48	+
D399R	49	+
D399H	50	+
K392D	51	+
K392E	52	+
K409D	53	+

(Ex. 1030 at Table 7.) Consistent with Example 13’s explanation that this “first step” involved only identical heavy chains, Table 7 makes clear that amino acid substitutions were made to a single CH3 domain in a single IgG heavy chain, which was then co-expressed with a light chain (in order to form the homodimer band of approximately 150 kDa), but *not* with a second, different heavy chain (Ex.

1030 at 54.) So, while Table 7 identifies modifications to positions 364 and 368, this table does not describe a heterodimeric antibody incorporating a pair of simultaneous amino acid substitutions to a “first human CH3 domain” and to a “second human CH3 domain,” as recited in claims 1-7 of the ’859 patent. Nor does the ’859 patent describe a single antibody comprising “a positively charged amino acid residue at position 364”, **and** “a negatively charged amino acid residue at position 368”, as recited in claims 1-7 of the ’859 patent.

114. Based on the results of the “first step” testing summarized in Table 7, Example 13 of the ’935 application went on to its second experiment, initially by selecting “[a] number of residues [that] were considered promising for further testing in combination.” (Ex. 1030 at 54.) None of the “promising” CH3 domain variants included any amino acid substitutions to positions 364 or 368—let alone combining an amino acid substitution at position 364 on a first CH3 domain and a second amino acid substitution at position 368 on a second CH3 domain. (Ex. 1030 at 54 (“A number of residues were considered promising for further testing in combination, including residues Q347, S354, Y349, L351, K360, T366, T394, and V397.”).)

115. Example 13 goes on to identify the amino acid substitutions that the inventors *did*, in fact make to a first and second CH3 domain, but again neither involved amino acid substitutions at positions 364 (on a first CH3 domain) or

position 368 (on a second CH3 domain)—let alone both substitutions. Table 8 of the '935 application – reproduced below – describes eight additional constructs that were made, focusing on the “promising” residues.

AA substitutions in CH3	construct #
L351K	61
T394K	62
L351D	63
T366D	64
S354D, Y349D	65
V397D	66
K360D	67

(Ex. 1030 at Table 8.)

116. Table 9, also reproduced below, defines which construct number (from Tables 7 or 8) was used in which vector (numbered XI through XX). It is clear from Tables 7 and 8 that none of the construct numbers cloned into these vectors comprised a mutation at either position 364 or 368. Thus, this second part of Example 13 does not describe or show possession of incorporating charged substitutions to position 364 of a first CH3 domain and to position 368 of a second CH3 domain, as is claimed in claims 1-7 of the '859 patent—none of the constructs used for the experiment contained any sort of mutation at either position.

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

(Ex. 1030 at Table 9.)

117. Table 10 of the '935 application—reproduced below—“depicts the transfection schedules and results” that the inventors did make and test. (Ex. 1030 at 55; Ex. 1030 at 57 (“Combinations of CH3 variants were expressed, and analyzed in SDS-PAGE (data not shown) and in native mass spectrometry (MS). Results are summarized in Table 10.”).)

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

(Ex. 1030 at Table 10.)

118. Tables 7, 8, and 9, together, provide the CH3 domain amino acid substitutions that were tested in Table 10, represented by the roman numerals under the column heading “Transfection of.” I have summarized the tested constructs below:

Construct #	Vector	AA substitutions in CH3
8	XI	Q347K
17	XII	S354K, Y349K
43	XIII	T366K
61	XIV	L351K
62	XV	T394K
63	XVI	L351D
64	XVII	T366D

65	XVIII	S354D, Y349D
66	XIX	V397D
67	XX	K360D

(Ex. 1030 at 52-57.) So, based on the disclosures of Tables 7-10, I have summarized the combined first and second CH3 domains incorporating an amino acid substitution below that were actually tested in Example 13 below:

Table 10:

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



Heterodimer Tested	AA Substitutions Tested
XIII + XVI	T366K + L351D

XIV + XVII	V397D + T366D
XII + XVIII	C354K/Y349K + S354D/Y349D
XV + XIX	T394K + V397D
XI + XX	Q347K + K360D

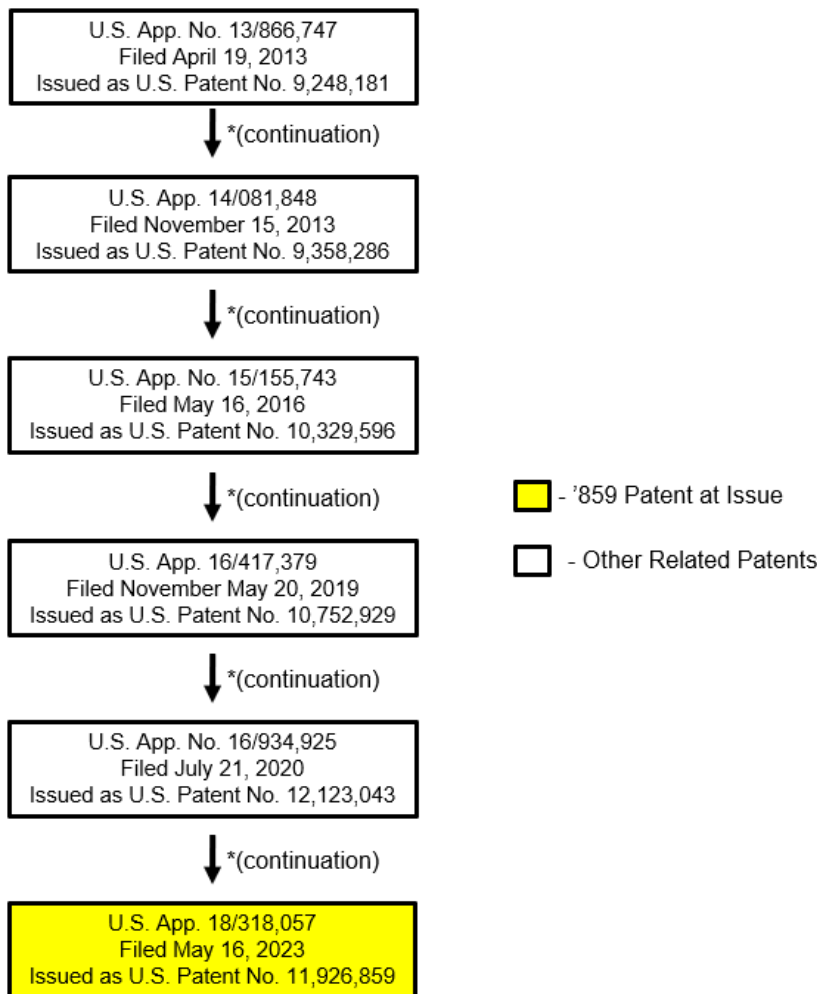
Again, none of the heterodimers tested included amino acid substitutions at either positions 364 or 368, let alone amino acid substitutions at position 364 on a first CH3 domain, and an amino acid substitution at position 368 on a second CH3 domain, as claimed in the '859 patent.

119. Therefore, it is my opinion that these disclosures in the '935 application would not have conveyed to a person of ordinary skill in the art that the individuals named as inventors on the face of the '859 patent were in possession of a heterodimeric antibody comprising a pair of modifications to positions 364 and 368 on two different CH3 domains, let alone the precise amino acids recited in claims 2 and 3 of the '859 patent.

C. No Support in Any Non-Provisional Application

120. The '859 patent further identifies five additional patent applications on its face, which I have summarized in the table below in the previously presented Demonstrative 9:

Demonstrative 9 – Continuation Applications Leading to the '859 Patent



121. As previously stated, I understand that patent owner contended during prosecution that Example 13 and Table 7 demonstrate possession of the claims of the '859 patent. Example 13 and Table 7 of the non-provisional applications identified on the face of the '859 patent are identical to those in the '935 application. And for the reasons discussed above in Section X.B, it is my opinion that the disclosures of Example 13 and Table 7 of the '935 application would not

indicate to a person of ordinary skill in the art that the named inventors were in possession of the claimed heterodimeric antibodies.

122. I understand that, as continuation applications, each of the non-provisional applications identified on the face of the '859 patent share an identical specification (or written disclosure). As compared to the '935 provisional application, these non-provisional applications include the additional examples 19-24, as well as figures 18-29. (Ex. 1001 at 52:30-67:2; Ex. 1001 at Figures 18-29.) However, these examples and figures likewise do not describe making an amino acid substitution at position 364 on a first CH3 domain, as well as an amino acid substitution at position 368 on a second CH3 domain. Therefore, it is my opinion that they likewise do not demonstrate possession of the heterodimeric antibodies claimed in the '859 patent.

XI. Ground 1: *Desjarlais* Teaches All of the Limitations of Claims 1-7

123. It is my opinion that each of the limitations of claims 1-7 is taught by *Desjarlais* for at least the reasons explained below.

A. Claim 1

1. “A heterodimeric antibody comprising”

124. It is my opinion that *Desjarlais* discloses a heterodimeric antibody.

125. As early as its abstract, *Desjarlais* teaches that “[t]he invention provides heterodimeric antibodies comprising a first heavy chain comprising a first

Fc domain and a single chain Fv region that binds a first antigen. The heterodimeric antibodies also comprise a second heavy chain comprising a second Fc domain, a first variable heavy chain and a first variable light chain, wherein the first and second Fc domains are different.” (Ex. 1036 at Abstract.)

126. Under the heading, “Detailed Description of the Invention,” *Desjarlais* confirms that “[t]he present invention is generally directed to the creation of heterodimeric proteins such as antibodies that can co-engage antigens in several ways, relying on amino acid variants in the constant regions that are different on each chain to promote heterodimeric formation and/or allow for ease of purification of heterodimers over the homodimers.” (Ex. 1036 at 8:28-33.)

127. As a way to promote heterodimerization, *Desjarlais* discloses “heterodimerization variants [that] include a number of different types of variants, including, but not limited to, steric variants (including charge variants)....” (Ex. 1036 at 20:58-62.) And, as discussed further below, the “steric variants” (and “heterodimerization variants”) taught in *Desjarlais* included heavy chain pairs in which a positively charged amino acid residue was substituted in at position 364 in a first CH3 domain, and a negatively charged amino acid residue was substituted in at position 368 in a second CH3 domain.

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

128. It is my opinion that *Desjarlais* discloses “a first human CH3 domain comprising a positively charged amino acid residue at position 364 according to the EU numbering system, and a second human CH3 domain comprising a negatively charged amino acid residue at position 368 according to the EU numbering system.”

129. As I noted in Section XI.A.1, *Desjarlais* teaches making amino acid substitutions so as to promote heterodimer formation. *Desjarlais* describes that “[t]he present invention is generally directed to the creation of heterodimeric proteins... [that] rely[] on amino acid variants in the constant regions that are different on each chain to promote heterodimeric formation and/or allow for ease of purification of heterodimers over the homodimers.” (Ex. 1036 at 8:28-33.)

130. *Desjarlais* further discloses specific “heterodimerization variants” and “steric variants” that “find particular use in the present invention.” (Ex. 1036 at 4:55-62.) These “variants” taught by *Desjarlais* include multiple heterodimer-promoting embodiments in which a positively charged amino acid residue is substituted in at position 364 in one human CH3 domain, and a negatively charged

amino acid residue is substituted in at position 368 in a second human CH3 domain, as recited in claim 1.

131. Figures 4A and 4B of *Desjarlais*—captioned “[p]referred steric variants that favor Fc heterodimerization” and “[s]pecifically preferred steric variants that favor Fc heterodimerization,” respectively—teach several such variants. I have annotated Figures 4A and 4B below to indicate precisely where *Desjarlais* provides combination of variants (Monomer 1 / Variant 1 and Monomer 2 / Variant 2) in which a positively charged amino acid residue is substituted in at position 364 (shown in green) in one human CH3 domain, and a negatively charged amino acid residue is substituted in at position 368 (shown in red) in a second human CH3 domain, as recited in claim 1.

Figure 4A

Preferred steric variants that favor Fc heterodimerization.

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

(Ex. 1036 at Figure 4A.)

Figure 4B

Specifically preferred steric variants that favor Fc heterodimerization.

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

(Ex. 1036 at Figure 4B.)

132. Figures 5A and 5B of *Desjarlais*, which share the heading “PREFERRED HETERODIMERIZATION VARIANTS,” likewise teach variants in which a positively charged amino acid residue is substituted in at position 364 on one human CH3 domain, and a negatively charged amino acid residue is substituted in at position 368 on a second human CH3 domain. Below, I have again annotated Figures 5A and 5B to show substitution in of a positively charged

amino acid residue at position 364 (in green) and substitution in of a negatively charged amino acid residue at position 368 (in red):

Figure 5A

PREFERRED HETERODIMERIZATION VARIANTS

Fc monomer 1 substitutions	Fc monomer 2 substitutions
Y407T	T366Y
F405A	T394W
T366Y/F405A	T394W/Y407T
Y407A	T366W
T366S/L368A/Y407V	T366W
T366S/L368A/Y407V/Y349C	T366W/S354C
K392D/K409D	E356K/D399K
K370D/K392D/K409D	E356K/E357K/D399K
Y349T	S364H
T394F	F405A
Y349T/T394F	S364H/F405A
K370E	T411K
K370E/T411D	T411K
K370E/T411E	K370R/T411K
L368E/K409E	L368K
Y349T/T411E	S364H/D401K
Y349T/T394F/S354C	S364H/F405A/Y349C
T411E	D401K
T411E	D401R/T411R
Q347E/K360E	Q347R
L368E	S364K
I199T/N203D/K247Q/R355Q/N384S/ K392N/V397M/Q419E/K447_ (deletion of K447)	Q196K/I199T/P217R/P228R/N276K
I199T/N203D/K247Q/R355Q/N384S/K3 92N/V397M/Q419E/K447_	Q196K/I199T/N276K
N384S/K392N/V397M/Q419E	N276K
D221E/P228E/L368E	D221R/P228R/K409R
C220E/P228E/L368E	C220R/E224R/P228R/K409R
F405L	K409R
T366i/K392M/T394W	F405A/Y407V
T366V/K409F	L351Y/Y407A
T366A/K392E/K409F/T411E	D399R/S400R/Y407A
Y349T	S364H
T394F	F405A
Y349T/T394F	S364H/F405A
K370E	T411K
K370E/T411D	T411K
K370E/T411E	K370R/T411K
L368E/K409E	L368K
Y349T/T411E	S364H/D401K
Y349T/T394F/S354C	S364H/F405A/Y349C
T411E	D401K
T411E	D401R/T411R

(Ex. 1036 at Figure 5A.)

Q347E/K360E	Q347R
L368E	S364K
L368E/K370S	S364K
L368E/K370T	S364K
L368E/D401R	S364K
L368E/D401N	S364K
L368E	E357S/S364K
L368E	S364K/K409E
L368E	S364K/K409V
L368D	S364K

(Ex. 1036 at Figure 5B.)

133. In addition, *Desjarlais* actually claims a heterodimer in which a positively charged amino acid residue is substituted in at position 364 in one CH3 domain, and a negatively charged amino acid residue is substituted in at position 368 in a second CH3 domain. (Ex. 1036 at claim 1.) More specifically, *Desjarlais* claims a heterodimer in which the positively charged amino acid inserted on one CH3 domain at position 364 is lysine (K), and the negatively charged amino acid inserted on a second CH3 domain at position 368 is aspartic acid (D):

We claim:

1. A heterodimeric protein comprising:
 - a) a first monomer comprising a first variant Fc domain, and
 - b) a second monomer comprising a second variant Fc domain,

wherein said first and second variant Fc domains comprise amino acid variant set L368D and S364K, according to the EU index as in Kabat.

(Ex. 1036 at claim 1.)

134. A person of ordinary skill in the art would further understand that the positions recited by the variants of *Desjarlais* are numbered “according to the EU numbering system,” as recited in claim 1. *Desjarlais* unequivocally states that

“[f]or all positions discussed in the present invention that relate to antibodies, unless otherwise noted, amino acid position numbering is according to the EU index. The EU index or EU index as in Kabat or EU numbering scheme refers to the numbering of the EU antibody.” (Ex. 1036 at 12:64-13:2.)

135. Finally, a person of ordinary skill in the art would readily understand that the disclosed variants are based on a human CH3 domain.¹⁷ *Desjarlais* teaches that “[t]he present invention is directed to the IgG class, which has several subclasses, including, but not limited to IgG1, IgG2, IgG3, and IgG4.” (Ex. 1036 at 15:63-66.) And *Desjarlais* instructs that the IgG sequence upon which the disclosed variants are based may be, more specifically, a “human” IgG sequence, stating that “[a]s described below, in some embodiments the parent polypeptide, for example an Fc parent polypeptide, is a human wild type sequence, such as the Fc region from IgG1, IgG2, IgG3 or IgG4....” (Ex. 1036 at 12:29-33.)

¹⁷ I note that if claim 1 is understood to require an entirely human CH3 domain sequence with respect to any ground, a person of ordinary skill in the art would not be able to understand this claim. Claim 1 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 CH3 domain” sequences. I therefore understand the claim’s requirement of a “a first human CH3 domain” and a “second human CH3 domain” to mean that the amino acid substitutions recited in the claim must be applied to a human CH3 domain sequence.

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

136. It is my opinion that *Desjarlais* discloses the heterodimeric antibody of claim 1, “wherein said positively charged amino acid residue at position 364 comprises a lysine (K) or an arginine (R) residue, and wherein said negatively charged residue at position 368 comprises an aspartic acid (D) or glutamic acid (E) residue.”

137. I have annotated the previously presented Figures 4 and 5 to indicate precisely where *Desjarlais* discloses variants in which the positively charged amino acid inserted at position 364 is lysine (K) or arginine (R) (both shown in green), and the negatively charged amino acid inserted at position 368 is aspartic acid (D) or glutamic acid (E) (both shown in red), as required by claim 2.

Figure 4A

Preferred steric variants that favor Fc heterodimerization.

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

(Ex. 1036 at Figure 4A.)

Figure 4B

Specifically preferred steric variants that favor Fc heterodimerization.

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

(Ex. 1036 at Figure 4B.)

Figure 5A

PREFERRED HETERODIMERIZATION VARIANTS

Fc monomer 1 substitutions	Fc monomer 2 substitutions
Y407T	T366Y
F405A	T394W
T366Y/F405A	T394W/Y407T
Y407A	T366W
T366S/L368A/Y407V	T366W
T366S/L368A/Y407V/Y349C	T366W/S354C
K392D/K409D	E356K/D399K
K370D/K392D/K409D	E356K/E357K/D399K
Y349T	S364H
T394F	F405A
Y349T/T394F	S364H/F405A
K370E	T411K
K370E/T411D	T411K
K370E/T411E	K370R/T411K
L368E/K409E	L368K
Y349T/T411E	S364H/D401K
Y349T/T394F/S354C	S364H/F405A/Y349C
T411E	D401K
T411E	D401R/T411R
Q347E/K360E	Q347R
L368E	S364K
I199T/N203D/K247Q/R355Q/N384S/ K392N/V397M/Q419E/K447_ (deletion of K447)	Q196K/I199T/P217R/P228R/N276K
I199T/N203D/K247Q/R355Q/N384S/K3 92N/V397M/Q419E/K447_	Q196K/I199T/N276K
N384S/K392N/V397M/Q419E	N276K
D221E/P228E/L368E	D221R/P228R/K409R
C220E/P228E/L368E	C220R/E224R/P228R/K409R
F405L	K409R
T366I/K392M/T394W	F405A/Y407V
T366V/K409F	L351Y/Y407A
T366A/K392E/K409F/T411E	D399R/S400R/Y407A
Y349T	S364H
T394F	F405A
Y349T/T394F	S364H/F405A
K370E	T411K
K370E/T411D	T411K
K370E/T411E	K370R/T411K
L368E/K409E	L368K
Y349T/T411E	S364H/D401K
Y349T/T394F/S354C	S364H/F405A/Y349C
T411E	D401K
T411E	D401R/T411R

(Ex. 1036 at Figure 5A.)

Q347E/K360E	Q347R
L368E	S364K
L368E/K370S	S364K
L368E/K370T	S364K
L368E/D401R	S364K
L368E/D401N	S364K
L368E	E357S/S364K
L368E	S364K/K409E
L368E	S364K/K409V
L368D	S364K

(Ex. 1036 at Figure 5B.)

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

138. It is my opinion that *Desjarlais* discloses the heterodimeric antibody of claim 2, “wherein said positively charged amino acid residue at position 364 comprises a lysine (K) residue, and wherein said negatively charged residue at position 368 comprises an aspartic acid (D).”

139. As shown in Figures 4 and 5, discussed previously with respect to claims 1 and 2, *Desjarlais* describes a heterodimeric antibody in which the positively charged amino acid inserted on one CH3 domain at position 364 is lysine (K), and the negatively charged amino acid inserted on a second CH3 domain at position 368 is aspartic acid (D), as required by claim 3. I have indicated in red boxes in Figures 4 and 5 where such substitutions were made.

Figure 4A

Preferred steric variants that favor Fc heterodimerization.

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

(Ex. 1036 at Figure 4A.)

Declaration of Leonard G. Presta, Ph.D.
U.S. Patent No. 11,926,859

Specifically preferred steric variants that favor Fc heterodimerization.

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

(Ex. 1036 at Figure 4B.)

Figure 5B

Q347E/K360E	Q347R
L368E	S364K
L368E/K370S	S364K
L368E/K370T	S364K
L368E/D401R	S364K
L368E/D401N	S364K
L368E	E357S/S364K
L368E	S364K/K409E
L368E	S364K/K409V
L368D	S364K

(Ex. 1036 at Figure 5B.) In fact, *Desjarlais* claims a heterodimer with these very amino acid substitutions, reciting:

We claim:

1. A heterodimeric protein comprising:

- a) a first monomer comprising a first variant Fc domain,
and
b) a second monomer comprising a second variant Fc domain,

wherein said first and second variant Fc domains comprise amino acid variant set L368D and S364K, according to the EU index as in Kabat.

(Ex. 1036 at claim 1.)

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

140. It is my opinion that *Desjarlais* discloses the heterodimeric antibody of claim 1, “wherein said heterodimeric antibody is a bispecific antibody.”

141. In its overview, *Desjarlais* describes that “[t]he present invention is directed to novel constructs to provide bispecific antibodies.... An ongoing problem in antibody technologies is the desire for ‘bispecific’ (and/or multispecific) antibodies that bind to two (or more) different antigens simultaneously, in general thus allowing the different antigens to be brought into proximity and resulting in new functionalities and new therapies.” (Ex. 1036 at 8:11-19.)

142. *Desjarlais* further instructs that “[t]he present invention is generally directed to the creation of heterodimeric proteins such as antibodies that can co-engage antigens in several ways, relying on amino acid variants in the constant regions that are different on each chain to promote heterodimeric formation and/or

allow for ease of purification of heterodimers over the homodimers.” (Ex. 1036 at 8:28-33.)

143. A person of ordinary skill in the art would readily understand *Desjarlais*' discussion of “heterodimeric proteins such as antibodies that can co-engage antigens” to include bispecific antibodies. (*E.g.*, Ex. 1007 at 1:31-32 (“Bispecific antibodies refer to antibodies having specificities for at least two different antigens.”).) In fact, *Desjarlais* says just that, detailing,

One avenue being explored [for improvement of antibody-based therapeutics] is the engineering of additional and novel antigen binding sites into antibody-based drugs such that a single immunoglobulin molecule co-engages two different antigens. Such non-native or alternative antibody formats that engage two different antigens are often referred to as bispecifics.

(Ex. 1036 at 1:48-53; *see also* Ex. 1036 at 15:41-45 (“The present invention is directed to the generation of multispecific, particularly bispecific binding proteins...”), 8:11-28.) And *Desjarlais* further expressly describes actually making the disclosed bispecific antibodies. (*See, e.g.*, Ex. 1036 at Example 1 (“Prototype ‘Triple F’ Bispecific Antibody”).)

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

144. It is my opinion that *Desjarlais* discloses the antibody of claim 1, “wherein said heterodimeric antibody is human IgG.”¹⁸

145. *Desjarlais* teaches that “[t]he present invention relates to the generation of multi-specific antibodies, generally therapeutic antibodies.” (Ex. 1036 at 15:47-48.) As to the identity of the sequence upon which the disclosed multi-specific, heterodimeric bodies are based, *Desjarlais* specifies that “[t]he present invention is directed to the IgG class, which has several sub-classes, including, but not limited to IgG1, IgG2, IgG3, and IgG4.” (Ex. 1036 at 15:63-66.) And *Desjarlais* instructs that the IgG sequence upon which the disclosed variants are based may be, more specifically, a “human” IgG sequence, stating that “[a]s described below, in some embodiments the parent polypeptide, for example an Fc

¹⁸ I note that if claim 5—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.

parent polypeptide, is a human wild type sequence, such as the Fc region from IgG1, IgG2, IgG3 or IgG4....” (Ex. 1036 at 12:29-33.)

146. Moreover, *Desjarlais* goes on to expressly claim a “heterodimeric protein [*i.e.*, antibody]... wherein said first and second variant Fc domains are selected from the group consisting of human IgG1, IgG2 and IgG4 variant Fc domains.” (Ex. 1036 at Claim 6.) And *Desjarlais*’s claim 6 depends from its claim 1 that recites the “L368D and S364K” charge pair that discloses the limitations in claim 1 of the ’859 patent. (*Id.*)

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

147. It is my opinion that *Desjarlais* discloses the heterodimeric antibody of claim 1, “wherein said heterodimeric antibody is human IgG1.”

148. As discussed above with respect to claim 5, *Desjarlais* teaches that the IgG sequence upon which its variants are based may be a “human” IgG sequence, stating that “[a]s described below, in some embodiments the parent polypeptide, for example an Fc parent polypeptide, is a human wild type sequence, such as the Fc region from IgG1, IgG2, IgG3 or IgG4.” (Ex. 1036 at 12:29-33.)

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

149. It is my opinion that *Desjarlais* discloses a pharmaceutical composition comprising the heterodimeric antibody of claim 1 “and a pharmaceutically acceptable carrier.”

150. For instance, *Desjarlais* states under the heading, “Summary of the Invention,” that “[t]he present invention provides compositions comprising immunoglobulin polypeptides described herein, and a physiologically or pharmaceutically acceptable carrier or diluent.” (Ex. 1036 at 4:17-22.) Further, under the heading, “Antibody Compositions for In Vivo Administration,” *Desjarlais* describes that “[f]ormulations of the antibodies used in accordance with the present invention are prepared for storage by mixing an antibody having the desired degree of purity with optional pharmaceutically acceptable carriers, excipients or stabilizers.” (Ex. 1036 at 47:40-45.) *Desjarlais* then goes on to list a range of known pharmaceutically acceptable “carriers, excipients or stabilizers” that may be used in formulating the heterodimeric antibodies described. (See Ex. 1036 at 47:47-67.)

151. A person of ordinary skill in the art would readily understand that the “antibodies used in accordance with the present invention” to be formulated in the

disclosed pharmaceutically acceptable carriers include the heterodimers discussed above in Section XI.A.2 with respect to claim 1.

* * *

152. For the reasons I discuss in Section XI above, it is my opinion that a person of ordinary skill in the art would have understood *Desjarlais* to teach every limitation of claims 1-7 of the '859 patent, as arranged in the claims.

XII. Ground 2: *Moore* Teaches All of the Limitations of Claims 1-7

153. In addition to understanding that *Desjarlais* teaches every limitation of claims 1-7 of the '859 patent, as discussed above in Section XI, it is my opinion that a person of ordinary skill in the art would have understood that *Moore* teaches every limitation of these same claims, as arranged in the claims.

A. Claim 1

1. “A heterodimeric antibody comprising”

154. It is my opinion that *Moore* discloses a heterodimeric antibody.

155. In fact, *Moore* is titled, “A robust heterodimeric Fc platform engineered for efficient development of bispecific antibodies of multiple formats.”

(Ex. 1038 at 38.) Consistent with that title, *Moore* details in its abstract that:

Bispecific monoclonal antibodies can bind two protein targets simultaneously and enable therapeutic modalities inaccessible by traditional [monoclonal antibodies]. Bispecific formats containing a heterodimeric Fc region are of particular interest.... We present a robust heterodimeric Fc platform, called the XmAb[®] bispecific

platform, engineered for efficient development of bispecific antibodies and Fc fusions of multiple formats.

(Ex. 1038 at 38.)

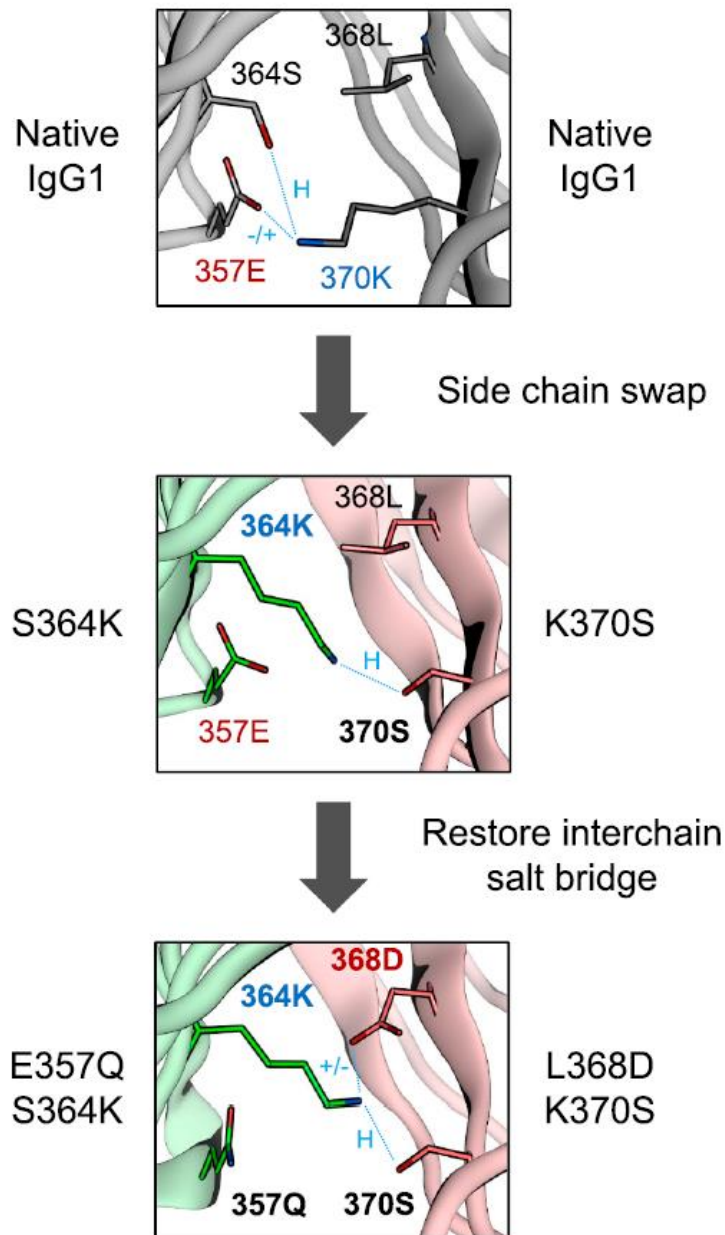
2. **“a first human CH3 domain comprising a positively charged amino acid residue at position 364 according to the EU numbering system, and a second human CH3 domain comprising a negatively charged amino acid residue at position 368 according to the EU numbering system”**

156. It is my opinion that *Moore* discloses “a first human CH3 domain comprising a positively charged amino acid residue at position 364 according to the EU numbering system, and a second human CH3 domain comprising a negatively charged amino acid residue at position 368 according to the EU numbering system.”

157. *Moore* “present[s] a heterodimeric Fc platform, called the XmAb[®] bispecific platform, engineered for efficient development of bispecific antibodies and Fc fusions of multiple platforms,” which incorporates amino acid substitutions “capable of achieving heterodimer yields over 95% with little change in thermostability.” (Ex. 1038 at 38.)

158. *Moore* goes on to teach that the amino acid substitutions described include inserting a positively charged amino acid residue at position 364 on a first human CH3 domain and inserting a negatively charged amino acid residue at position 368 on a second human CH3 domain. Specifically, *Moore* teaches in

Figure 5 (reproduced below) making the following amino acid substitutions: on one chain, (1) *positively charged lysine (K)* replaces *neutral serine (S) at position 364*, and (2) neutral glutamine (Q) replaces negatively charged glutamic acid (E) at position 357; and on the second chain, (3) *negatively charged aspartic acid (D)* replaces *neutral leucine (L) at position 368*, and (4) neutral serine (S) replaces positively charged lysine (K) at position 370. (Ex. 1038 at 42.)



(Ex. 1038 at Figure 5.) *Moore* refers to this construct as the “E357Q/S364K-L368D/K370S heterodimer” with positions “numbered according to the EU index.” (Ex. 1038 at 39, 42.) And *Moore* further teaches that the disclosed

substitutions were introduced into distinct native human heavy chain IgG1

sequences. (Ex. 1038 at Figure 5; *see also* Ex. 1038 at 39.)

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

159. It is my opinion that *Moore* discloses the heterodimeric antibody of claim 1, “wherein said positively charged amino acid residue at position 364 comprises a lysine (K) or an arginine (R) residue, and wherein said negatively charged residue at position 368 comprises an aspartic acid (D) or glutamic acid (E) residue.”

160. In Figure 5, *Moore* teaches: (1) on one CH3 domain, replacing serine with lysine (K) at position 364; and (2) replacing leucine with aspartic acid (D) at position 368. (Ex. 1038 at Figure 5.) *Moore* refers to this construct as the “E357Q/S364K-L368D/K370S heterodimer.” (Ex. 1038 at 39, 42.)

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

161. It is my opinion that *Moore* discloses the heterodimeric antibody of claim 2, “wherein said positively charged amino acid residue at position 364

comprises a lysine (K) residue, and wherein said negatively charged residue at position 368 comprises an aspartic acid (D).”

162. As discussed above with respect to claims 1 and 2 in Sections XII.A and XII.B, *Moore* teaches: (1) on one CH3 domain, replacing serine with lysine (K) at position 364; and (2) replacing leucine with aspartic acid (D) at position 368. (Ex. 1038 at Figure 5.) *Moore* refers to this construct as the “E357Q/S364K-L368D/K370S heterodimer.” (Ex. 1038 at 39, 42.)

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

163. It is my opinion that *Moore* discloses the heterodimeric antibody of claim 1, “wherein said heterodimeric antibody is a bispecific antibody.”

164. The very title of *Moore*, for instance, is “A robust heterodimeric Fc platform engineered for efficient development of *bispecific antibodies* of multiple formats.” (Ex. 1038 at 38 (emphasis added).) Consistent with its title, *Moore* summarizes in its Abstract that:

Bispecific monoclonal antibodies can bind two protein targets simultaneously and enable therapeutic modalities inaccessible by traditional [*i.e.*, monoclonal antibodies]. Bispecific formats containing a heterodimeric Fc region are of particular interest.... We present a robust heterodimeric Fc platform, called the XmAb[®] bispecific platform, engineered for efficient development of bispecific antibodies and Fc fusions of multiple formats.

(Ex. 1038 at 38; *see also* Ex. 1038 at 39 (“In this paper, we present a robust heterodimeric Fc, called the XmAb[®] bispecific platform, engineered for efficient development of bispecific antibodies and Fc fusions of multiple formats.”).)

165. One specific heterodimer generated by the “XmAb[®] bispecific platform” is the heterodimer described in Figure 5, captioned “Structural models confirming feasibility of heterodimeric Fc design rationale.” (Ex. 1038 at 48.)

Figure 5, as I have previously noted, describes: (1) on one CH3 domain, replacing serine with lysine (K) at position 364; and (2) replacing leucine (L) with aspartic acid (D) at position 368. (Ex. 1038 at Figure 5.)

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

166. It is my opinion that *Moore* discloses a heterodimeric antibody, “wherein said heterodimeric antibody is human IgG.”

167. *Moore* teaches modifying position 364 to a positively charged amino acid residue on a first human CH3 domain and modifying position 368 to insert a negatively charged amino acid residue on a second human CH3 domain, as discussed above with respect to claim 1. (Section XII.A.2.) Further, *Moore* states that the disclosed substitutions were introduced into distinct native human heavy chain IgG1 sequences. (Ex. 1038 at Figure 5; *see also* Ex. 1038 at 39.)

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

168. It is my opinion that *Moore* discloses the heterodimeric antibody of claim 1, “wherein said heterodimeric antibody is human IgG1” for the reasons discussed above with respect to claims 1 and 5. (Sections XII.A, XII.E.)

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

169. It is my opinion that *Moore* discloses a pharmaceutical composition comprising the heterodimeric antibody of claim 1 “and a pharmaceutically acceptable carrier.”

170. As an initial matter, I note that the '859 patent defines “pharmaceutically acceptable carrier” very broadly. Per the '859 patent, “[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 29:12-18.)

171. The authors of *Moore* state that its disclosed “heterodimeric Fc” technology has been used to “produce” several clinical therapeutic drug candidates. (Ex. 1038 at 49.) A person of ordinary skill in the art would readily understand that, in order to be tested in humans, heterodimeric antibodies like those taught in

Moore must be formulated with pharmaceutically acceptable carriers as part of a pharmaceutical composition.

172. *Moore* further teaches that its disclosed heterodimers have been assessed in final liquid formulations that are part of regulatory filings, and therefore are biologically compatible. (Ex. 1038 at 47 (“Ongoing stability assessments on the final liquid formulations for multiple TAA × CD3 molecules indicate that they are very stable, with no impact on aggregation, heterodimer/homodimer ratios and bioactivity over long periods of refrigerated and frozen storage.”).) This demonstrates that *Moore* teaches placing the heterodimeric antibody in a pharmaceutically acceptable carrier, and thus *Moore* teaches the limitation in Claim 7.

* * *

173. 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 *Moore* to teach every limitation of claims 1-7, as arranged in the claims.

XIII. Ground 3: *Lazar* Alone or in view of *Kannan* Teaches or Suggests Every Limitation of Claims 1-7

174. A person of ordinary skill in the art would have understood that *Desjarlais* and *Moore* both taught every limitation of claims 1-7 of the '859 patent, as discussed above in Sections XI and XII by May 2023.

175. Additionally, a person of ordinary skill in the art would have understood that *Lazar*—or at least the combination of *Lazar* and *Kannan*—discloses or suggests every limitation of claims 1-7 by April 2012.

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

176. I have previously summarized the disclosures of *Lazar* and *Kannan*, which are both directed to techniques for enhancing the yield of heterodimeric antibodies. (Sections VII.C-D.) Each of these references teaches a framework for more efficiently developing heterodimeric antibodies for numerous applications. (Sections VII.C-D.) And as I explain below, the respective teachings of *Lazar* and *Kannan* could readily be combined by a person of ordinary skill in the art by April 2012 with a reasonable expectation of success, using well-established techniques.

177. **Lazar**: *Lazar* teaches enhancing the yield of heterodimers through amino acid substitutions in the CH3 domain of antibodies, resulting in Fc modifications that favor heterodimerization and disfavor unwanted homodimerization. (Ex. 1004 at ¶¶120-125 (identifying “Fc modifications that Favor Heterodimerization”), 241(teaching “[a] number of designed variants [that] increased the content of heterodimer relative to that of the native parent Fc region” and identifying “[p]referred and most preferred variants”), Tables 1-2 (listing “Preferred” and “Most preferred” “CH3 domain variants that favor Fc heterodimerization”).) Further, *Lazar* expressly incorporates *Kannan* “by

reference,” identifying it by its International Application Number. (Ex. 1004 at ¶125 (“Other Fc variants that favor heterodimerization that may find use in the creation of the antibody analogs of the invention have been described...

PCT/US2009/000071 [(i.e., the International Application Number of *Kannan*)]; all entirely incorporated herein by reference.”).)

178. **Kannan**: *Kannan* describes “a strategy for altering a pair of CH3 domains to reduce the ability of each domain to interact with itself but to increase the ability of the domains to interact with each other, i.e., form heterodimers.”

(Ex. 1007 at 2:33-35.) In order to promote heterodimerization, *Kannan* teaches “replacing one or more residues that make up the CH3-CH3 interface in both CH3 domains with a charged amino acid such that homodimer formulation is electrostatically unfavorable but heterodimerization is electrostatically favorable.”

(Ex. 1007 at 2:35-37.) *Kannan* continues:

[A] charged amino acid in each CH3 domain is replaced with an amino acid with an opposite charge. For example, a positive-charged amino acid may be replaced with a negative charged amino acid in the first CH3 domain and a negative charged amino acid may be replaced with a positive-charged amino acid in the second CH3 domain.... [T]he reversed charges are electrostatically favorable, i.e., opposing charges in the interface, for heterodimerization formation.

(Ex. 1007 at 2:37-3:7.)

179. Like *Lazar*, *Kannan* identifies specific amino acid mutations that could be made so as to promote heterodimerization. At Table 2, for instance,

Kannan teaches “possible mutations involving charge change” (Ex. 1007 at 9:15-16), and states that the “mutations can be combined to enhance the electrostatic effects.” (Ex. 1007 at 9:16-17.) In Table 2, *Kannan* teaches that, where a negative charge is being introduced, either aspartic acid (“Asp” or “**D**”) or glutamic acid (“Glu” or “**E**”) may be substituted in. Similarly, where a positive charge is being introduced, either of lysine (“Lys” or “**K**”) or arginine (“Arg” or “**R**”) may be substituted in. (Ex. 1007 at 9:18-19 (Table 2a); *see also* Ex. 1007 at 10:6-7 (“Each positively charged residue (Lys and Arg) can be mutated to two negatively charged residues (Asp or Glu) and vice versa.”).)

180. Additionally, *Kannan* instructs that its charge-engineering strategy can be extended to substituting in complementary charged amino acid residues for neutral residues to promote heterodimerization. (Ex. 1007 at 10:16-18 (“This strategy can also be extended to modifying uncharged [*i.e.*, neutral] residues to charged residues at the CH3 domain interface.”).)

B. Claim 1

1. “A heterodimeric antibody comprising”

181. It is my opinion that *Lazar*—or at least the combination of *Lazar* and *Kannan*—discloses or suggests a heterodimeric antibody.¹⁹

182. *Lazar* teaches that “[t]he present disclosure provides novel antibody analog compositions that simultaneously co-engage antigens.... The novel antibody analogs described preferably utilize heterodimeric Fc regions.” (Ex. 1004 at ¶2; *see also* Ex. 1004 at ¶42 (“Optionally, but preferred in some embodiments, the two heavy chains also differ from each other by the presence of amino acid substitutions in the Fc domain that favors heterodimeric formation over homodimers.”).) *Lazar* further teaches that “[a] number of designed variants increased the content of heterodimer relative to that of the native parent Fc region,” with “[p]referred and most preferred variants” listed in Tables 1 and 2 of *Lazar*. (Ex. 1004 at ¶241, Tables 1-2.)

¹⁹ I further note that the '859 patent broadly refers to an “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 11:39-48.)

183. *Kannan* equally teaches heterodimeric antibodies. The reference summarizes in its Abstract that the disclosure “relates to methods of making Fc-heterodimeric proteins or polypeptides.” (Ex. 1007 at Abstract; *see also* Ex. 1007 at 2:33-35.)

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

184. It is my opinion that *Lazar*—or at least the combination of *Lazar* and *Kannan*—discloses or suggests a heterodimeric antibody including “a first human CH3 domain comprising a positively charged amino acid residue at position 364 according to the EU numbering system, and a second human CH3 domain comprising a negatively charged amino acid residue at position 368 according to the EU numbering system.”

185. *Lazar* teaches “[a] number of designed variants” that “increased content relative to that of the native parent Fc region” and lists “[p]referred CH3 domain variants that favor Fc heterodimerization” in Table 1. (Ex. 1004 at ¶241.) As I have annotated using the red box below, Table 1 describes engineering an electrostatic interaction between two heavy chains by substituting a charged amino acid residue at position 364 on a first CH3 domain and an oppositely charged amino acid residue at position 368 on a second CH3 domain:

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

(Ex. 1004 at Table 1 (annotation added).) This pair of modified chains is identified by *Lazar* as a “[p]referred CH3 domain variant[] that favor[s] Fc heterodimerization.” (Ex. 1004 at Table 1.) Moreover, the “S364E” / “L368K” heterodimer is subsequently called out in Figures 5 and 6 of *Lazar*, along with a second heterodimer incorporating a charged amino acid residue at position 364 on a first CH3 domain and an oppositely charged amino acid residue at position 368

on a second CH3 domain: the “S364^D” / “L368^K” heterodimer. (Ex. 1004 at Figures 5 and 6.)

186. Based on these disclosures, a person of ordinary skill in the art would understand *Lazar* as teaching positions 364 and 368 as an advantageous pairing of positions (on a first and second CH3 domain) for substituting in oppositely charged amino acid residues as part of an electrostatic engineering approach. (Ex. 1004 at Table 1, Figures 5-6; *see also* Ex. 1007 at 7:19-8:7 (Table 1) (identifying positions 364 and 368 on a “[I]ist of CH3 domain interface residues in the first chain (A) and their contacting residues in the second chain (B)”)).

187. And while in Table 1, *Lazar* provides a substitution of a negatively charged amino acid residue at position 364 (insertion of the negatively charged glutamic acid (^E)) on a first chain and a positively charged amino acid residue at position 368 (insertion of the positively charged leucine (^K)), the teachings of *Lazar* disclose or suggest substituting in the reverse pair of charges. That is, the teachings of *Lazar* disclose (or, at the very least, suggest) exchanging the charges of the “[p]referred” “S364^D” / “L368^K” heterodimer and instead substituting a *positively* charged amino acid residue at position 364 on a first CH3 domain and a *negatively* charged amino acid residue at position 368 on a second CH3 domain—*e.g.*, reversing the substitutions of the preferred heterodimer to yield a “S364^K” / “L368^D” variant, for example.

188. For instance, *Lazar* teaches both positively charged and negatively charged amino acid substitutions at these very positions. I have annotated the modifications provided in paragraph 52, below, to indicate substitution of a positively charged (in green) amino acid residue and a negatively charged amino acid residue (in red) at position 364 on a first chain and position 368 on a second chain:

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

(Ex. 1004 at ¶123.) *Lazar* describes these as “preferabl[e]” substitutions that “can be used individually or in any combination.” (Ex. 1004 at ¶123.)

189. Based on *Lazar*’s teachings in paragraph 123, a person of ordinary skill in the art would understand that either a complementary charge pair of amino acid residues could be substituted in at positions 364 and 368 of a first and second CH3 domain—positive/negative *or* negative/positive. Therefore, while *Lazar*

identifies a “[p]referred” “S364^D” / “L368^K” (negatively / positively charged) heterodimer, a person of ordinary skill in the art would appreciate that the “preferabl[e]” amino acid substitutions of paragraph 123 could equally be applied at those positions to form a “S364^H / L368^E” or “S364^R / L368^E” (positively / negatively charged).

190. In addition to *Lazar*’s teachings, *Kannan* describes a “strategy for altering a pair of CH3 domains to reduce the ability of each domain to interact with itself but to increase the ability of the domains to interact with each other, i.e., form heterodimers.” (Ex. 1007 at 2:33-35.) The disclosed strategy involves “replacing one or more residues that make up the CH3-CH3 interface in both CH3 domains with a charged amino acid such that homodimer formation is electrostatically unfavorable but heterodimerization is electrostatically favorable.” (Ex. 1007 at 2:35-37.)

191. To promote heterodimer formation, *Kannan* expressly teaches swapping negative and positive charges on a CH3 domain interface. *Kannan* states:

[D]escribed herein is a strategy for altering a pair of CH3 domains to reduce the ability of each domain to interact with itself but to increase the ability of the domains to interact with each other, i.e., form heterodimers. This can be achieved by replacing one or more residues that make up the CH3-CH3 interface in both CH3 domains with a charged amino acid such that homodimer formation is electrostatically unfavorable but heterodimerization is electrostatically favorable. In

certain embodiments, a charged amino acid in each CH3 domain is replaced with an amino acid with an opposite charge. ***For example, a positive-charged amino acid may be replaced with a negative charged amino acid in the first CH3 domain and a negative charged amino acid may be replaced with a positive-charged amino acid in the second CH3 domain.*** By reversing the charge of the amino acid, homodimer formation is reduced.

(Ex. 1007 at 2:33-3:5 (emphasis added).)

192. As a result, the combination of *Lazar* and *Kannan* teaches the amino acid substitutions of claim 1. *Lazar* discloses heterodimeric antibodies in which a negatively charged amino acid residue (glutamic acid (E)) is substituted in at position 364, and a positively charged amino acid residue (lysine (K)) is substituted in at position 368 on a second CH3 domain—yielding a 364E / 368K heterodimer. (Ex. 1004 at Table 1.) And *Kannan* teaches that a negatively charged amino acid residue on one CH3 domain may be substituted for a positively charged amino acid residue, with a corresponding charge change (*i.e.*, positive-for-negative) on the second CH3 domain—*i.e.*, inserting complementary charged amino acids. (Ex. 1007 at 2:33-3:7.) Applying *Kannan*'s teachings, a person of ordinary skill in the art would have readily understood before April 2012 that the charges of the “preferred” variant of *Lazar* could be flipped to yield, for instance, a 364K / 368E heterodimer.

193. Finally, *Lazar* teaches CH3 domain variants based on a human CH3 domain sequence, and that the positions on such CH3 domains are numbered

according to the EU numbering system, as recited in claim 1. *Lazar* expressly instructs that “the 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.” (Ex. 1004 at ¶118 (“Unless otherwise noted, constant region and Fc positions discussed herein are numbered according to the EU index or EU numbering scheme”).)

194. **Motivation to Combine:** A person of ordinary skill in the art would have been motivated to synthesize a heterodimeric antibody made up of a “a first human CH3 domain comprising a positively charged amino acid residue at position 364” and a “second human CH3 domain comprising a negatively charged amino acid residue at position 368” based on the teachings of *Lazar*, or at least based on the combined teachings of *Lazar* and *Kannan*.

195. *Lazar* teaches that “[o]f particular benefit to the immunoglobulins of the invention are Fc variants that favor heterodimerization of the Fc region 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.” (Ex. 1004 at ¶120.) *Lazar* further provides “[p]referred CH3 domain variants” that accomplish the stated goal of “favor[ing]

heterodimerization,” a number of which a person of ordinary skill in the art would have recognized to involve substituting in corresponding positively and negatively charged amino acid residues so as to promote electrostatic interactions between the two distinct CH3 domains. (Ex. 1004 at ¶241, Tables 1-2.)

196. For example, I have annotated Table 1 from *Lazar* to demonstrate variants in which neutral amino acids were replaced with positively charged amino acid residues (highlighted in yellow and green, respectively) and corresponding neutral amino acids that were replaced with negatively charged amino acid residues (highlighted in yellow and red, respectively):

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

(Ex. 1004 at Table 1.) Based on *Lazar*'s disclosure and the knowledge in the field by April 2012, a person of ordinary skill in the art would readily understand the use of complementary charged amino acid substitutions to promote heterodimerization.

197. When applying the electrostatic steering techniques described in the prior art, a person of ordinary skill in the art would further have had good reason to make charge modifications at position 364 (on a first chain) and 368 (on a second chain), as recited in claim 1. In fact, *Lazar*'s Table 1 teaches just that. Table 1 identifies a heterodimer incorporating CH3 domains with amino acid substitutions at those very positions—*i.e.*, position 364 and position 368—as a “[p]referred CH3 domain variant[] that favor[s] heterodimerization.” (Ex. 1004 at Table 1.) *Lazar* discloses that this very heterodimer was further “designed and screened,” and determined to be “[p]referred” on this basis.

198. And while Table 1 of *Lazar* identifies a heterodimer incorporating CH3 domains substituting in 364E (negatively charged) on a first CH3 domain and 368K (positively charged) on a second CH3, *Lazar* would have provided a person of ordinary skill in the art good reason to pursue amino acid substitutions with opposite charges—*e.g.*, 364K and 368E. As I have previously noted, paragraph 123 of *Lazar* teaches substituting both negatively and positively charged amino acid substitutions at positions 364 and 368. (Ex. 1004 at ¶123.) Equally, Figures 5-7 of *Lazar* depict various heterodimers with corresponding negative/positive and positive/negative amino acid substitutions at contact residues to measure impact on heterodimer formation. For instance, as shown below, Figure 5 tested both

“S364^D / K370^R” (negative/positive substitution) and “S364^R / K370^D”
(positive/negative substitution):

Figure 5

Lane	Empty-Fc	scFv-Fc	Empty -M	Empty -D	Hetero	scFv -D	scFv -M
1	IgG1 WT	IgG1 WT	2%	33%	42%	23%	0%
2	S364D	Y349K	0%	6%	73%	21%	0%
3	S364E	Y349K	0%	7%	75%	18%	0%
4	S364F	Y349A	0%	13%	59%	29%	0%
5	S364G	Y349W	0%	26%	52%	23%	0%
6	S364H	Y349T	0%	0%	65%	35%	0%
7	S364Y	Y349A	0%	2%	51%	47%	0%
8	S364Y	Y349S	0%	2%	56%	42%	0%
9	S364D	L368K	6%	31%	51%	12%	0%
10	S364E	L368S	4%	37%	54%	5%	0%
11	S364E	L368K	3%	19%	64%	14%	0%
12	K409D	L368K	0%	4%	73%	23%	0%
13	K409E	L368K	4%	24%	70%	1%	0%
14	S364D	K370R	0%	24%	38%	38%	0%
15	S364F	K370G	0%	22%	65%	13%	0%
16	S364H	K370S	0%	0%	35%	65%	0%
17	S364R	K370D	19%	11%	59%	11%	0%

(Ex. 1004 at Figure 5.)

199. Applying this teaching to *Lazar*'s Table 1 heterodimers, *Lazar* provides good reason to reverse the charge of the “[p]referred” “S364^E”/“L368^K” (negative / positive) heterodimer of Table 1, and substitute in a *positively* charged amino acid residue at position 364 on a first CH3 domain chain and a *negatively* charged amino acid residue at position 368.

200. *Kannan*'s teachings would have provided a person of ordinary skill in the art with further motivation to reverse the charges of the same “[p]referred” “S364^E”/“L368^K” heterodimer. As an initial matter, *Kannan*'s teachings are

identified as incorporated “by reference” into *Lazar*, providing a person of ordinary skill in the art with good reason to combine the teachings of *Kannan* with those of *Lazar*. (See Ex. 1004 at ¶125 (“Other Fc variants that favor heterodimerization that may find use in the creation of the antibody analogs of the invention have been described... PCT/US2009/000071 [(i.e., the International Application Number of *Kannan*)]; all entirely incorporated herein by reference.”).)

201. And at Table 1, *Kannan* provides a “[l]ist of CH3 domain interface residues in the first chain (A) and their contacting residues in the second chain (B).” (Ex. 1007 at 7:19-8:7 (Table 1).) As shown below in yellow highlighting, one of these contact residue pairs is position 364 (on chain A) and position 368 (on chain B):

Table 1: List of CH3 domain interface residues in the first chain (A) and their 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' PRO B 352' PRO B 353' SER B 354' THR B 366'
SER A 354	TYR B 349' THR B 350' LEU B 351'
<i>ARG A 355^b</i>	THR B 350'
ASP A 356	TYR B 349' LYS B 439'
GLU A 357	TYR B 349' LYS B 370'
<i>LYS A 360^b</i>	GLN B 347' TYR B 349'
SER A 364	LEU B 368' LYS B 370'

(Ex. 1007 at 7:19-8:7 (Table 1) (annotation added).) Of the “CH3 domain interface residues” identified by *Kannan*’s Table 1, *Lazar* teaches the insertion of complementarily charged amino acids at positions 364 and 368 on a first and second CH3 domain—the “[p]referred” S364E / L368K variant. (Ex. 1004 at ¶241.)

202. *Kannan* expressly making electrostatic steering amino acid modifications at these “contacting residues” (or “interfaces”), stating, “When the replacements are coordinated properly, the reversed charges are electrostatically favorable, i.e., opposing charges in the interface, for heterodimerization formation.” (Ex. 1007 at 3:5-7; *see also* Ex. 1007 at 2:33-37 (“Further described herein is a strategy for altering a pair of CH3 domains to reduce the ability of each domain to interact with itself but to increase the ability of the domains to interact with each other, i.e., form heterodimers. This can be achieved by replacing one or more residues that make up the CH3-CH3 interface in both CH3 domains with a charged amino acid such that... heterodimerization is electrostatically favorable.”).) Therefore, *Kannan*’s teachings would provide a person of ordinary skill in the art with good reason to pursue amino acid mutations at position 364 (on a first CH3 domain) and position 368 (on a second CH3 domain) in order to promote heterodimerization, just as taught in *Lazar* and *Kannan*.

203. Moreover, *Kannan* teaches swapping positive/negative charges in a pair of CH3 domains. Specifically, *Kannan* discloses that to promote heterodimer formation, “a charged amino acid in each CH3 domain is replaced with an amino acid with an opposite charge. *For example, a positive-charged amino acid may be replaced with a negative charged amino acid in the first CH3 domain and a negative charged amino acid may be replaced with a positive-charged amino acid in the second CH3 domain.*” (Ex. 1007 at 3:1-4 (emphasis added).)

204. Based upon *Kannan*'s disclosures, a person of ordinary skill would have good reason to swap the charges of *Lazar*'s “[p]referred” “S364E”/“L368K” heterodimer. For instance, *Kannan* teaches that the positively charged lysine (K) at position 368 “may be replaced with a negative charged amino acid in the first CH3 domain” and the negatively charged glutamic acid (E) at position 364 “may be replaced with a positive-charged amino acid in the second CH3 domain.” (Ex. 1007 at 3:1-4.) In other words, a person of ordinary skill in the art would appreciate that the teachings of *Lazar* and *Kannan* contemplate, and encourage, reversing charge pairs in heterodimer synthesis—yielding, for instance, a “S364K”/“L368E” heterodimer.

205. **Reasonable Expectation of Success:** A person of ordinary skill in the art would have reasonably expected success in combining the teachings of *Lazar* and *Kannan*. As an initial matter, the synthesis of bispecific, heterodimeric

antibodies dates back to the 1980s, almost thirty years before April 2012. (*See, e.g.,* Ex. 1004 at ¶4.) Equally, methods of promoting heterodimer formation by modifying CH3 domain sequences had been used for decades by April 2012. (*See, e.g.,* Ex. 1007 at 2:5-21.)

206. Based on this long-standing experience, a person of ordinary skill in the art would have reasonably expected to successfully synthesize a heterodimeric antibody including “a first human CH3 domain comprising a positively charged amino acid residue at position 364 according to the EU numbering system, and a second human CH3 domain comprising a negatively charged amino acid residue at position 368 according to the EU numbering system,” as recited in claim 1. *Lazar* demonstrates the successful design and synthesis of a heterodimeric antibody incorporating a pair of complementary charged amino acid mutations at positions 364 and 368 on two respective CH3 domains. (Ex. 1004 at ¶241, Table 1.) Again, *Lazar* reports that such a variant was successfully “designed and screened.” (Ex. 1004 at ¶241.) *Lazar*, in fact, demonstrates the successful synthesis and screening of additional variants, which involve substituting in both positively charged and negatively charged amino acids—consistent with *Kannan*’s own teaching that charged amino acid substitutions may be interchangeable or even combined. (*See, e.g.,* Ex. 1007 at 9:15-17 (“Table 2 lists many possible mutations involving charge change, and the mutations can be combined to enhance the electrostatic effects.”).)

Accordingly, a person of ordinary skill in the art would reasonably expect success in exchanging the charges of *Lazar*'s Table 1, and therefore arrive at the antibody claimed in claim 1.

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

207. It is my opinion that *Lazar*—or at least the combination of *Lazar* and *Kannan*—discloses or suggests the heterodimeric antibody of claim 1, “wherein said positively charged amino acid residue at position 364 comprises a lysine (K) or an arginine (R) residue, and wherein said negatively charged residue at position 368 comprises an aspartic acid (D) or glutamic acid (E) residue.”

208. As discussed above in Section XIII.B, *Lazar*—or at least the combination of *Lazar* and *Kannan*—discloses or suggests the heterodimeric antibody of claim 1. *Lazar* teaches a 364^E / 368^K heterodimer. (Ex. 1004 at Table 1.) And *Lazar* further teaches or suggests reversing the charges in such an antibody. (Section XIII.B; Ex. 1004 at ¶123, Figures 5-7.)

209. Moreover, *Kannan* teaches that a negatively charged amino acid residue on one CH3 domain may be substituted for a positively charged amino acid residue, with a corresponding charge change (*i.e.*, positive-for-negative) on a second CH3 domain. (Section XIII.B; Ex. 1007 at 2:33-3:5.) Applying *Kannan*'s

teachings, a person of ordinary skill in the art would have readily understood before April 2012 that the charges of the “preferred” variant of *Lazar* could be flipped, with a positive amino acid residue substituted in at position 364 on a first CH3 domain, and a negative amino acid residue substituted in at position 368 on a second CH3 domain.

210. When making such a charge mutation, *Kannan* further teaches substituting in lysine (K) or arginine (R) as the *positively* charged amino acid to be introduced, as well as substituting aspartic acid (D) or glutamic acid (E) as the *negatively* charged amino acid to be introduced, as recited in claim 2.

211. As an initial matter, *Kannan* explains—and a person of ordinary skill in the art would have known, regardless—that aspartic acid (D) and glutamic acid (E) are the only negatively charged amino acids, and that lysine, arginine, and histidine are the only positively charged amino acids. (Ex. 1007 at 2:27-29; *see also* Ex. 1001 at 13:39-41 (’859 patent recognizing that aspartic acid and glutamic acid are the only two negatively charged amino acid residues).) So, substituting in a negatively charged amino acid *necessarily* involves substituting in aspartic acid (D) or glutamic acid (E).

212. Meanwhile, substituting in a positively charged amino acid *necessarily* involves substituting in lysine (K), arginine (R), or histidine (H). (Ex. 1007 at 2:26-29; *see also* Ex. 1001 at 13:37-39 (’859 patent recognizing arginine,

lysine, and histidine are the only three positively charged amino acid residues.)
And of those three positively charged amino acids, *Kannan* provides good reason to focus on lysine (K) and arginine (R), specifically, teaching that “[e]ach positively charged residue (Lys[ine] and Arg[inine]) can be mutated to two negatively charged residues (Asp[artic acid] or Glu[tamic acid]) *and vice versa*.” (Ex. 1007 at 10:6-7.) Echoing this, Tables 2a and 2b disclose exchanging the negatively charged aspartic acid or glutamic acid for lysine or arginine, as shown below:

Table 2a: List of some possible pair-wise charge residue mutations to enhance heterodimer formation^a

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

^aCombinations of the above pair-wise charge residue mutations could also be used. For example Lys409 --- Asp399' interaction pair mutations could be combined with Lys439 --- Asp356' pair mutations.

Table 2b: Additional single charge residue mutations to enhance electrostatic steering effects^a

Position in Chain 1	Mutation	Position in Chain 2	Mutation
Arg355	Asp or Glu	Arg355'	Asp or Glu
Lys360	Asp or Glu	Lys360'	Asp or Glu

^aThese single residue mutations could be combined with the Table 2a pair-wise mutations to enhance the heterodimer formation (Figure 6d).

(Ex. 1007 at 9:15-10:4 (Tables 2a, 2b).)

213. Applied to *Lazar*'s “[p]referred” “S364E”/“L368K” heterodimer, *Kannan* teaches substituting in lysine (K) or arginine (R) (positively charged) in place of the negatively charged glutamic acid (S) at position 364—yielding a first S364K or S364R variant. Paired with that first charge substitution, *Kannan* teaches introducing the complementary charged aspartic acid (D) or glutamic acid (E) (negatively charged) in place of the positively charged lysine (K) at position 368—yielding a L368D or L368E, and a S364K or S364R / L368D or L368E heterodimer. As that is all claim 2 requires, the combination of *Lazar* and *Kannan* teaches (or, at the very least, suggests) each limitation of claim 2.

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 apply the teachings of *Lazar* or combine the teachings of *Lazar* and *Kannan* to create a heterodimeric antibody with a positively charged amino acid residue at position 364 on a first CH3 domain chain and a negatively charged amino acid residue at position 368. (Section XIII.B.) A person of ordinary skill in the art would further have good reason to substitute in lysine (K) or arginine (R) as the positively charged amino acid residue at position 364, as well as aspartic acid (D) or glutamic acid (E) as the negatively charged residue at position 368.

215. *Kannan* instructs substituting in those very amino acids for purposes of promoting heterodimer formation using electrostatic steering. Again, *Kannan* teaches a person of ordinary skill that “[e]ach positively charged residue (Lys[ine] and Arg[inine]) can be mutated to two negatively charged residues (Asp[artic acid] or Glu[tamic acid]) and vice versa.” (Ex. 1007 at 10:6-7.) Tables 2a and 2b of *Kannan* further teach a person of ordinary skill in the art that: (1) when a positively charged amino acid residue is substituted into a CH3 domain to promote heterodimer formation, lysine (K) or arginine (R) should be utilized; and (2) when a negatively charged amino acid residue is substituted into a CH3 domain to promote heterodimer formation, aspartic acid (D) or glutamic acid (E) should be used, as shown below:

Table 2a: List of some possible pair-wise charge residue mutations to enhance heterodimer formation^a

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

^aCombinations of the above pair-wise charge residue mutations could also be used. For example Lys409 --- Asp399' interaction pair mutations could be combined with Lys439 --- Asp356' pair mutations.

Table 2b: Additional single charge residue mutations to enhance electrostatic steering effects^a

Position in Chain 1	Mutation	Position in Chain 2	Mutation
Arg355	Asp or Glu	Arg355'	Asp or Glu
Lys360	Asp or Glu	Lys360'	Asp or Glu

^aThese single residue mutations could be combined with the Table 2a pair-wise mutations to enhance the heterodimer formation (Figure 6d).

(Ex. 1007 at 9:15-10:4 (Tables 2a, 2b).)

216. Moreover, a person of ordinary skill would readily understand that glutamic acid and aspartic acid are the *only two* negatively charged amino acids, and that lysine (K) and arginine (R) are *two of only three* positively charged amino acids, and the only two that do not comprise the complicating factor of an aromatic ring. So when substituting in a negatively charged amino acid at position 368 of *Lazar*'s "[p]referred" "S364E"/"L368K" heterodimer, a person of ordinary skill would necessarily insert one of aspartic acid (D) or glutamic acid (E) (as recited in claim 2). Meanwhile, when substituting a positively charged amino acid at position 364, a person of ordinary skill in the art would have good reason to incorporate lysine (K) or arginine (R) as two of three positively charged options. Even more so in view of *Kannan*'s warning that "mutating negatively charged residues (Asp to Glu) to H[istidine] [(i.e., the only other positively charged amino acid)] will lead to increase in side chain volume which may cause steric issues."

(Ex. 1007 at 10:11-12.)

217. Further, a person of ordinary skill in the art would have reasonably expected success in combining the teachings of *Lazar* and *Kannan* to arrive at the antibody recited in claim 2 using known synthesis methods for the reasons discussed above with respect to claim 1. (Section XIII.B.)

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

218. It is my opinion that *Lazar*—or at least the combination of *Lazar* and *Kannan*—discloses or suggests the heterodimeric antibody of claim 2, “wherein said positively charged amino acid residue at position 364 comprises a lysine (K) residue, and wherein said negatively charged residue at position 368 comprises an aspartic acid (D).”

219. As discussed above in Section XIII.B, *Lazar*—or at least the combination of *Lazar* and *Kannan*—discloses or suggests a heterodimeric antibody in which a positively charged amino acid residue is substituted in at position 364 on a first human CH3 domain, and a negatively charged amino acid residue is substituted in at position 368 on a second CH3 domain. Further, for the reasons discussed above in Sections XIII.B and XIII.C, the combination of *Lazar* and *Kannan* teach or suggest that the positively charged amino acid substituted in at position 364 on a first CH3 domain is a lysine (K) residue, and that the negatively

charged amino acid residue substituted in at position 368 is an aspartic acid (D) residue.

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

A person of ordinary skill in the art would have been motivated to select lysine and aspartic acid as the positively and negatively charged (respectively) amino acid residues to be incorporated when applying *Lazar*'s and/or *Kannan*'s charge reversal technique to *Lazar*'s "[p]referred" "S364E"/"L368K" heterodimer.

221. As I have previously discussed, *Lazar* teaches or suggests reversing the charges in such an antibody. (Section XIII.B; Ex. 1004 at ¶123, Figures 5-7.) Additionally, *Kannan* teaches that "[e]ach positively charged residue (Lys[ine] and Arg[inine]) can be mutated to two negatively charged residues (Asp[artic acid] or Glu[tamic acid]) and vice versa." (Ex. 1007 at 10:6-7; *see also* Ex. 1007 at 2:33-3:4 ("Further described herein is a strategy for altering a pair of CH3 domains to reduce the ability of each domain to interact with itself but to increase the ability of the domains to interact with each other, i.e., form heterodimers.... For example, a positive-charged amino acid may be replaced with a negative charged amino acid in the first CH3 domain and a negative charged amino acid may be replaced with a positive-charged amino acid in the second CH3 domain.").) *Kannan*'s instruction results in four potential amino acid substitutions that could be made in the context of *Lazar*'s "[p]referred" "S364E"/"L368K" heterodimer:

- S364K / L368D
- S364R / L368D
- S364K / L368E
- S364R / L368E

As indicated in the bold and underlined text above, the first of these reverse charges of *Lazar*'s "[p]referred" "S364E"/"L368K" heterodimer is the antibody recited in claim 3.

222. In fact, even if a person of ordinary skill in the art included every possible charge-swapping alternative (*i.e.*, the positive amino acid, histidine, were included), a limited, finite number of amino acid substitutions would have remained. This, of course, ignores *Kannan*'s teaching that "mutating negatively charged residues (Asp or Glu) to H... will lead to increase in side chain volume which may cause steric issues," which would have led a person of ordinary skill in the art to pursue lysine or arginine (both positively charged) substitutions, instead. (Ex. 1007 at 10:11-12.) Regardless, including histidine (H) would result in only six possible charge-swapping substitutions when applied to *Lazar*'s "[p]referred" "S364E"/"L368K" heterodimer:

- S364K / L368D
- S364R / L368D
- S364K / L368E

- S364**R** / L368**E**
- S364**H** / L368**D**
- S364**H** / L368**E**

Again, one of this limited, finite set of charge substitutions is the combination later claimed in the '859 patent (as indicated in bold and underline above).

223. Further, a person of ordinary skill in the art would have reasonably expected success in combining the teachings of *Lazar* and *Kannan* to arrive at the antibody recited in claim 3 using known synthesis methods for the reasons discussed above with respect to claim 1. (Section XIII.B.)

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

224. It is my opinion that *Lazar*—or at least the combination of *Lazar* and *Kannan*—discloses or suggests the heterodimeric antibody of claim 1, “wherein said heterodimeric antibody is a bispecific antibody.”

225. First, as discussed above in Section XIII.B, *Lazar*—or at least the combination of *Lazar* and *Kannan*—discloses or suggests the heterodimeric antibody of claim 1.

226. 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.) 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 readily understood that *Lazar*’s teachings of such heterodimers that target two antigens to refer to “bispecific” antibodies, as recited in claim 4. (*See, e.g.*, Ex. 1007 at 1:31-32 (“Bispecific antibodies refer to antibodies having specificities for at least two different antigens.”).)

227. *Kannan* likewise teaches applying its disclosed electrostatic engineering techniques to heterodimeric, bispecific antibodies. For instance, *Kannan* recognizes at the outset of its disclosure that “it is desirable to create a molecule that contains the Fc portion of an antibody but comprises a heterodimer. An important application of Fc heterodimeric molecules is the generation of bispecific antibodies.... The use of bispecific antibodies for immunotherapy of cancer has been extensively reviewed in the literature.” (Ex. 1007 at 1:29-37.) Further, *Kannan* notes that “[p]referred embodiments of the invention include... a bispecific antibody....” (Ex. 1007 at 4:17-18.)

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

By April 2012, a person of ordinary skill in the art would have been motivated to combine the teachings of *Lazar* and *Kannan* to synthesize a bispecific,

heterodimeric antibody. 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 (“During the past decade, dual targeting with bispecific antibodies has emerged as an alternative to combination therapy or use of mixtures. The concept of dual targeting with bispecific antibodies is based on the targeting of multiple disease-modifying molecules with one drug. From a technological and regulatory perspective, this makes development less complex because manufacturing, preclinical and clinical testing is reduced to a single, bispecific molecule. Therapy with a single dual-targeting drug rather than combinations should also be less complicated for patients.”).)

229. And when creating such a bispecific antibody, a person of ordinary skill in the art would have been motivated to utilize the heterodimer synthesis techniques taught in *Lazar* and *Kannan* to improve heterodimer yield. (Section XIII.B; Ex. 1007 at 1:29-31 (“In certain instances, it is desirable to create a molecule that contains the Fc portion of an antibody but comprises a heterodimer.

An important application of Fc heterodimeric molecules is the generation of bispecific antibodies (BsAbs).”.)

230. Further, a person of ordinary skill in the art would have reasonably expected success in combining the teachings of *Lazar* and *Kannan* to arrive at the antibody recited in claim 4 using known synthesis methods for the reasons discussed above with respect to claim 1. (Section XIII.B.)

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

231. It is my opinion that *Lazar*—or at least the combination of *Lazar* and *Kannan*—discloses or suggests the heterodimeric antibody of claim 1, “wherein said disclosed heterodimer antibody is a human IgG.”

232. First, as discussed above in Section XIII.B, *Lazar*—or at least the combination of *Lazar* and *Kannan*—discloses or suggests the heterodimeric antibody of claim 1.

233. Finally, *Lazar* and *Kannan* both teach applying the disclosed heterodimer-promoting techniques discussed with respect to claim 1 (Section XIII.B) to sequences derived from human IgG—specifically, human IgG1. *Lazar* instructs that “the 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.” (Ex. 1004 at ¶118.) Moreover, *Lazar* further

describes that the variants of Table 1 (including the “[p]referred” “S364E”/“L368K” heterodimer) are based on an IgG1—*i.e.*, a human IgG1—sequence. (Ex. 1004 at ¶239.)

234. *Kannan* likewise provides that the electrostatically-engineered “CH3-containing polypeptide comprises an IgG Fc region, preferably derived from a wild-type *human IgG* Fc region.” (Ex. 1007 at 3:25-26; *see also* Ex. 1007 at 3:32-34 (“In certain embodiments, the polypeptide containing the CH3 region is an IgG molecule and further contains a CH1 and CH2 domain. Exemplary *human IgG* sequences comprise the constant regions of IgG1”), 10:15-18.)

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

Both *Lazar* and *Kannan* would have motivated a person of ordinary skill in the art by April 2012 to apply the disclosed heterodimeric enhancement techniques to human IgG sequences, including human IgG1. Again, both teach 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 *Kannan’s* teachings. Both references expressly exemplify their disclosed techniques to human IgG1 sequences. (Ex. 1004 at ¶¶ 238-239; Ex. 1007 at 3:32-4:2.)

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

236. It is my opinion that *Lazar*—or at least the combination of *Lazar* and *Kannan*—discloses or suggests the heterodimeric antibody of claim 1, “wherein said heterodimeric antibody is human IgG1.”

237. First, as discussed above in Section XIII.B, *Lazar*—or at least the combination of *Lazar* and *Kannan*—discloses or suggests the heterodimeric antibody of claim 1.

238. Moreover, *Lazar* and *Kannan* both teach applying the disclosed heterodimer-promoting techniques discussed with respect to claim 1 (Section XIII.B) to sequences derived from human IgG1 for the reasons discussed above with respect to claim 5. (Section XIII.F.)

239. **Motivation to Combine and Reasonable Expectation of Success:** Both *Lazar* and *Kannan* would have motivated a person of ordinary skill in the art—with a reasonable expectation of doing so successfully—by April 2012 to apply the disclosed heterodimeric enhancement techniques to human IgG1 sequences for the reasons discussed above with respect to claim 5. (Section XIII.F)

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

240. It is my opinion that *Lazar*—or at least the combination of *Lazar* and *Kannan*—discloses or suggests a pharmaceutical composition comprising the heterodimeric antibody of claim 1 “and a pharmaceutically acceptable carrier.”

241. First, as discussed above in Section XIII.B, *Lazar*—or at least the combination of *Lazar* and *Kannan*—discloses or suggests the heterodimeric antibody of claim 1.

242. *Lazar* teaches heterodimeric antibodies formulated with a physiologically or pharmaceutically acceptable carrier or diluent. (Ex. 1004 at ¶55 (“The present invention provides compositions comprising antibody analog polypeptides described herein, and a physiologically or pharmaceutically acceptable carrier or diluent.”).) *Lazar* further includes 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.) *Kannan* similarly instructs that the disclosed “heterodimeric proteins may be particularly useful in therapeutic compositions. In certain embodiments, a heterodimeric protein may be formulated in a composition that includes one or more pharmaceutically acceptable buffer or excipient.” (Ex. 1007 at 4:23-27.) Particularly where the ’859 patent

defines “pharmaceutically acceptable carrier” as “includ[ing] any and all solvents, salts, dispersion media, coatings, antibacterial and antifungal agents, isotonic and absorption delaying agents, and the like,” a person of ordinary skill in the art would readily understand that both *Lazar* and *Kannan* teach a “pharmaceutically acceptable carrier.” (Ex. 1001 at 29:12-16.)

243. **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 *Kannan*, 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 known techniques to carry out the disclosures of *Lazar* and *Kannan*.

* * *

244. For the reasons I discuss in Section XIII above, it is my opinion that a person of ordinary skill in the art would have understood that *Lazar*—or at least the combination of *Lazar* and *Kannan*—discloses or suggests every limitation of claims 1-7.

XIV. Conclusion

245. 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. 11,926,859

Executed on: *Feb 11, 2025*

By: *Leonard G Presta*

Leonard G. Presta, Ph.D.