

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

MERCK SHARP & DOHME LLC,
Petitioner,

v.

SURROZEN OPERATING, INC.,
Patent Owner.

Case No. PGR2026-00027
Patent No. 12,297,278

DECLARATION OF DR. JAMES McDONNELL

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GLOSSARY

<i>Bold and italicized</i>	Emphasis added unless otherwise indicated
Garcia	International Patent Publication No. WO 2016/040895 A1
POSA	Person of ordinary skill in the art

I. INTRODUCTION

1. I, James McDonnell, Ph.D., have been retained by Finnegan, Henderson, Farabow, Garrett & Dunner, LLP on behalf of Merck Sharp & Dohme LLC (“Merck”) as an independent expert in the field of antibody design and engineering to provide my opinions related to the U.S. Patent No. 12,297,278 (“’278 patent”), including its invalidity and the relevant state of the art.

II. SUMMARY OF MY OPINIONS

2. It is my opinion that claims 1-5 (all claims) of the ’278 patent are deficient for three separate reasons: lack of written description, lack of enablement, and indefiniteness. Claims 1 and 4 are additionally anticipated by a prior art reference, referred to as Garcia (EX1004) here in my declaration.

3. *Lack of Written Description*: The claims of the ’278 patent are directed to a genus of soluble, tetravalent, multispecific Wnt surrogate molecule that comprises two Fzd binding regions that bind to two Fzd receptors and two Lrp5/6 binding regions that bind to a Lrp5 and/or a Lrp6, wherein each of the Fzd binding regions and the Lrp5/6 binding regions comprises an antibody or antigen-binding fragment, and each of the two Lrp5/6 binding regions is fused to one of the two Fzd binding regions via a linker moiety.

4. The scope of these claims is extraordinarily broad—as they are defined almost entirely by their functions of binding to Fzd and LRP5/6 receptor

combinations and activating the Wnt signaling pathway. Even for the antigen-binding components of the claimed molecules, the claims impose no limitations on specific structures or amino acid sequences or even their target epitopes. My conservative calculation illustrates that claim 1, for example, encompasses more than 130 million distinct tetravalent molecular formats and over 35,000 different Fzd and Lrp5/6 target combinations, constructed from an effectively unknowable number of possible Fzd- and Lrp5/6-binding region amino acid sequences.

5. In contrast, the disclosures of the '278 patent are narrow. The specification evaluated only a small set of closely related molecules, representing 29 formats and targeting a limited number of Fzd and Lrp5/6 target combinations. A POSA would have concluded that these molecules are not representative of other, untested molecules that differ in either format or Fzd and Lrp5/6 target combination. Further, from these limited disclosures, a POSA could not identify any common structural feature that correlates with the claimed function of activating Wnt signaling. To the contrary, the data in the specification demonstrate that no such structure-function relationship exists.

6. Thus, it is my opinion that claims 1-5 lack written description support.

7. Lack of Enablement: It is also my opinion that claims 1-5 fail to satisfy the enablement requirement.

8. As of 2017, the field of multivalent, multispecific antibody engineering was both nascent and highly unpredictable. There was no universally effective multivalent, multispecific format suitable across all biological systems, much less for Wnt signaling. As Dr. Kahn explains, Wnt signaling is more complicated than other biological systems, and was not well understood as of the effective filing date.

9. The specification, however, provides only minimal—and clearly insufficient—guidance regarding which molecules, among the vast number of potential candidate molecules with millions of tetravalent formats and linker configurations, would be capable of activating Wnt signaling. Thus, in order to make and use the full scope of claimed tetravalent, multispecific Wnt surrogate molecules, a POSA would have been required to undertake extensive, iterative trial-and-error experimentation to identify molecules that activate Wnt signaling pathway from a sea of potential candidates. Claims 1-5 are not enabled.

10. Indefiniteness: In my opinion, claims 1-5 are also indefinite. The specification fails to identify or endorse any specific assay capable of measuring both canonical and noncanonical Wnt signaling, and further fails to define the conditions for numerous variables that affect the assay for measuring Wnt signaling activity. Because the determination of whether a candidate molecule is “biologically active” in activating Wnt signaling depends on unspecified assay- and condition-dependent variables, a POSA would not be able to determine, with reasonable

certainty, whether a given candidate molecule qualifies as a claimed “Wnt surrogate molecule.”¹

11. Anticipation: Lastly, it is my opinion that claims 1 and 4 of the ’278 patent are anticipated. The reasoning is straightforward: the prior art reference Garcia (EX1004) expressly discloses a “Wnt signaling agonist” that is a “dimer” of monomeric molecules that each possess an antibody binding region for Fzd and an antibody binding region for Lrp5/6. As confirmed by the named inventor, the dimeric aggregation of two monomeric molecules, which corresponds to “two . . . binding domains for FZD and two . . . binding domains for LRP in one molecule,” was “associated with Wnt activity.” EX1008, 4171. Thus, Garcia’s “dimer” constitutes a tetravalent Wnt surrogate molecule satisfying each and every limitation

¹ As discussed below, it is my opinion that the claim term “each of the two LRP5/6 binding regions is fused to one of the two Fzd binding regions via a linker moiety” requires that each of the two LRP5/6 binding regions is directly connected to one and only one Fzd binding regions via a linker moiety. To the extent that the term is construed more broadly (e.g., allowing indirect connections or binding to one or both Fzd binding regions), it leads to additional reasons for the challenged claims to lack written description, lack enablement, and be indefinite, as discussed below. *See infra* §§ VIII.E.2, IX.A.7, X.A.5, XI.B.

of claims 1 and 4. As explained below, Patent Owner's characterization during prosecution that Garcia does not disclose a tetravalent Wnt surrogate molecule is not correct.

III. QUALIFICATIONS

12. I am a Professor of Molecular Immunology in the Randall Centre for Cell & Molecular Biophysics at King's College London. I have been researching immunoglobulins (antibodies) and cytokines involved in immunological and inflammatory disorders for nearly 40 years. My research focuses mainly on molecules that regulate allergy and asthma. In the course of that research, I have had numerous occasions to not only evaluate regulation of cellular signaling pathways, but also to design, use, and evaluate antibodies and their biological impact on these signaling pathways, including involvement in more than a dozen distinct antibody projects, about half of which were programs to develop therapeutic antibodies in collaboration with industrial partners. In the course of that work, I have gained extensive experience in engineering and screening of antibodies and antibody fragments, including those targeting cellular signaling pathways.

13. I obtained my B.S. in Microbiology from the University of Massachusetts at Amherst and my Ph.D. in 1993 from the Department of Immunology at Thomas Jefferson University. From 1993 to 1996, I did my first postdoctoral research at King's College London, conducting biophysical analyses of

IgE-receptor interactions. From 1996 to 2000, I worked as a Senior Research Associate at the Rockefeller University, studying the molecular structures and interactions of proteins by NMR spectroscopy. From 2000 to 2010, I was a University Lecturer in the Department of Biochemistry at the University of Oxford. In 2010, I joined King's College London as a Professor of Molecular Immunology and continued my research on molecular recognition and intervention in pathological immune responses.

14. I have published about 100 scholarly articles. Approximately 80 of these are primary papers in peer-reviewed journals, while the others are invited review papers, book chapters, and meeting reports. These include publications focused on antibody crystal structures, binding properties and therapeutic potential. I sit on the editorial boards of several scientific journals, including Antibodies, Frontiers of Molecular Biosciences, and Biomedical Spectroscopy and Imaging. I am also currently a reviewer of numerous prestigious journals on structural biology and drug development, including recently the journals Biochemistry, Cell, Current Opinion in Immunology, FEBS Letters, European Biophysics Journal, Journal of Biological Chemistry, Journal of Molecular Biology, Nature, Nature Reviews Drug Development, and PLoS ONE.

15. I have lectured, organized, and taught multiple courses on antibody structure and function, protein structure, molecular interactions, and structure-based

drug design. Based on my research and publications, I have been awarded numerous funding grants from national scientific organizations including the Medical Research Council (MRC), the Biotechnology and Biological Sciences Research Council (BBSRC), the Wellcome Trust, and the National Institutes for Health to investigate, among other topics, antibody structure and function, as well as cellular signaling pathways related to asthma and allergy.

16. My professional qualifications are described in further detail in my curriculum vitae, which is attached as **Appendix A**.

17. I am being compensated for the time I spend on this matter, but my compensation is not contingent in any way upon my opinions, my performance, or the outcome of this or any other proceeding. I have no current or past financial ties with Merck outside of my engagement in this proceeding.

IV. MATERIALS CONSIDERED

18. I provide opinions in this declaration based on my education, training, background, and experience, as well as the documents I have reviewed to date. Those documents, and the other materials cited in this declaration, are listed in **Appendix B**. I may consider additional documents and information in forming any supplemental opinions. To the extent I am provided with additional documents or information, including any declarations in this proceeding, I may modify or expand

upon my opinions based on any new information that may arise and in response to any additional reports and testimony.

V. LEVEL OF ORDINARY SKILL IN THE ART

19. I have been informed that that my analysis of the '278 patent claims must be conducted from the perspective of a person of ordinary skill in the art ("POSA") as of the "effective filing date" of the patent claims. As discussed below, I was instructed to assume that December 19, 2017 is the effective filing date of the '278 patent claims.

20. I understand that the level of ordinary skill in the art is determined by looking at: (1) the type of problems encountered in the art; (2) the prior-art solutions to those problems; (3) the rapidity with which innovations are made; (4) the sophistication of the technology; and (5) the educational level of active workers in the field. In this case, the art and field relate to multivalent, multispecific antibody engineering, in particular with respect to the Wnt signaling pathway.

21. In my opinion and based on my experience in the field at the relevant time, a POSA for the subject matter of the '278 patent would have had a Ph.D. degree in immunology, molecular biology, chemistry, or biochemistry with at least five years of experience in antibody engineering or Wnt signaling. A POSA with respect to the '278 patent may also have had access to other POSAs with complementary experience in antibody engineering or Wnt signaling.

VI. LEGAL STANDARDS

22. In preparing this declaration, certain patent law concepts have been explained to me, including the legal standard for interpreting claims, as well as those for assessing written description, enablement, indefiniteness, and anticipation.

A. Claim Construction

23. I have been informed by counsel that terms in a patent claim are interpreted (“construed”) from the perspective of a POSA at the time of the effective filing date. I understand that claim terms are interpreted in light of the claim language itself, the specification, and the prosecution history, collectively referred to as “intrinsic evidence.” I also understand that “extrinsic evidence” other than the patent and its prosecution history can be relevant in determining how a POSA would understand terms of art used in the claims. I have been informed, however, that extrinsic evidence may not be used to contradict the meaning of the claims as described in the intrinsic evidence, that is, evidence in the claim language itself, the specification, and the prosecution history.

24. In addition, I understand that if the intrinsic evidence provides an explicit definition of a claim term, i.e., the inventors acted as lexicographers, that definition controls even if it differs from the plain and ordinary meaning that it would otherwise have to a POSA. For all other terms, I understand that their plain and ordinary meaning applies.

25. I also understand that in an independent claim, a claim term that appears before the first “comprises” or “comprising” language is referred to as a “preamble.” I understand that the preamble is construed as limiting (i.e., it limits the scope of the claim) if it is necessary to give life, meaning, and vitality to the claim, and the intrinsic evidence shows that the inventors regarded the preamble as an important feature of their invention.

B. Written Description

26. I understand that a claim in a patent must satisfy certain disclosure requirements. I understand that one such requirement is referred to as the “written description” requirement, which requires that the patent’s disclosure (including its specification and figures) provide sufficient information for a POSA to recognize that the named inventors in fact invented what is claimed.

27. I understand that to satisfy the written description requirement, a POSA reading the patent’s disclosure must recognize that the named inventors were in possession of the full scope of the claimed subject matter as of the effective filing date. I further understand that a number of factors are considered for evaluating the adequacy of the disclosure, including the existing knowledge in the particular field, the extent and content of the prior art, the maturity of the science or technology, and the predictability of the aspect at issue.

28. To satisfy the written description requirement for claims directed to a genus of molecules that include functionally-defined limitations, like the claims of the '278 patent, I have been informed that the specification must at least disclose either: (1) a representative number of species falling within the scope of the claimed genus; or (2) structural features common to the members of the genus such that a POSA can “visualize or recognize” the members of the claimed genus.

C. Enablement

29. I understand that another disclosure requirement is referred to as the “enablement” requirement, which requires that the specification of a patent enable a POSA to make and use the full scope of the claimed subject matter without undue experimentation as of its effective filing date. I further understand that the specification may call for a reasonable amount of experimentation to make and use a patented invention, and that what is reasonable in any case depends on the nature of the invention and the underlying art.

30. To determine whether or not the disclosure of a patent would require undue experimentation, I have been informed by counsel to consider (1) the breadth of the claims, (2) the nature of the claimed subject matter, (3) the state of the prior art, (4) the level of predictability in the art, (5) the level of one of ordinary skill, (6) the amount of direction or guidance provided by the named inventors, (7) the presence or absence of working examples, and (8) the quantity of experimentation

needed to make or use the claimed subject matter based on the content of the disclosure.

D. Indefiniteness

31. I have also been informed by counsel that a claim must particularly point out and distinctly claim the subject matter that the named inventors regard as their invention. I understand that a claim is indefinite when the claim, read in light of the specification and the prosecution history, fails to inform a POSA about the scope of the claim with reasonable certainty. I further understand that a claim term is indefinite when it can be measured in different ways that would yield different results, with no express guidance from the patent or its prosecution history as to which measurement method to use.

E. Anticipation

32. I understand that a claim is anticipated when a single prior art reference discloses, either expressly or inherently, each and every claim limitation arranged in the order specified by the claim. I understand that where a claim is directed to a genus encompassing multiple species, the claim is anticipated if even a single species falling within the genus was known in the prior art.

VII. BACKGROUND AND STATE OF THE ART

A. Antibody Technical Background

33. Proteins play a critical role in the biological functions of the human body. Cells contain and produce many different types of proteins, each with

specialized biological activities. In nature, proteins are assembled from the same group of twenty building blocks called amino acids. Amino acids are linked together to form chains called polypeptide chains. Individual amino acids in the polypeptide chain are connected via a peptide bond between the amino group of one amino acid and the carboxyl group of another. The beginning of a polypeptide chain is referred to as the amino- or N-terminal end and the last amino acid in a chain is referred to as the carboxyl- or C-terminal end. The order of amino acids in a polypeptide chain, from the N-terminal end to the C-terminal end, are referred to as the “amino acid sequence.”

34. An antibody, which is also known as an immunoglobulin (Ig), is a specialized protein that recognizes and binds to a target molecule, referred to as an “antigen.” EX1039, 61. Intact antibodies typically consist of four polypeptide chains: two identical “heavy chains” and two identical “light chains,” arranged in a characteristic Y-shaped structure, as illustrated in **Figure 1** below. Each heavy chain is paired with a light chain to form one of the two arms of the Y shape. The terms “heavy chain” and “light chain” refer to their relative molecular weights, with each heavy chain containing additional amino acids at its C-terminus. Within each arm, the heavy and light chains are linked by disulfide bonds, and the two heavy-light chain pairs are themselves joined by disulfide bonds, together giving rise to the Y-shaped architecture.

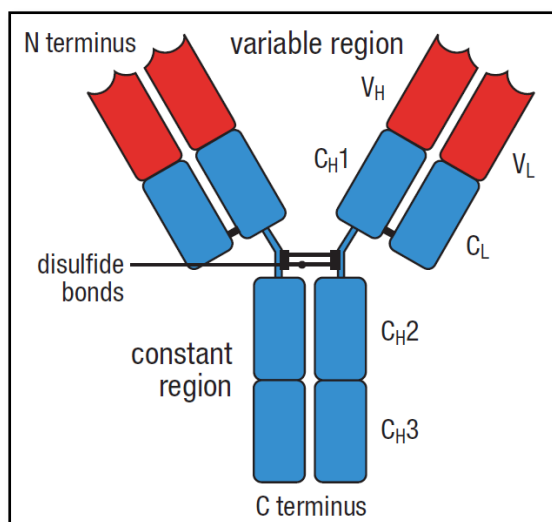


Figure 1. Exemplary Antibody (IgG) (EX1039, 56)

35. Each heavy chain and each light chain contain a variable domain and one or more constant domains. EX1039, 56-57. In a typical antibody, the constant domains of the heavy (C_H1, C_H2, C_H3) and light (C_L) chains, located at the lower portions of the two arms and the stem of the Y-shaped structure, together form the constant region of the antibody (shown in blue in the figure above). The constant region primarily mediates interaction with cellular receptors in the body and contributes to downstream biological functions, including cellular cytotoxicity. *Id.*, 57, 101-02.

36. Antibodies may be categorized into various classes based on the structure of their constant regions. Specifically, there are two classes of light chains: kappa (κ) and lambda (λ), and five classes of heavy chains, α , δ , ϵ , γ and μ , each defining antibody isotypes IgA, IgD, IgE, IgG, and IgM, respectively. EX1039, 56-57. IgG is the most abundant immunoglobulin in human plasma. *Id.*, 57. In IgG,

two constant domains (C_{H2} and C_{H3} in the above figure) of each of the two heavy chains together constitute the stem of the Y-shape structure, which is also referred to an “Fc region.”

37. The regions located at the upper portions of the two arms of a typical Y-shaped antibody (shown in red in the figure above) control antigen specificity and the strength, primarily via segments known as the complementarity determining regions (“CDRs”). Because the amino acid sequences of these regions vary significantly from one antibody to another, they are referred to as “variable regions.” EX1039, 61. In a typical antibody, each variable region is formed from a pair of variable domains located at the N-terminal regions of the heavy and light chains. The variable domain of the light chain (“ V_L ”) pairs with the variable domain of the heavy chain (“ V_H ”) to form a specific three-dimensional structure capable of binding a target antigen. A typical antibody contains two identical V_H - V_L pairs, one on each arm of the Y-shaped structure.

38. Although sequence diversity is present throughout the variable domains, specific segments within both the heavy and light chains exhibit particularly high variability in their amino acid sequences. These hypervariable segments, known as CDRs, directly interact with antigens by forming a complementary binding surface. EX1039, 62-63. Each heavy chain contains three CDRs, designated HCDR1, HCDR2, and HCDR3, and each light chain likewise contains three CDRs,

designated LCDR1, LCDR2, and LCDR3. Together, all six CDRs from the paired heavy and light chain variable domains form the antigen-binding pocket and are the primary determinants of antigen specificity and binding affinity. *Id.*

39. The antigen-binding pocket of an antibody typically interacts with only a small region on the surface of its target antigen. The part or parts of the antigen that are recognized and bound by an antibody are referred to as an “epitope.” EX1039, 63. An epitope can consist of a linear stretch of the target antigen’s amino acid sequence. Alternatively, protein folding can bring together non-adjacent segments of the antigen to form the three-dimensional structure of the epitope. *Id.*, 63-64. Antigen may have multiple epitopes that are bound by different antibodies.

B. Antibody Engineering Was Unpredictable in 2017

40. As of 2017, a POSA could not reliably predict which antibody would bind a particular target antigen (or epitope therein). Determining antibody-antigen specificity thus required empirically generating and testing candidate antibodies. EX1064, 2; EX1047, 12-13. This unpredictability stems from the extraordinary diversity of antibody sequence and structure, and how this influences antibody-antigen interactions.

41. Antibodies are capable of binding to a vast range of antigens because of the amino acid sequence hypervariability exhibited in their antigen-binding regions, allowing different antibodies to provide binding pockets with different

shapes and properties that interact with distinct antigens and epitopes. EX1039, 61-63. Even minor changes in the amino acid sequence in the variable domains, particularly in the CDRs, can produce large and unpredictable effects on antigen specificity or binding affinity. A study from Xu and Davis, for example, reported that differences at just a few amino acid positions in only one of the three heavy chain CDR regions (HCDR3) caused otherwise identical antibodies to bind very different antigens. EX1079, 2-3.

42. Conversely, antibodies with highly dissimilar variable region sequences may nonetheless fold into structures capable of binding the same antigen. For example, two monoclonal antibodies binding the same 12 amino acid residues on a lysozyme antigen were shown to have no sequence homology at any of their CDRs. EX1049, 7. In addition, most antigens present multiple distinct epitopes, each of which may be recognized by different antibodies, further expanding the range of antibody sequences capable of binding a given antigen. EX1039, 31. In view of this extensive variability and inherent unpredictability, by 2017 it was virtually impossible to predict with any reliability which antibody sequences would bind a particular antigen. Identifying a specific antibody-antigen pair required empirical testing on candidate antibodies. EX1064, 2; EX1047, 12-13.

43. As of 2017, a POSA likewise could not determine, without empirical experimentation, the biological effect of an antibody on the function of a specific

target antigen or, in turn, on the functions of the cellular signaling pathways regulated by that antigen. In general, antibody binding can “agonize” (enhance) one or more functions of a target antigen, or “antagonize” (inhibit) or even completely block those functions. Alternatively, binding of an antibody to an antigen may have little or no functional effect at all.

44. For example, a study with anti-Lrp6 antibodies from Gong and colleagues illustrated this unpredictability. EX1027, Abstract. In this study, several antibodies against Lrp6 were generated. Notably, antibodies binding different sites of Lrp6 unpredictably impacted Wnt signaling activity. *Id.*, 2-3. Among 24 antibodies binding to the E1E2 sites and 22 antibodies binding to the E3E4 sites, none of the E1E2 binders and six E3E4 binders inhibited Wnt3a-induced signaling in HEK293 cells, whereas five E1E2 binders and two E3E4 binders potentiated Wnt3a-induced signaling in HEK293 cells. *Id.* The biological effects of these antibodies also depended on whether the antibodies were intact or fragmented. For example, a full-length anti-Lrp6 antibody bound to two Lrp6 molecules and potentiated Wnt signaling, but a fragment of that same antibody that bound to only one Lrp6 molecule inhibited Wnt signaling. *Id.*, 7. This study demonstrated that an antibody’s function unpredictably depended on its biological target, binding site, amino acid sequence, and ability to bind one or more target molecules.

45. Because there was no reliable way to predict from an antibody's amino acid sequence whether it would bind to its intended antigen and whether and how it would affect the biological activity of the antigen, one needed to make and test each candidate antibody. By 2017, several methods for making antibodies against an antigen of interest in the laboratory were known in the art. As discussed below, each method was labor-intensive and subject to variable known and unknown factors that could unpredictably impact the successful generation of candidate antibodies.

46. One such method was to administer a target antigen to an animal (such as a mouse, rat, rabbit, or goat). EX1039, 133-34. This process, generally referred to as "immunization," elicits an immune response in the animal, causing B cells to produce a pool of antibodies against the injected antigen. *Id.*, 134. The administration route, dose, and form in which the antigen is administered can profoundly affect whether and how the immune response occurs. *Id.*, 125-28.

47. If and when a sufficient immune response is achieved, B cells from the immunized animal are collected and fused to cancer cells to obtain hybrid cells known as "hybridomas." *Id.*, 134. Because each hybridoma is derived from a single B cell fused to a single cancer cell, all of the antibody molecules produced by that hybridoma clone are identical in sequence and are referred to as "monoclonal" antibodies. *Id.* Generating a single monoclonal antibody by this approach typically takes several weeks to months.

48. Another method known in 2017 was to create a library of different antibodies and to screen that library for potential candidate antibodies. For example, gene segments encoding the antigen-binding variable domains of antibodies can be fused to genes encoding the coat protein of a bacteriophage. EX1039, 134-35. Bacteriophages containing such gene fusions were used to infect bacteria, and the resulting phage particles had coats that display the antigen-binding domain on the surface of the phages. *Id.*, 135. A collection of recombinant phages, each displaying a different antigen-binding domain on the surface, is known as a phage display library. *Id.* Phages expressing antigen-binding domains specific for a particular antigen could then be isolated by selecting the phages in the library for binding to that antigen. *Id.* Because the exact nature of the variable domain repertoire in the library was unknown, the usefulness of the library for obtaining antibodies specific to a target antigen could only be determined empirically on a trial-and-error basis.

49. In many cases, an antibody obtained from immunization or a phage-display library is commonly derived from a non-human source. These antibodies may induce immunogenic responses in a human subject as the body recognizes them as foreign pathogens. Thus, those antibodies needed to be “humanized,” a process that substitutes non-human sequences with human sequences. This process, however, could reduce the binding affinity of antibodies and thus would require additional engineering to restore binding affinity. EX1010, 4. The humanization

process in 2017 was both time-consuming and costly, minimally adding months to the time already taken for immunization or phage screening.

50. Obtaining a candidate antibody, however, was only the beginning. Each antibody needed to be evaluated for its ability to bind its intended antigen, and additionally for its ability to affect the biological function of the antigen, if a particular functional property (e.g., antagonism) was desired. Indeed, assessing the functional impact of a given antibody required a detailed understanding of the biological function of the target antigen and careful empirical testing in an appropriate biological system capable of modeling that function. For example, where a target antigen is involved in Wnt signaling, a suitable Wnt signaling model system needed to be established to determine empirically whether an antibody agonizes or antagonizes the Wnt signaling pathway by binding to that target antigen. As confirmed by Dr. Kahn, assessing Wnt signaling induced by candidate molecules was particularly complex for a POSA in 2017. EX1003, ¶¶76-112; *see infra* § VII.E.

C. A Wide Variety of Antigen-Binding Fragments Were Known in the Art

51. Antibodies produced in the human body are typically full-length antibodies, as discussed above. EX1039, 55-56. But by 2017, researchers recognized that some biological applications may require different antibody structures, for example, those that are larger than full-length antibodies or contain only parts of full-length antibodies. Thus, researchers used laboratory techniques to

modify and dissect full-length antibodies to generate various antibody-derived fragments that retain the portions needed for antigen-binding but structurally differ from full-length antibodies. EX1017, 1-2. Researchers also turned to non-human mammals such as camels that produce atypical, smaller antibodies. EX1078, 2. This additional layer of antibody engineering required sophisticated designing strategies and recombination techniques, adding more time and effort to the work needed to make typical, full-length antibodies.

52. By 2017, a wide variety of antigen-binding fragments had been generated and reported in the literature. These fragments may or may not retain the function of a full-length antibody because “[f]ragmentation of antibodies results in altered physiochemical features” of the antibody molecules. EX1059, 2. **Figure 2** depicts some of those fragments. Each fragment is briefly discussed below.

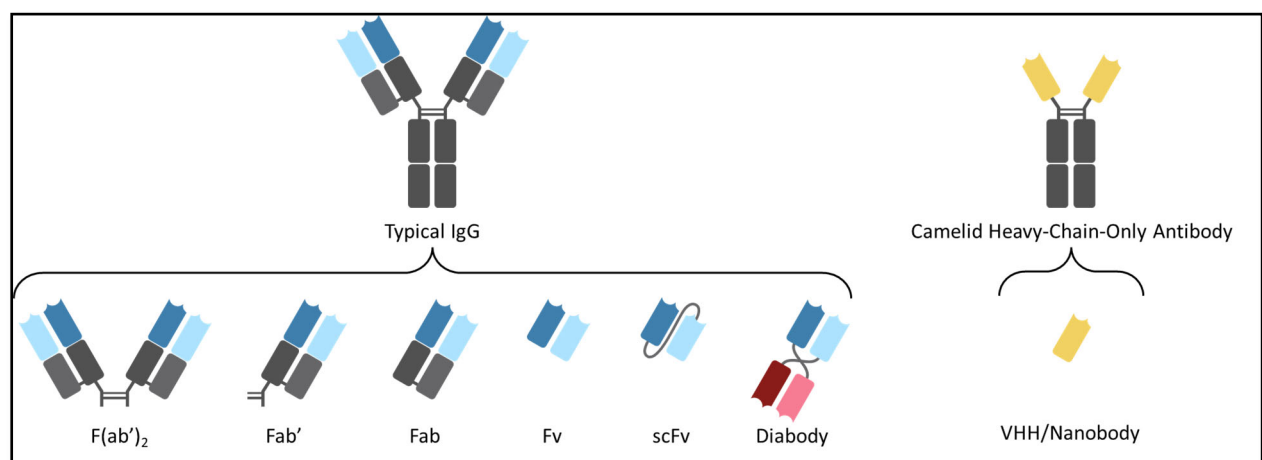


Figure 2. Exemplary Antigen-Binding Fragments

53. *F(ab')₂*: In a *F(ab')₂*, the two antigen-binding arms of the Y-shaped antibody molecule remain linked by disulfide bonds, but the remaining parts of the

heavy chains are removed. A $F(ab')_2$ may maintain the antigen-binding characteristics as the original antibody but is unable to interact with effector molecules that would otherwise bind the Fc domain. Thus, the $F(ab')_2$ may be used experimentally to separate an antibody's antigen-binding functions from other effector functions. EX1039, 59.

54. Fab': A Fab' comprises an antigen binding region formed by a complete light chain paired with the variable domain and one constant domain of the heavy chain, corresponding to one arm of the Y-shaped structure of a typical antibody. A Fab' retains the disulfide bridge thiol functional group near its C-terminus. Like $F(ab')_2$, Fab' lacks the Fc domain so while it may maintain the antigen-binding characteristics as the original antibody, it is also unable to interact with effector molecules that would otherwise bind the Fc domain.

55. Fab: A Fab is similar to a Fab' in that it also comprises an antigen binding region formed by a complete light chain paired with the variable domain and one constant domain of the heavy chain, which corresponds to one arm of the Y-shaped structure of a typical antibody. Unlike a Fab', a Fab does not retain the disulfide bridge thiol functional group. EX1039, 59. Compared to full-size antibodies, Fab' and Fab fragments generally permit more effective tissue penetration but have significantly shorter circulating half-lives. EX1059, 2.

56. Fv: A Fv comprises a V_H domain and a V_L domain, i.e., the tip of one arm of the Y-shaped structure of a typical antibody. In a Fv, a V_H domain and a V_L domain associate each other via non-covalent bonds, similar to how a V_H domain and a V_L domain would typically interact in a full-length antibody. However, due to the lack of covalent bonds, Fv fragments by themselves are unstable because the V_H and V_L domains can rapidly dissociate, resulting in drastically reduced binding affinity and often aggregation. EX1013, 1-2.

57. ScFv: A single-chain Fv, also known as scFv, is similar to a Fv, except that a V_H domain is linked to a V_L domain by a synthetic peptide (also referred to as a peptide “linker”). EX1059, 3. The function of scFv depends on the orientation of the V_H and V_L domains, as well as the length and composition of the linker. EX1009, 2-3. When an appropriate linker is used, the scFv may retain the three-dimensional structure of the variable region of a typical antibody and the associated ability to bind a target antigen. *Id.*, 2.

58. Diabody: A diabody combines two scFv fragments to form a noncovalently associated dimer with two antigen-binding regions, each consisting of a V_H domain and a V_L domain derived from different scFv fragments. EX1059, 4.

59. VHH, sdAb, or Nab: A VHH is derived from species that naturally produce heavy-chain-only antibodies, such as llamas, alpacas, and camels, and

consist of a single heavy-chain variable domain. EX1059, 4. The recombinant version of a VHH fragment is called a “single-domain antibody” (“sdAb”) or a “nanobody” (“Nab”). EX1089, 2.

D. Engineered Multivalent, Multispecific Antibodies Present Heightened Demands for More Sophisticated Empirical Evaluation

60. Antibody molecules may be characterized by their valency and specificity. In antibody biology, valency refers to the number of antigen-binding regions in an antibody molecule, that is, how many epitopes, whether identical or different, the antibody can bind simultaneously. Specificity, on the other hand, refers to the number of distinct epitopes an antibody is capable of recognizing. An antibody that binds only a single epitope is termed monospecific, regardless of the number of antigen-binding regions it contains. Conversely, an antibody capable of binding two or more different epitopes, whether on the same antigen or on different antigens, is termed multispecific.²

² For example, an antibody with four binding regions (tetravalent), which collectively target two different epitopes (bispecific), is termed “tetravalent, bispecific.” An antibody with four binding regions (tetravalent), but collectively targeting three (trispecific) or four (tetraspecific) different epitopes, is termed “tetravalent, trispecific,” and “tetravalent, tetraspecific,” respectively.

61. As discussed above, a typical IgG antibody contains two antigen-binding variable regions. Each variable region is formed by the pairing of variable domains located at the N-termini of the heavy (V_H) and light (V_L) chains. Because a typical IgG antibody consists of two identical heavy chains and two identical light chains, it contains two identical V_H - V_L pairs and thus two identical variable regions. These identical variable regions have the capacity to recognize and bind the same epitope on a target antigen. Accordingly, a typical IgG antibody, which has two antigen-binding regions that bind the same epitope, is a bivalent, monospecific antibody and can potentially engage two identical antigens. EX1039, 57-58.

62. By 2017, antibody engineers could join antibodies and antigen-binding fragments to create synthetic antibody-like molecules that incorporate multiple antigen-binding regions. EX1017, 1-2; EX1051, 2-3. Using antibodies and their antigen-binding fragments as modular building blocks, antibody engineers have developed a wide range of antibody formats containing two or more antigen-binding regions (i.e., multivalent), each designed to bind to a different epitope (i.e., multispecific), either on the same antigen molecule or on different antigen molecules. EX1017, 2; EX1051, 2-3. Indeed, by 2017, approximately 100 such structurally distinct multivalent, multispecific antibody formats had been generated and characterized, as illustrated in the reproduced figure below. EX1017, 1, Fig. 2; EX1051, 2-3, Fig. 1.

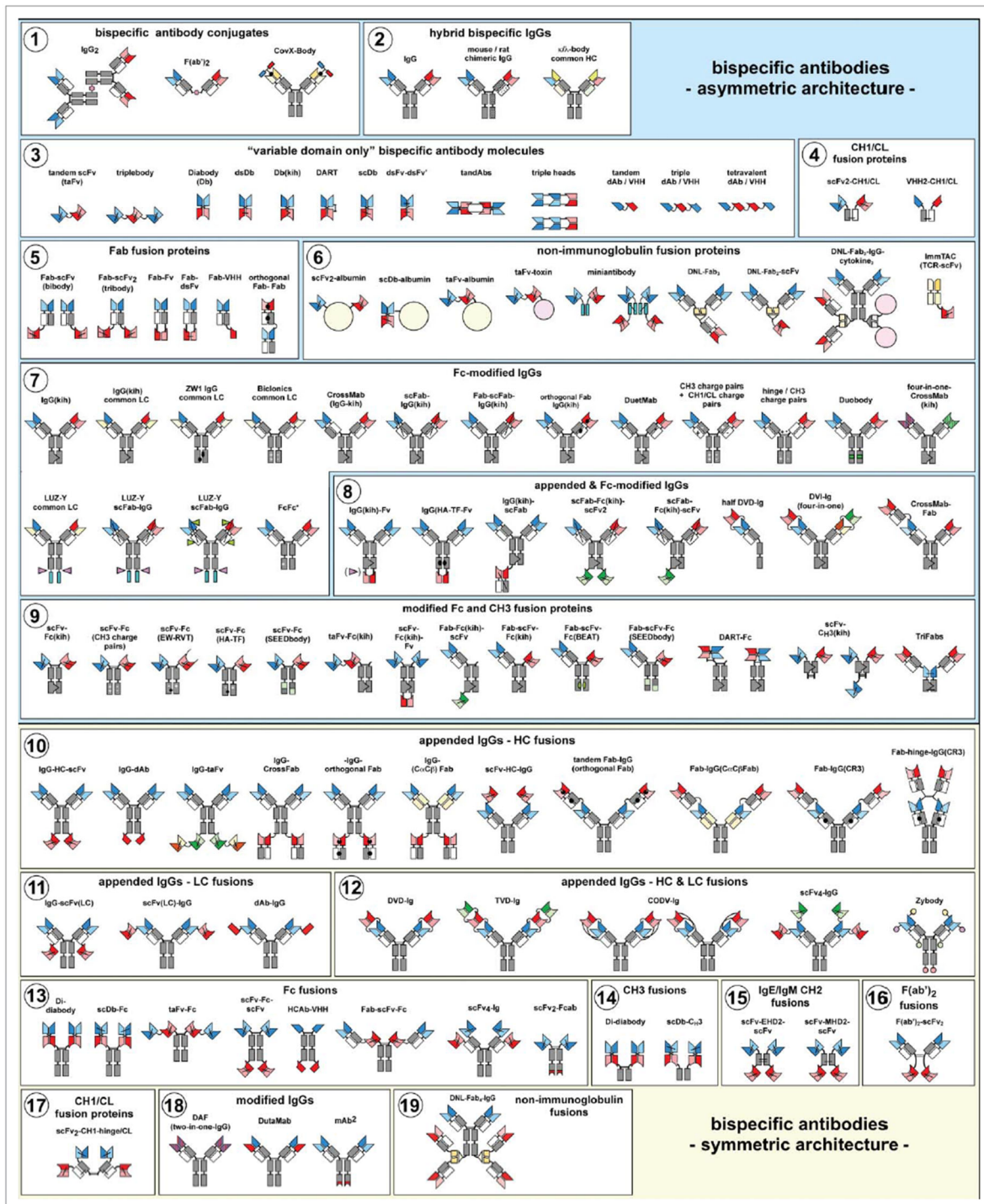


Figure 3. A Variety of Multivalent, Multispecific Antibody Formats Had Been Generated (the Different Antigen-Binding Regions Are Illustrated in Blue, Red, Green, and Purple Colors) (See EX1017, Fig. 2)

63. The multivalent, multispecific antibody formats that had been generated and preliminarily characterized by 2017 represent only a small subset of the formats that could, in principle, be engineered. The potential diversity of multivalent, multispecific antibody formats stems from multiple independent variables. Beyond primary sequence variation, these formats exhibit vast topological and geometric diversity, defined by the spatial arrangement of constituent modules, the valency of engagement, and the conformational constraints imposed by linkers that tether disparate binding regions within a single format.

64. *First*, antibody formats may differ in valency. As illustrated in the reproduced figure below, a multivalent antibody molecule may be, for example, bivalent, trivalent, or tetravalent. The valency is generally determined by the number of antigen-binding regions present in each format.

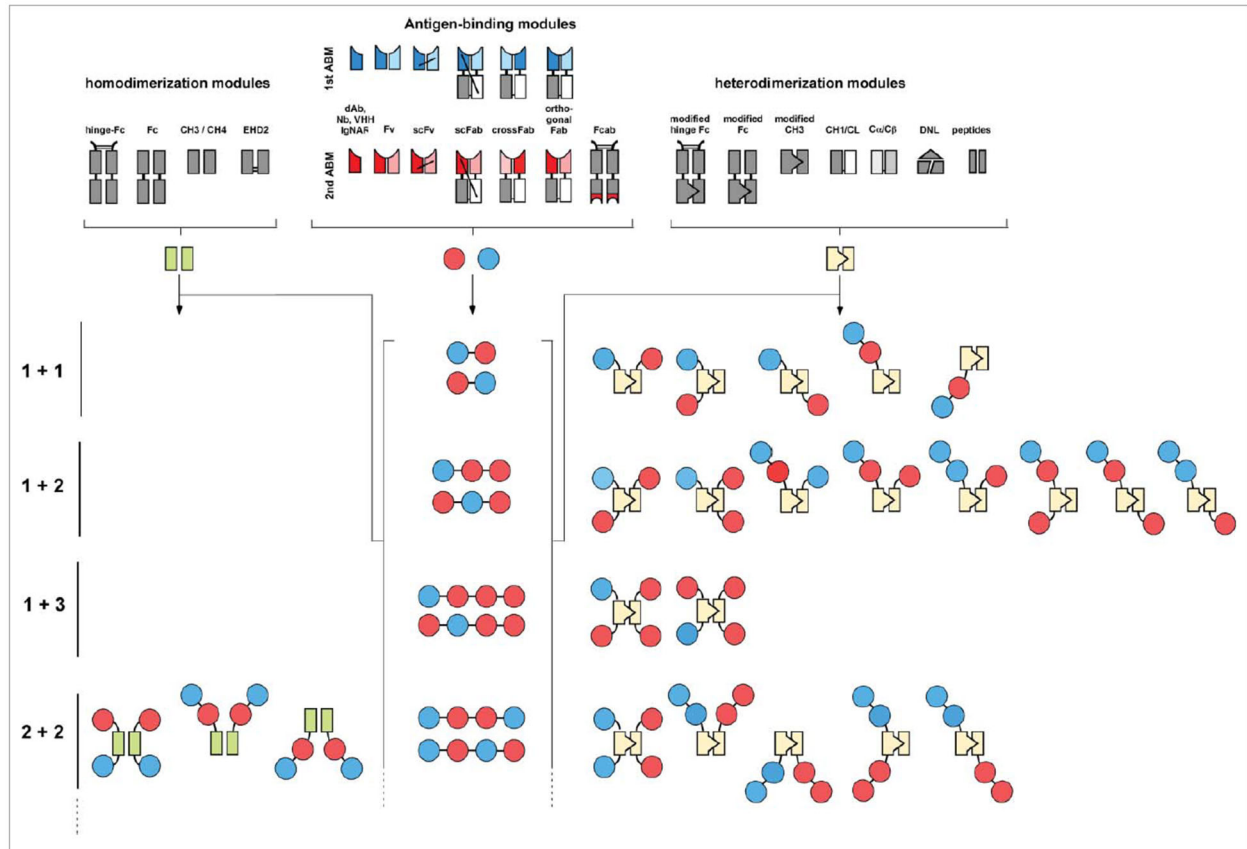


Figure 4. Variability in Valency, Specificity, and Stoichiometry Results in Different Multivalent, Multispecific Antibody Formats (*See EX1017, Fig. 1*)

65. *Second*, for any given valency, both specificity and stoichiometry may vary. For example, a tetravalent multispecific antibody may be bispecific, trispecific, or tetraspecific, having two, three, or four distinct epitope binding regions, respectively. Even within a tetravalent, bispecific format, the two binding regions may bind epitopes in different stoichiometries, such as 1:3 (the first binding region binding to the first epitope and the other three binding regions binding to the second epitope), 2:2 (two binding regions binding to the first epitope and the other two binding regions binding to the second epitope), and 3:1 (the first three binding

regions binding to the first epitope and the last binding region binding to the second epitope). Even with a 2:2 stoichiometry, the arrangement of the binding regions may vary when the tetravalent multispecific antibody adopts an asymmetrical topology. The specificity and stoichiometry are primarily determined by the amino acid sequences of antigen-binding regions present in each format and, for some antibody formats, the accessibility of the epitopes.

66. *Third*, each antigen-binding region may be independently selected from a wide array of antibodies and antibody fragment types (as discussed above), and those regions can be arranged in different orders and orientations within the same construct. EX1017, Fig. 1. In addition, the antigen-binding regions can be connected using linkers of varying lengths, compositions, and flexibility, with no inherent constraints on linker design. *Id.*, 4-5. As of 2017, both linkers made of amino acids (peptidic) and chemical moieties (non-peptidic) had been used for multivalent, multispecific antibody formats. EX1051, 8-9 (discussing both peptide linkers and azetidinone linker).

67. Given these multiple layers of variability and the extensive toolbox of available antibody and antigen-binding fragment building blocks, the number of possible multivalent, multispecific antibody formats was, by 2017, enormous.

68. As of 2017, although interest in using multivalent, multispecific antibody molecules as therapeutic agents was increasing, researchers faced

significant challenges in harnessing the full potential of such molecules because the structural complexity and functional unpredictability of these antibody molecules are substantially greater than those of conventional antibodies. Consider, for example, a bivalent, bispecific IgG antibody. Unlike a typical, monospecific IgG antibody that is made of two identical heavy chains and two identical light chains, a bispecific IgG antibody is made of two *different* heavy chains and two *different* light chains.

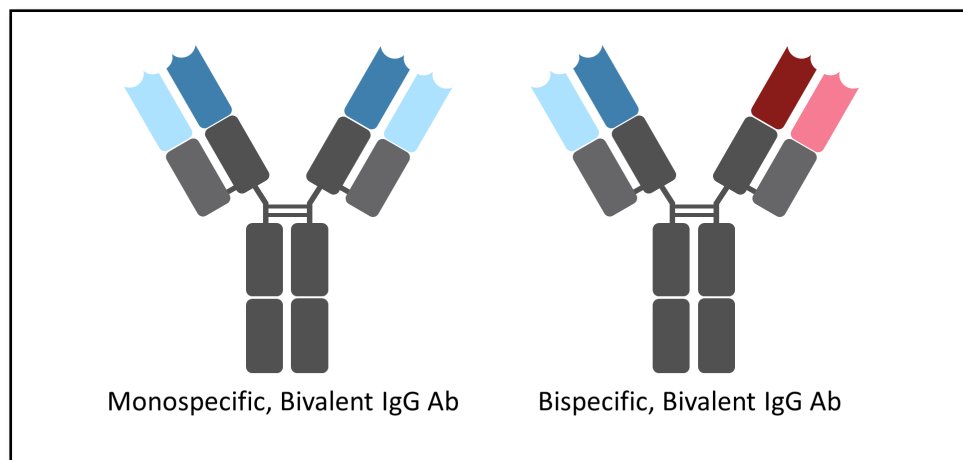


Figure 5. Comparison of Monospecific versus Bispecific IgG Antibodies

69. To produce a typical, monospecific IgG antibody, cells only need to produce two different chains (one heavy chain and one light chain), which would naturally pair together and result in a homogenous population of properly paired antibody molecules. In contrast, producing a bispecific IgG antibody requires co-expression of four different chains in cells, which, as illustrated below, can theoretically yield 16 different heavy-light chain pairings, corresponding to 10 distinct antibody species, due to promiscuous pairing of heavy and light chains.

Only one of these 10 species—representing two of the 16 possible pairings—forms the intended bivalent, bispecific IgG antibody; the remaining pairings give rise to monospecific or otherwise nonfunctional molecules. In this example, only 12.5% of the antibodies produced are the desired bispecific construct. As valency and specificity increase, the ratio of correctly assembled multivalent, multispecific antibody molecules further decreases.

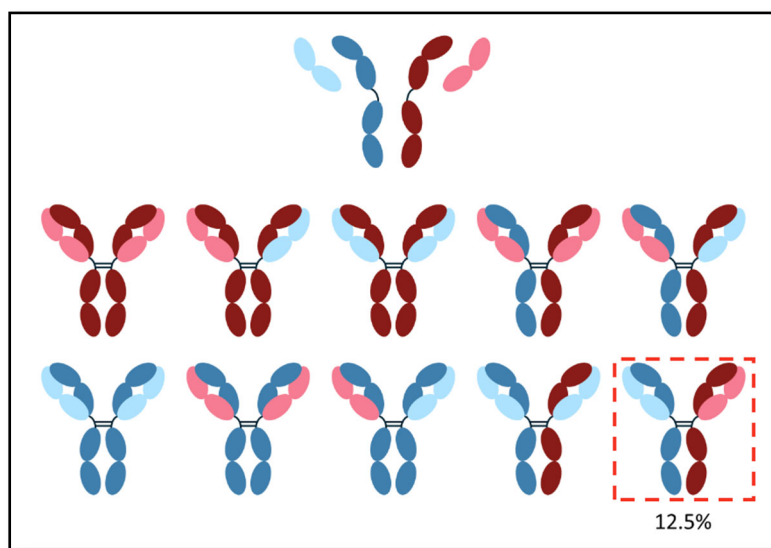


Figure 6. Challenges in Producing Multivalent, Multispecific Molecules

(See EX1017, 2)

70. Moreover, for multivalent, multispecific antibody molecules, there was no “one size fits all” format capable of achieving “the plethora of desired functionalities and applications.” EX1017, 21. Instead, empirical evaluations were required to determine how specific molecular architectures, including format selection and linker design, affected the functional performance of multivalent, multispecific antibody molecules. *Id.*

71. This need for empirical evaluation in part resulted from the varied properties of the target antigens for multivalent, multispecific antibody molecules, including the spatial “arrangement or size of the different target antigens” and “the target densities on cell surfaces.” EX1017, 21. Take bispecific antibodies as an example: when two antigens are expressed at low levels, their sparse distributions on the cell surface may require a bispecific antibody to adopt a format having greater flexibility and extended reach to interact effectively with both antigens. Conversely, when the two antigens are expressed at high levels, their relatively dense distribution may tolerate, or even necessitate, more compact formats to achieve effective bispecificity. These and other target-specific properties—including unknown properties—also affect which antibody formats, e.g., bivalent, trivalent, or higher-order, may be applicable to achieve binding to one or both antigens, whether simultaneously or in a mutually exclusive manner. *Id.* Consequently, a format that may have proven effective for one set of antigen-binding regions or one cell type could fail for another. Indeed, the art recognized that even relatively small format variations, such as changes in “linker length or composition,” were “crucial determinants for functionality.” *Id.*

72. Pharmacokinetic and pharmacodynamic behaviors are also important factors that were understood to influence the functionality of multivalent, multispecific antibodies. For example, while multivalent, multispecific antibody

molecules using smaller antigen-binding fragments may provide advantages such as effective tissue penetration and distribution and the ability to be tightly controlled, their small size could also lead to a shorter serum half-life, lesser tissue retention, and rapid clearance from the blood through kidneys. EX1017, 21; EX1051, 11.

73. As a result, predicting in advance how a particular multivalent, multispecific antibody format would function in vitro, in vivo, and ultimately in humans, was impossible in 2017. Instead, each candidate multivalent, multispecific antibody molecule needed to be individually designed, produced, and empirically tested to determine whether it satisfied the relevant functional requirements and desired characteristics both for each target antigen and for the target signaling pathway as a whole. EX1017, 21 (“suitable formats must be identified by generating and comparing the functionalities of different formats”). Tellingly, there were only two bivalent, bispecific molecules approved by FDA as of 2017. *Id.*, Table 3; EX1090. No molecules with higher valency or specificity had been approved by the FDA as of 2017. In fact, I am not aware of any tetravalent molecules approved by the FDA even today.

E. The Wnt Signaling Pathway Was Complex but Poorly Understood

74. Based on my extensive training and research experience in cellular signaling pathways, I have a general understanding of the molecular mechanisms

and regulation of the Wnt signaling pathway. As a basis for my opinions, I have also reviewed relevant scientific publications as well as Dr. Kahn's declaration.

75. As explained in Dr. Kahn's declaration, Wnt signaling plays a role in numerous biological processes, and aberrant Wnt signaling has been linked to a wide range of disorders, including various cancers, metabolic diseases, and neurodegenerative conditions. EX1003, ¶¶76-79; EX1063, 1; EX1043, 1.

76. The Wnt signaling pathway is complex, involving multiple ligands and receptors that interact simultaneously. EX1003, ¶¶80-89. By 2017, more than fifteen receptors and co-receptors had been reported to participate in Wnt signaling, and nineteen Wnt ligands were known. EX1043, 1. Among the receptors and co-receptors involved in Wnt signaling are ten Frizzled (Fzd) receptors, Fzd1-10, and two low-density lipoprotein receptor-related proteins (Lrp), Lrp5 and Lrp6. EX1063, 1, 3. In addition, several non-Wnt ligands, such as Norrin, were known to bind and activate a subset of these receptors, while secreted R-spondin proteins were recognized to potentiate Wnt signaling. *Id.*, 3-5.

77. The activity of Wnt signaling is influenced not only by these ligands and receptors but also by cell type, development stage, and other contextual factors. EX1003, ¶¶90-100. As of 2017, it was understood that Wnt and non-Wnt ligands exert tissue-specific effects, and that loss of Wnt genes produces unique or partially overlapping phenotypes corresponding to the expression patterns of these ligands.

EX1063, 1. Moreover, Wnt and non-Wnt ligands can trigger different types of cellular responses, including “canonical” activation of the β -catenin and T-cell factor (“TCF”) transcription complex and alternative “noncanonical” pathways that do not involve this complex. EX1043, 1, 3.

78. By 2017, the mechanism of action of the Wnt signaling pathway remained poorly understood. EX1003, ¶¶79-100. It was postulated that canonical Wnt signaling is activated when Wnt and non-Wnt ligands simultaneously bind and bring together a Fzd receptor (Fzd1-10) and an Lrp receptor (Lrp5 or Lrp6). EX1063, 3. However, the precise interactions between individual ligands and their corresponding receptors were not yet elucidated. EX1003, ¶¶79-100. For example, no crystallization of the complete Wnt-Fzd-Lrp complex had been reported as of 2017. Instead, available crystal structures included only subcomponents of the complex, such as Norrin dimers, or, in some cases, non-mammalian proteins like *Xenopus* Wnt8 complexed with a portion of a Fzd receptor. See EX1044, 2-4; EX1038, 1. As the interactions between subcomponents in isolation do not necessarily reflect their interactions in a functional Wnt signaling complex, these crystal structures do not provide a sufficient foundation for designing the full scope of the Wnt surrogate molecules.

79. The roles of Fzd and Lrp receptors in noncanonical Wnt signaling were also poorly characterized. EX1003, ¶¶92-95. In certain cases, Fzd-Lrp interactions

inhibited rather than activated noncanonical signaling. EX1066, 1. Accordingly, it was believed that “differences in affinities of different Wnt and Frizzleds and their local concentrations . . . would determine to which signaling branch a particular Wnt couples.” EX1065, 4.

80. By 2017, no single assay was universally applicable to all Wnt systems for determining pathway activation. EX1003, ¶¶101-12. Instead, there were “multiple ways in which WNT signaling [was] read out (such as nuclear β -catenin levels, reporter assays and endogenous gene expression), which are highly cell-type dependent.” EX1043, 11; EX1003, ¶¶101-12. Only some assays were capable of measuring both canonical and noncanonical responses. EX1003, ¶102. Even assays designed to measure canonical activity, such as the TOPFlash reporter assay, could not “capture all the important transcriptional changes caused by activated WNT signaling.” EX1043, 3; EX1003, ¶¶108-12. Furthermore, variability and inconsistency across experimental systems made it difficult to determine definitively whether a molecule functions as a Wnt agonist, antagonist, both, or neither and under what conditions. EX1056, 2-5, 11; EX1003, ¶¶101-12, 136.

VIII. THE '278 PATENT

A. Disclosures of the '278 Patent

81. The '278 patent purports to disclose “Wnt pathway agonists and related compositions.” EX1001, Abstract. The specification of the '278 patent states that

“Wnt surrogate molecules of the present invention are **biologically active** in binding to one or more Fzd receptor and to one or more of LRP5 and LRP6, and **in activation of Wnt signaling**, i.e., the Wnt surrogate molecule is a Wnt agonist.” *Id.*, 16:52-56. The ’278 patent further explains that “Wnt agonists typically initiate a reaction or activity that is similar to or the same as that initiated by the receptor’s natural ligand.” *Id.*, 16:61-63.

82. The specification of the ’278 patent states that “the Wnt signaling pathway is a canonical Wnt signaling pathway or a noncanonical Wnt signaling pathway,” and that the “ability of the Wnt surrogate molecules and other Wnt agonists disclosed herein to mimic the activity of Wnt can be confirmed by a number of assays.” EX1001, 4:49-51, 16:58-61. According to the ’278 patent, these assays include: “Wnt/ β -catenin target gene expression; TCF reporter gene expression; β -catenin stabilization; LRP phosphorylation; Axin translocation from cytoplasm to cell membrane and binding to LRP.” *Id.*, 117:40-44. These assays are for evaluating the canonical Wnt signaling pathway. *Id.*, 117:39-40; EX1003, ¶¶103-09. As confirmed by Dr. Kahn, I understand that the ’278 patent does not name specific assays for evaluating noncanonical Wnt signaling. *Id.*, ¶¶19, 121.

83. Table 1A of the ’278 patent provides a list of “antibodies or fragments thereof that bind to one or more Fzd receptor.” EX1001, 22:37-38. While there are about 450 clones listed in Table 1A, these clones were evaluated for “Initial Binding.”

Thus, Table 1A only provides preliminary Fzd binding data for each of these 450 clones. *Id.*, Table 1A. A subset of the clones listed in Table 1A were further tested for their binding ability to Fzd (“Confirmed Binding”). *Id.*, Table 1B. Many of the clones listed in Table 1B are marked with “n.b.,” indicating that these clones lack the ability to bind to any Fzd molecules. Even for the clones with “Confirmed Binding,” the ’278 patent does not disclose any parameters reflecting their binding affinity (e.g., K_D). *Id.* Notably, Table 1B lists the heavy and/or light sequences for only 39 clones. *Id.* Neither Table 1A nor Table 1B discloses the listed clones’ Wnt agonist activity. The specification does not explain how these clones were made, e.g., via immunization or phage-display library screening. *See generally id.*

84. Table 2A of the ’278 patent discloses a list of “antibodies or fragments thereof that bind to LRP5 and/or LRP6.” EX1001, 80:42-43. Table 2A lists about 250 clones and indicates whether they bind to Lrp5 or Lrp6 (“Confirmed Binding”). *Id.*, Table 2A. However, no binding affinity data is disclosed in the ’278 patent. *Id.* Table 2B discloses the heavy chain sequences of 24 clones. Among the 24 clones, only one clone is reported to bind Lrp5. *Id.*, Table 2B. Table 2B also does not provide any light chain sequences. *Id.* In addition, neither Table 2A nor Table 2B discloses the listed clones’ Wnt agonist activity. Again, the specification does not explain how these clones were made. *See generally id.*

85. The '278 patent includes 26 examples (Examples 1-26). Example 1 lists “illustrative Wnt surrogate molecule formats” in Table 3. EX1001, cols. 150-155. Table 3 of the '278 patent lists 104 potential “Wnt surrogate” molecules. *Id.*, Table 3. Notably, despite being encompassed by the claims, no trispecific or tetraspecific molecules are listed in Table 3. *See id.* Nor does the '278 patent disclose any trispecific or tetraspecific molecules. Indeed, I reviewed and searched the specification of the '278 patent for, but did not find, the words “trispecific” or “tetraspecific” or other disclosures of such species. *See generally* EX1001.

86. Examples 2-18 evaluate potential Wnt surrogate molecules using the TOPFlash assay with multiple cell types. EX1001, cols. 155-161. While some molecules were evaluated both in the presence and absence of R-spondin, many were evaluated only in the presence of R-spondin. *See, e.g., id.*, 157:35-50. Two of those molecules (R2M3-26 and R2M3-32) were further tested for binding to the extracellular domain of Fzd1. *Id.*, cols. 155-156. However, the '278 patent does not identify the epitopes bound by those two molecules or any other molecules. Examples 19-26 disclose *in vivo* mouse experiments for three of the tested Wnt surrogate molecules (R2M3-26, 1R-C07-3, and 1R-C07-26) and a prior-art Wnt agonist reported in Garcia (18R5-DKK1c-FlagHis). *Id.*, cols. 161-172.

87. Based on my review, the molecules evaluated in the '278 patent only represent 29 different formats, with 18 different Fzd binding regions, 23 different

Lrp5/6 binding regions, and 3 linker types. As discussed below, many of the molecules evaluated in the '278 patent share the same format and structurally are very similar. *See infra* § IX.A.4. Moreover, as I explain in detail below, these molecules and examples of the '278 patent effectively demonstrate the unpredictability in making and identifying Wnt surrogate molecules, even within the limited subset of highly similar materials that were tested. *See infra* §§ IX.A.5; XI.A.

B. Effective Filing Date

88. The '278 patent claims priority to three provisional applications, filed December 19, 2017, March 9, 2018, and June 4, 2018, respectively. EX1001, item (60). From my review, it appears that each of the three provisional applications discloses *less* than the '278 patent itself. For example, the first provisional application (EX1005) filed on December 19, 2017 did not evaluate candidate Wnt surrogate molecules disclosed in Examples 14-18 of the '278 patent. The first provisional application also did not include any of the *in vivo* studies discussed in Examples 20-26 of the '278 patent.

89. Although I believe none of these provisional applications adequately describe or enable the challenged claims (for at least the same reasons discussed below), I was asked to assume the December 19, 2017 filing date as the effective filing date of the '278 patent for the purposes of my opinions set forth herein. My

opinion would not change, however, if the effective filing date is December 19, 2018, the filing date of the first non-provisional application.

C. Challenged Claims

90. The '278 patent contains one independent claim and four dependent claims. Claim 1 recites:

1. A soluble, tetravalent, multispecific Wnt surrogate molecule, wherein the Wnt surrogate molecule comprises:

(i) two Fzd binding regions that specifically bind to two Frizzled (Fzd) receptors, wherein each of the two Fzd binding regions comprises an antibody or antigen-binding fragment of the antibody; and

(ii) two LRP5/6 binding regions that specifically bind to a Low-density lipoprotein (LDL) receptor-related protein 5 (LRP5) and/or a Low-density lipoprotein (LDL) receptor-related protein 6 (LRP6), wherein each of the two LRP5/6 binding regions comprises an antibody or antigen-binding fragment of the antibody, and

wherein each of the two LRP5/6 binding regions is fused to one of the two Fzd binding regions via a linker moiety.

EX1001, cl. 1. The dependent claims, which are also reproduced below, recite that the Fzd binding regions comprise a full IgG and the Lrp5/6 binding regions comprise

a VHH (claim 2), fusion locations (claims 3 and 5), or pharmaceutical compositions (claim 4).

2. The Wnt surrogate molecule of claim 1, wherein the Fzd binding regions comprise a full immunoglobulin G (IgG), comprising two light chains and two heavy chains, and the LRP5/6 binding regions comprise a VHH.

3. The Wnt surrogate molecule of claim 2, wherein the LRP5/6 binding region is fused to the N-terminus or the C-terminus of the heavy chain or is fused to the N-terminus or the C-terminus of the light chain.

4. A pharmaceutical composition comprising a physiologically acceptable excipient, diluent, or carrier, and the Wnt surrogate molecule according to claim 1.

5. The Wnt Surrogate molecule of claim 2, wherein each of the two LRP5/6 binding regions is fused to one of the light chains via a linker moiety.

91. Notably, none of the five claims includes any limitation specifying the amino acid sequences of the claimed Wnt surrogate molecules, or even the Fzd or Lrp5/6 binding regions within those molecules. Moreover, as confirmed by Dr. Kahn, the claims cover molecules that can bind to one or more of Fzds 1-10 and to one or both of Lrp5 and Lrp6. EX1003, ¶¶114-18. As discussed in detail below, each of these five claims potentially encompass a tremendous number of soluble,

tetravalent, multispecific Wnt surrogate molecules. *See infra* §§ IX.A.1, IX.A.2, X.A.1.

D. Prosecution History of the '278 Patent

92. In rendering my opinion, I have also reviewed the prosecution history of the '278 patent. I noticed that the claims originally submitted for examination are substantively similar to the issued claims of the '278 patent. EX1008, 274, 1396. In the Office Action issued on June 13, 2024, the Examiner rejected the then-pending claims as obvious over Garcia US (EX1011) in view of Wu (EX1012). *Id.*, 2973. I understand that Garcia US is a publication of the U.S. patent application corresponding to Garcia (EX1004) and is substantively identical to Garcia (EX1004).

93. In that Office Action, the Examiner contended that Garcia US discloses molecules that “are water soluble; bind with high affinity to both (i) frizzled (Fzd) proteins and (ii) Lrp5/6; and directly activate canonical wnt pathway signaling.” EX1008, 2973. While the rejected claims were not limited to any specific tetravalent format, the Examiner narrowly focused on a “dual variable domain (DVD) format,” stating that Garcia US does not teach this particular format. *Id.* The Examiner then contended that Wu renders this particular format obvious because Wu taught that the “DVD-Ig format bispecific antibody is highly stable and exhibits excellent, IgG-like physicochemical and pharmacokinetic properties.” *Id.*, 2974.

94. Applicant responded that Garcia US teaches “bivalent and bispecific” Wnt agonist molecules rather than “tetravalent, multispecific” antibodies. EX1008, 3955-56. Applicant further argued that Garcia did not disclose a Wnt surrogate molecule containing an anti-Lrp5/6 antibody, because the Wnt agonist molecules in Garcia US used “a decoy protein based on DKK1.” *Id.*, 3955.

95. In the final Office Action dated on December 27, 2024, the Examiner again rejected the pending claims as obvious over Garcia US and Wu, contending that the “LRP5/6 binding domain taught by Garcia [US] is NOT limited only to DDK1” and instead encompasses “any domain that binds Lrp5/6 at high affinity,” which would include an anti-Lrp5/6 antibody or antibody fragment. EX1008, 3985.

96. In response to the final Office Action, Applicant contended that “the Wnt surrogates disclosed in Garcia [US] include one Fzd binding region and one LRP binding region, and are bivalent, bispecific molecules comprised of a single polypeptide and having a stoichiometry of 1:1 Fzd binder:LRP5/6 binder.” EX1008, 4005 (emphasis in original). Applicant further argued that “Garcia [US] does not disclose or contemplate any other stoichiometry between Fzd binding regions and LRP5/6 binding regions.” *Id.* According to Applicant, this is different from the claimed “tetravalent, multispecific Wnt surrogate molecule comprising two Fzd binding regions and two Lrp5/6 binding regions, thus having a 2:2 stoichiometry of 2 Fzd binders:2 LRP5/6 binders (2:2 Fzd binders/Lrp5/6 binders).” *Id.* (emphasis in

original). With the response, Applicant submitted a declaration from named-inventor Dr. Yang Li, who also stated that “Garcia [US] **only** described Wnt surrogate molecules having 1:1 Fzd binder: Lrp5/6 binder stoichiometry.” *Id.*, 4168. In his declaration, Dr. Li also asserted that “Garcia’s research group not only continued to teach the original 1:1 Fzd binder:Lrp5/6 binder stoichiometry, but also presented arguments **against** the superiority of the tetravalent format.” *Id.* (citing EX1014).

97. As discussed below, I disagree with the characterization of Garcia US by Applicant and Dr. Li. In my opinion, Garcia US (and Garcia) does disclose a “dimer” molecule consisting of two Fzd binding regions and two Lrp5/6 binding regions. *E.g.*, EX1004, [0056]; *see infra* § XII.A. In addition, contrary to Dr. Li’s assertion, not only does Garcia US (and Garcia) expressly disclose Wnt agonist molecules “multimerized” through “an Fc domain,” *id.*, [0018], Dr. Garcia’s later patent applications continued to disclose Wnt agonist molecules with higher valency, *i.e.*, a Wnt agonist “multimerized” through “an Fc domain.” *E.g.*, EX1014, [0009]; *see infra* § XII.A.

98. In an attempt to distinguish Wu, both Applicant and Dr. Li contended that “the teachings of Wu relate to bivalent molecules that allowed the simultaneous blockade of multiple targets,” which is “very different than the claimed molecules”

that “agonize the canonical Wnt signaling cascade.” EX1008, 4006, 4168 (emphasis in original).

99. The Examiner then allowed the claims but did not provide any reasons for the allowance. EX1008, 4212-14. Based on my review of the prosecution history of the '278 patent, I confirm that the Examiner never rejected any of the pending claims as being inadequately described, not enabled, indefinite, or anticipated.

E. Claim Construction

100. I was asked to opine on the meaning of the following two claim terms: (1) “Wnt surrogate molecule,” which appears in the preamble of claim 1; and (2) “wherein each of the two LRP5/6 binding regions is fused to one of the two Fzd binding regions via a linker moiety,” which is the last “wherein” clause of claim 1. I also considered whether the preamble term “Wnt surrogate molecule” is limiting. Below I provide my analysis of these terms, applying the claim construction principles provided by counsel.

101. I have read all other claim terms as having their ordinary meaning as understood by a POSA as of December 2017.

1. “Wnt Surrogate Molecule”

102. The term “Wnt surrogate molecule” first appears in the preamble of claim 1. In my opinion, the preamble term “Wnt surrogate molecule” means a “molecule that is biologically active in binding to one or more Fzd receptor and to

one or more of LRP5 and LRP6, and in activation of Wnt signaling, i.e., the molecule is a Wnt agonist” as expressly defined in the ’278 patent. This is consistent with Dr. Kahn’s reading of the term and the specification. EX1003, ¶¶66-75. The specification of the ’278 patent states:

Wnt surrogate molecules of the present invention are biologically active in binding to one or more Fzd receptor and to one or more of LRP5 and LRP6, and ***in activation of Wnt signaling***, i.e., the Wnt surrogate molecule is a ***Wnt agonist***.

EX1001, 16:52-56; EX1003, ¶¶67-68.

103. The statement makes it clear that the inventors expressly characterized a “Wnt surrogate molecule” as having these functional properties as the “present invention,” and the inventors therefore acted as lexicographers and assigned the term this specific meaning. EX1003, ¶¶67-68.

104. I agree with Dr. Kahn’s opinion that the preamble term “Wnt surrogate molecule” is limiting, i.e., it limits claim 1 to molecules that are “biologically active in binding to one or more Fzd receptor and to one or more of LRP5 and LRP6, and in activation of Wnt signaling, i.e., the molecule is a Wnt agonist” and excludes others that are not biologically active. EX1003, ¶69. Both the specification and the prosecution history confirm that this preamble is necessary to give life, meaning, and vitality to the claim. *Id.*, ¶¶69-75.

105. As discussed above, the '278 patent defines its alleged “invention” as a “Wnt agonist,” and it repeatedly emphasizes that the invention is directed to “Wnt signaling pathway *agonists*.” *E.g.*, EX1001, Abstract; *see also id.*, 1:34-35 (the “present invention relates generally to *Wnt signaling pathway agonist molecules*”); 16:55-56 (“the Wnt surrogate molecule *is a Wnt agonist*”). As Dr. Kahn summarized, every example where candidate molecules were evaluated invariably focuses on their ability to activate the Wnt signaling pathway. *Id.*, cols. 155-161 (Examples 2, 3, 5-11, 13-18 (“activate” or “activated” Wnt signaling)); EX1003, ¶¶20-36, 72. The specification thus demonstrates that the named inventors regarded these “biologically active” “agonist” functional properties to be the important characteristics of the claimed molecules.

106. I also agree with Dr. Kahn’s opinion that the prosecution history of the '278 patent supports the limiting nature of this preamble term. EX1003, ¶¶73-74. During prosecution, Applicant repeatedly relied on the preamble to overcome a prior art rejection based on Wu. *See supra* § VIII.D. For example, Applicant argued for “an important biological distinction between the molecules of Wu and those presently claimed.” EX1008, 4006. Applicant emphasized that Wu related to molecules “that allow the simultaneous blockade of multiple targets,” “which is very different than the claimed molecules” that “agonize the canonical Wnt signaling cascade.” *Id.* (emphasis in original). Applicant further characterized its alleged

invention as a “Wnt agonist molecule capable of agonizing a Wnt signaling pathway in cells.” *Id.* (emphasis in original). Consistent with these arguments, inventor Li asserted in a sworn declaration that there is an “important biological distinction” between Wu’s molecules and the claimed agonist molecules. The former resulted in a “blockade of multiple targets,” while the latter “agonize” Wnt signaling. EX1008, 4168 (emphasis in original). The Examiner allowed the pending claims in response to these arguments. *Id.*, 4212-14. Thus, I agree with Dr. Kahn that by successfully distinguishing prior-art molecules in Wu based on the preamble term, Applicant made it clear that the preamble term limits the scope of claim 1. EX1003, ¶¶73-75.

107. In view of the intrinsic evidence and consistent with Dr. Kahn’s opinion, I adopt the express definition of a “molecule that is biologically active in binding to one or more Fzd receptor and to one or more of LRP5 and LRP6, and in activation of Wnt signaling, i.e., the molecule is a Wnt agonist” as the meaning of the term “Wnt surrogate molecule” and treat this preamble term as limiting in rendering my opinions herein. EX1003, ¶¶66-75.

2. “Wherein Each of the Two LRP5/6 Binding Region Is Fused to One of the Two Fzd Binding Regions via a Linker Moiety”

108. The last “wherein” clause of claim 1 recites: “wherein each of the two LRP5/6 binding regions is *fused to one of the two Fzd binding regions **via a linker moiety***.” EX1001, cl. 1 (emphasis added). In my opinion, this “wherein” clause

means “each of the two LRP5/6 binding regions is *connected directly via a linker moiety* to one and only one Fzd binding region.”

109. “*fused . . . via a linker moiety*”: The term “fused” is not expressly defined in the specification. In my opinion, a POSA would have understood that being “fused . . . via a linker moiety” in claim 1 requires being connected directly via the linker moiety.

110. Throughout the specification, the term “fused” is consistently used to connote direct connections, rather than indirect connections mediated by features such as disulfide bonds that are present within or between the polypeptide chains of Wnt surrogate molecules. The specification’s characterization of various formats is illustrative. For example, Figure 1A of the specification depicts four formats, which are reproduced and annotated below. Referring to these formats, the specification states that “the Nab binder can be *fused* to any of the 4 available termini” and distinguishes the four formats based on how different parts are directly connected to each specific terminus: “the Nab binder can be *fused* to the N-terminus of the IgG light chain” (upper left), the “N-terminus of the IgG heavy chain” (upper right), the C-terminus of the heavy chain (lower left), and the C-terminus of the light chain (lower right). EX1001, 150:37-44.

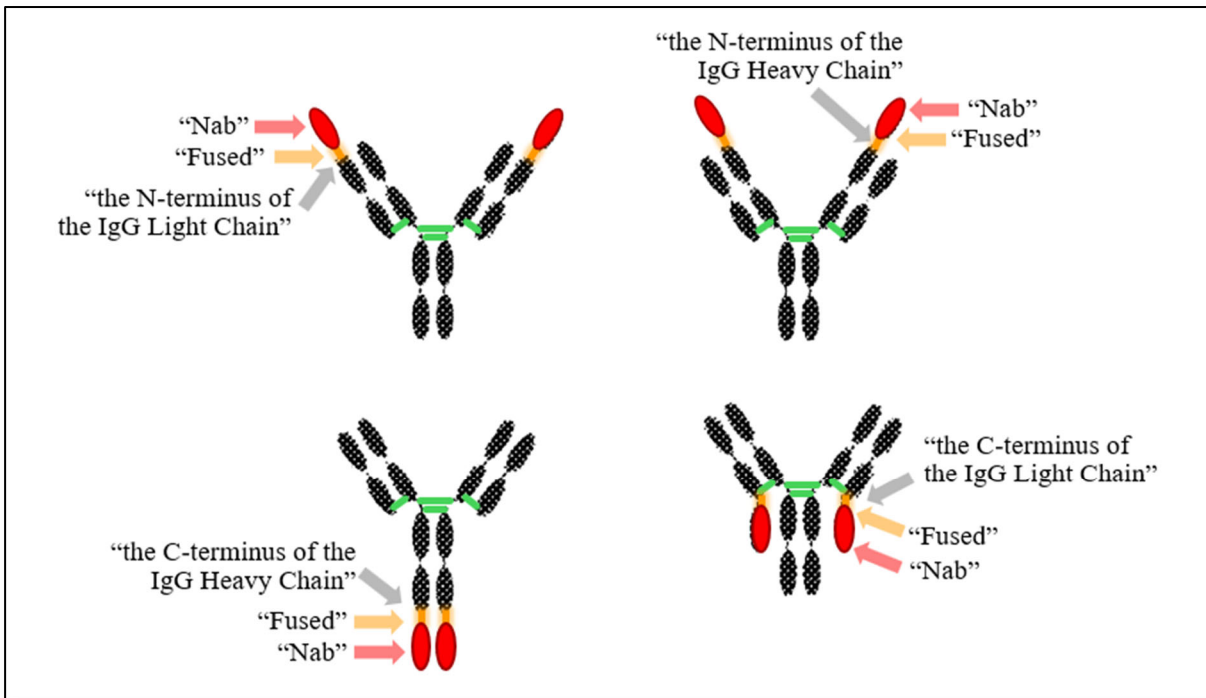


Figure 7. Annotated Figure 1A of the '278 patent

111. In my opinion, reading the term “fused . . . via a linker moiety” in claim 1 to encompass indirect connections (e.g., through interchain disulfide bonds) would be inconsistent with the specification. As shown above, the Nab fragment in each of the four depicted formats is *indirectly* connected, via the linker, interchain disulfide bonds, and the heavy and light chains themselves, to (i) both the IgG heavy and light chains (ii) both the C-terminal and N-terminal ends. In other words, the Nab fragments are indirectly connected to all four termini. If the term “fused” as used in claim 1 and the specification were to encompass indirect connections, distinguishing these four formats based on the Nab fragment being “fused” to a specific terminus becomes impossible and the specification’s characterization and

distinguishing of these formats likewise become incomprehensible. *See also infra* § XI.B.

112. The specification's characterization of the format depicted in Figure 1B again confirms that the term "fused" means a direct connection. Referring to that format, the specification explains that "one Fab binder is first reformatted to a full IgG format" (shown in black and blue) while the "second Fab binder" (shown in white and red) "can be fused to the N-terminus of the IgG." EX1001, 150:62-64. The specification further states that the "two HC can be fused together with a linker in between" but the "LCs can be fused or unfused." *Id.*, 150:64-65. If the term "fused" in this sentence permitted indirect connections, the term would become indistinguishable from "unfused" and lose any significance because the LCs would be fused to one another, directly or indirectly, in either case.

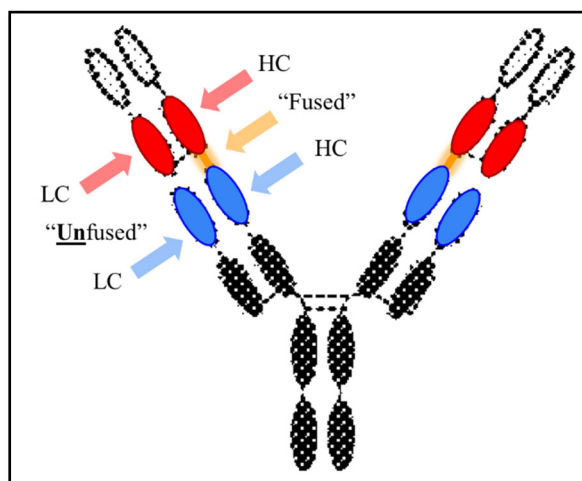


Figure 8. Annotated Figure 1B of the '278 patent

113. For at least these reasons, the term “fused . . . via a linker moiety” in claim 1 encompasses only direct connections and therefore means “connected directly via a linker moiety.”

114. “one of the two *Fzd binding regions*”: A POSA would have understood that claim 1 requires that each of the two LRP5/6 binding regions is fused to *one and only one* Fzd binding region, not both Fzd binding regions. Both the claim language and the specification support this understanding.

115. Claim 1 expressly uses the restrictive phrase, “one of the two,” as opposed to nonrestrictive phrases such as one or both or even a generic “a” or “an.” By specifically choosing the claimed phrase over nonrestrictive phrases, claim 1 makes it clear that a one-to-one connection is required: each Lrp5/6 binding region is directly connected, via a linker moiety, to one and only one Fzd binding region, rather than to both Fzd binding regions. Permitting a Lrp5/6 binding region to be directly connected to two Fzd binding regions would effectively make the term “one of the two” meaningless.

116. Similar phrases used in other claims also support this reading. Claim 2 recites that “the Fzd binding regions comprise a full immunoglobulin G (IgG), comprising two light chains and two heavy chains” and “the LRP5/6 binding regions comprise a VHH.” EX1001, cl. 2. Claim 5, which depends from claim 2, recites that “each of the two LRP5/6 binding regions is fused to *one of the light chains* via

a linker moiety.” *Id.*, cl. 5. A POSA would have understood that “**one** of the light chains” as recited in claim 5 means **one and only one** light chain, which aligns with the formats shown in Figure 1A. Likewise, a POSA would have understood that claim 5 does not encompass molecules in which each VHH is connected to both light chains. Indeed, the ’278 patent depicts no molecules in which each VHH is connected to both light chains.

117. The specification reinforces this reading in two ways. *First*, the specification consistently uses nonrestrictive phrases like “one or more” to denote multiple options, whereas it uses the restrictive phrase “one of” to denote a singular option. *Compare* EX1001, 20:65-67 (“one of the binding regions is a VHH or sdAb and the other is an scFv”), *with id.*, 21:36-38 (“any of these formats may comprise one or more scFvs in place of one or more VHH or sdAb”). Consistent with this, a POSA would have understood that had claim 1 been written to allow each of the two Lrp5/6 binding regions to be fused to more than one Fzd binding region, it would not have used the restrictive phrase “one of the two.”

118. *Second*, the tetravalent, multispecific molecules tested in the specification confirm that “one of the two” means “one and only one.” Specifically, all of the molecules evaluated in the Examples include a linear peptide linker that directly connects one of the two Fzd binding regions to one of the two Lrp5/6 binding regions. *See, e.g.*, EX1001, Figure 1. The ’278 patent does not depict, let alone

evaluate, any molecules in which one of the two Lrp5/6 binding regions is directly connected to both Fzd binding regions via a linker moiety.

119. For at least the reasons discussed above, a POSA would have understood that the last “wherein” clause of claim 1 means “wherein each of the two LRP5/6 binding regions is connected directly via a linker moiety to one and only one Fzd binding region.” I have also applied that meaning in rendering my opinions.³

IX. CLAIMS 1-5 LACK WRITTEN DESCRIPTION

A. Claim 1 Lacks Written Description

1. Claim 1 Is Exceedingly Broad in Scope

120. Claim 1 is directed to a genus of tetravalent, multispecific Wnt surrogate molecules that comprise two Fzd binding regions, two Lrp5/6 binding regions. According to claim 1, each of these four Fzd and Lrp5/6 binding regions comprises “an antibody or antigen binding fragment of the antibody.” Claim 1 adds no restriction on the specific epitope, binding affinity, or amino acid sequence for

³ As discussed below, to the extent that the term is construed more broadly (e.g., allowing indirect connections or binding to one or both Fzd binding regions), it leads to additional reasons for the challenged claims to lack written description, lack enablement, and be indefinite. *See infra* §§ IX.A.7, X.A.5, XI.B.

any of the Fzd or Lrp5/6 binding regions, each of which can broadly comprise either an antibody or antigen-binding fragment of the antibody.

121. The only claim element that seemingly limits the structure of the claimed tetravalent, multispecific Wnt surrogate molecules is the last wherein clause, namely, that “each of the two LRP5/6 binding regions is fused to one of the two Fzd binding regions via a linker moiety.” But this clause also imposes no meaningful structural limitation for composition, length, or properties. Instead, the specification expressly states that the claimed “linker moiety” can essentially be of any type, length, or flexibility. According to the specification, the claimed linker moiety encompasses, “but [is] not limited to,” polypeptide and non-peptidic linkers, rigid and flexible linkers, and any length without limitation. EX1001, 17:49-54, 116:40-65.

122. Without any meaningful structural limitations, it is difficult to contemplate fully or articulate the extensive breadth of claim 1. Nevertheless, to conceptualize how a POSA would have viewed the scope of claim 1, I calculated the number of tetravalent, multispecific topologies and formats that are encompassed by claim 1 based on the disclosures of the '278 patent. I use the term “topology” to refer to the spatial arrangement of the claimed components: Lrp5/6 binding regions, Fzd binding regions, and linker moieties, and I use the term “format” to refer to the types of antibody-derived segments and linkers as arranged. As explained below,

my conservative calculation, which does not even account for the amino acid variations available for each format, reveals that claim 1 encompasses at least **130 million** distinct tetravalent, multispecific formats. Accordingly, a POSA would have concluded that the scope of claim 1 is exceedingly broad.

a. Claim 1 Encompasses More Than 130 Million Tetravalent Formats

123. “Wnt Surrogate Molecule” Topologies: As shown in the figure below, I identified 21 possible tetravalent topologies that correspond to the genus of tetravalent molecules recited in claim 1. I use the term “topology” to refer to the spatial arrangement of the claimed components: Lrp5/6 binding regions (red ball), Fzd binding regions (blue ball), and linker moieties (orange line) each directly connecting one Lrp binding region to one Fzd binding region. In this figure, each topology is drawn in the orientation from the N-terminus to the C-terminus. I treat connections via N-terminus and connections via C-terminus differently, as the orientation of the binding regions arrangement may affect the function of the Wnt surrogate molecules. EX1017, 21, Fig. 2. The '278 patent also recognizes this distinction. For example, Figure 1A of the '278 patent depicts four different formats, and the specification distinguishes the format in which the Nab binder is connected to “the N-terminus of the IgG light chain” with the format in which the Nab binder is connected to “C-terminus of [light chain]”. EX1001, 150:32-44. As another example, in Figure 13D of the '278 patent, the molecules “26:Fc:17SB9” and

“17SB9:Fc:26” have the same binding regions arranged in opposite N-C orientations. The specification treats them as different molecules, describing them as having binding regions “arranged in different tandem formats or on different ends of the Fc fragment.” *Id.*, 158:64-159:3.

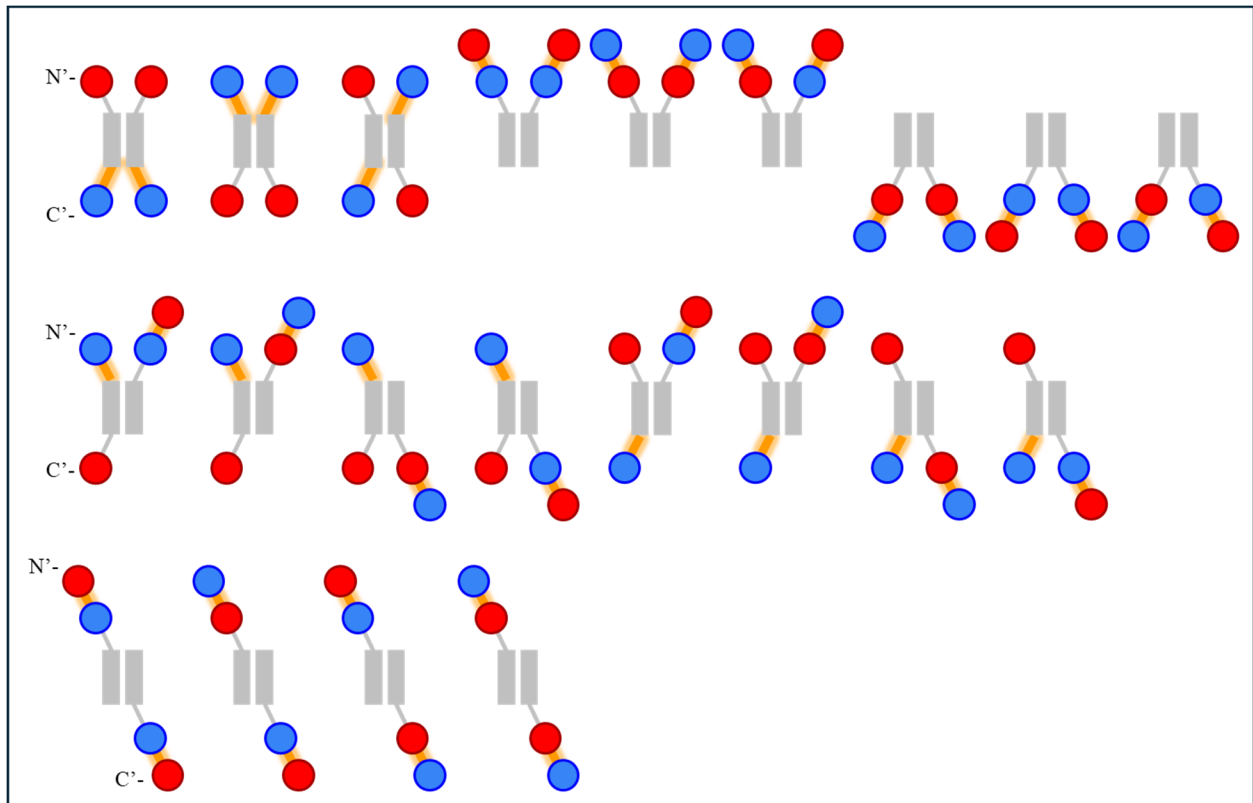


Figure 9. Possible Tetravalent Topologies

124. In each topology, I used grey blocks to represent constant domains that the specification explains are “necessary” to hold different polypeptide chains together. EX1001, 124:5-13 (antibody variable domains can be “fused to immunoglobulin constant domain sequences” that are “necessary for light chain bonding”), 17:55-18:25 (discussing “disulfide bonds, and/or noncovalent

interactions” and “knob-into-hole” modifications to facilitate “heterodimerization of the heavy chains”). I treated arrangements where constant domains are differently located among Fzd and Lrp binding regions as different topologies because the specification does so. For example, the specification separately groups formats in which Fc regions are placed at the end of both Fzd and Lrp binding regions as Figure 1A and those in which Fc regions are placed between Fzd and Lrp binding regions as Figure 1C. *Compare* EX1001, 18:48-67 (Figure 1A), *with id.*, 20:62-21:37 (Figure 1C). In other words, the specification distinguishes arrangements based on where these constant domains are placed within each format, e.g., at the end of both Fzd and Lrp binding regions (as those shown in the last six topologies in the top row in **Figure 9**) or between Fzd and Lrp binding regions (as those shown in the first three topologies in the top row and those in the bottom two rows in **Figure 9**).

125. “Antibody or Antigen-Binding Fragment”: Each generic topology can include multiple, distinct types of antibody-derived segments and linkers. Thus, I considered how many combinations of binding region types are available for each tetravalent topology. As discussed above, claim 1 allows each of the four Fzd and Lrp5/6 binding regions to comprise “an antibody or antigen-binding fragment of the antibody.” EX1001, cl. 1. The specification in turn defines an “antibody” as follow:

As used herein, the term encompasses not only intact polyclonal or monoclonal antibodies, but also *fragments thereof (such as dAb, Fab, Fab', F(ab')₂, Fv), single*

chain (scFv), VHH or sdAb, synthetic variants thereof, naturally occurring variants, fusion proteins comprising an antibody or an antigen-binding fragment thereof, humanized antibodies, chimeric antibodies, and any other modified configuration of the immunoglobulin molecule that comprises an antigen-binding site or fragment (epitope recognition site) of the required specificity.

Id., 11:25-38.

126. Among the listed types of antigen-binding fragments, a VHH fragment contains only a single heavy chain variable domain, meaning that it can be connected to another binding region through its heavy chain only. In contrast, the other four fragments (Fab, Fab', Fv, scFv) are made of two binding domains, one from the heavy chain and the other from the light chain. Thus, when any of the claimed binding regions comprises one of these four antigen-binding fragment types, the binding region can be “fused . . . via a linker moiety” either through its heavy chain or its light chain. Notably, the specification explicitly recognizes being fused via the heavy chain versus the light chain as two different structural options. *See, e.g.*, EX1001, 150:32-44 (a Nab binder is connected to “the N-terminus of the IgG light chain” (“NL”) or the “N-terminus of the IgG heavy chain” (“NH”)). Overall, accounting for the two connectivity options for Fab, Fab', Fv, and scFv, and the single connectivity option for VHH, these five antigen-binding fragment types give rise to nine distinct options for each of the four Fzd and Lrp5/6 binding regions.

127. For my calculation, I conservatively assumed that each of the four Fzd and Lrp5/6 binding regions can independently be chosen from these nine options, even though the term “antibody” is defined to encompass many more options, including, e.g., “synthetic variants thereof.” EX1001, 11:33. With that, I arrived at a total of **6,531** different binding region type combinations for the four claimed binding regions: 9 options for the first Fzd binding region $\times$ 9 options for the second Fzd binding region $\times$ 9 options for the first Lrp5/6 binding region $\times$ 9 options for the second Lrp5/6 binding region.

128. This number represents the possible combinations for *each* topology. Accordingly, for all 21 tetravalent topologies within the claim scope, there are at least **137,781** possible different tetravalent formats: 6,531 binding region combinations for each tetravalent topology $\times$ 21 possible tetravalent topologies.

129. Linker Moiety: This number does not yet account for the diversity of the claimed “linker moiety.” For each of the 137,781 different tetravalent formats, two linker moieties are required by claim 1, each connecting one Lrp5/6 binding region to one Fzd binding region.

130. As discussed above, the specification does not meaningfully limit the scope of linker moieties. Instead, the specification broadly distinguishes two types of linker moieties: “a polypeptide linker, or a non-peptidic linker.” EX1001, 116:46-48. For peptide linkers, the specification discloses that the length of the peptide

linker can range from “about 1” to “30 or more” amino acids, and can have every intermediate length “less than about 100 angstroms, less than about 90 angstroms, less than about 80 angstroms, less than about 70 angstroms, less than about 60 angstroms, or less than about 50 angstroms.” *Id.*, 116:52-64. In any event, for simplicity, I conservatively assumed 31 options for each linker, including 30 different peptide lengths plus one non-peptidic linker.

131. Accounting for the linker moiety options for each of the two required linkers, claim 1 encompasses at least **132,407,541** possible tetravalent formats: 137,781 tetravalent formats $\times$ 31 options for the first linker moiety $\times$ 31 options for the second linker moiety.

132. Accordingly, a POSA would have concluded that the scope of claim 1 is exceedingly broad.

b. My Calculation of Tetravalent Formats Understates the True Scope of Claim 1

133. It is important to note that my calculation is conservative in many ways and therefore significantly underestimates the number of tetravalent formats encompassed by claim 1.

134. As noted above, I assumed only 31 options for each linker moiety (orange line) even though both claim 1 and the specification do not limit the claimed linker moieties by type, length, or flexibility. Even for a single linker moiety made of 5 amino acids, there are 3,200,000 possible different amino acid sequences (= 20

amino acids per each position, which corresponds to 20^5 options), illustrating how my assumption of 31 options for each linker is extremely conservative.

135. I also limited my calculation to 9 different binding region type options for each binding region (red or blue ball), even though both claim 1 and the specification encompass many more types, for example, “synthetic variants thereof,” “fusion proteins,” and “any other modified configuration.” EX1001, 11:33-36. Each of these categories encompasses a tremendous number of binding fragment types. It is virtually impossible to calculate the number of tetravalent formats encompassed by claim 1, if I were to account for the possibilities set forth in the text of the ’278 patent.

136. Furthermore, I did not separately calculate the number of possible constant domains (grey blocks) that are used to hold polypeptide chains together. As discussed above, the specification recognizes that domains such as constant regions, which are part of “antibody or antigen-binding fragment,” are “necessary” for light or heavy chain pairing. *See, e.g.*, EX1001, 124:5-13; 11:25-38 (“antibody” includes “any other modified configuration of the immunoglobulin molecule”). The specification identifies different types of constant regions, including those derived from “different classes of antibodies including IgA (which includes subclasses IgA1 and IgA2), IgD, IgE, IgG (which includes subclasses IgG1, IgG2, IgG3, and IgG4), and IgM.” *Id.*, 122:13-19. The specification explains that these constant regions

may be used in whole or in part and further modified with features such as “knob-into-hole” to promote heterodimerization of polypeptide chains of certain Ig isotypes. *Id.*, 18:6-25.

137. Accounting for all of these various options would exponentially increase the number of possible tetravalent formats encompassed by claim 1 and reinforce my conclusion that a POSA would also have concluded that the scope of claim 1 is exceedingly broad.

* * *

138. In sum, my conservative calculation produced a precise number: **132,407,541** possible tetravalent formats encompassed by claim 1. It must be noted that this total accounts only for structural and topological format variability; it does not begin to address the astronomical sequence-level diversity inherent in the individual antigen-binding regions themselves. Consequently, this number significantly underestimates the actual scope of claim 1, as the true number of all possible tetravalent constructs—once both format and sequence variability are considered—is effectively incalculable. Given the magnitude of these combinatorial possibilities, the only possible conclusion that a POSA would have drawn is that the scope of claim 1 is exceedingly broad.

2. Claim 1 Is Broad in Many Other Ways, Including Fzd/Lrp Binding Combinations and Unknowable Amino Acid Sequence Options

139. As discussed above, I calculated the number of tetravalent formats encompassed by claim 1 to illustrate the exceedingly broad scope of claim 1. But the broad scope of claim 1 can be illustrated in several other ways, including the wide variety of targets and amino acid sequence variability it encompasses.

140. *Targets*: Claim 1 recites that each Lrp5/6 binding region specifically binds to Lrp5 “and/or” Lrp6. Thus, there are three target options for each Lrp5/6 binding region: Lrp5, Lrp6, or both.

141. Claim 1 also recites that each claimed Wnt surrogate molecule comprises two Fzd binding regions that specifically bind to two Fzd receptors. As explained by Dr. Kahn, there were 10 different Fzd receptors known in the art. EX1063, 1, 3; EX1003, ¶82. Yet, claim 1 does not limit to which Fzd(s) the claimed Fzd binding region specifically binds. Instead, the specification expressly allows each Fzd binding region to bind one or more Fzd receptors. EX1003, ¶¶113-15. Specifically, the specification states that each Fzd binding region can cross-react with “one or more” or “two or more” of Fzds 1-10. EX1001, 2:31-46. Binding a single Fzd means that there are 10 target options, and binding any two Fzds means that there are 45 target options. The specification also calls out 8 different combinations of three or more Fzds that each Fzd binding region can cross-react

with. *Id.* Just based on the specification, one can identify a total of 63 binding possibilities per Fzd binding region ($10 + 45 + 8 = 63$).⁴

142. Collectively, each tetravalent molecule can bind to one of at least **35,721** target combinations: 63 target options for the first Fzd binding region $\times$ 63 target options for the second Fzd binding region $\times$ 3 target options for the first Lrp5/6 binding region $\times$ 3 target options for the second Lrp5/6 binding region. Stated differently, claim 1 encompasses more than 35,000 possible target combinations for each tetravalent format. This calculation is confirmed by Dr. Kahn. EX1003, ¶¶113-18.

143. This conservative calculation underestimates the number of potential target combinations because, as discussed above (*see supra* § VII.B) each Fzd and Lrp5/6 receptor may present multiple epitopes that the Fzd and Lrp5/6 binding regions can target. *See* EX1027, 2. If these different Fzd and Lrp5/6 epitopes are

⁴ For example, a tetravalent molecule comprising two Fzd binding regions, each of which cross-reacts with Fzd1, Fzd2, and Fzd7, would bind to two Fzd molecules, each selected from Fzd1, Fzd2, and Fzd7. If the Fzd binding region reacts with Fzd1 only, however, the tetravalent molecule would still bind to two Fzd molecules, but both are Fzd1. EX1003, ¶115.

considered, the number of potential target combinations would increase exponentially.

144. Amino Acid Sequences: As discussed above, claim 1 imposes no limitation on the specific epitope, binding affinity, or amino acid sequence of any of the four binding regions. Each region is defined solely by its function—binding to Fzd or Lrp5/6—rather than by its sequence. This stands in stark contrast to Patent Owner’s related U.S. Patent No. 11,773,171, in which the claimed Fzd and Lrp5/6 binding regions are defined by the CDR amino acid sequences. EX1091, cl. 1. Although the ’278 patent lists exemplary CDR amino acid sequences for the Fzd and Lrp5/6 binding regions (EX1001, Tables 1A & 2A), claim 1 of the ’278 patent is not limited in any way to any of these listed amino acid sequences.

145. A POSA would have concluded that the exemplary anti-Fzd or Lrp5/6 antibody sequences disclosed in the ’278 patent are only a fraction of the total number of antibody sequences potentially capable of binding Fzd or Lrp5/6. As I explained above, antibody biology is highly unpredictable. *See supra* § VII.B. Even minor changes in the amino acid sequence of the variable domains, particularly in the CDRs, could result in significant and unpredictable changes in antigen binding or affinity. *Id.* Conversely, two very different sequences can bind to the same target. *Id.* Given the extraordinary diversity of antibody sequences a POSA would have

understood that the total number of antibody sequences potentially capable of binding Fzd or Lrp5/6 likely far exceeds what's disclosed in the '278 patent.

146. Notably, the specification of the '278 patent does not explain how the antibody sequences listed in Table 1A and Table 2A were generated. *See generally* EX1001. This is problematic because different antibody generation methods can result in sequences that are not representative of one another. For example, antibody sequences derived from immunization undergo somatic mutation whereas those derived from synthetic library screening do not. Here, there is no indication whether the antibody sequences listed in Table 1A or Table 2A were made from diverse antibody generation methods, which further illustrates the lack of representativeness.

147. It is also important to note that a POSA would not be able to discern any common sequence or structural feature from the '278 patent that correlate with Fzd binding or Lrp5/6 binding function. For Fzd binding, Table 1B of the '278 patent lists a total of 106 different antibody clones with "confirmed" Fzd binding. As shown in the Table below, even for the antibodies that have the same Fzd target specificity (e.g., Fzd1, Fzd2, Fzd7), the amino acid sequences and length of their CDR regions are not identical, indicating that there is no common sequence or structural feature from these sequences that correlates with Fzd binding.

Clone ID	CDRH1	CDRH2	CDRH3	CDRL1	CDRL2	CDRL3
	1 10	1 10	1 10	1 10	1 7	1 10
001S-E02	GSISGNNYYWG	GSIFY-TGGTYYN	CAR-----VMLITDAFDIW	RSSQSLHSNGYNYLD	LGSNRAS	CMQGTG--WPYTF
001S-G02	GAISGTSYFWG	GSIIY-TGNTYYN	CAR-----IGIAVAAPVDHW	RASQS-----VGTYLT	DASNRAT	CMQATQ--FPLTF
001S-H02	GSISSSSYWG	GYIYY-SGSTYYN	CAR-----ATYGGDAFDIW	TRSSSNI-GAGYDVH-	GNSIRPS	CGTWDSSLSAWVF
001S-B03	ASEFG--HYWT	GEIDH-TGSTNYE	CAR---GGQGGYDWGHYHGLDVW	-SGDK---VGHKYAS	EDSQRPS	CQAWDSSTD-VVF
014S-A01	YTFTS--YYMH	GWVSPSSGNTAYA	CAR-----DEGAGYYYYMDVW	RASQS-----ISSYLN	AASSLQS	CQQSYS--TPLTF
014S-C03	YTFTNN--FMH	GIIZPGGGRTIYA	CAK-----GDYGALDYW	RASQ-----SISSYLN	AASSLQS	CQQSYS--TPLTF
029S-D01	YTFTR--YYIH	GWMNPNSGNTGYA	CAR-----VRFLEEMDVW	RASQ-----SLSSWLA	DASTLQS	CQQAIS--FPLTF
029S-C02	GTFSS--YGIS	GIINPSGGSTSYA	CARGDIVATMGMKVDYYYYMDVW	RASQ-----DISNNLN	GASHLQT	CQQANS--FPVTF
001S-A01	YTFTS--YGIS	GWISAYNGNTNYA	CAR-----ASAWTPYGAFDIW	-SGSSSNIG-SHTVS-	SNYQRPS	CAAWDGSFLGHWVT
001S-H01	GSISSGGYYWS	GYIYY-SGSTYYN	CAR-----HAGFYGLADYFDYW	RSSQSLHSNGYNYLD	LGSKRAS	CMQALQ--IPPTF

Table 1. Alignment of CDR Amino Acid Sequences for Clones Having Confirmed Binding to Fzd1, Fzd2, Fzd7.

148. The lack of common sequence is also observed for Lrp5/6 binding. Table 2B of the '278 patent discloses 24 different antibody clones with “confirmed” Lrp5/6 binding. EX1001, Table 2B. For Lrp5 binding, Table 2B lists only one antibody (008S-D01). *Id.* A POSA would not be able to discern a “common” sequence that correlates with Lrp5 binding ability from a single clone. Nor would a POSA believe that this single antibody is representative of many other undisclosed Lrp5 binding antibodies. For Lrp6 binding, Table 2B provides 7 antibodies for the Lrp6 e1e2 epitope and 16 antibodies for Lrp6 e3e4 epitope. To illustrate the lack of common sequences, I have compared the amino acid sequences of the CDR regions for the Lrp6 e1e2 binding antibodies. As shown in the Table below, both the CDR amino acid sequences and lengths vary across these antibodies. This observation again demonstrates that the CDR amino acid sequences for Lrp5/6 binding are not uniform, and there is no common sequence or structural feature from these sequences that correlates with Lrp5/6 binding.

Clone ID	CDRH1	CDRH2	CDRH3
	1 9	1 10	1 10
001S-F11	RTFSSYAMS	AVIGRSGGIKYA	CATRRPFNSYNTEQSYDSW
009S-G02	SIFSIYAMG	AVITSGGKT-VYA	CYADSRSS--WYDEYLEHW
009S-A03	RTFSVYGVG	AAVSASGGYTWYA	CKAAPRW---GGATA--YW
009S-D03	SIFSDGAMG	AVI-SGGRT-GYA	CNTYPFPIYKKGYP---FW
009S-F03	RTFSSYAMS	AVIGRSGGIKYA	CATRRPFNSYNTEQSYDSW
009S-H03	SIFSINTMG	AVITSGGKT-VYA	CYADSRSS--WYDEYLEHW
009S-A04	RTLSAYDMG	GGIRWSGGTTLYP	CYARTVIGGFGAFFRA--HW

Table 2. Alignment of CDR Amino Acid Sequences for Clones Having Confirmed Binding to Lrp6 e1e2.

149. Moreover, the exemplary CDR amino acid sequences for the Fzd and Lrp5/6 binding regions disclosed in the '278 patent are also not representative of the vast scope of all potential CDR amino acid sequences that confer Fzd and Lrp5/6 binding capabilities. For example, Table 1B of the '278 patent discloses only one antibody each for confirmed Fzd2 binding (003S-E07), Fzd3 binding (030S-F04), and Fzd5 binding (004S-H04). EX1001, Table 1B. A POSA would have concluded that a single antibody is not representative of substantially many more antibodies that could also bind the same Fzd. Similarly, Table 2B of the '278 patent only discloses one antibody (008S-D01) that showed confirmed binding for Lrp5. *Id.*, Table 2B. Moreover, each of the antibodies listed in Table 2B has only a heavy chain, i.e., each binds to its target through a heavy chain only. A POSA would have concluded that these antibodies are not representative of typical antibodies that rely on both heavy and light chains to bind their targets. In addition, the CDR3 domains of these heavy-chain-only antibodies are much longer than those of typical antibodies and often stabilized by additional disulfide bonds. EX1078, 2, Fig. 2. Given the structural distinction, a POSA would not have considered these heavy-chain-only antibodies to be representative of antibodies that have typical CDR3 domains.

150. As such, when accounting for both the diversity of binding targets and the variability in amino acid sequences, even a single tetravalent format gives rise to an extraordinarily large number of tetravalent, multispecific molecules within the scope of claim 1. Combined with the conservative estimate of over 130 million possible tetravalent formats, the overall scope of claim 1 is exceptionally broad.

3. The '278 Patent Fails to Address the Unpredictability for Multivalent, Multispecific Antibody Molecules

151. As of 2017, identifying a multivalent, multispecific molecule capable of modulating a biological pathway of interest required multiple levels of trial-and-error experimentation. This unpredictability stemmed from distinct variables inherent to each biological pathway, including different receptors and ligands involved in the pathway, as well as their varying stoichiometric relationships, their divergent spatial and structural configurations, and their expression profiles such as the location and density of target antigens. EX1017, 21. These variables, both independently and interdependently, dictate the valency, specificity, molecular reach, and conformational flexibility necessary for a multivalent, multispecific molecule to function effectively. *Id.* As a result, there was no “one best format,” and “no single format [was] suitable for all, or even most of, the desired applications.” *Id.*, 1, 21. Instead, even for relatively simple signaling pathways, identifying functional multivalent, multispecific molecules required empirical trial-and-error investigation.

152. As Dr. Kahn explains, the Wnt signaling pathway is particularly complex, involving multiple ligands and receptors interacting simultaneously. EX1003, ¶¶76-100; EX1043, 1; EX1063, 1, 3. Yet, the mechanism of action for Wnt signaling was poorly understood by 2017, and the '278 patent failed to provide sufficient disclosures to bridge the knowledge gap. EX1003, ¶¶76-100, 124-35. As a result, it is my opinion that, without trial-and-error experimentation, a POSA would not have been able to determine, for any particular combination of Fzd and Lrp5/6 binding regions, which of the more than 130 million possible tetravalent formats would yield a functional Wnt surrogate molecule. *Id.*, ¶¶113-35.

153. Wnt Signaling Components: As Dr. Kahn confirms, as of 2017, the mechanism by which each Wnt and non-Wnt ligand engaged specific Fzd and Lrp5/6 molecules to trigger Wnt signaling was poorly understood, and the mechanisms varied from ligand to ligand. EX1003, ¶¶79-100. Notwithstanding this, the specification merely directs a POSA to target one or both of Lrp5 and Lrp6 and one or more of Fzds 1-10. EX1001, 2:2-9, 2:31-46. These disclosures encompass more than 35,000 different Fzd/Lrp target combinations that fall within the scope of claim 1 (*see supra* § IX.A.2). As Dr. Kahn explains, other than a handful of combinations tested in the specification, the specification fails to teach how a POSA could identify other Fzd/Lrp target combinations that could lead to Wnt signaling activation. EX1003, ¶¶113-43. Consequently, a POSA reading the specification would not be

able to identify Wnt surrogate molecules without empirically testing each of these Fzd/Lrp target combinations.

154. Wnt Signaling Stoichiometries: As confirmed by Dr. Kahn, I understand that there was no consensus in 2017 regarding “the stoichiometry of the putative Wnt-FZD-LRP6 (or LRP5) complex.” EX1054, 8; EX1003, ¶¶85-86. But as Dr. Kahn agrees, the ’278 patent provides no guidance on the stoichiometric relationships between Fzd and Lrp molecules necessary to activate Wnt signaling. EX1003, ¶¶128-30. Instead, claim 1 broadly covers tetravalent, multispecific molecules in which (i) two Fzd-binding regions bind to two Fzd receptors and (ii) each Lrp5/6-binding region binds to Lrp5 and/or Lrp6, resulting in five possible stoichiometric combinations. Specifically, if both Lrp-binding regions recognize the same Lrp5 epitope, they must bind two different Lrp5 molecules because each Lrp5 molecule has only one epitope available for one Lrp-binding region. The same applies to Lrp6: if both Lrp-binding regions recognize the same Lrp6 epitope, they must bind two different Lrp6 molecules. In contrast, if the two Lrp-binding regions recognize different epitopes, they may bind two distinct epitopes on the same Lrp5 molecule, the same Lrp6 molecule or on two different Lrp5/6 molecules. Thus, each tetravalent molecule that falls within the scope of claim 1 could engage Fzd and Lrp5/6 molecules in five different stoichiometries: (1) two Fzds and one Lrp5; (2) two Fzds and two Lrp5; (3) two Fzds and one Lrp6; (4) two Fzds and two Lrp6; or

(5) two Fzds, one Lrp5, and one Lrp6. Neither the prior art nor the '278 patent teaches, for any particular tetravalent format and particular combination of Fzd and Lrp5/6 binding regions, which stoichiometries are required to activate Wnt signaling, so a POSA would need to test each possibility empirically.

155. Wnt Signaling Component Expression Profiles and Structures: Dr. Kahn further explained that the expression profiles of Fzd and Lrp5/6 vary across tissues and developmental stages, which would substantially affect the spatial distance between these molecules across tissues and over time. EX1003, ¶¶98-99, 131-33. As a result, the flexibility and reach required for a tetravalent, multispecific molecule must be determined case by case, based on the expression levels of Fzd and Lrp5/6. *See* EX1017, 21. As discussed above, when Fzd and Lrp5/6 are expressed at low levels, their sparse distributions may require a functional Wnt surrogate molecule to have greater flexibility and extended reach to interact effectively with both Fzd and Lrp5/6. By contrast, when Fzd and Lrp5/6 are expressed at high levels, the dense distributions may tolerate, or even favor, more compact formats for functional Wnt surrogate molecules. *See supra* § VII.D.

156. The specification provides no guidance to account for the variability and unpredictability of Wnt agonist activity arising from differing expression profiles of Fzd and Lrp5/6. For example, the specification has no disclosure regarding the expression levels of any of the Fzd and Lrp5/6 receptors in the multiple

different cell lines used in the TOPFlash assays. Although the specification states that the “distance between binding domains” must be “enforced,” EX1001, 116:52-56, there is no meaningful guidance in the specification on how to achieve that requirement. Instead, the specification broadly contemplates the use of virtually any linker (“not limited to any of those disclosed herein”) and merely suggests that a wide range of linker compositions and lengths might be effective, including peptidic or non-peptidic linkers of “less than about 100 angstroms,” whether “rigid” or “flexible.” *Id.*, 17:52-54, 116:52-58.

157. Mirroring this open-ended disclosure, claim 1 broadly recites any “linker moiety” connecting the Fzd binding regions and the Lrp5/6 binding regions. EX1001, cl. 1. Claim 1 does not even impose any structural limitations on how the two Fzd binding regions are connected to one another within the tetravalent molecule. *Id.* Claim 1 is also silent on how the two Lrp5/6 binding regions are connected to one another within the tetravalent molecule. *Id.* Because the requisite information is found neither in the prior art nor the ’278 patent, a POSA would again have to rely on extensive trial-and-error experimentation to identify functional Wnt surrogate configurations capable of accommodating varying levels and types of Fzd and Lrp5/6 expression.

158. Other Wnt Signaling Variables: As explained by Dr. Kahn, I also understand that different Wnt and non-Wnt ligands were known to interact with their

receptors at different epitopes and with different affinities. EX1003, ¶¶82-84, 134-35. But the specification of the '278 patent provides no meaningful guidance on how to account for this substantial variability in epitope targeting or binding affinity across different Wnt systems.

159. With respect to epitopes, the specification recognizes that the claimed Wnt surrogate molecule “specifically bind to two or more different epitopes, e.g., one or more Fzd receptor, and LRP5 and/or LRP6.” EX1001, 17:11-14. But the specification does not teach which epitopes within Fzd or Lrp5/6 correlate with Wnt signaling activation. Indeed, the specification does not even disclose the specific epitopes targeted by any of the tested putative Wnt surrogate molecules. *See id.*, Table 3. As such, a POSA reading the '278 patent would not be able to obtain any insight on which epitope to target for a given Wnt system. EX1003, ¶¶134-35.

160. The specification is similarly deficient with respect to binding affinity. While the specification states that a Wnt surrogate molecule must “specifically” bind Fzd or Lrp5/6, EX1001, 2:1-9, it defines “specific binding” only in broad, qualitative terms—binding “more frequently, more rapidly, with greater duration and/or with greater affinity”—without identifying which of these parameters, or what specific values, are necessary to activate Wnt signaling. *Id.*, 120:66-121:3. The specification also fails to provide quantitative binding data, such as affinity measurements, for the tested putative Wnt surrogate molecules. *See id.*, Table 3. Binding affinity data for

Fzd antibodies and Lrp5/6 antibodies in the prior art provided little help as incorporation of antibodies or antibody fragments into multivalent, multispecific molecule may affect their functional affinity. EX1020, 2. To the extent the specification indicates that the claimed Wnt surrogate molecules bind to Fzd or Lrp5/6 “with a K_D of 50 μ M or lower,” EX1001, 4:39-44, this exceedingly broad range does not provide a POSA with any meaningful guidance. Indeed, a K_D of 50 μ M reflects a very weak antibody-antigen interaction and is generally inconsistent with what a POSA would regard as biologically meaningful antibody binding. The specification provides no explanation why Wnt surrogate molecules with an affinity within this exceedingly broad range would be biologically active in activation of Wnt signaling; nor does the specification provide any direction, in terms of binding affinity, for distinguishing molecules capable of activating the Wnt signaling pathway from those that would not.

161. In sum, in 2017, finding a functional tetravalent, multispecific molecule for a biological system required trial-and-error experimentation. This would have been particularly true for Wnt signaling pathway, which Dr. Kahn explains was known to be complex, variable, and poorly understood. As illustrated above, the '278 patent lacks any meaningful guidance for a POSA to avoid trial-and-error experimentation. In my opinion, the '278 patent at most provides a research plan

for a POSA to find other functional tetravalent, multispecific Wnt surrogate molecules that are undisclosed in the specification.

4. The '278 Patent Does Not Disclose a Representative Number of Species Across the Scope of Claim 1

162. While claim 1 encompasses an exceedingly broad genus of tetravalent, multispecific molecules that function as Wnt surrogates, the specification of the '278 patent discloses only a tiny fraction of molecules within the genus, both in terms of molecular formats and biological targets. In my opinion, these molecules are not representative of other Wnt surrogate molecules that fall within the scope of claim 1.

a. Lack of Representative Tetravalent Topologies

163. As explained above, there are at least 21 possible tetravalent topologies encompassed by claim 1. *See supra* § IX.A.1. In contrast, the specification of the '278 patent discloses only five topologies, which are marked with a red box in **Figure 10** below. The specification of the '278 patent leaves the remaining 16 topologies untested.

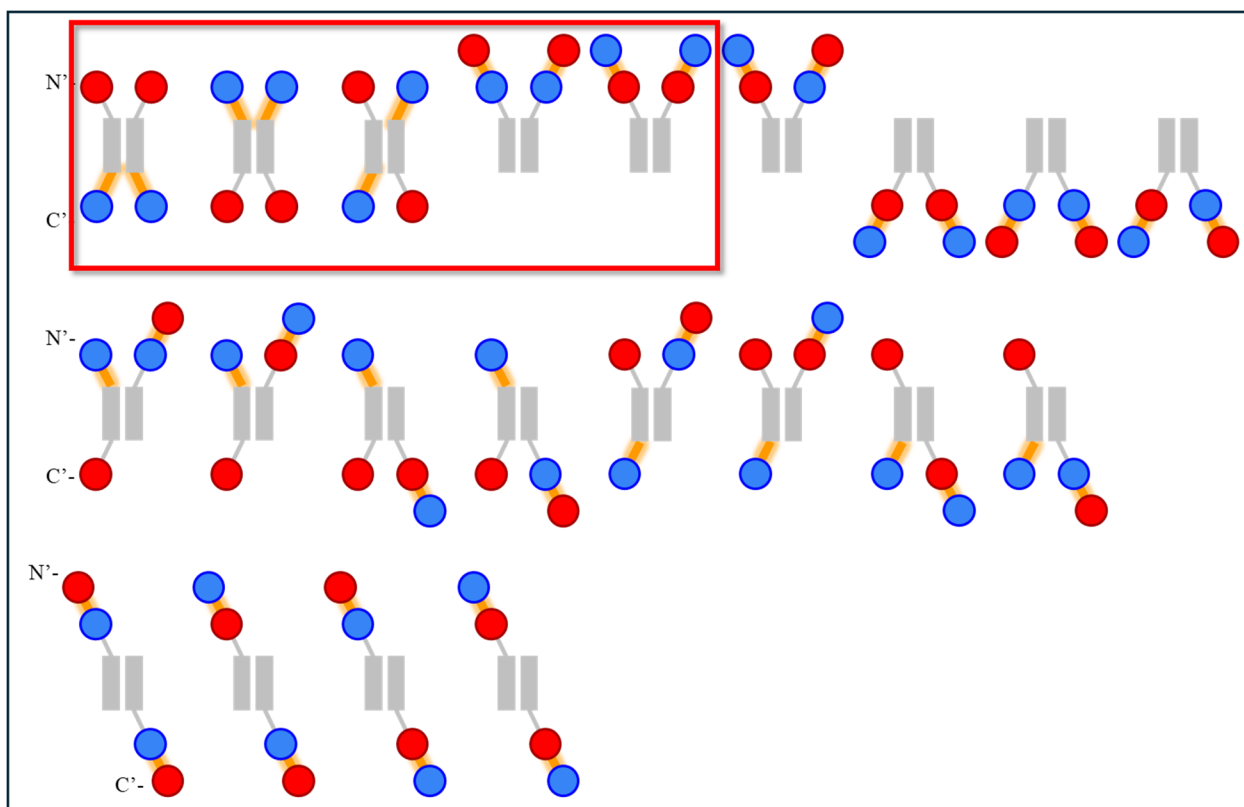


Figure 10. Tested Topologies (Red Box) Among Possible Topologies

Encompassed by Claim 1

164. The five tested topologies differ significantly from the 16 undisclosed topologies and therefore cannot be considered representative of unevaluated topologies within the claimed genus. As an example, for the four topologies shown in the bottom row of **Figure 10**, one set of Fzd and Lrp5/6 binding regions is oriented opposite to the other set. This topological arrangement increases the spatial separation between the two sets of Fzd and Lrp5/6 binding regions, providing a greater capacity to engage sparsely distributed Fzd and Lrp5/6 receptors than any of the five topologies evaluated in the '278 patent. This distinction is significant

because, as Dr. Kahn explains, variations in receptor expression profiles can cause the spatial distance between Fzd and Lrp5/6 receptors to differ substantially across tissues and over time, and the agonist activity in Wnt signaling depends on the simultaneous engagement of multiple receptors. EX1003, ¶¶98-99, 131-33. Thus, differences in topological configuration would be expected to produce unpredictable effects on Wnt signaling activation. A POSA therefore would conclude that the limited set of topologies evaluated in the '278 patent is not representative of other, untested topologies, including those capable of providing different reach and flexibility.

b. Lack of Representative Tetravalent Formats

165. As discussed above, claim 1 encompasses more than 130 million different tetravalent formats. *See supra* § IX.A.1. In my opinion, the small number of specific tetravalent formats evaluated in the specification is not representative of the other 130 million possible tetravalent formats that are encompassed claim 1 but not evaluated in the specification. As illustrated below, the '278 patent discloses and tests only 29 tetravalent formats. These formats are not representative of the diverse landscape of claim 1's tetravalent formats for several reasons.

Topology	Tested Formats															
	 = Nab = 5-AA = Nab	1	 = ScFv = 5-AA = ScFv	2												
	 = Fv = 5-AA = Nab	3	 = Fv = 5-AA = Nab	4	 = Nab = 5-AA = Nab	5	 = ScFv = 5-AA = ScFv	6								
	 = Nab = 5-AA = Nab									7						
	 = Nab = 5-AA = Fv (L)	8	 = Nab = 5-AA = Fv (H)	9	 = Fv = 5-AA = Fv	10	 = Nab = 5-AA = Fab'	11	 = ScFv = 5-AA = ScFv	12	 = ScFv = 10-AA = ScFv	13	 = ScFv = 15-AA = ScFv	14	 = Nab = 5-AA = Nab	15
	 = Nab = 10-AA = Nab	16	 = Nab = 15-AA = Nab	17	 = Fab (L) = 5-AA = Fv	18	 = Fab (L) = 10-AA = Fv	19	 = Fab (H) = 5-AA = Fv	20	 = Fab (H) = 10-AA = Fv	21	 = Fab (H) = 15-AA = Fv	22		
	 = ScFv = 5-AA = ScFv	23	 = ScFv = 10-AA = ScFv	24	 = ScFv = 15-AA = ScFv	25	 = Fab (H) = 5-AA = Fv	26	 = Fab (H) = 10-AA = Fv	27	 = Fab (H) = 15-AA = Fv	28	 = Fab (L) = 5-AA = Fv	29		

Figure 11. Tested Formats in the '278 Patent

166. *First*, there is limited diversity in the types of antigen-binding fragments. Although each of the four Fzd and Lrp5/6 binding regions can independently adopt any one of five fragment types (Fab, Fab', Fv, scFv, VHH/Nab) and different connectivity (e.g., through heavy or light chain), in all 29 evaluated formats, the two Fzd binding regions comprise the same fragment type with the same connectivity, and the two Lrp5/6 binding regions likewise comprise the same type with the same connectivity. Because each fragment type has distinct spatial and binding properties, a POSA would not consider formats with identical fragment types representative of formats in which the two Fzd or two Lrp5/6 binding regions adopt different fragment types.

167. *Second*, there is limited diversity in the arrangement and order of the antigen-binding regions. In all but one (No. 7 in the figure above) of the 29 evaluated formats, the mode and order of the connection between the first Fzd binding region and the first Lrp5/6 binding region is identical to the mode and order of the connection between the second Fzd binding region and the second Lrp5/6 binding region. The '278 patent itself demonstrates that arrangement and orientation can profoundly affect the agonistic activity of Wnt surrogate molecules. *See, e.g.*, EX1001, Figs. 9A, 9C. A POSA would therefore not consider formats with identical connections representative of formats with differing arrangements and orientations.

168. *Third*, all but one (No. 7 in figure above) of the 29 disclosed tetravalent formats are symmetrical, whereas the vast majority of the tetravalent formats encompassed by claim 1 are asymmetrical. *See supra* § IX.A.1. Because fragment type, arrangement, and orientation all impact how tetravalent molecules interact with Fzd and Lrp5/6 receptors, a POSA would not view symmetrical formats as representative of asymmetrical ones.

169. The '278 patent itself demonstrates that one tetravalent format is not representative of another, even for the same pair of Fzd and Lrp5/6 binding region sequences. For example, the '278 patent evaluates four formats in Figures 9A and

9C using the same pair of Fzd and Lrp5/6 binding region sequences.⁵ In these formats, the Lrp5/6 binding regions are connected to the Fzd binding regions in different arrangements and orientations: (1) the N-terminus of the light chain (“NL”); (2) the N-terminus of the heavy chain (“NH”); (3) the C-terminus of the heavy chain (“CH”); and (4) the C-terminus of the light chain (“CL”). As shown in Figure 9A, which uses the same sequence pair (R2M3-26) for all four formats evaluated, three formats (NL, NH, and CH) produced responses in a TOPFlash assay, whereas the CL format failed to do so. EX1001, Fig. 9A. But the ’278 patent provides no explanation or other guidance for why the CL format failed despite using the same Fzd and Lrp5/6 sequences as the other three formats. A similar pattern was observed with another sequence pair (18R5-26) in Figure 9C. *Id.*, Fig. 9C.

170. These observations would have made clear to a POSA that, for any given pair of Fzd and Lrp5/6 binding region sequences, the ability to activate Wnt signaling is highly unpredictable across different tetravalent formats. Thus, a POSA would not consider one format to be representative of another, even when the underlying Fzd and Lrp5/6 binding region sequences are identical.

⁵ For clarity, instead of using the black-and-white figures of the ’278 patent, I have used corresponding color figures from one of the provisional applications that was provided to me by counsel. EX1007.

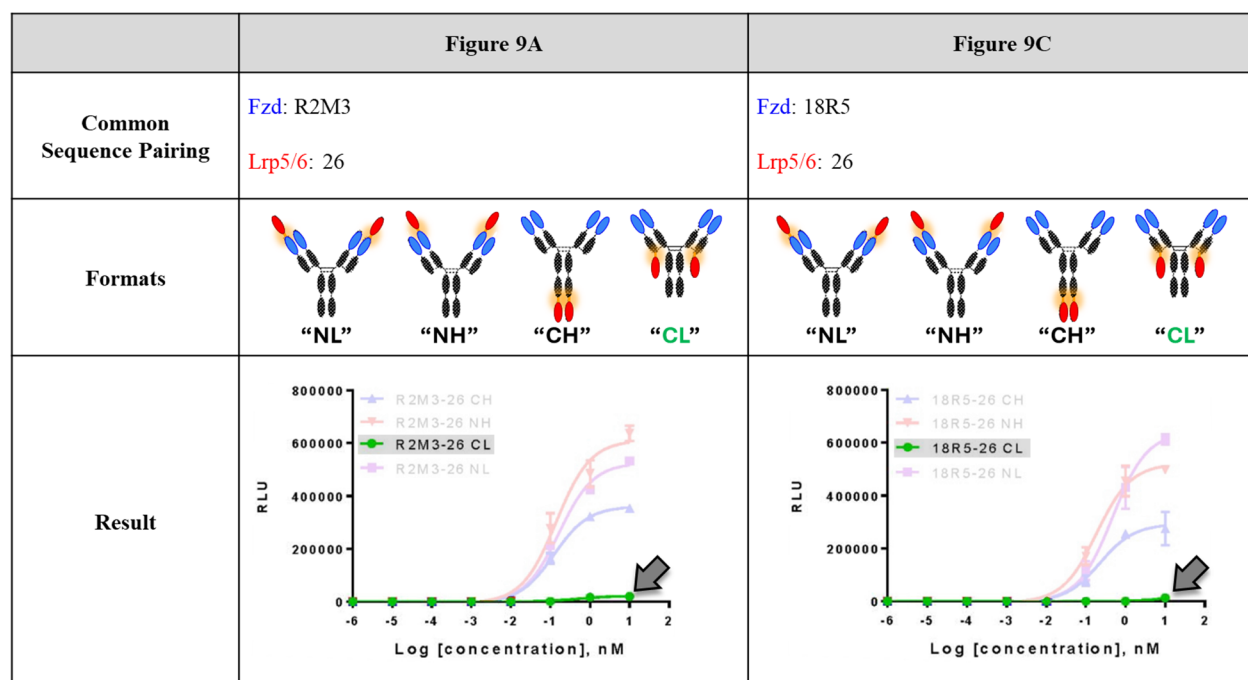


Figure 12. Inactive Tetravalent, Multispecific Molecules (Annotated)

171. I have also reviewed tetravalent, multispecific molecules made and tested after the assumed effective filing date of the '278 patent. Those molecules further confirm my opinion that the specific tetravalent, multispecific molecules disclosed in the patent are not representative of the full scope of claim 1. Specifically, I reviewed a patent publication from one of the named inventors of the '278 patent, Yang Li. EX1081 (“Li”). Figure 11A of Li discloses two sets of tetravalent, multispecific molecules comprising the same pair of anti-Fzd and anti-Lrp5/6 antibody sequences (18R5 and 1115.3, respectively) and compares their ability to activate the Wnt signaling pathway. EX1081, 181-82, Table 6A, Fig. 11A.

172. As illustrated below, the two sets of molecules are identical except for the relative positioning of the Fzd and Lrp5/6 binding regions. In the first set, the

Fzd binding regions are positioned C-terminal relative to the Lrp5/6 binding regions (“L1:5:F1:Fc,” “L1:10:F1:Fc,” “L1:15:F1:Fc”), whereas in the second set, the Fzd binding regions are positioned N-terminal relative to the Lrp5/6 binding regions (“F1:5:L1:Fc,” “F1:10:L1:Fc,” “F1:15:L1:Fc”). EX1081, 187. These molecules were evaluated in a TOPFlash assay under identical conditions. *Id.*, 13, 187. Notably, while the first set of molecules produced responses in this assay, the second set of molecules did not. *Id.*, Fig. 11A. These results again confirm that even for molecules with the same Fzd and Lrp5/6 binding sequences, one tetravalent format cannot be considered representative of another.

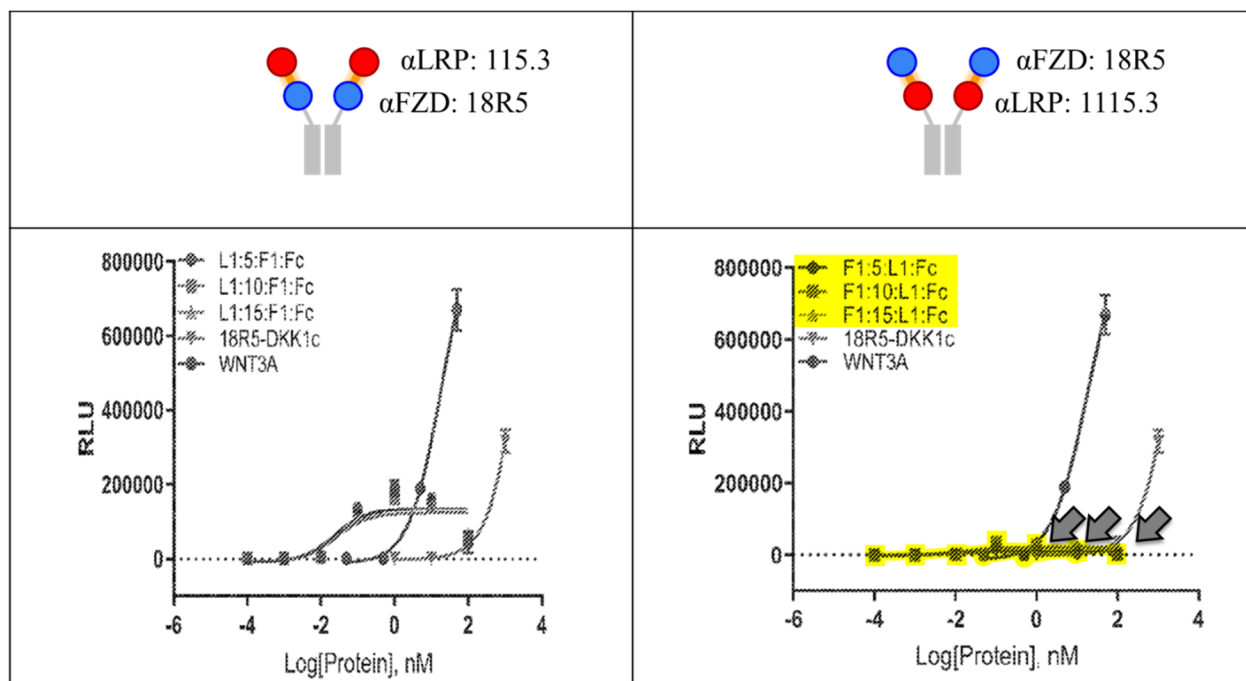


Figure 13. Inactive Tetravalent, Multispecific Molecules (Annotated; Wnt3A and 18R5-DKK1c Are Positive Controls)

173. The tetravalent formats evaluated in the specification are also narrow in terms of linkers. Indeed, all of these formats contain a single class of linkers: peptide linkers consisting exclusively of glycine (G) and serine (S) residues, with lengths of only 5, 10, or 15 amino acids. EX1001, Table 3, Fig. 19. In my opinion, tetravalent molecules containing flexible, G/S-rich linkers of 5-15 amino acids are not representative of molecules containing non-peptidic, rigid, or peptidic linkers of substantially different lengths.

174. The prior art evaluating and comparing different linker types further supports my opinion. For example, DiGiammarino and colleagues compared linkers of different types and lengths, including G-rich linkers and linkers composed of other amino acids in DVD-Ig molecules. EX1024, 2, Table 1. Although the study found that, on average, tetravalent formats with higher target binding affinity possessed longer linkers than those that exhibited lower affinity, it also reported a “surprising” finding that a “hinge” linker and a G-rich linker “have nearly identical linker lengths, but show >4-fold difference” in binding affinity for TNF α . *Id.*, 5. DiGiammarino noted that the G-rich linker was expected to “be the most flexible of linker designs for a given length and provide the greatest degree of freedom,” and the mechanism for the “hinge” linker’s unpredictable success required “[f]uture structural studies.” *Id.* This unpredictability arising from linker composition in the

context of a single target antigen (TNF α) would be expected, if not amplified, in the Wnt surrogate molecules, given the complexity of the Wnt signaling pathways.

175. The unpredictability was also observed within the subset of G/S linkers themselves, where variations in linker length and glycine content altered linker flexibility in non-linear and unexpected ways. For example, van Rosmalen and colleagues demonstrated that the observed increase in linker stiffness with reduced glycine content is “much less pronounced than that predicted by a classical model.” EX1074, 1. van Rosmalen explained that the linker flexibility does not decrease linearly as glycine content is reduced because increased serine content allows the linker to adopt alternative conformations and better accommodate different spatial orientations among binding domains. *Id.*, 7-8.

176. Consistent with this, the prior art also recognized that linkers have unpredictable and substantial effects on the properties of tetravalent molecules: “Small format variations, such as minor changes in linker length or composition or ‘switch’ of domains, can be crucial determinants for functionality.” EX1017, 21. In view of the prior art, a POSA would have concluded that the narrow set of formats with highly similar linkers evaluated in the specification of the ’278 patent is not representative of the full spectrum of other claimed formats with unevaluated linkers.

177. For these reasons, the limited number of tetravalent formats tested in the specification is not representative of the vast majority of other, undisclosed formats covered by claim 1.

c. Lack of Representative Target Specificities

178. The Wnt surrogate molecules evaluated in the specification are not representative of claimed but undisclosed molecules for several other reasons.

179. *First*, every tetravalent molecule evaluated in the specification is limited to bispecific binding. *See* EX1001, Table 3. Claim 1, however, encompasses trispecific and tetraspecific molecules capable of simultaneously binding multiple distinct epitopes on Fzd and/or Lrp5/6. The '278 patent does not present any experimental data demonstrating that such higher-order multispecific molecules are capable of activating Wnt signaling; nor does it offer meaningful guidance on how to design trispecific or tetraspecific molecules that could activate Wnt signaling. A POSA would have recognized that this absence of information is significant, particularly given the understanding in the art that the functionality of multivalent antibody molecules depends critically on how multiple binding domains recognize and engage their targets. Indeed, as the prior art explains, key determinants of activity include whether binding is bivalent, trivalent, or multivalent, and whether interactions with one or more antigens occur simultaneously or in a mutually exclusive fashion. EX1017, 21 (factors determining functionality in a tetravalent,

multispecific molecule include “bivalent, trivalent or multivalent binding to one or both antigens in a simultaneous or mutually exclusive manner”).

180. *Second*, the tetravalent Wnt surrogate molecules evaluated in the '278 patent use a limited set of anti-Fzd antibody sequences that target only a subset of Fzd receptors, whereas claim 1 broadly encompasses molecules in which each Fzd binding region is capable of binding any one or more Fzd receptors. As discussed above, the specification identified at least 63 distinct Fzd combinations to which each Fzd binding region can bind. *See supra* § IX.A.2. However, the '278 patent disclosed only 17 of those 63 target options as having “confirmed binding” activities: 10 individual Fzds, only two of the 45 different two-Fzd combinations (Fzd 5, 8 and Fzd 9, 10), and only 5 of the 8 different three or more-Fzd combination (Fzd 1, 2, 7; Fzd 1, 2, 7, 9; Fzd 1, 2, 5, 7, 8; Fzd 2, 6, 3; and Fzd 1, 2, 7, 5). EX1001, Table 1B. The specification does not disclose binding regions for the remaining 46 of the 63 specifically identified Fzd targets; nor does it teach a POSA how to identify such binding regions other than through making and testing each candidate Fzd binding region individually.

181. Problematically, the '278 patent evaluated even a narrower subset of Fzd combinations as part of tetravalent, multispecific molecules. Indeed, as summarized in Table 3 of the '278 patent, only 14 anti-Fzd antibody sequences were tested as part of tetravalent, multispecific molecules, and those sequences are

reported to bind just eight Fzd combinations: (1) Fzd2; (2) Fzd4; (3) Fzd8; (4) Fzd9; (5) Fzd5 and Fzd8; (6) Fzd1, Fzd2, and Fzd7; (7) Fzd1, Fzd2, Fzd7, and Fzd9; and (8) Fzd1, Fzd2, Fzd5, Fzd7, and Fzd8. EX1001, Tables 1B & 3. Thus, the '278 patent provides no example or evidence that a tetravalent, multispecific molecule binding to any of the remaining 55 expressly recognized Fzd combinations (Fzd3, Fzd6, and Fzd10, for example) can activate Wnt signaling.

182. The manner in which tetravalent, multispecific molecules are evaluated in the specification is also limited. Indeed, the only *in vitro* assay used in the specification is the TOPFlash assay, which, as Dr. Kahn explains, measures responses only in connection with the canonical Wnt signaling pathway. EX1003, ¶¶19, 108-112, 121, 137; EX1001, Examples 2-18. As such, the '278 patent does not test or demonstrate possession of any tetravalent, multispecific molecules capable of activating noncanonical Wnt signaling, even *in vitro*. EX1003, ¶¶19, 121, 137.

183. In my opinion, this narrow disclosure is insufficient to support the full scope of claim 1. As explained by Dr. Kahn, as of 2017, different Fzd receptors were known to play distinct functional roles, with some activating canonical Wnt signaling, others activating noncanonical signaling, and still others capable of activating both. EX1003, ¶¶93-95; EX1077, 4-6. Therefore, a molecule that binds a particular Fzd or Fzd combination and activates canonical Wnt signaling would

not have been understood to be representative of molecules binding different Fzds or Fzd combinations. EX1003, ¶¶113-21, 125-35.

184. The inability to extrapolate across molecules with different Fzd target specificities is confirmed by Li. EX1081. As reproduced below, Li compared two molecules sharing the same tetravalent format: “R2M3-26” and “4SC10-3.” *Id.*, Fig. 5A. The R2M3-26 molecule binds Fzd1, Fzd2, Fzd5, Fzd7, and Fzd8, whereas 4SC10-3 binds only Fzd6. *Id.*, 178. Despite their identical format, R2M3-26 produced responses in a TOPFlash assay, but 4SC10-3 “was **not** able to effectively activate beta-catenin-dependent signaling in 293STF reporter cells.” *Id.* These results further confirm that a Wnt surrogate molecule that binds a particular Fzd or Fzd combination is not representative of other molecules that bind different Fzds or Fzd combinations.

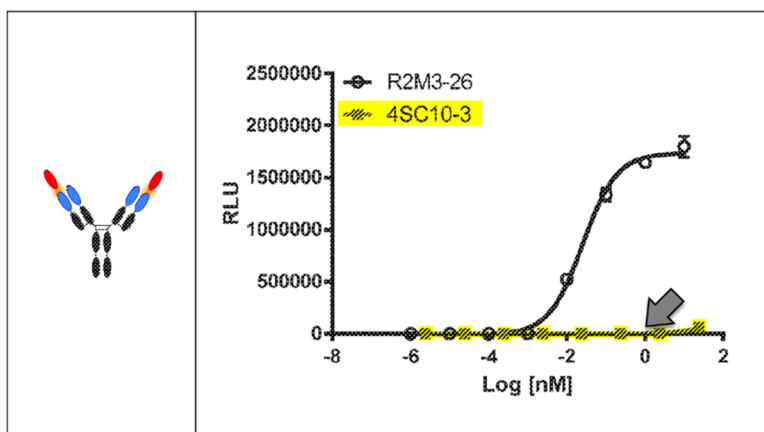


Figure 14. Inactive Tetravalent, Multispecific Molecules (Annotated)

185. For at least the reasons discussed above, the '278 patent discloses only a small and narrow set of tetravalent, multispecific molecules that, in both number and diversity, are not representative of the full scope of claim 1.

5. The '278 Patent Fails to Disclose a Common Structural Feature Correlating to Wnt Signaling Activation

186. As discussed above, the Wnt surrogate molecules encompassed by claim 1 are a combination of multiple functional features: tetravalent, multispecific molecules capable of activating Wnt signaling, which comprise two binding regions for Fzd and two binding regions for Lrp5/6. The only arguable structural limitation in claim 1 is that each of the two Lrp5/6 binding regions is connected directly to one, and only one, Fzd binding region via a “linker moiety.” EX1001, cl. 1. A POSA, however, would have understood that this minimal structural requirement alone is insufficient to confer the activation capability for the claimed “Wnt surrogate molecules.” Indeed, the '278 patent itself demonstrates the absence of any correlation between this generalized structural arrangement and Wnt surrogate activity.

187. In the reproduced figure below, several molecules (R2M3-26, R2M3-32, 18R5-28, 26-17SB9) that possess the claimed structural feature—namely, each of the two Lrp5/6 binding regions is connected directly to one and only one Fzd binding region via a linker moiety—failed to produce responses in the absence of R-

spondin in a TOPFlash assay. EX1001, Figs. 2D, 3D, 6A, 13B.⁶ Dr. Kahn explains that endogenous Wnt and non-Wnt ligands can activate downstream signaling without the aid of a molecular potentiator such as R-spondin. EX1003, ¶¶36, 88; EX1063, 5; EX1093, 1-3. As such, I agree with Dr. Kahn that the inability of these molecules to do so raises serious questions as to whether they can properly be characterized as Wnt “surrogates.” EX1003, ¶¶148-49. The ’278 patent does not provide any explanation for the dependence on R-spondin, and thus fails to teach whether these molecules are biologically active as required by claim 1. EX1001, 16:52-56; *see infra* § XI.A. Indeed, by focusing on TOPFlash responses only in the presence of R-spondin, the specification creates confusion as to what is required to be a Wnt surrogate molecule. *See infra* § XI.A.

⁶ I noticed that Figure 13B of the ’278 patent appears to be an incorrect duplicate of Figure 13E. I was provided with Figure 13B of the underlying provisional application (EX1007), which appears to match the description of that figure in the specification.

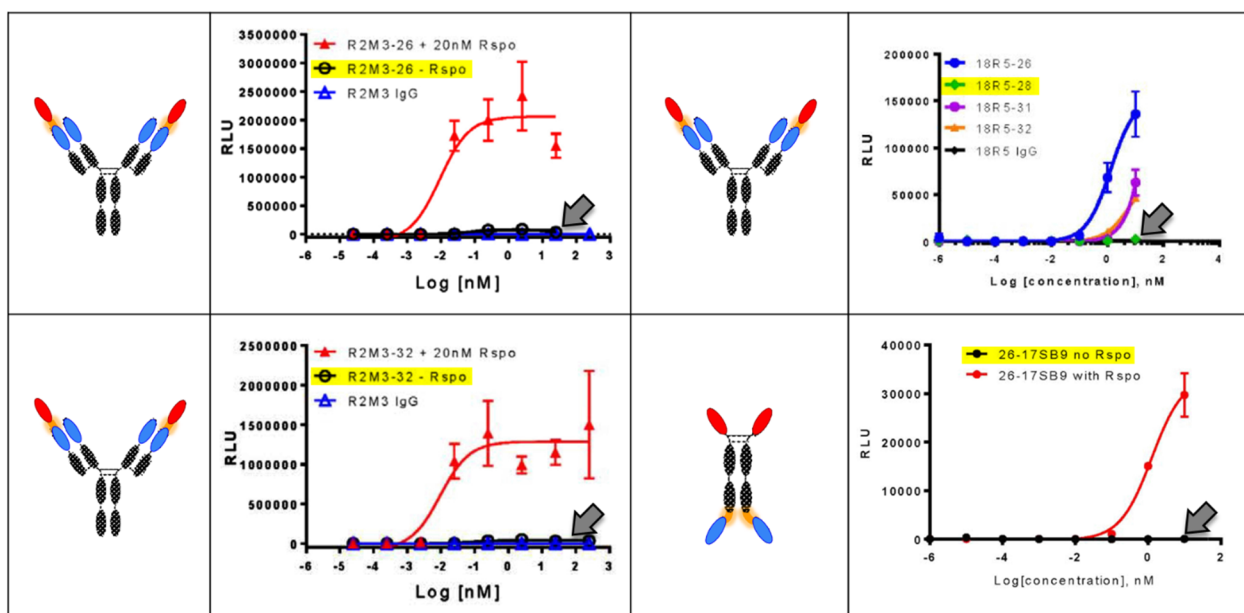


Figure 15. Inactive Tetravalent, Multispecific Molecules (Annotated)

188. Notably, the '278 patent reports that even in the presence of R-spondin, several tetravalent, multispecific molecules that satisfy the claimed structure feature also failed to activate Wnt signaling. As shown in the reproduced figure below, although each tested molecule included two Lrp5/6 binding regions, each directly connected to one and only one Fzd binding region via a linker moiety, several of these molecules (R2M3-25, R2M3-27, 1R-G05-26) failed to produce responses in a TOPFlash assay. EX1001, Figs. 5B, 8B. The specification of the '278 patent completely ignores these inactive molecules. *See id.*, 156:32-52, 157:14-29. Consequently, a POSA would not be able to distinguish active tetravalent, multispecific molecules from inactive ones and would instead be required to make and test each candidate molecule empirically.

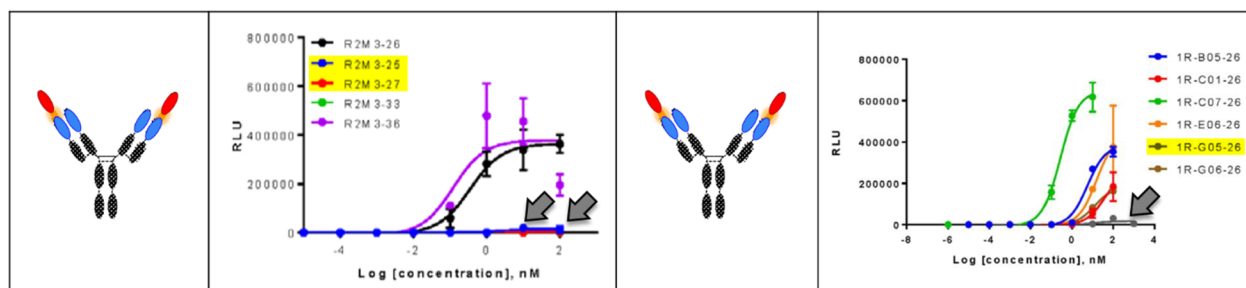


Figure 16. Inactive Tetravalent, Multispecific Molecules (Annotated)

189. The '278 patent also demonstrates that even when molecules share the same tetravalent format, their activity depends unpredictably on the specific antibody fragments used and their relative orientation. Figure 9 of the '278 patent, reproduced below, illustrates this point. In that experiment, four tetravalent formats, designated “NL,” “NH,” “CH,” and “CL,” were evaluated in a TOPFlash assay. EX1001, Fig. 9. In these formats, the Lrp5/6 binding region is connected respectively to (1) the N-terminus of the light chain of the Fzd binding region (“NL”); (2) the N-terminus of the heavy chain of the Fzd binding region (“NH”); (3) the C-terminus of the heavy chain of the Fzd binding region (“CH”); and (4) the C-terminus of the light chain of the Fzd binding region (“CL”). *Id.*, 157:35-42. Notably, the “CL” format exhibited TOPFlash responses only when the format incorporated a particular combination of anti-Fzd and anti-Lrp5/6 binding region sequences (R2M3 and 32, respectively), even though other binding region combinations (e.g., R2M3 and 26, or 18R5 and 26) showed TOPFlash responses in the other three formats (“NL,” “NH,” and “CH”).

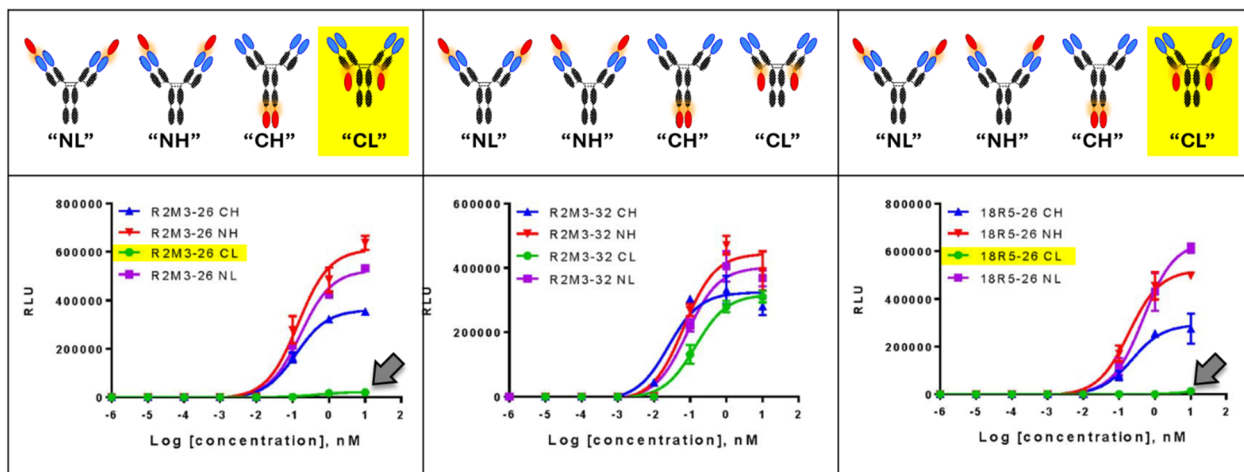


Figure 17. Inactive Tetravalent, Multispecific Molecules (Annotated)

190. In my opinion, this unpredictable variability demonstrates that the claimed “Wnt surrogate” activity depends on structural features that are neither recited in the claims nor adequately disclosed in the specification, for example, the specific amino acid sequences employed and their spatial arrangement within the tetravalent format. Indeed, in discussing the results shown in Figure 9, the specification expressly acknowledges that: “the attachment location of the fusion and the geometry between the Fzd and LRP binding domains play roles in the ability of the Wnt surrogates to activate Wnt signaling.” EX1001, 157:47-50. In my opinion, this acknowledgement confirms that even if a particular “attachment location” or “geometry” is effective for one pair of Fzd and Lrp binding regions, a POSA would still be required to determine the appropriate “attachment location” and “geometry” empirically for each new pair of Fzd and Lrp binding regions.

191. There are other confounding factors that affect how each molecule activates Wnt signaling pathway. For example, during the prosecution history of the '278 patent, both the Applicant and its declarant argued that the claimed molecules must “simultaneously engage two cell surface coeffector molecules (Fzds and Lrp5/6) required to agonize the canonical Wnt signaling cascade.” EX1008, 4006, 4168. The specification, however, does not teach any common structural feature that confers the ability to “simultaneously engage two cell surface coeffector molecules.” Indeed, as discussed above, several tetravalent, multispecific molecules (R2M3-26, R2M3-32, 18R5-28, 26-17SB9) failed to produce TOPFlash responses in the absence of R-spondin in a TOPFlash assay, and several other tetravalent, multispecific molecules (R2M3-25, R2M3-27, 1R-G05-26) failed to produce TOPFlash responses even in the presence of R-spondin. *See supra* **Figs. 15, 16.**

192. Without guidance in the specification, a POSA would not have known how to account for a “hook” effect, where biological activity is lost at higher concentrations. This occurs because the desired effect of a multivalent molecule depends on avidity, the multivalent molecule’s ability to bridge multiple targets simultaneously. At low concentrations, the molecule favors multivalent interactions and crosslinks its receptors. However, as the concentration approaches the intrinsic K_D of an individual binding arm, monovalent binding events begin to compete with multivalent interactions. Instead of one tetravalent molecule bridging four receptors,

each tetravalent molecule begins to engage receptors monovalently, effectively “hooking” the system and preventing activation. The threshold at which this competition occurs is a function of the complex interplay between intrinsic affinity, epitope density, and construct geometry, none of which are predictable from the specification. Thus, the determination of which candidate antibodies are susceptible to this “hook” effect requires empirical experimentation.

193. The '278 patent in fact confirms that some, but not all, tetravalent, multispecific antibodies designed for Wnt agonism are susceptible to a “hook” effect. As shown in the figure below, several candidate molecules evaluated in the '278 patent produced responses in a TOPFlash assay at lower concentrations, but their ability diminished or disappeared at higher concentrations. EX1001, Figs. 14A, 15G. This is a classic sign of a “hook” effect.

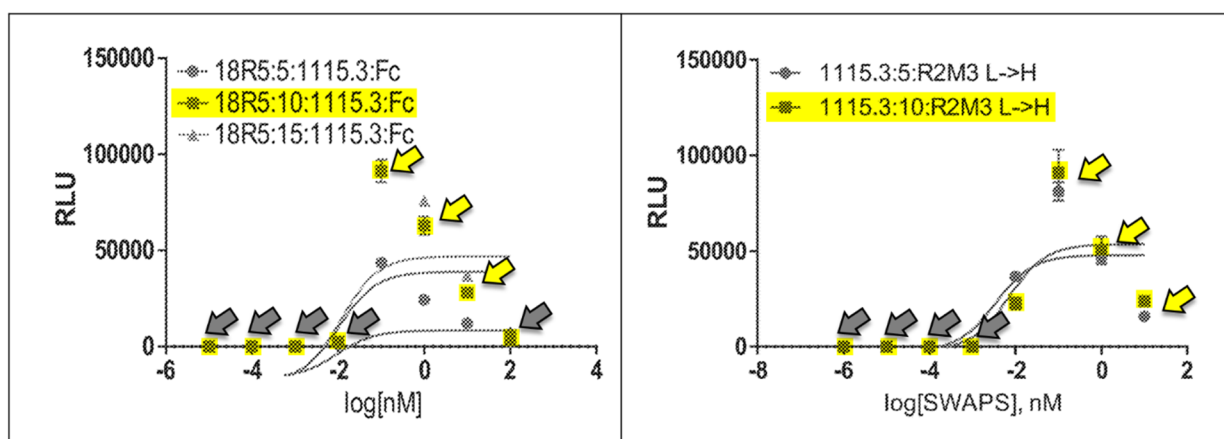


Figure 18. Annotated Figures 14A (Left) and 15G (Right) of the '278 Patent

194. The specification, however, offers no explanation for this unpredictable behavior, much less why some, but not all, candidate molecules exhibited a hook

effect. EX1001, 159:27-39, 160:41-49. Collectively, the data in the specification confirms that “Wnt surrogate” activity is not an inherent property of the claimed molecules, but rather depends on various extrinsic factors, both known and unknown to a POSA by 2017. In other words, beyond the elements recited in claim 1, other, unidentified elements are required for, and therefore correlated with, the claimed Wnt agonist functionality.

195. The absence of a disclosed structure-function correlation in the '278 patent is further illustrated by tetravalent, multispecific molecules made and tested after the assumed effective filing date of the '278 patent. As discussed above and summarized in **Figure 19** below, Li reported multiple tetravalent, multispecific molecules (4SC10-3, F1:5:L1:Fc, F1:10:L1:Fc, F1:15:L1:Fc) that were inactive despite possessing the claimed structural feature. EX1081, 178, 187, Figs. 5A, 11A. Referring to those molecules, Li stated that “the effects of orientation on the reporter activity is not due to impact of format on binding but rather the geometry of the receptors assembled by the surrogate molecules.” *Id.*, 187. Li’s statement confirms that features beyond those required by claim 1 of the '278 patent, such as orientation and geometry, have an unpredictable impact on the ability of tetravalent, multispecific molecules to activate Wnt signaling.

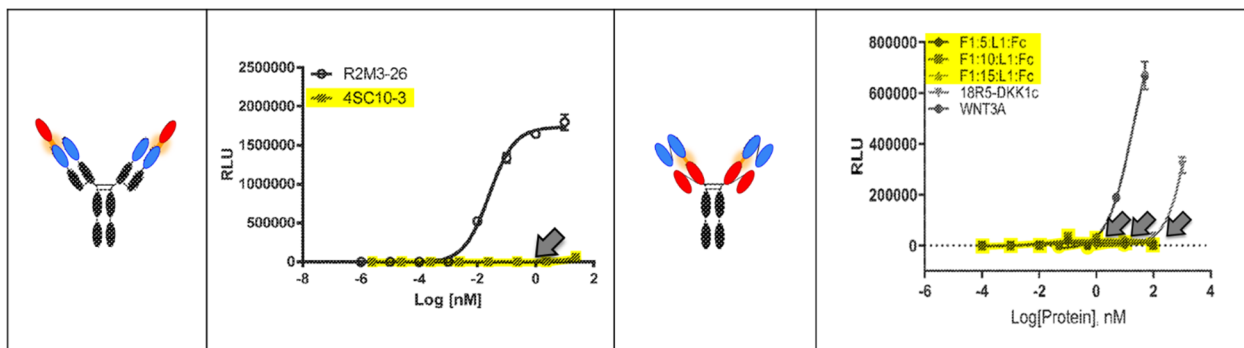


Figure 19. Inactive Tetravalent, Multispecific Molecules (Annotated)

196. In sum, the '278 patent fails to disclose a common structural feature that correlates with the claimed “Wnt surrogate” function. Numerous candidate molecules evaluated in the '278 patent confirm that no such correlation is disclosed. Indeed, the specification specifically acknowledges that “the attachment location of the fusion and the geometry between the Fzd and LRP binding domains play roles in the ability of the Wnt surrogates to activate Wnt signaling,” but remains silent on which attachment location or geometry leads to Wnt signaling activation. EX1001, 157:47-50. Without a meaningful structure-function correlation, a POSA would be forced to make and test each candidate molecule.

6. The '278 Patent Are Deficient for Other Reasons

197. As discussed above, claim 1 of the '278 patent covers a genus of tetravalent, multispecific Wnt surrogate molecules that comprise two Fzd binding regions and two Lrp5/6 binding regions, and each of the four binding regions is defined by their functions: the Fzd binding regions specifically bind to Fzd receptors and the LRP5/6 binding regions bind to Lrp5 and/or Lrp6. *See supra* §§ IX.A.1,

IX.A.2. In my opinion, however, the specification of the '278 patent does not provide adequate written description for these functional elements.

198. As I have explained, claim 1 encompasses, and the specification expressly contemplates, at least 63 distinct Fzd combinations to which each Fzd binding region can bind. *See supra* § IX.A.2; *see also* EX1003, ¶¶113-15. However, the specification of '278 patent disclosed only 17 of those 63 target options as having “confirmed binding” activities: 10 individual Fzds, only two of the 45 different two-Fzd combinations (Fzd 5, 8 and Fzd 9, 10), and only 5 of the 8 different three or more-Fzd combinations (Fzd 1, 2, 7; Fzd 1, 2, 7, 9; Fzd 1, 2, 5, 7, 8; Fzd 2, 6, 3; and Fzd 1, 2, 7, 5). EX1001, Table 1B; *see supra* § IX.A.4. The specification neither discloses binding regions for the remaining 46 of the 63 specifically identified Fzd targets nor teaches a POSA how to identify such binding regions other than through making and empirically testing each candidate Fzd binding region.

199. In my opinion, because the '278 patent shows that the named inventors obtained Fzd binding regions targeting only a minority (17 in 63) of the identified Fzd targets or target combinations, a POSA reading the specification would have understood that the named inventors did not possess the full scope of claimed Fzd binding regions.

7. A Construction of the “Wherein” Clause Broader Than My Proposed Construction Would Further Exacerbate the Written Description Problem

200. As discussed above, in my opinion, the last “wherein” clause of claim 1 means “wherein each of the two LRP5/6 binding regions is connected directly via a linker moiety to one and only one Fzd binding region.” *See supra* § VIII.E.2. I was asked by counsel to consider that Patent Owner may disagree with my construction, contending, for example, that claim 1 encompasses molecules in which each Lrp5/6 binding region may be (1) connected indirectly to at least one Fzd binding region and/or (2) connected via linker moiety to both Fzd binding regions.

201. In my opinion, this construction would significantly broaden the scope of claim 1, sweeping in tetravalent formats that were unknown to a POSA as of 2017 and not described, much less exemplified, in the specification. For example, in 2019, a separate research group at the University of Toronto published a study, evaluating tetravalent bispecific and trispecific formats that fundamentally differed from the Wnt surrogate formats disclosed in the ’278 patent. EX1072 (“Tao”). In the formats reported in that study, the four binding regions comprised antibody fragments known as “diabody.” *Id.*, 2. As discussed earlier, a diabody is formed by pairing two scFv fragments to create a dimer with two antigen-binding regions. Importantly, each of the two antigen-binding regions comprises a V_H domain and a V_L domain from *different* scFv fragments. *See supra* § VII.C. As illustrated below, a POSA would

have understood that, in Tao's formats, each of the two Lrp5/6 binding regions is directly linked via a linker moiety to **both** Fzd binding regions. EX1072, Fig. 1.

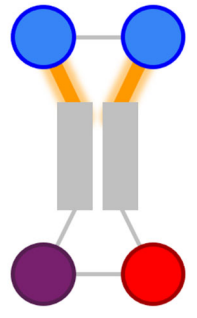
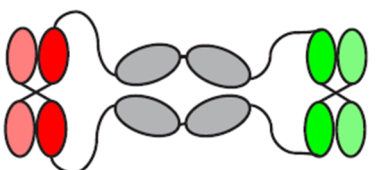
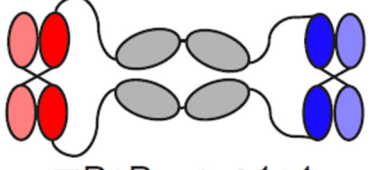
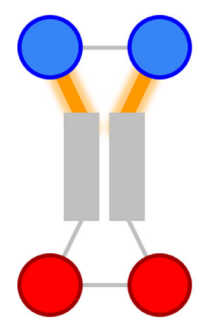
Formats from EX1072	Corresponding Topology
 <p>FP+P - L6¹⁺³</p> <p>“F^P” = Fzd binding region</p> <p>“L6¹” = Lrp6 binding region (targeting Wnt1 binding site)</p> <p>“L6³” = Lrp6 binding region (targeting Wnt3A binding site)</p>	 <p>● = Fzd Binding Region</p> <p>● = Lrp5/6 Binding Region 1</p> <p>● = Lrp5/6 Binding Region 2</p>
 <p>FP+P - L6³⁺³</p>  <p>FP+P - L6¹⁺¹</p>	 <p>● = Fzd Binding Region</p> <p>● = Lrp5/6 Binding Region</p>

Figure 20. Tetraivalent Formats Arising After the Patent

202. This mode of connection is not disclosed in the '278 patent. As shown in the figure below, in all tetravalent formats evaluated in the patent, each of two Lrp5/6 binding regions is connected directly via a linker moiety to one and only one Fzd binding region, and never to both. The '278 patent does not evaluate any format in which each Lrp5/6 binding region is directly linked to both Fzd binding regions. Nothing in the specification indicates that the named inventors were in possession of formats like Tao's, much less envisioned that such formats are possible. For the same reason, nothing in the specification would have led a POSA to molecules with formats like Tao's.

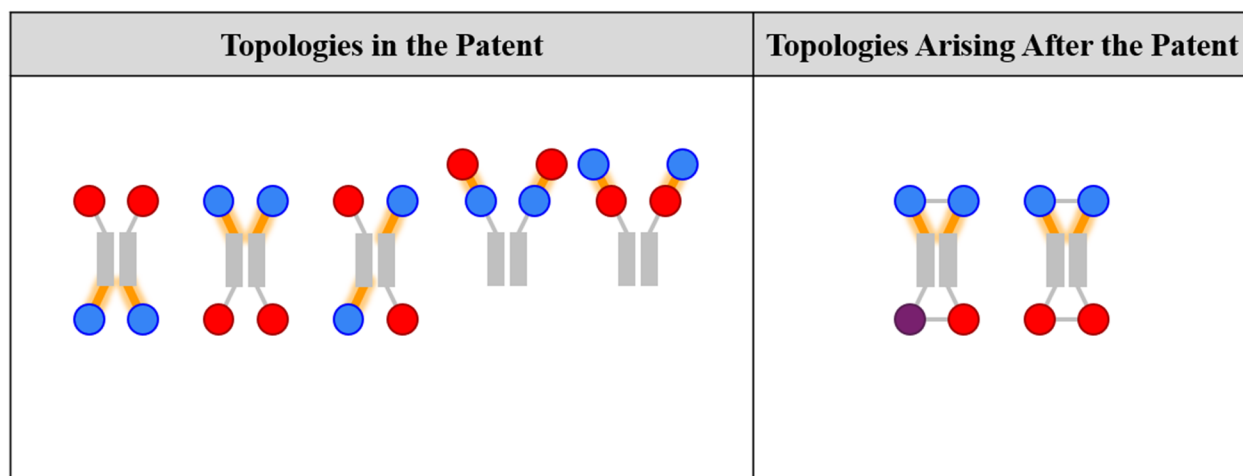


Figure 21. Topologies Tested in the Patent Versus Those Arising After

203. In sum, a POSA reading the '278 patent would not have believed that the named inventors were in possession of molecules with formats like Tao's. The construction of the "wherein" clause broader than my proposed construction thus makes the written description deficiency even worse for the '278 patent.

B. Claims 2-5 Also Lack Written Description

1. Claims 2, 3, and 5

204. Claim 2 recites that “the Fzd binding regions comprise a full immunoglobulin G (IgG), comprising two light chains and two heavy chains, and the LRP5/6 binding regions comprise a VHH.” EX1001, cl. 2. Claims 3 and 5 depend from claim 2. Claim 3 further recites that the “LRP5/6 binding region is fused to the N-terminus or the C-terminus of the heavy chain or is fused to the N-terminus or the C-terminus of the light chain,” and claim 5 recites that “each of the two LRP5/6 binding regions is fused to one of the light chains via a linker moiety.” *Id.*, cls. 3, 5. It is my opinion that these additional limitations do not resolve the lack of written description support for these claims.

205. As with claim 1, the specification fails to disclose a representative number of species within the scope of these dependent claims. *See supra* § IX.A.4. For example, as explained earlier, each of these claims encompasses trispecific and tetraspecific molecules, whereas all molecules evaluated in the specification are bispecific. *See supra* § IX.A.4. Each of these dependent claims also covers molecules that bind to one or more of ten Fzd receptors, while the disclosed species are limited to only a subset of these Fzd receptors and combinations. *See supra* § IX.A.4. Likewise, each of these dependent claims encompasses the use of essentially any peptidic or non-peptidic linkers, but the disclosed species employ

only two highly similar peptidic linkers of the same length (GSGGS or GSGSG). EX1001, Table 3, Fig. 19.

206. The specification also fails to disclose any common structural feature that correlates to the claimed function of Wnt signaling activation, and this problem for claim 1 is not solved by the narrowing limitations of claims 2, 3, and 5. Many of the molecules that demonstrate the lack of structure-function correlation for claim 1 also include the additional features recited in claims 2, 3, and 5. *See supra* § IX.A.5. As illustrated below, several molecules (R2M3-26, R2M3-32, 18R5-28) that satisfy all of the additional limitations of claims 2, 3, and 5 still failed to produce TOPFlash responses in the absence of R-spondin. EX1001, Figs. 2D, 3D, 6A.

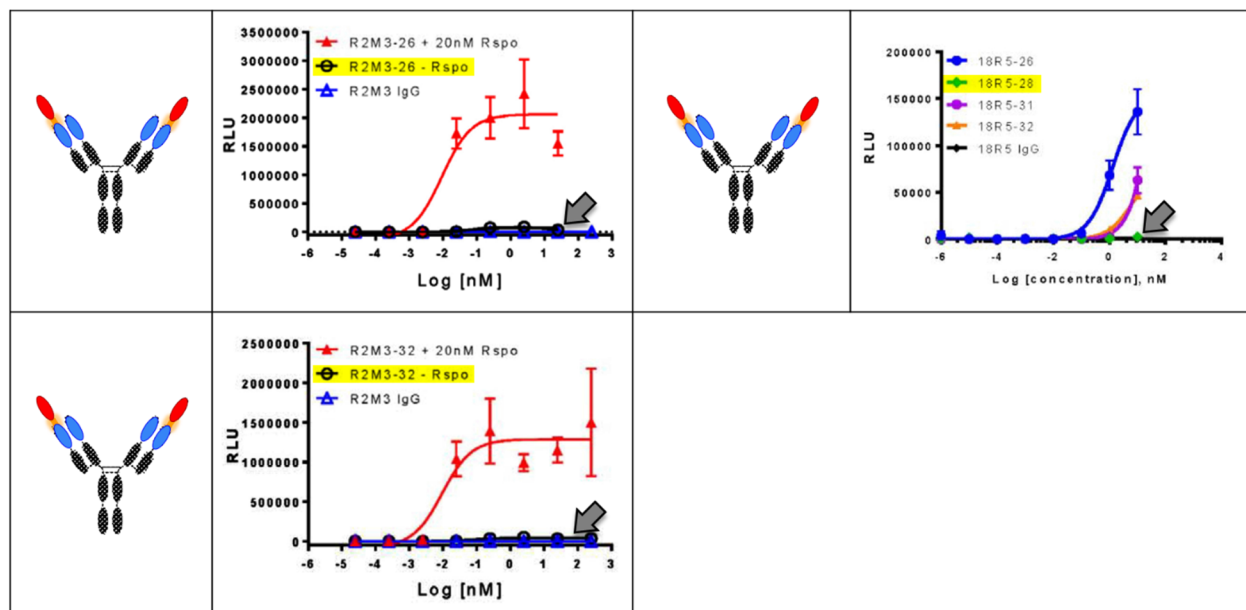


Figure 22. Inactive Molecules in the Absence of R-spondin (Annotated)

207. Likewise, as illustrated below, several molecules (R2M3-25, R2M3-27, 1R-G05-26, R2M3-26 CL, 18R5-26 CL) that satisfy all of the additional limitations

of claims 2, 3, and 5 also failed to produce TOPFlash responses even in the presence of R-spondin. EX1001, Figs. 5B, 8B, 9A, 9C.

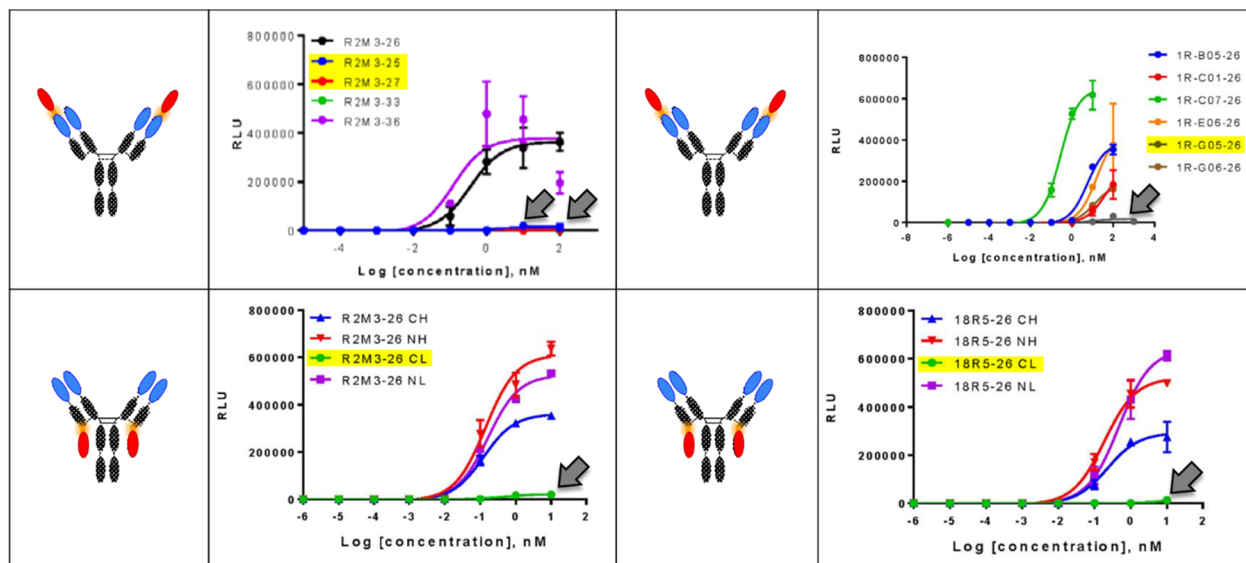


Figure 23. Inactive Molecules in the Presence of R-spondin (Annotated)

208. These molecules, which satisfy the structural requirements of claims 2, 3, and 5 but do not exhibit the claimed function, confirm the lack of correlation between the additional features recited in these claims and the claimed Wnt surrogate activity.

209. For these reasons, it is my opinion that claims 2, 3, and 5 are invalid for lack written description.

2. Claim 4

210. Claim 4 recites a “pharmaceutical composition comprising a physiologically acceptable excipient, diluent, or carrier, and the Wnt surrogate molecule according to claim 1.” EX1001, cl. 4. Claim 4 does not narrow the

exceedingly broad scope of the tetravalent, multispecific Wnt surrogate molecules encompassed by claim 1 and, therefore, is invalid for the same reasons as claim 1.

X. GROUND 2: CLAIMS 1-5 LACK ENABLEMENT

A. Claim 1 Is Not Enabled

1. Claim 1 Is Exceedingly Broad in Scope and Functional in Nature

211. As discussed above, claim 1 covers a genus of tetravalent, multispecific Wnt surrogate molecules that comprise two Fzd binding regions and two Lrp5/6 binding regions. *See supra* §§ IX.A.1, IX.A.2. Each of the four binding regions is defined solely by function, with no limitations on structural features. *See supra* §§ IX.A.1, IX.A.2.

212. As also discussed above, while claim 1 imposes an arguable structural limitation on the claimed genus, namely, “each of the two LRP5/6 binding regions is fused to one of the two Fzd binding regions via a linker moiety,” there is no structural limitation on the linker moiety itself. The linker moiety may be of any type, any length, and any level of flexibility. *See supra* §§ IX.A.1, IX.A.2. The ’278 patent confirms that the linker moiety encompasses, “but [is] not limited to,” polypeptide and non-peptidic linkers, rigid and flexible linkers, and linkers of any length. *See* EX1001, 17:49-54, 116:40-65.

213. As explained above, the scope of claim 1 is exceedingly broad. *See supra* §§ IX.A.1, IX.A.2. Claim 1 encompasses over 35,000 target combinations

and more than 130 million tetravalent formats. *See supra* §§ IX.A.1, IX.A.2. Because the amino acid sequences of the Fzd and Lrp5/6 binding regions are undefined and these regions are open to any and all possible types (e.g., synthetic variants), the total number of Wnt surrogate molecules potentially falling within the scope of the claim is far greater, and likely indefinite. *See supra* §§ IX.A.1, IX.A.2.

2. The Specification Only Provided Limited Working Examples and Guidance

214. In my opinion, compared to the expansive scope of claim 1, the disclosure of the '278 patent is simply too narrow. As discussed above, the specification evaluated only 5 of 21 possible topologies and 29 of more than 130 million tetravalent formats. *See supra* § IX.A.4. All of these evaluated formats are exclusively bispecific, use only one type of linker (G/S flexible linkers), and bind to only a subset of Fzd molecules and their combinations. *See supra* § IX.A.4. These limited working examples provide no teaching as to whether, or how, other unevaluated tetravalent formats, linker structures, target combinations, or binding region sequences would yield functional Wnt surrogate molecules. *See supra* §§ IX.A.3-6.

215. The remainder of the specification provides no adequate guidance to remedy these deficiencies. *See supra* §§ IX.A.3-6. The specification provides no meaningful direction for determining the appropriate flexibility, valency, or specificity for each candidate molecule, other than via empirical trial-and-error

experimentation. *See supra* §§ IX.A.3-6. Indeed, while the specification acknowledges that “the attachment location of the fusion and the geometry between the Fzd and LRP binding domains play roles in the ability of the Wnt surrogates to activate Wnt signaling,” EX1001, 157:47-50, it provides no indication of which attachment location or geometry for each Fzd and Lrp5/6 pair would confer the activation capability for the claimed “Wnt surrogate molecules.” *See supra* §§ IX.A.3-6.

216. The specification also speculates that an exceedingly broad range of “enforced” distances (e.g., “less than about 100 angstroms”), specificities (e.g., “a K_D of 50 μ M or lower”), and valencies (e.g., all possible combinations of two Fzd molecules, one or two Lrp5 molecules, one or two Lrp6 molecules, or one Lrp5 and one Lrp6 molecules) may impact activation of Wnt signaling. *See supra* §§ IX.A.3-6. As explained above, these open-ended suggestions offered in the specification are largely meaningless, as they could be satisfied by virtually any candidate molecule, regardless of its actual ability to activate the Wnt signaling pathway. *See supra* §§ IX.A.3-6.

3. The Relevant Art Was Nascent and Unpredictable

217. As discussed above, the field of multivalent, multispecific antibodies was both nascent and unpredictable in 2017. *See supra* §§ VII.E, IX.A.3. Contemporary publications consistently emphasized that no single format could

accommodate different biological contexts, and that effective formats could only be identified by generating multiple candidates and empirically evaluating their performance. EX1017, 21. The regulatory landscape at the time further reflected the early stage of development in this field. By 2017, the FDA had approved only two bispecific antibodies, the first (blinatumomab) targeting CD19 and CD3, and the second (emicizumab-kxwh) targeting activated factor IX (FIXa) and factor X (FX). *Id.*, Table 3; EX1090. There was no FDA-approved bispecific (let alone tri or tetraspecific) antibody targeting Fzd and Lrp5/6. *Id.* No trispecific or tetraspecific antibodies had been approved for any indication, and no tetravalent antibody has been approved even today. *See supra* §§ VII.E, IX.A.3.

218. As explained by Dr. Kahn, the field of Wnt signaling regulation was also nascent and unpredictable as of 2017. EX1003, ¶¶76-112. Contemporary review articles characterized the Wnt signaling pathway as exceptionally complex and described therapeutic efforts to modulate the activity of this pathway as being in their infancy. EX1043, 1, 15; EX1003, ¶¶76-100. As Dr. Kahn further explained, it was well understood that cellular context and local environmental conditions could substantially alter the outcomes of Wnt signaling. EX1003, ¶¶83, 98-99. Critical mechanistic questions also remained unanswered by 2017, including the stoichiometry of the proposed Wnt–FZD–LRP5/6 signaling complex. *Id.*, ¶¶80-86; EX1054, 8.

219. These scientific uncertainties were compounded by practical limitations. As Dr. Kahn noted, available assays for measuring Wnt agonist activity were known to be incomprehensive and highly cell-type dependent, making it difficult to assess reliably whether a given candidate molecule truly functioned as a Wnt agonist. EX1003, ¶¶101-12; EX1043, 10-11. Reflecting these challenges, no molecule specifically designed to activate Wnt signaling had received FDA approval by 2017, and none has to date. EX1043, 11, Table 1; EX1003, ¶89.

220. Given the complexity of the Wnt signaling pathway, a POSA could not have drawn any general rule or set of parameters for designing tetravalent, multispecific molecules capable of activating Wnt signaling. Instead, a POSA would have been required to make and test each candidate molecule through empirical, trial-and-error experimentation.

4. The Amount of Experimentation Required Was Undue

221. In my opinion, the amount of experimentation required to make and use the full scope of claim 1 would have been undue.

222. At the outset, a POSA would have been required to generate and experimentally evaluate antibodies capable of binding Lrp5 and/or Lrp6, as well as antibodies binding one or more of Fzds 1-10, including antibodies exhibiting cross-reactivity across multiple Fzd molecules. *See* EX1001, 2:31-46. As explained above, as of 2017, there was no reliable method for predicting, from amino acid sequence

alone, whether an antibody would bind a desired target antigen. EX1064, 2; EX1047, 12-13; *see supra* § VII.B. Consequently, each candidate antibody would have had to be individually produced and assessed in binding assays, a process that was both time and resource intensive. *See supra* § VII.B.

223. As Dr. Kahn explained, Wnt signaling presents additional complexities. It was recognized in the art that Wnt and non-Wnt ligands can bind Fzd and Lrp5/6 at different epitopes. EX1003, ¶¶82-84, 134-35; *see supra* § VII.B, IX.A.2. As a result, a POSA seeking to develop Fzd- and Lrp5/6-binding sequences would need to account for multiple potential epitopes rather than focus on a single binding site.

224. As discussed above, it took several weeks to months to generate candidate antibodies against a target of interest, with no guarantee of finding an antibody that is usable. *See supra* § VII.B. In other words, finding suitable antibody sequences for tetravalent, multispecific molecules as claimed would have been an iterative, trial-and-error process.

225. The '278 patent illustrates the iterative nature of this process. The specification shows that antibodies exhibiting apparent binding capability in an initial screen may fail to bind their intended targets upon further evaluation, which necessitated additional rounds of antibody generation and testing. *Compare* EX1001, Table 1A (reporting “initial binding” of “004S-C12” and “004C-D12” to Fzd6), *with id.*, Table 1B (reporting “n.b.” for both clones). In my opinion, extending this

iterative process across the more than 35,000 distinct Lrp-Fzd target combinations encompassed by claim 1 would have required undue experimentation.

226. Even this substantial amount of work would only identify suitable Fzd and Lrp5/6 binding regions, not the creation of functional tetravalent, multispecific molecules that could activate the Wnt signaling pathway. After identifying a pair of Fzd and Lrp5/6 binding sequences, a POSA would then have to incorporate these sequences into tetravalent, multispecific formats. In my opinion, this would have been a particularly difficult task as of 2017. As discussed above, generating tetravalent, multispecific formats in 2017 requires coordinated expression and assembly of multiple distinct heavy and/or light chains. *See supra* § VII.D. During production, these chains often mispaired with unintended partners, significantly reducing the yield of correctly assembled tetravalent, multispecific molecules. *See supra* § VII.D; EX1017, 2.

227. While heterodimerization strategies mitigated heavy-chain mispairing, they did not resolve light-chain mispairing, which remained a persistent and significant problem as of 2017. EX1017, 11. Addressing these issues often required “sophisticated upfront engineering,” and even then the assembly of tetravalent, multispecific formats was “not invariably successful.” EX1069, 5-6. As a result, producing sufficient quantities of even a single correctly assembled molecule for testing was challenging. Scaling this process across more than 130 million potential

tetravalent, multispecific formats, combined with the vast universe of possible binding region sequences, would have required undue experimentation.

228. As Dr. Kahn explains, testing those candidate molecules would have also required an unreasonable amount of experimentation. EX1003, ¶¶101-12, 136-43. Dr. Kahn has explained that the TOPFlash assay, the primary *in vitro* assay used in the '278 patent, measures only canonical Wnt signaling. *See supra* § VII.E; EX1043, 3; EX1003, ¶¶19, 121. Thus, a POSA seeking a Wnt surrogate molecule capable of activating noncanonical Wnt signaling would need to test candidate molecules with assays not disclosed in the specification. *See* EX1001, 117:26-118:36 (listing assays used for “measuring the level of canonical Wnt/β-catenin signaling” only); EX1003, ¶¶19, 121.

229. Even with the TOPFlash assay, Dr. Kahn further explains that a candidate molecule could produce inconsistent responses depending on the assay and experimental conditions, making the determination of Wnt signaling activation even more difficult. *See supra* § VII.E; EX1003, ¶¶110-11, 136-43. This variability would have required a POSA to test each candidate molecule in multiple cell types, at multiple concentrations, and with or without additional potentiators, such as R-spondin. EX1003, ¶¶110-11, 136-38. Further, according to Dr. Kahn’s conservative estimate, each TOPFlash assay takes about a week: from seeding cells, treating cells with an agent of interest, and reading signals generated from the cells. EX1003,

¶¶108, 140-42. Dr. Kahn also explains that while it was possible to scale up the assay to test several agents of interest simultaneously in 2017 (e.g., using 384-well plates), this strategy could create more background noise and inconsistent results because the number of cells per well becomes too small and the signal intensity generated per well likewise becomes too weak to differentiate from background noise. *Id.*, ¶140. This is consistent with my experience in using an *in vitro* assay that is similar in principle to the TOPFlash assay.

230. If a POSA were to evaluate a single molecule for each tetravalent format using the TOPFlash assay, the amount of work needed to evaluate all candidate molecules would have required undue experimentation. Consider that one candidate molecule per tetravalent format is tested in only two cell types at two concentrations with R-spondin and the assays are done using a 384-well plate per each run. That would mean that, after synthesis, just 96 candidate molecules can be evaluated per run. Applying Dr. Kahn's conservative estimate that each run takes a week, testing candidate molecules across more than 130 million different tetravalent, multispecific formats for their ability to activate Wnt signaling would require nearly 1.4 million assays ran consecutively, amounting to more than 26,000 years' worth of work: $(132,407,541 \text{ candidates} / 96 \text{ candidates per run}) = \text{about } 1,379,245 \text{ runs} = \text{about } 1,379,245 \text{ weeks} = 26,524 \text{ years}$. Notably, this estimate does not account for the substantial time and effort required to generate the candidate molecules

themselves; nor the uncertainty and variability of assay outcomes under different experimental conditions. EX1003, ¶¶141-43.

231. For at least these reasons, it is my opinion that practicing the full scope of the claimed tetravalent, multispecific Wnt surrogate molecules would have required undue experimentation.

5. The Construction of the “Wherein” Clause Broader Than My Proposed Construction Would Further Exacerbate the Enablement Problem

232. To the extent the last “wherein” clause of claim 1 is construed to encompass an indirect connection via a linker moiety, or to allow each Lrp5/6 binding region to be connected to both Fzd binding regions via a linker moiety, such a construction would only magnify the enablement defect. *See supra* §§ VIII.E.2, IX.A.7. Under the broader construction, claim 1 would cover Wnt surrogate molecules with tetravalent formats that were unknown to a POSA in 2017. *See supra* § IX.A.7. A POSA would be required to design, generate, and test these additional, previously unknown formats, on top of the more than 130 million tetravalent formats already within the claim scope, without any meaningful guidance or representative working examples in the specification. *See supra* § IX.A.7. Thus, in my opinion, claim 1 is not enabled under either Petitioner’s proposed construction or any broader construction that Patent Owner may advance.

B. Claims 2-5 Are Also Not Enabled

1. Claims 2, 3, and 5

233. Claim 2 recites that “the Fzd binding regions comprise a full immunoglobulin G (IgG), comprising two light chains and two heavy chains, and the LRP5/6 binding regions comprise a VHH.” EX1001, cl. 2. Claims 3 and 5 depend from claim 2. Claim 3 further recites that the “LRP5/6 binding region is fused to the N-terminus or the C-terminus of the heavy chain or is fused to the N-terminus or the C-terminus of the light chain,” and claim 5 recites that “each of the two LRP5/6 binding regions is fused to one of the light chains via a linker moiety.” *Id.*, cls. 3, 5. It is my opinion that none of claims 2, 3, and 5 is enabled for all of the reasons discussed above.

234. For example, as discussed above, multiple tetravalent, multispecific molecules satisfying the additional limitations recited in these dependent claims failed to produce TOPFlash responses, both in the presence and absence of R-spondin. *See supra* § IX.B.1. For molecules satisfying the additional requirements of these dependent claims, the specification provides no meaningful guidance for distinguishing those that activate Wnt signaling from those that do not. *See supra* §§ IX.B.1, X.A; Thus, like claim 1, these dependent claims also require extensive trial-and-error experimentation and are thus not enabled. *See supra* § X.A.

2. Claim 4

235. Claim 4 recites a “pharmaceutical composition comprising a physiologically acceptable excipient, diluent, or carrier, and the Wnt surrogate molecule according to claim 1.” EX1001, cl. 4. Claim 4 does not narrow the scope of the tetravalent, multispecific Wnt surrogate molecules encompassed by claim 1. Claim 4 is therefore unpatentable for the same reasons as claim 1.

XI. GROUND 3: CLAIMS 1-5 ARE INDEFINITE

A. “Wnt Surrogate Molecule” Lacks Reasonable Certainty

236. Each of claims 1-5 of the '278 patent recite a “Wnt surrogate molecule.” According to the specification of the '278 patent, this term is defined as being “biologically active . . . in activation of Wnt signaling, i.e., the Wnt surrogate molecule is a Wnt agonist.” EX1001, 16:52-56; *see supra* § VIII.E.1. As discussed below, biological activity in activation of Wnt signaling can depend on a range of factors, including the identity and receptor specificity of the potential Wnt and non-Wnt agonist, the agonist’s concentration, and the expression levels of the receptors that varies by cell type and development stage. Further, there was no standard assay to determine biological activity in activating Wnt signaling, and results could vary depending on the assay and its conditions. Complicating matters still further, the specification discloses multiple conflicting assays and assay conditions that lead to different results. Taken together, the specification fails to provide a POSA with

reasonable certainty on how to determine whether a candidate molecule is “Wnt surrogate molecule” that is “biologically active . . . in activation of Wnt signaling, i.e., the Wnt surrogate molecule is a Wnt agonist.” Therefore, it is my opinion that claims 1-5 are indefinite.

237. As confirmed by Dr. Kahn, the Wnt signaling pathway is complex, involving multiple ligands and receptors that interact simultaneously. EX1003, ¶¶76-100; EX1063, 1, 3; EX1043, 1. By 2017, it was recognized that the identity, receptor specificity, and concentration of potential Wnt agonists could affect their biological activity in activation of Wnt signaling. EX1003, ¶¶76-100; EX1063, 1, 3; EX1043, 1. It was also understood that Wnt and non-Wnt ligands could exert different effects depending on tissue, cell type, and development stage. EX1003, ¶¶98-99, 131-32; EX1063, 1, 3; EX1043, 1.

238. As Dr. Kahn explains, by 2017, no single assay was universally applicable to all Wnt systems for determining pathway activation. EX1003, ¶¶101-12. Instead, there were “multiple ways in which WNT signaling [was] read out (such as nuclear β -catenin levels, reporter assays, and endogenous gene expression), which are highly cell-type dependent.” EX1043, 11; EX1003, ¶¶101-12. As confirmed by Dr. Kahn, it was understood in 2017 that assays designed to measure the activation of canonical Wnt signaling (e.g., TOPFlash assay) generally do not measure the activation of noncanonical Wnt signaling, and *vice versa*. EX1003, ¶¶101-02. As a

result, the same candidate molecule could produce opposite responses depending on the assay employed and the specific assay conditions. *Id.*, ¶¶101-12. Dr. Kahn illustrated this problem using Wnt5, explaining that the same molecule may appear to be an agonist, inactive, or an antagonist depending entirely on the assay and assay conditions used, rather than on any inherent property of the molecule itself. *Id.*, ¶¶110-11,136-38. Thus, variability and inconsistency across experimental systems made it difficult to determine definitively whether a molecule functions as a Wnt agonist, antagonist, both, or neither. EX1056, 2-5, 11; EX1003, ¶¶101-12, 136-38, 144-55.

239. As Dr. Kahn agrees, the specification and prosecution history, fail to provide guidance for determining whether a molecule qualifies as a claimed “Wnt surrogate molecule” to overcome the actual and potential inconsistencies among available assay methods and between canonical and noncanonical signaling pathways. EX1003, ¶¶136-38, 144-55. To the contrary, the specification compounds this ambiguity by (1) defining the Wnt signaling pathway as either “a canonical Wnt signaling pathway *or* a non-canonical Wnt signaling pathway” and (2) open-endedly allowing that the “ability of the Wnt surrogate molecules of the invention to mimic the activity of Wnt can be confirmed by *a number of assays*.” EX1001, 4:47-51, 117:28-30, 16:59-61. Indeed, as confirmed by Dr. Kahn, the specification identifies assays only for assessing canonical Wnt signaling, and even

for those canonical Wnt signaling assays, the specification discloses multiple assay conditions that produce inconsistent results. EX1003, ¶¶19, 121, 144-55.

240. While the '278 patent employed a TOPFlash assay most frequently, **none** of the TOPFlash assays reported in the specification defines a threshold for “biologically active” or includes a biologically relevant positive control, such as a Wnt protein. See EX1001, Examples 2-18, Figs. 2-18; EX1003, ¶¶36, 145-49. Without any defined threshold or appropriate positive control, a POSA would be unable to determine whether, for example, a low-level TOPFlash signal reflects a molecule that is, in fact, “biologically active.” EX1003, ¶¶145-49.

241. This lack of certainty is evident in the candidate molecule “18R5:Fc:1115.3.” EX1001, Fig. 14E; EX1003, ¶147. Although the specification describes this molecule as “activat[ing] Wnt signaling” in the specific reporter assay in 293 cells employed (EX1001, 159:27-39), as shown in the reproduced figure below, the reported response is minuscule and presented without any positive control for comparison. EX1001, Fig. 14E. As a result, I agree with Dr. Kahn that the specification of the '278 patent fails to provide a POSA with reasonable certainty as to whether this response satisfies the requirement for a “biologically active” Wnt surrogate molecule. EX1003, ¶147.

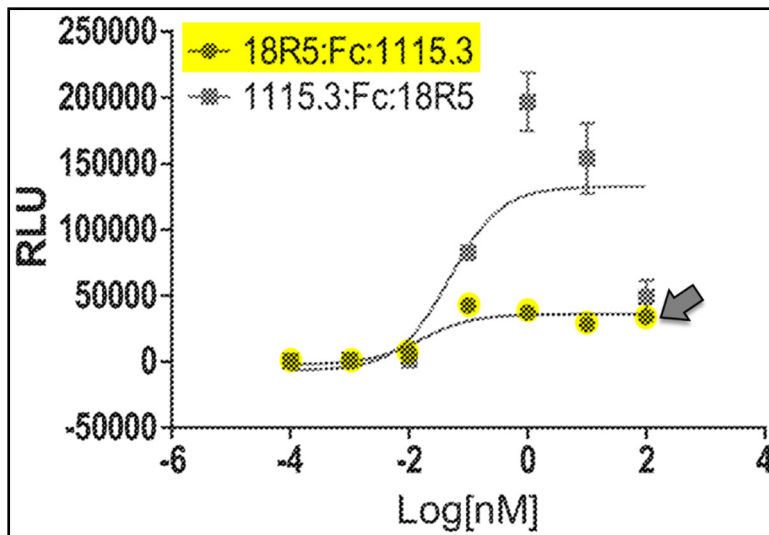


Figure 24. Annotated Figure 14E of the '278 Patent

242. Dr. Kahn further explained that Wnt and non-Wnt ligands in nature are capable of activating Wnt signaling without the need for additional potentiating factors such as R-spondin. EX1003, ¶¶36, 148; EX1063, 5; EX1093, 1-3. However, as shown in the reproduced figure below, several candidate molecules disclosed in the specification (R2M3-26, R2M3-32, 26-17SB9) failed to produce responses in the absence of R-spondin in TOPFlash assays, demonstrating that, unlike natural Wnt and non-Wnt ligands, they are not “biologically active.” EX1003, ¶¶148-49; *see supra* § IX.A.5. Nevertheless, based solely on the positive responses observed in the presence of R-spondin, the '278 patent characterizes these molecules as “induc[ing] canonical Wnt signaling.” EX1001, 158:54-63. This characterization creates ambiguity as to whether these molecules qualify as “Wnt surrogate molecules.” Given these conflicting condition-dependent results and the

specification's characterization that ignores the "biologically active" requirement, a POSA would be unable to determine, with reasonable certainty, as to whether these molecules or other unevaluated candidate molecules would fall within the scope of the claimed Wnt surrogates. EX1003, ¶¶148-49.

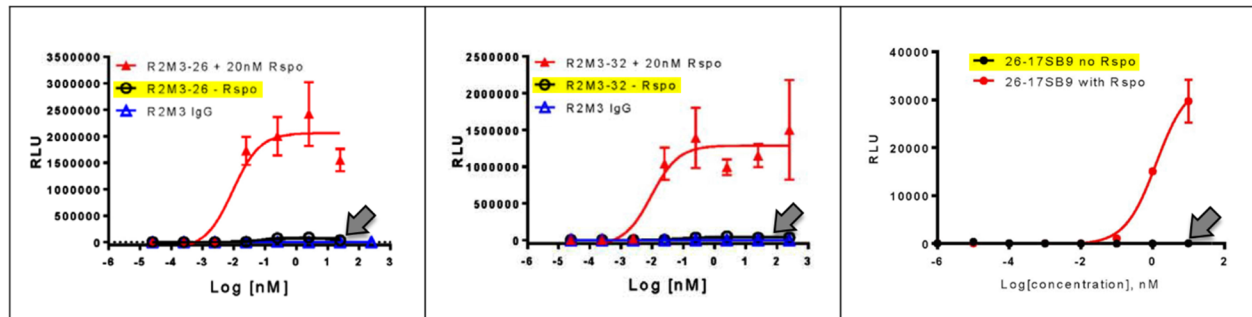


Figure 25. Annotated Figures 2D, 3D, 13B⁷ of the '278 patent

243. Dr. Kahn also confirms that, as of 2017, it was well known that both Wnt and non-Wnt ligands perform tissue-specific roles. EX1003, ¶¶98-99, 131-33, 150-51. Thus, the same "Wnt surrogate" molecule may activate Wnt signaling in one biological context yet fail to do so in another, depending on its biological targets and the Fzd/Lrp molecules expressed in the tissue of interest. EX1056, 2-5, 11; EX1003, ¶¶98-99, 131-33, 150-51. As Dr. Kahn noted, this uncertainty is reflected

⁷ I noticed that Figure 13B of the '278 patent appears to be an incorrect duplicate of Figure 13E. I was provided with Figure 13B of the underlying provisional application (EX1007), which appears to match the description of that figure in the specification.

in the '278 patent itself, which reports inconsistent responses across different cell types. EX1003, ¶¶150-51. Specifically, as shown in the reproduced figure below, the candidate molecule “18R5-28” failed to produce TOPFlash responses in 293 cells in the absence of R-spondin, but produced TOPFlash responses in A375 cells under the same conditions. EX1001, Figs. 6A, 6B; EX1003, ¶¶150-51. Thus, because a candidate molecule that failed to produce TOPFlash responses in one cell type can nonetheless potentially produce TOPFlash responses in another cell type, the '278 patent does not provide a POSA with reasonable certainty as to whether a candidate molecule that exhibits cell-type dependent Wnt activity qualifies as a Wnt surrogate molecule. EX1003, ¶¶150-51.

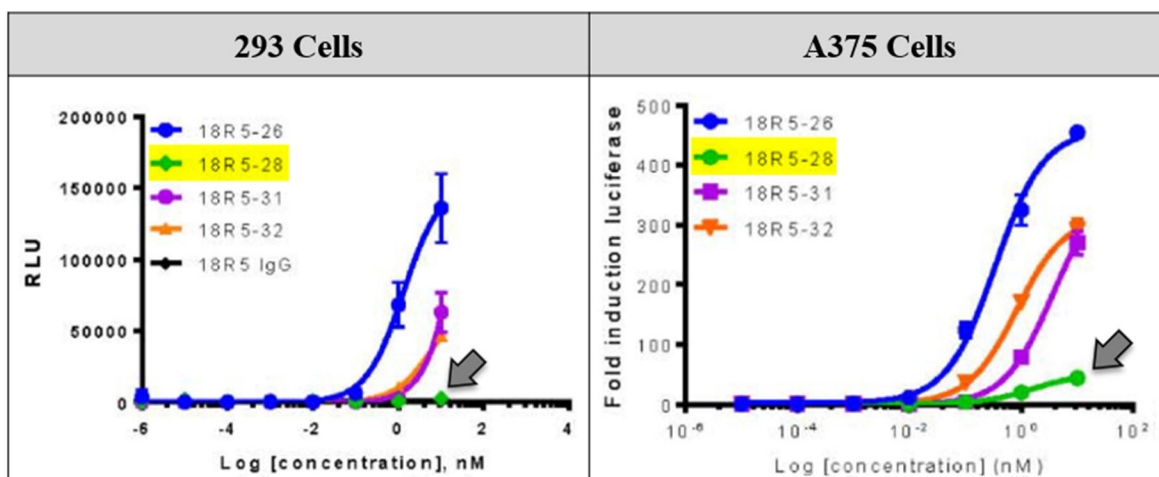


Figure 26. Annotated Figures 6A and 6B of the '278 Patent

244. Finally, the TOPFlash assay data disclosed in the specification demonstrate that assay outcomes depend on concentration and can behave unpredictably rather than in a consistent dose-dependent manner. This

unpredictability introduces an additional layer of indefiniteness, because whether a given species appears “active” in the assay can vary based solely on the concentration tested. The patent provides no guidance as to which concentration or range of concentrations is relevant to determining whether a candidate molecule qualifies as a “Wnt surrogate molecule.” EX1003, ¶¶152-53.

245. As discussed above, several candidate molecules exhibit so-called “hook” effects, further underscoring the unpredictable relationship between concentration and measured Wnt activity. *See supra* § IX.A.5. The specification offers no explanation for how such effects should be interpreted or accounted for. As a result, a POSA would be unable to determine whether a molecule that exhibits no activity at one concentration, or across a range of concentrations, would exhibit activity at higher or lower concentrations, particularly where the specification does not expressly disclose a standard concentration range. A POSA would also be unable to determine whether molecules that do not behave in a dose-dependent manner, and that unpredictably lose agonistic activity at higher concentrations, nonetheless qualify as Wnt surrogate molecules. EX1003, ¶¶152-53.

246. In sum, as also confirmed by Dr. Kahn, the specification fails to identify or endorse any specific assay capable of measuring both canonical and noncanonical Wnt signaling, and further fails to define the conditions for numerous variables that materially affect the assay that measures Wnt signaling activity. EX1003, ¶¶137-39,

144-55. Because the determination of whether a candidate molecule is “biologically active” in activating Wnt signaling turns on assay-dependent and condition-dependent results, a POSA would not be able to determine, with reasonable certainty, whether a given candidate molecule qualifies as a Wnt surrogate molecule. Accordingly, it is my opinion that claims 1-5 of the ’278 patent are indefinite.

B. A Broader Construction of the “Linker” Limitation Would Make the Challenged Claims Incomprehensible

247. As explained above, in my opinion, the last “wherein” clause of claim 1 means that each of the two LRP5/6 binding regions is connected directly via a linker moiety to one and only one Fzd binding region. *See supra* §§ VIII.E.2. If Patent Owner advances a claim construction that does not require a direct connection via the linker to one and only one Fzd binding region, it is my opinion that such a claim construction would render all claims of the ’278 patent incomprehensible and indefinite.

248. A claim construction that does not require “connected directly” renders claim 1 incomprehensible and thus lacking reasonably certainty for its scope for several reasons. *See supra* § VIII.E.2.

249. *First*, this construction would make the specification’s characterization of different molecular formats incomprehensible. In discussing formats shown in Figure 1A, for example, the specification explains that the Nab fragment is “fused” to “the C-terminus of HC” in the left format while the Nab fragment is “fused” to

“the C-terminus of LC” in the right format. EX1001, 150:37-44. If “fused” were interpreted to include indirect connections, that distinction would collapse, because the Nab fragment would effectively be “fused” to every terminus, eliminating any meaningful differentiation between the disclosed formats.

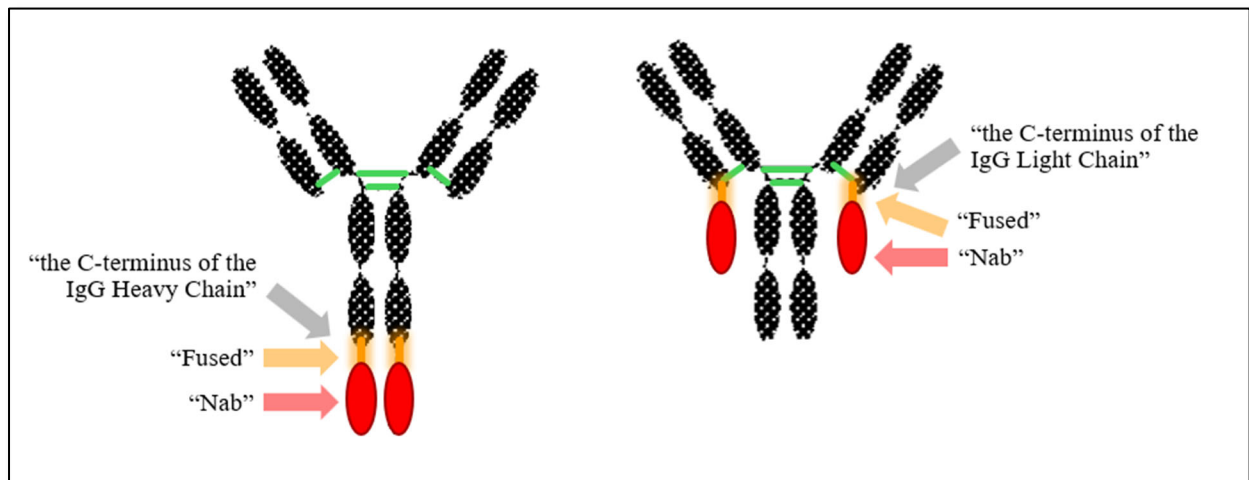


Figure 27. Annotated Figure 1A of the '278 patent

250. *Second*, if the “fused” term in claim 1 allows for the binding regions to be connected indirectly, a POSA would be unable to determine, for any given molecule, where the claimed binding regions begin and end or where the claimed linker moiety is located. For example, in the molecules depicted above, a POSA could not discern whether a binding region within the IgG portion begins or ends at the C-terminus of the IgG heavy chain, at the hinge region, at the C-terminus of the IgG light chain, or at some indeterminate location in between.

251. *Third*, if “fused” in claim 1 allows for indirect connections, the claim would become internally inconsistent and therefore impossible to practice. Under

such a construction, each of the two Lrp5/6 binding regions would be required to be fused to only “one of the two Fzd binding regions,” as mandated by the claim language, while simultaneously being permitted to be fused to both Fzd binding regions via indirect connections, creating an irreconcilable contradiction.

252. This broader construction would also make the challenged dependent claims incomprehensible. Claim 3, for example, recites that “the LRP5/6 binding region is fused to the N-terminus or the C-terminus of the heavy chain or is fused to the N-terminus or the C-terminus of the light chain.” EX1001, cl. 3. If indirect connections were permitted, the Lrp5/6 binding region would necessarily be fused to both the N-termini and C-termini of both the heavy and light chains, stripping this limitation of any meaning. The same defect applies to claim 5, which recites that “each of the two LRP5/6 binding regions is fused to one of the light chains via a linker moiety.” *Id.*, cl. 5. Under the broader construction, each Lrp5/6 binding region would be fused to both light chains, rendering the words “each” and “one” meaningless.

XII. GROUND 4: CLAIMS 1 AND 4 ARE ANTICIPATED BY GARCIA

253. In my opinion, claims 1 and 4 of the '278 patent are additionally invalid because they are anticipated by Garcia, a prior art reference published on March 17, 2016. EX1004, item (43). As I explain below, Garcia discloses each and every limitation of claim 1 and claim 4.

A. Claim 1 Is Anticipated by Garcia

1. Garcia Discloses “a Soluble, Tetravalent, Multispecific Wnt Surrogate Molecule” Comprising “Two Fzd Binding Regions” and “Two LRP5/6 Binding Regions”

254. As summarized above, during prosecution of the application that led to the '278 patent, both Applicant and named inventor Dr. Yang Li repeatedly argued that Garcia does not disclose this limitation because Garcia's disclosure is limited to “bivalent, bispecific molecules comprised of a single polypeptide and having a stoichiometry of 1:1 Fzd binder:LRP5/6 binder.” EX1008, 4005, 4168 (emphasis in original). The examiner was persuaded by this argument and allowed the claims of the '278 patent. *See supra* § VIII.D.

255. I disagree with Applicant and Dr. Li's characterization of Garcia because the reference *does* disclose this “tetravalent, multispecific” limitation.

256. Garcia expressly states that “Wnt signaling agonist compositions and methods for their use are provided.” EX1004, Abstract. Garcia further explains that those compositions are “water soluble” and “directly activate canonical wnt pathway signaling.” *Id.*, [0009]. Garcia therefore discloses soluble Wnt surrogate molecules.

257. Garcia states that it discloses “water soluble” “Wnt signaling agonist” molecules that can be tetravalent and multispecific. Specifically, Garcia states that the “wnt surrogate can be *a polypeptide*, where a binding domain for Fzd is joined to a binding domain for Lrp5/6.” EX1004, [0056]. Garcia further states that the

“polypeptide wnt surrogate may be a single chain, *dimer*, or higher order multimer.”

Id. Because each polypeptide, as disclosed by Garcia, comprises a binding region for Fzd and a binding region for Lrp5/6, a dimer formed from two such polypeptides contains two binding regions for Fzd and two binding regions for Lrp5/6. Because this dimer contains four antigen-binding regions, it is a tetravalent molecule. This tetravalent dimer is also multispecific because it can bind to at least two different epitopes: the Fzd binding regions bind an epitope on Fzd and the Lrp5/6 binding regions bind a distinct epitope on Lrp5/6. Thus, Garcia discloses this limitation.

258. My opinion that Garcia discloses this limitation is supported by the testimony of one co-inventor of the '278 patent, Dr. Yang Li. In particular, Dr. Li confirmed that the Garcia's disclosure does provide, via dimerization, a tetrameric, multispecific Wnt surrogate molecule.

259. During prosecution of the '278 patent, Dr. Li submitted a declaration stating that he had made compositions comprising a “tandem scFv format” with “a single scFv Fzd binding linked to a single scFv Lrp5/6 binding” as “described by Garcia.” EX1008, 4170. In the declaration, Dr. Li further stated that the “aggregation of two . . . monomeric tandem scFv molecules,” corresponding to “two . . . binding domains for FZD and two . . . binding domains for LRP in one molecule,” was “associated with Wnt activity.” *Id.*, 4171. In my opinion, these statements confirm that—consistent with Garcia's express teaching of dimers—

dimers are formed from the polypeptides disclosed in Garcia, and that such dimers comprise two Fzd binding regions and two Lrp5/6 binding regions, and are capable of activating the Wnt signaling pathway. Thus, Dr. Li's testimony confirms that Garcia discloses this limitation.

2. Garcia Discloses "Two Fzd Binding Regions that Specifically Bind to Two [Fzd] Receptors, Wherein Each of the Two Fzd Binding Regions Comprises an Antibody or Antigen-Binding Fragment of the Antibody"

260. Garcia teaches that "[i]n polypeptide embodiments, the Fzd binding domain may be selected from any domain that binds Fzd at high affinity" and that "[s]uitable Fzd binding domains include," for example, "antibody derived binding proteins, e.g., scFv, Fab, etc. and other portions of antibodies that specifically bind to one or more Fzd proteins." EX1004, [0011]. Garcia further explains that the term "antibody" as used in Garcia encompasses, e.g., "intact IgG." *Id.*, [0099]. Thus, Garcia discloses that each of the two Fzd binding regions in a dimeric Wnt surrogate molecule can comprise an antibody or antigen-binding fragment of the antibody that specifically binds Fzd.

3. Garcia Discloses "Two LRP5/6 Binding Regions that Specifically Bind to a [LRP5] and/or a [LRP6], Wherein Each of the Two LRP5/6 Binding Regions Comprises an Antibody or Antigen-Binding Fragment of the Antibody"

261. Garcia states that "[i]n polypeptide embodiments, the Lrp5/6 binding domain or element may be selected from any domain that binds Lrp5/6 at high

affinity” and that “[s]uitable Lrp5/6 binding domains include,” for example, “antibody derived binding proteins, e.g. scFv, Fab, etc. and other portions of antibodies that specifically bind to one or more Fzd [sic] proteins.” EX1004, [0013]; *see id.*, [0099] (the term “antibody” encompasses, e.g., “VHHs”). These types of antigen-binding proteins, such as scFv, Fab, and VHH, are recognized in the field of antibody engineering as antibodies or antigen-binding fragments of the antibodies. This understanding is consistent with the disclosure of the ’278 patent, which states that the term “antibody” encompasses, among other things, “dAb, Fab, Fab’, F(ab’)2, Fv), single chain (scFv), VHH or sdAb, synthetic variants thereof, naturally occurring variants, fusion proteins comprising an antibody or an antigen-binding fragment thereof.” EX1001, 11:25-51. Thus, it is my opinion that Garcia discloses this limitation.

4. Garcia Discloses that “Each of the Two LRP5/6 Binding Regions is Fused to One of the Two Fzd Binding Regions via a Linker Moiety”

262. The tetravalent dimeric Wnt surrogate molecule disclosed in Garcia satisfies this limitation. Garcia explains that, in each bivalent polypeptide component of the tetravalent dimer, the “Fzd binding domain and the Lrp5/6 binding domain may be directly joined, or may be separated by a linker, e.g., a polypeptide linker, or a non-peptidic linker, etc.” EX1004, [0056]. Thus, it is my opinion that

Garcia teaches that each of the two Lrp5/6 binding regions in the dimer is directly connected to one of the two Fzd binding regions via an intervening linker moiety.

263. As such, Garcia discloses each and every limitation of claim 1. Claim 1 is therefore anticipated by Garcia.

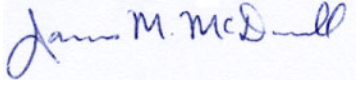
B. Claim 4 Is Anticipated by Garcia

264. Claim 4 recites a “pharmaceutical composition comprising a physiologically acceptable excipient, diluent, or carrier, and the Wnt surrogate molecule according to claim 1.” EX1001, cl. 4. Garcia discloses a composition comprising “an effective dose of a wnt signaling agonist in a pharmaceutically acceptable excipient.” EX1004, [0019]; *see also id.*, cl. 34 (claiming a “pharmaceutical composition comprising a wnt signaling agonist of any one of Claims 1-33, and a pharmaceutically acceptable excipient”). It is my opinion that Garcia discloses each and every limitation of claim 4 and thus anticipates the claim.

XIII. CONCLUSION

265. I hereby declare that all statements made herein of my own knowledge are true and that statements made on information and belief are, to the best of my knowledge, believed to be true; and further that these statements are 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.

Dated: _11 February, 2026

By: A handwritten signature in blue ink, appearing to read "James M. McDonnell", is written over a light blue rectangular background.

Dr. James M. McDonnell

Appendix A

James M. McDonnell, PhD
Professor of Molecular Immunology
Randall Centre for Cell & Molecular Biophysics, King's College London
Email: james.mcdonnell@kcl.ac.uk Tel. +44 207 848 6970

Research Experience

- 2010-present Molecular recognition and intervention in pathological immune responses
Professor of Molecular Immunology,
Head, Section of Molecular Biophysics, Randall Centre for Biophysics
King's College London
- 2000-2010 Immunological molecular interactions and signal transduction
University Lecturer, Department of Biochemistry
University of Oxford
- 1996-2000 Molecular structure and interaction analysis by NMR spectroscopy
Senior Research Associate, Laboratory of Physical Biochemistry
The Rockefeller University
- 1993-1996 Biophysical studies of IgE-receptor interactions
Postdoctoral Fellow, Biophysics Unit
King's College London
- 1989-1993 Structure/function studies of peptide antagonists of CD4
PhD Student, Department of Immunology
Thomas Jefferson University

Research Interests

Understanding how specific molecular recognition events regulate immunological disorders. Detailed analysis of molecular interactions, conformation and dynamics using structural, biophysical and chemical biology approaches. Application of this information in the identification of inhibitors of molecular interactions, using either structure-based design or library screening methods, and the development of these inhibitors as therapeutic or diagnostic agents.

Overview of Grant Funding

Medical Research Council: Project Grant (2021-2025), Programme Grant (2012-2017), Capital Award (2013-2014), Project Grant (2005-2008), Career Establishment Grant (2002-2007), Cooperative Grant (2003-2008); six PhD studentships

The Wellcome Trust: Capital Award Grants (2009-2015, 2017-2022), Programme Grant (2007-2012), Equipment Grant (2005-2010), Project Grant (2003-2007); five PhD studentships

Biotechnology and Biological Sciences Research Council: Equipment Grant (2022-2027), Equipment Grant (2020-2025), Project Grant (2017-2021); one PhD studentship

National Institute for Health Research: Biomedical Research Centre Project Grant (2012-2018)

European Union: FP6 Consortium Grant (2004-2009)

Arthritis Research Campaign: Studentship Grant (2008-2011)

Asthma UK: Foundation Grant (2010-2011)

Darwin Trust: two PhD studentships

E.P. Abraham Research Fund: Project Grant (2001-2002)

The Royal Society: Equipment Grant (2001-2002)

US Army Breast Cancer Research Award (1998-2000)

Pharmacia Allergy Research Foundation Fellowship (1998)

Burroughs Wellcome Fund: Hitchings-Elion Fellowship (1993-1996)

Industrial support [*details confidential*] (2009-present)

Developed drugs in clinical trials

Small molecule anti-IgE (UCB8600): in Phase 1/1b (NCT04444466)

Small molecule MDM2 antagonist (ASTX295): in Phase 1/2 (NCT03975387)

Biologic anti-IgE: awaiting clinical trial authorisation

Biologic anti-IgE: in preclinical development, and species homologs being used for veterinary therapeutic studies (with Peacock Biotherapeutics Ltd.)

Patents

- 2017 Anti-IgE antibodies (US patent no. US-20220235146-A1)
- 2013 Variant IgE with reduced affinity to CD23 (WO2014009707A1)
- 2006 Immunomodulatory peptide fragments of CD23 and uses therefor (WO2006067406A1)
- 2000 IgE antagonists for the treatment of allergic diseases (US patent no. 5,962,634)
- 1997 Compounds that inhibit T cell proliferation and methods for using the same (US patent no. 5,589,458)

60 Structures deposited in the Protein Databank

1A6S, 1C4B, 1DDB, 1G84, 1T8C, 1T8D, 1XBH, 2BO2, 2BOU, 2BOX, 2WMA, 2WMB, 2WQR, 2XXS, 2Y7Q, 4B53, 4EZM, 4G96, 4G9A, 4GI0, 4GKO, 4GK1, 4GJ0, 4GJX, 4J4P, 4J6K, 4J6J, 4J6L, 4J6M, 4J6N, 4J6Q, 4J6P, 5O9K, 5O9L, 5O9M, 5G64, 5LGK, 5LGJ, 5MOI, 5MOJ, 5MOK, 5MOL, 5OTJ, 6EYN, 6EYO, 6TCN, 6TCO, 6TCM, 6TCP, 6TCQ, 6TCR, 6TCS, 6Y0L, 6Y0M, 8OJS, 8OJT, 8OJU, 8OJV, 8Q6K, 9FMB

Teaching experience

Programme and course leadership:

Course Organiser, *Protein Structure and Function* (2011-present)

Common Year One, Organisation Committee (2013-2019)

Course Organiser, *Chemistry for Biosciences* (2013-2017)

Organiser, Year 1, *Biological Chemistry* curriculum (2008-2010)

Organiser, Year 2-3, *Structure and Function of Macromolecules* exam paper (2009-2010)

Lectures, Practicals and Workshops:

First Year Topics: Biochemical Thermodynamics, Biomolecular Spectroscopy, Chemistry and Structure of Proteins, Reaction Mechanisms, Reaction Kinetics

Second Year Topics: Data Analysis and Interpretation, Enzymology, Molecular Graphics, Protein Structure, Protein Folding, Protein Allostery, Protein-Nucleic Acid Interactions, Interaction Proteomics, Structure and Function of Antibodies

Third Year Topics: Programmed Cell Death, Quantitative Data Handling

M.Res./M.Sc. Topics: Antibody Structure and Function, Biomolecular Mass Spectrometry, Immunological Signal Transduction, NMR Spectroscopy, Structure-Based Drug Design

University Committees, Management and Administration

Head, Molecular Biophysics Section, Randall Centre for Cell & Molecular Biophysics (2023-present)

Lead, KCL Antibody Research Interest Group (2023-present)

Postgraduate Coordinator, Randall Centre (2012-2022)

Deputy Head, Asthma & Allergy Section, Randall Centre (2014-2022)

King's College London Core Facilities Committee (2011-2017)

KCL Mass Spectrometry Steering Committee (2012-2018)

Biochemistry Teaching Committee (2010-present)

Dean, Somerville College, Oxford University (2007-2009)

Somerville College, Oxford: Governing Body, Education Committee, Housing & Welfare Committee, Library Committee, Buildings Committee (2000-2010)

Department of Biochemistry, Oxford University: Teaching Committee, Steering Committee, Core Services and Equipment Committee (2000-2010)

Numerous admissions, examinations, recruitment and appointment committees (2000-present)

External Examiner, Department of Biochemistry, Edinburgh University (2018-2024)

Grant and Journal reviewing

Journal Editorial Boards: Antibodies, *Frontiers in Molecular Biosciences*

Journal reviewing (in the last two years) for *Acta Crystallographica* Section D, *Antibodies*, *Biochemistry*, *Cell*, *Cellular and Molecular Life Sciences*, *Current Opinion in Chemical Biology*, *Current Opinion in Immunology*, *FEBS Letters*, *European Biophysics Journal*, *Journal of Biological Chemistry*, *Journal of Molecular Biology*, *Journal of the American Chemical Society*, *mAbs*, *Nature*, *Nature Communications*, *Nature Reviews Drug Development*, *PLoS ONE*, *Spectroscopy*

Grant reviewing (in the last two years) for BBSRC, EPSRC, MRC, National Health Service, The Wellcome Trust, Asthma + Lung UK, Austrian Science Fund, Research Foundation Flanders, Swiss National Science Foundation

Publications

- A.M. Chenoweth, A. Cheung, J. Chauhan, R. Adams, G. Osborn, K. Stoker, M. Grandits, R. Laddach, J. Trendell, A. McCraw, B. Esapa, S. Haider, J. Quist, K.M. Ilieva, A.M. Davies, P. Romero-Clavijo, T. Senard, J. Cheeseman, R.A. Gardner, D. I. R. Spencer, S. Tsoka, S. Irshad, J.M. McDonnell, A. Grigoriadis, A.N.J. Tutt and S.N. Karagiannis (2025) An Fc-engineered glycomodified antibody supports immune effector cell pro-inflammatory activation and restricts breast cancer growth. **Cancer Research** 85:4521-4540 (doi: 10.1158/0008-5472.CAN-24-3174)
- A.I. Adam, B.J. Sutton and J.M. McDonnell (2025) Biophysical and functional characterization of an IgE interactions with a malaria antigen. **Biochem Biophys Research Comm** 792:152938 (doi: 10.1016/j.bbrc.2025.152938)
- S.K. Vester, R.L. Beavil, A. Alexandrovich, H.J. Gould, A.J. Beavil, B.J. Sutton, and J.M. McDonnell (2025) Anti-IgD nanobodies as novel tools for studying human IgD biology. **Scientific Reports** 15: 24455 (doi: 10.1038/s41598-025-09118-4)
- A.M. Davies, T.T.T. Bui, R. Pacheco-Gómez, S.K. Vester, A.J. Beavil, H.J. Gould, B.J. Sutton and J.M. McDonnell (2024) The crystal structure of human IgD-Fc reveals unexpected differences with other antibody isotypes. **Proteins** 93:786-800 (doi:10.22541/au.172490476.65094176)
- C.A. Whitehead, B.D. Wines, A.M. Davie, J.M. McDonnell, H.M. Trist, S.E. Esparon and P.M. Hogarth (2024) Stellabody: A novel hexamer-promoting mutation for improved IgG potency. **Immunological Reviews** 328:438-455 (doi: 10.1111/imr.13400)
- A.J. McCraw, L.C. Palhares, J. Hendel, A. Santaolalla, S. Crescioli, J.M. McDonnell, M.V. Hemelrijck, A. Chenoweth, D.I.R. Spencer, G.K. Wagner and S.N. Karagiannis (2024) IgE Glycosylation and Impact on Structure and Function: A Systematic Review. **Immunology** 23:13455 (doi: 10.1111/all.16259)
- S.K. Vester, A.M. Davies, R.L. Beavil, B.S. Sandhar, A.J. Beavil, H.J. Gould, B.J. Sutton and J.M. McDonnell (2023) Expanding the Anti-Phl p 7 Antibody Toolkit: An Anti-Idiotypic Nanobody Inhibitor. **Antibodies** 12:75 (doi: 10.3390/antib12040075)
- A.M. Davies, R.L. Beavil, M. Barbolov, B.S. Sandhar, H.J. Gould, A.J. Beavil, B.J. Sutton and J.M. McDonnell (2023) Crystal structures of the human IgD Fab reveal insights into C_H1 domain diversity. **Mol Immunol** 159:28-37 (doi: 10.1016/j.molimm.2023.05.006)
- J.M. McDonnell, B. Dhaliwal, B.J. Sutton and H.J. Gould (2023) IgE, IgE Receptors and Anti-IgE Biologics: Protein Structures and Mechanisms of Action. **Annual Review of Immunology** 41:255-275 (doi: 10.1146/annurev-immunol-061020-053712)
- A.J. McCraw, R.A. Gardner, A.M. Davies, D.I.R. Spencer, M. Grandits, G.K. Wagner, J.M. McDonnell, S.N. Karagiannis, A. Chenoweth, S. Crescioli (2022) Generation and Characterization of Native and Sialic Acid-Deficient IgE. **Int J Mol Sci** 23:13455. (doi: 10.3390/ijms232113455)
- C. Pollard, M. Hudson, J.M. McDonnell, P.G. Royall, and K. Wolff (2022) Development of a point-of-care test for the detection of MDMA in latent fingerprints using surface plasmon resonance and lateral flow technology. **Drug Test Anal** 14:613-621 (doi: 10.1002/dta.3196)
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- S.K. Vester, R.L. Beavil, S. Lynham, A.J. Beavil, D.S. Cunningham-Graham, J.M. McDonnell and T.J. Vyse (2021) Nucleolin acts as the receptor for C1QTNF4 and supports C1QTNF4-mediated innate immunity modulation. **J. Biol. Chem.** 296:100513 (doi: 10.1016/j.jbc.2021.100513)
- S.V. Benjamin, P.I. Creeke, A.J. Henry and J.M. McDonnell (2020) NMR backbone assignment of the Cε4 domain of immunoglobulin E. **Biomolecular NMR Assignments** 14:1-5 (doi: 10.1007/s12104-020-09936-9)
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- A.N. Mitropoulou, T. Ceska, J.T. Heads, A.J. Beavil, A.J. Henry, J.M. McDonnell, B.J. Sutton and A.M. Davies (2020) Engineering the Fab Fragment of the anti-IgE Omalizumab to Prevent Fab Crystallization and Permit IgE-Fc Complex Crystallization. **Acta Crystallogr F** 76:116-129 (doi: 10.1107/S2053230X20001466)
- G. Bucaite, T. Kang-Pettinger, J. Moreira, H.J. Gould, J.K. James, B.J. Sutton, and J.M. McDonnell (2019) Interplay between Affinity and Valency in Effector Cell Degranulation: A Model System with Polcalcin Allergens and Human Patient-Derived IgE Antibodies. **J. Immunol.**, 203:1693-1700 (doi: 10.4049/jimmunol.1900509)
- S. Dimeloe, L.V. Rice, H. Chen, C. Cheadle, J. Raynes, P. Pfeffer, P. Lavender, D.F. Richards, M.P. Nyon, J.M. McDonnell, C. Kemper, B. Gooptu and C.M. Hawrylowicz (2019) Vitamin D (1,25(OH)2D3) induces α -1-antitrypsin synthesis by CD4+ T cells, which is required for 1,25(OH)2D3-driven IL-10. **J Ster Bioch Mol Biol** 189:1-9 (doi: 10.1016/j.jsbmb.2019.01.10.014)
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- K.A. Doré, A.M. Davies, N. Drinkwater, A.J. Beavil, J.M. McDonnell and B.J. Sutton (2017) Thermal sensitivity and flexibility of the C ϵ 3 domains in immunoglobulin E. **Biochim Biophys Acta** 1865:1336-1247 (doi: 10.1016/j.bbapap.2017.08.005)
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Appendix B

LIST OF MATERIALS CONSIDERED

Exhibit	Description
1001	U.S. Patent No. 12,297,278
1003	Declaration of Michael Kahn, Ph.D.
1004	International Patent Publication No. WO 2016/040895 A1
1005	U.S. Provisional Application No. 62/607,875
1006	U.S. Provisional Application No. 62/641,217
1007	U.S. Provisional Application No. 62/680,522
1008	File History of U.S. Patent No. 12,297,278
1009	Zuhaida A. Ahmad, et. al., <i>scFv antibody: principles and clinical application</i> , 2012 CLIN. DEV. IMMUNOL. 1-15 (2012).
1010	Vahideh Ahmadzadeh, et al., <i>Antibody humanization methods for development of therapeutic applications</i> , 33 MONOCLON. ANTIB. IMMUNODIAGN. IMMUNOTHER. 67-73 (2014).
1011	U.S. Publication No. 2017/0306029 A1 (“Garcia US”)
1012	Chengbin Wu, et al., <i>Simultaneous targeting of multiple disease mediators by a dual-variable-domain immunoglobulin</i> , 25 NAT. BIOTECH. 1290-1297 (2007).
1013	Tapan K. Bera, et al., <i>A bivalent disulfide-stabilized Fv with improved antigen binding to erbB2</i> , 281 J. MOL. BIOL. 475-483 (1998).
1014	International Patent Publication No. WO 2020/018445 A1
1017	Ulrich Brinkmann and Roland E. Kontermann, <i>The making of bispecific antibodies</i> , 9 MABS 182-212 (2017).
1020	Angel M. Cuesta, et al., <i>Multivalent antibodies: when design surpasses evolution</i> , 28 TRENDS BIOTECHNOL. 355-362 (2010).

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1024	Enrico L. DiGiammarino, et al., <i>Ligand association rates to the inner-variable-domain of a dual-variable-domain immunoglobulin are significantly impacted by linker design</i> , 3 MABS 487-494 (2011).
1027	Yan Gong, et al., <i>Wnt isoform-specific interactions with coreceptor specify inhibition or potentiation of signaling by LRP6 antibodies</i> , 5 PLoS ONE e12682 (2010).
1038	Claudia Y. Janda, et al., <i>Structural basis of Wnt recognition by Frizzled</i> , 337 SCIENCE 59-64 (2012).
1039	Kenneth Murphy and Casey Weaver, JANEWAY'S IMMUNOBIOLOGY (9th ed. 2017).
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1044	Jiyaun Ke, et al., <i>Structure and function of Norrin in assembly and activation of a Frizzled 4-Lrp5/6 complex</i> , 27 GENES DEV. 2305-2319 (2013).
1047	Daisuke Kuroda, et al., <i>Computer-aided antibody design</i> , 25 PROTEIN ENG. DES. 507-521 (2012).
1049	Julien Lescar, et al., <i>Crystal structure of a cross-reaction complex between Fab F9.13.7 and guinea fowl lysozyme</i> , 270 J. BIOL. CHEM. 18067-18076 (1995).
1051	Hongyan Liu, et al., <i>Fc engineering for developing therapeutic bispecific antibodies and novel scaffolds</i> , 8 FRONT. IMMUNOL. 1-15 (2017).
1054	Bryan T. MacDonald and Xi He, <i>Frizzled and Lrp5/6 receptors for Wnt/β-catenin signaling</i> , 4 COLD SPRING HARB. PERSPECT. BIOL. 1-23 (2012).

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1056	Amanda J. Mikels and Roel Nusse, <i>Purified Wnt5a protein activates or inhibits β-catenin-TCF signaling depending on receptor context</i> , 4 PLoS BIOL. 570-582 (2006).
1059	Aaron L. Nelson, <i>Antibody fragments</i> , 2 MABS 77-83 (2010).
1063	Roel Nusse and Hans Clevers, <i>Wnt/β-catenin signaling, disease, and emerging therapeutic modalities</i> , 169 CELL 985-999 (2017).
1064	Mattia Pedotti, et al., <i>Computational docking of antibody-antigen complexes, opportunities and pitfalls illustrated by influenza hemagglutinin</i> , 12 INT. J. MOL. SCI. 226-251 (2011).
1065	Tata P. Rao and Michael Kuhl, <i>An updated overview on Wnt signaling pathways</i> , 106 CIRC. RES. 1798-1806 (2010).
1066	Dan-ni Ren et al., <i>Lrp5/6 directly bind to Frizzled and prevent Frizzled-regulated tumour metastasis</i> , 6 NAT. COMM. 1-13 (2015).
1069	Christoph Spiess, et al., <i>Alternative molecular formats and therapeutic applications for bispecific antibodies</i> , 67 MOL. IMMUNOL. 95-106 (2015).
1072	Yuyong Tao, et al., <i>Tailored tetravalent antibodies potently and specifically activate Wnt/Frizzled pathways in cells, organoids and mice</i> , 8 ELIFE e46134 (2019).
1074	Martijn van Rosmalen, et al., <i>Tuning the flexibility of glycine-serine linkers to allow rational design of multidomain proteins</i> , 56 BIOCHEM. 6565-6574 (2017).
1077	Yanshu Wang, et al., <i>Frizzled receptors in development and disease</i> , 117 CURR. TOP. DEV. BIOL. 1-28 (2016).
1078	Janusz Wesolowski, et al., <i>Single domain antibodies: promising experimental and therapeutic tools in infection and immunology</i> , 198 MED. MICROBIOL. IMMUNOL. 157-174 (2009).

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1079	John L. Xu and Mark M. Davis, <i>Diversity in the CDR3 region of V_H is sufficient for most antibody specificities</i> , 13 IMMUNITY 37-45 (2000).
1081	International Patent Publication No. WO 2020/010308 (“Li”)
1089	Peter Bannas, et al., <i>Nanobodies and nanobody-baed human heavy chain antibodies as antitumor therapeutics</i> , 8 FRONT. IMMUNOL. 1-13 (2017).
1090	<i>FDA approves emicizumab-kxwh for prevention and reduction of bleeding in patients with hemophilia A with factor VIII inhibitors</i> , (c. Nov. 16, 2017) U.S. FDA, https://www.fda.gov/drugs/resources-information-approved-drugs/fda-approves-emicizumab-kxwh-prevention-and-reduction-bleeding-patients-hemophilia-factor-viii (Retrieved on Feb. 9, 2026).
1091	U.S. Patent No. 11,773,171
1093	Wim de Lau, et al., <i>Lgr5 homologues associate with Wnt receptors and mediate R-spondin signalling</i> , 476 NATURE 293-298 (2011).