

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

U.S. PATENT NO. 12,297,278

DECLARATION OF DR. JEFFREY RAVETCH

TABLE OF CONTENTS

I.	INTRODUCTION	1
II.	SUMMARY OF OPINIONS.....	1
III.	QUALIFICATIONS.....	2
IV.	MATERIALS CONSIDERED	8
V.	LEVEL OF ORDINARY SKILL IN THE ART	8
VI.	LEGAL STANDARDS.....	9
A.	Claim Construction	9
B.	Written Description	10
C.	Enablement.....	11
D.	Indefiniteness.....	13
E.	Anticipation	13
VII.	BACKGROUND AND THE STATE OF THE ART	14
A.	Antibody Engineering Was a Mature Field in 2017	14
B.	A POSA Could Generate a Wide-Range of Antigen-Binding Fragments Using Known Methods.....	27
C.	Multivalent, Multispecific Antibodies Could Be Synthesized, But Required Specific Structural Guidance	32
D.	The Wnt Signaling Pathway Was Well-Characterized and Extensively Studied as of 2017	43
VIII.	THE '278 PATENT	49
A.	Disclosures of the '278 Patent.....	49
B.	Effective Filing Date	59
C.	Challenged Claims	59

D.	Prosecution History of the '278 Patent	61
IX.	CLAIM CONSTRUCTION.....	66
A.	“Wnt Surrogate Molecule”	67
B.	“Wherein Each of the Two LRP5/6 Binding Regions Is Fused to One of the Two Fzd Binding Regions via a Linker Moiety”	72
1.	“Fused ... via a Linker Moiety”	73
2.	“One of the Two Fzd Binding Regions”	81
X.	CLAIMS 1-5 ARE SUPPORTED BY ADEQUATE WRITTEN DESCRIPTION.....	88
A.	Claim 1 Is Supported By Adequate Written Description.....	88
1.	Claim 1’s Breadth Is Bounded By Several Features, and Is Supported By Representative Examples in the Specification.....	88
2.	The '278 Patent Discloses Its Claimed Structure Reliably Agonizes Wnt Signaling	144
3.	The '278 Patent Discloses Structural Features Common to the Full Scope of Claim 1	158
4.	Dr. McDonnell’s “Other Reasons” Are Duplicative and Do Not Render the '278 Patent Deficient	169
5.	The Presence of Purportedly Later-Arising Formats Does Not Change My Written Description Opinions	170
B.	Claims 2–5 Are Supported By Adequate Written Description.....	172
1.	Claims 2, 3, and 5	172
2.	Claim 4	174
XI.	CLAIMS 1-5 ARE ENABLED	174
A.	Claim 1 Is Enabled	174

1.	Claim 1 Is Structurally and Functionally Bounded in Scope.....	174
2.	The Specification Provides Ample Working Examples and Guidance.....	177
3.	The Relevant Art Was Mature	183
4.	The Level of Skill in the Art Was High.....	186
5.	The Amount of Experimentation Required Was Not Undue	186
6.	The Presence of Purportedly Later-Arising Formats Does Not Change My Enablement Opinions.....	194
B.	Claims 2–5 Are Enabled	195
XII.	CLAIMS 1-5 ARE DEFINITE	196
A.	“Wnt Surrogate Molecule” Has Reasonable Certainty	196
B.	My Construction of the “Linker” Limitation Does Not Make the Claims Incomprehensible	213
XIII.	CLAIMS 1 AND 4 ARE NOT ANTICIPATED BY GARCIA	218
A.	Garcia Does Not Anticipate Claim 1	218
1.	Garcia Does Not Disclose “a Soluble Tetravalent, Multispecific Wnt Surrogate Molecule” Comprising “Two Fzd Binding Regions” and “Two LRP5/6 Binding Regions”	218
2.	Garcia Does Not Disclose “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”	227
3.	Garcia Does Not Disclose “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	228
4. Garcia Does Not Disclose That “Each of the Two LRP5/6 Binding Regions Is Fused to One of the Two Fzd Binding Regions via a Linker Moiety”	229
B. Garcia Does Not Anticipate Claim 4	230
XIV. CONCLUSION	231

I. INTRODUCTION

1. My name is Jeffrey Ravetch, Ph.D. I have been retained by Surrozen Operating, Inc. (“Surrozen” or “Patent Owner”) as an independent expert in the field of immunology and molecular biology, including antibody design/engineering, in connection with this post-grant review proceeding. I understand this proceeding concerns Surrozen’s U.S. Patent No. 12,297,278 (the “’278 Patent”). The ’278 Patent covers tetravalent Wnt surrogate molecules that contain two Frizzled receptor (“Fzd”) binding regions and two low-density lipoprotein receptor-related protein 5 or 6 (“LRP5/6”) binding regions. *See* EX1001 at cls. 1–5.

2. I understand from counsel for Surrozen that on February 12, 2026, Merck Sharp & Dohme LLC (“Merck” or “Petitioner”) filed a Petition seeking post-grant review of U.S. Patent No. 12,297,278 and cancellation of its claims. I understand Merck alleges that claims 1–5 of the ’278 Patent are invalid for lack of enablement, inadequate written description, and indefiniteness, and that claims 1 and 4 are anticipated by International Patent Publication No. WO 2016/040895 A1 (“Garcia,” EX1004).

II. SUMMARY OF OPINIONS

3. I understand that Merck has retained the following experts:

- Professor James McDonnell, Ph.D., who provided an expert declaration dated February 11, 2026 (“McDonnell Declaration”); and

- Professor Michael Kahn, Ph.D., who provided an expert declaration dated February 10, 2026 (“Kahn Declaration”).

4. I have been asked by Counsel for Surrozen to provide my opinions regarding the validity of the '278 Patent, and to respond to the opinions of Merck's experts regarding the validity of the '278 Patent.

5. It is my opinion that claims 1–5 (all claims) of the '278 Patent are not invalid for lack of written description, lack of enablement, or indefiniteness. In addition, it is my opinion that Garcia does not anticipate either of claims 1 and 4. It is also my opinion that Merck's experts have failed to show that claims 1–5 are invalid under any of the grounds for invalidity asserted by Merck's experts (including anticipation, written description, enablement, and indefiniteness).

III. QUALIFICATIONS

6. My Curriculum Vitae, which contains information pertaining to my education, experience, and qualifications in the field of immunology, microbiology, cellular biology, and molecular genetics, as well as a list of my publications within at least the preceding 10 years, and publications on relevant subject matter, is provided as EX2013.

7. I am an M.D./Ph.D. specializing in molecular genetics and immunology and particularly the structure and function of antibodies and the interactions between antibodies and their receptors on immune cells. My research has focused on the

mechanisms by which antibodies generate diversity and the translation of that diversity into physiological responses. As a result of my work on antibody diversification of effector responses, novel therapeutic antibodies have been developed and approved for the treatment of inflammatory and neoplastic diseases. I have over 40 years of academic and research experience in the area of immunology. Currently, I am the Theresa and Eugene M. Lang Chair and head of the Leonard Wagner Laboratory of Molecular Genetics and Immunology at The Rockefeller University (“Rockefeller”).

8. I earned a Bachelor of Science degree at Yale University in 1973 in molecular biophysics and biochemistry. In 1978, I earned a Ph.D. at Rockefeller, where I completed my research in the Laboratory of Genetics under Norton Zinder and Peter Model. In 1979, I completed my M.D. at Cornell University Medical College.

9. From 1979 to 1982, I completed postdoctoral training in the Laboratory of Molecular Genetics at the National Institutes of Health under Philip Leder. Dr. Leder was a pioneering researcher in molecular genetics, helping to determine the genetic code and elucidate genes underlying immune proteins and genes involved in cancer. During my postdoctoral studies, I characterized genes for human antibodies and genetic elements involved in producing variability in the variable domains and heterogeneity in the constant domain of antibodies. Those studies established the

genetic elements involved in diversification of the variable domains and the mechanisms by which effector domains are diversified.

10. In 1982, I established my own laboratory at Memorial Sloan-Kettering Cancer Center (“MSKCC”). I was an Assistant Faculty Member of the Division of Molecular Biology at MSKCC from 1982 to 1986, an Associate Faculty Member from 1986 to 1990, and a Full Faculty Member from 1990 to 1996. My laboratory researched the genetics of the immune system with a particular focus of understanding how effector functions are triggered by antibodies. Under my leadership, the laboratory characterized the structure and function of the “Fc” domains of antibodies as well as the Fc receptors (“FcRs”) that recognize them. We further characterized the regulation of the expression of antibodies and different domains of antibodies, including in response to signaling molecules like interferon- γ . Our studies resulted in a new paradigm to account for the inflammatory properties of antibodies that are triggered by the engagement of specific Fc domains to Fc receptors. These interactions underlie the basis for inflammatory diseases caused by autoantibodies, as are found in autoimmune diseases like lupus and rheumatoid arthritis and form the basis for the therapeutic activity of anti-tumor antibodies like Herceptin and Rituximab.

11. From 1986 to 1990, I served as the Associate Attending in the Division of Medical Oncology, Hematology-Lymphoma Service, Department of Medicine, at

MSKCC. From 1990 to 1996, I served as an Attending in the Division of Hematologic Oncology in the Department of Medicine at Memorial Hospital for Cancer and Allied Diseases.

12. In 1996, I returned to Rockefeller as a Professor and was named the Theresa and Eugene M. Lang Chair in 1997. Since 1996 and continuing today, my laboratory studies the mechanisms of Fc and FcR interactions as well as the role these interactions play in coordinating immune system responses and treatments for disease. We have advanced novel therapeutic antibodies into clinical trials, optimized for their activity by selective modification of the Fc domain to engage specific Fc receptors.

13. I have published over 250 peer-reviewed scientific articles and book chapters, the vast majority of which are related to immunoglobulin G (“IgG”) antibodies, Fc and FcR structure and function, and regulation of the immune system. I have published several articles and book chapters over the past 30 years studying Fc structure, Fc function, and modifications of the Fc domain to alter the function of antibodies in disease and treatment of disease. *See e.g.*, Stylianos Bournazos, et al., Fc-optimized antibodies elicit CD8 immunity to viral respiratory infection, 588 Nature 485 (2020) (“Bournazos 2020”); Stylianos Bournazos, et al., Human IgG Fc Domain Engineering Enhances Antitoxin Neutralizing Antibody Activity, 124 J. Clinical Investigation 725 (2014) (“Bournazos 2014”); Lucie Baudino, et al., Impact

of a Three Amino Acid Deletion in the CH2 Domain of Murine IgG1 on Fc-Associated Effector Functions, 181 J. Immunology 4107 (2008); Toshiyuki Takai, et al., FcR γ Chain Deletion Results in Pleiotropic Effector Cell Defects, 76 Cell 519 (1994). I further published two highly cited reviews on FcRs including a review in Nature Reviews Immunology titled “Fc γ Receptors as Regulators of Immune Responses” (cited over 2750 times) and a review in Annual Review of Immunology titled “Fc receptors” (cited over 2190 times). See Falk Nimmerjahn and Jeffrey V. Ravetch, Fc γ receptors as regulators of immune responses, 8 Nature Reviews Immunology 151 (2008); Jeffrey V. Ravetch and Jean-Pierre Kinet, Fc receptors, 9 Ann. Rev. Immunology 457 (1991).

14. I am also a named inventor on several patents on engineered antibodies and FcRs. For example, I am a named inventor on U.S. Patent No. 8,618,251 titled “Fc mutants” and on U.S. Patent No. 7,038,031 titled “DNA encoding Fc γ R receptor protein on NK cells.”

15. For my work, I have been recognized with several international awards. In 2006, I was elected a member of the National Academy of Sciences in the section of Immunology and Inflammation. In 2008, I was elected a Fellow of the American Academy of Arts and Sciences. In 2012, I received both the Gairdner International Award and the Sanofi-Institut Pasteur Award. The Gairdner International Award recognizes “outstanding researchers whose unique scientific contributions have

increased the understanding of human biology and disease” while the Sanofi-Institut Pasteur Award recognizes “scientists for their past or ongoing research demonstrating real scientific progress in the life sciences.” Most recently, I received the Wolf Prize in Medicine (2015), the Ross Prize (2017), the Robert Koch Award (2018) and the William Paul Memorial Award (2021) and the Emory Max Cooper Prize in Immunology (2025) for my contributions to dissecting the mechanisms of antibody effector function and its role in antibody therapeutics. For my work in immunology, I received an honorary doctorate from the Friedrich-Alexander-University Erlangen-Nuremberg in 2013.

16. I am a consultant and a member of the scientific advisory boards for a variety of biotechnology and pharmaceutical companies in the area of antibody design and their therapeutic applications. I have founded several biotechnology companies in the area of therapeutic antibody discovery.

17. I am a frequent lecturer at academic conferences and university seminars and have served on the advisory boards of several philanthropic organizations focused on biomedical research.

18. I am being compensated at my usual consulting rate of \$1,500 per hour for my work on this matter. I also am being reimbursed for reasonable and customary expenses associated with my work and testimony in this investigation. My

compensation is not dependent upon my opinions or testimony or the outcome of this proceeding.

IV. MATERIALS CONSIDERED

19. In forming my opinions, I reviewed and considered the materials cited in this report, in addition to those listed in Appendix A. I have also relied on my education, background and significant experience of more than 40 years in the field of immunology and molecular biology. I have also considered the information and expert opinions provided in the Expert Declaration of Dr. Karl Willert, dated May 22, 2025 (“Willert Declaration”) (EX2010).

V. LEVEL OF ORDINARY SKILL IN THE ART

20. I have been informed that patents are to be read from the perspective of a person of ordinary skill in the art (“POSA”) at the time of the invention, and I have been asked to respond to Dr. McDonnell’s opinion regarding the level of skill in the relevant art.

21. Dr. McDonnell asserts that a POSA would have been someone having “a Ph.D. degree in immunology, molecular biology, chemistry, or biochemistry[,] with at least five years of experience in antibody engineering or Wnt signaling.” EX1002

¶ 21. Given the claimed invention’s focus on antibody-derived structures, however, in my opinion, a POSA would have had a Ph.D. degree in immunology, molecular biology, chemistry, or biochemistry with at least five years of experience in antibody

engineering and either (i) would themselves have at least two years of experience with Fzd and/or LRP receptors and/or Wnt signaling, or (ii) have access to someone with such experience in Fzd and/or LRP receptors and/or Wnt signaling, or would be part of a team whose members collectively have equivalent experience. The person of ordinary skill in the art may also have access to other persons of ordinary skill in the art with complementary experience in antibody engineering, Fzd and LRP receptors, and/or Wnt signaling.

22. As discussed above, I meet the definition of a POSA for the '278 Patent as of December 2017 under Dr. McDonnell's definition and under my own definition, with access to Professor Willert's complementary experience in Fzd and LRP receptors and Wnt signaling. *See* ¶¶ 6–17, above; EX2010 ¶¶ 4–10. For the purposes of my opinions below, I apply my own definition of a POSA. I note, however, that my opinions would not change under Dr. McDonnell's definition.

VI. LEGAL STANDARDS

23. Counsel for Surrozen have informed me of certain relevant legal principles relating to patent validity, which I apply in my analysis as set forth herein.

A. Claim Construction

24. I understand from counsel for Surrozen that terms in a patent claim are to be interpreted or construed as understood by a POSA at the time of the effective filing date—here, December 19, 2017. I also understand that claim terms are generally to

be given their plain and ordinary meaning, which is the meaning that a POSA would ascribe when reading the term in context of the claim, specification, and prosecution history.

25. I understand that an interpretation of a claim term may depart from its plain and ordinary meaning only under certain circumstances, and that one such instance is when the inventors acted as lexicographers by providing a specific definition in the patent specification. I understand, however, that for the inventors to have acted as their own lexicographers, they must have clearly set forth a definition of a claim term other than its plain and ordinary meaning and must have clearly defined the term.

26. In addition, I understand that patent claims may contain an introductory phrase or “preamble” before the claim’s technical features or “limitations.” I understand that preamble language that merely states the purpose or intended use of an invention is generally not treated as a claim limitation (*i.e.*, it does not limit the scope of the claim) and thus need not be construed.

B. Written Description

27. I understand that, pursuant to the “written description” requirement, the patent’s specification must offer sufficient description of the claimed invention to convey to a POSA that the patentee was in possession of the claimed invention at the time the patent application was filed.

28. I have been informed that the level of detail required to fulfill the written description requirement varies according to what was already known in the art. I have also been informed that the specification does not need to include every aspect known in the art to establish that the inventors possessed the claimed invention.

29. I understand that there are a variety of ways to satisfy the written description requirement, including by words, structures, figures, diagrams, or formulas that fully set forth the claimed invention and show the applicant was in possession of the claimed invention. I have been informed that the specification is not required to include an actual reduction to practice or working examples. I have been informed that the specification is not required to show physical possession of every species and/or embodiment of the claimed invention.

30. I have also been informed that the written description requirement may be satisfied for genus claims if the specification discloses a representative number of species or structural features common to the members of the genus, such that a POSA can recognize or visualize the members of the genus.

31. I understand that the adequacy of a patent's written description is assessed as of the patent's priority date.

C. Enablement

32. I understand that, pursuant to the "enablement" requirement, a patent specification must teach a POSA how to make and use the invention claimed without

undue experimentation. I also understand that, in evaluating whether undue experimentation would be required, the following factors, known as the *Wands* factors, may be considered: (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims.

33. I understand the specification is not required to disclose every species encompassed by the claims, even if the invention is in an unpredictable art, and does not need to describe how to make and use every possible embodiment of the claims.

34. I understand the specification is not required to teach what is well known in the art. I have been informed that the fact that necessary experimentation may be complex or time-consuming does not necessarily make it undue if it applies known methods and/or the specification guides how the invention is practiced.

35. I understand the enablement analysis considers each claim as a whole, rather than each element in isolation.

36. I understand that the inventor need not have carried out each aspect of a claim, nor does each aspect need to be exemplified in the specification. I have also been informed that working examples are not required for enablement where a POSA would be able to practice the invention without undue experimentation based

on the disclosures in the patent's specification. Additionally, I understand that it is not required for enablement that a skilled artisan could practice the entire scope of the claims within a short period of time.

37. I understand that the enablement requirement is assessed as of the patent's priority date.

D. Indefiniteness

38. I understand that the specification must conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the inventor or a joint inventor regards as the invention. I understand that the "definiteness" requirement requires a patent, read in light of the specification and prosecution history, to inform a POSA of the scope of the invention with reasonable certainty.

E. Anticipation

39. I understand that a claim may be invalid as "anticipated" only if a single prior art reference (e.g., a product, patent, publication, etc.) discloses each and every limitation of the claim, arranged as in the claim, either expressly or inherently. I understand that a reference is not anticipatory as to an asserted claim if any limitation of that claim is not disclosed, either expressly or inherently.

40. For a prior art reference to disclose a claim limitation inherently, I understand the limitation must necessarily result from the reference's disclosures,

and that a mere possibility or probability that the limitation results from the reference's disclosures is not sufficient for anticipation.

41. I understand that anticipation is evaluated based on the publicly available prior art at the time the invention was made.

42. I understand that a prior art reference must enable a POSA to practice the claimed invention without undue experimentation in order to be anticipatory.

VII. BACKGROUND AND THE STATE OF THE ART

43. Dr. McDonnell's declaration purports to provide background information on the state of the art as of 2017 with respect to antibody engineering and Wnt signaling mechanisms. My responses to Dr. McDonnell's discussion of the state of the art are given throughout this report, but I directly address several of his characterizations in this section.

A. Antibody Engineering Was a Mature Field in 2017

44. Paragraphs 40–50 of Dr. McDonnell's report address the alleged unpredictability in the field of antibody research in 2017. Specifically, Dr. McDonnell asserts that "[a]s of 2017, a POSA could not reliably predict which antibody would bind a particular target antigen (or epitope therein)," EX1002 ¶ 40, but omits that making such predictions is neither necessary nor used in the field to generate antibodies that bind particular antigens. Instead, as the '278 Patent makes clear, in 2017, a POSA would have been able to use the wealth of information at

their disposal—developed from more than four decades of research in the field—and apply methods that were known at the time to successfully obtain antibodies that bound specific epitopes, including those on Fzd and LRP5/6 antigens. *See* ¶¶ 89–98, below.

45. Dr. McDonnell correctly acknowledges that “[b]y 2017, several methods for making antibodies against an antigen of interest in the laboratory were known in the art.” EX1002 ¶ 45; *see also* EX1001 at 13:32–33 (listing several antibody generation methods, “e.g., by hybridoma, phage selection, recombinant expression, transgenic animals, etc.”). But Dr. McDonnell then inaccurately states that “each method was labor-intensive and subject to variable known and unknown factors that could unpredictably impact the successful generation of candidate antibodies.” *Id.* I disagree. By 2017, once a target antigen was known, methods of antibody generation existed that efficiently and reliably created target-antigen binding candidate molecules with a high degree of success. *See* ¶¶ 46–53, below; EX1001 at 13:30–16:35.

46. Dr. McDonnell also discusses immunization methods of generating antibodies, called “monoclonal” antibodies or “hybridoma-derived” antibodies. *See* EX1002 ¶ 47; *see also* EX1001 at 13:14–17 (“A ‘monoclonal antibody’ refers to a homogeneous antibody population wherein the monoclonal antibody is comprised of amino acids (naturally occurring and non-naturally occurring) that are involved

in the selective binding of an epitope.”). The first antibodies made using this technique were produced in 1975. EX2023 at 1. And, as Dr. McDonnell’s own cited reference from 2017 explains, “[e]xperimental immunizations [we]re routinely carried out by injecting the test antigen into the animal or human subject.” EX1039 at 125. Thus, by 2017, researchers in the field had the benefit of over four decades of literature on how to generate antibodies that bind to a specific antigen using immunization methods. Further, while Dr. McDonnell alleges that “[g]enerating a single monoclonal antibody by this approach typically takes several weeks to months,” he omits that by 2017, techniques such as phage display were capable of discovering new antibodies in a shorter time span, and that recombinant expression methods could be used to quickly generate antibodies whose sequences were already known. *See* ¶¶ 48–50, below.

47. While Dr. McDonnell observes that “[t]he administration route, dose, and form in which the antigen is administered [in the hybridoma method] can profoundly affect whether and how the immune response occurs,” EX1002 ¶ 46, his own cited references acknowledge that by 2017, scientists knew how to administer an antigen to generate hybridoma-derived antibodies. For example, Dr. McDonnell’s own reference states that subcutaneous administration was the “method most commonly used when the object of the experiment is to elicit specific antibodies or T cells against a given antigen.” EX1039 at 127. Similarly, researchers in the field had

designed various injection mixtures known as “adjuvants” that could enhance the immune system’s response to the antigen and could be used to modulate the immune system’s response in various ways. *See* Table 1, below. These variables were thus not a source of unpredictability in the hybridoma process, as Dr. McDonnell implies.

Table 1: Exemplary Adjuvants as of 2017 (see EX1039 at 127)

Adjuvants that enhance immune responses		
Adjuvant name	Composition	Mechanism of action
Incomplete Freund’s adjuvant	Oil-in-water-emulsion	Delayed release of antigen; enhanced uptake by macrophages
Complete Freund’s adjuvant	Oil-in-water emulsion with dead mycobacteria that stimulate C-type lectin receptors	Delayed release of antigen; enhanced uptake by macrophages; induction of co-stimulators in macrophages
Freund’s adjuvant with MDP	Oil-in-water emulsion with muramyl dipeptide (MDP), a constituent of mycobacteria that stimulates NOD-like receptors	Similar to complete Freund’s adjuvant
Alum (aluminum hydroxide)	Aluminum hydroxide gel	Delayed release of antigen; enhanced macrophage uptake
Alum plus <i>Bordetella pertussis</i>	Aluminum hydroxide gel with killed <i>B. pertussis</i>	Delayed release of antigen; enhanced uptake by macrophages; induction of co-stimulators

Immune stimulatory complexes (ISCOMs)	Matrix of Quil A containing viral proteins	Delivers antigen to cytosol; allows induction of cytotoxic T cells
TLR agonists	Lipopolysaccharide, flagellin, lipopeptides, ds-RNA, unmethylated DNA	Inflammatory cytokine production, induction of co-stimulators, enhanced antigen presentation to T cells
NOD-like receptor (NLR) agonists	Muramyl dipeptide (bacterial cell wall constituent)	Inflammatory cytokine production, induction of co-stimulators, enhanced antigen presentation to T cells
C-type lectin receptor agonists	Mycobacterial cell wall component trehalose-6,6'-dimycolate	Inflammatory cytokine production

48. Dr. McDonnell acknowledges that by 2017 another method practitioners in the field used to generate antibodies that bind to a specific antigen was the phage-display approach. EX1002 ¶ 48. This method involves systematically selecting antibodies from a vast “library” of antibody sequences based on their ability to bind specific antigens. *See id.*

49. The first step in the phage-display approach is to obtain the antibody library that will be screened to identify the desired antibodies. *See* EX1002 ¶ 48. By 2017, a POSA could rely on several established antibody libraries to identify antigen-binding sequences. *See* Table 2, below; EX2024 at 4. These libraries typically each contained antibody sequences on the order of 10^{10} , allowing a POSA to simultaneously screen *tens of billions* of antibodies at a time. *See* Table 2, below;

EX2024 at 7–8. By 2017, these libraries had been extensively characterized and successfully used to identify antibodies that bound a specific antigen. *See id.* at Table 2. Dr. McDonnell is thus incorrect that “the exact nature of the variable domain repertoire” in these libraries was “unknown,” and that “the usefulness of the library for obtaining antibodies specific to a target antigen could only be determined empirically on a trial-and-error basis.” EX1002 ¶ 48.

**Table 2: Examples of Antibody Libraries Available to a POSA as of 2017
(Excerpted From EX2024 at Table 2)**

	Library Name (year)	Organization	Format	Library Type	Framework	Library Size	Key Feature	Highest affinity (nM) (format) ^a
First generation library	N/A (1996)	Cambridge Antibody Technology	ScFv	Naïve	Naïve	1.4×10^{10}	* Repertoires from 43 healthy donors	4.2 (scFv)
	N/A (1994)	MRC Centre for Protein Engineering	Fab	Synthetic	49 V _H frameworks; 26 V _L frameworks; 21 V _κ frameworks	6.5×10^{10}	- Fully randomized CDR3 - Heavy and light chains assembled using combinatorial infection	7 (Fab)
	HAL (2015)	Technical University of Braunschweig	ScFv	Naïve	Naïve	1.5×10^{10}	- Repertoires from 98 healthy donors - Optimized Myc/His tag - Improved antibody production by removal of C-terminal phenylalanine of V_κ light chain	0.9 (IgG)
	CAT2.0 (2009)	MedImmune	ScFv	Naïve	Naïve	1.29×10^{11}	* Repertoires from 160 healthy donors	N/A
	n-CoDeR (2000)	Biolinvent	ScFv	Naïve	Single V _H framework; single V _L frameworks	2×10^9	* Rearranged 6 CDR segments from natural repertoire in single light and heavy chain frameworks	0.9 (scFv) ^b
Second generation library	ETH2-GOLD (2005)	ETH Zurich	ScFv	Synthetic	Single V _H framework; 2 V _L frameworks	3×10^9	- Fully randomized CDR3 - CDR diversity concentrated in the center of antigen binding region	23.6 (scFv)
	PHILODiam ond (2014)	ETH Zurich	ScFv	Synthetic	Single V _H framework; 2 V _L frameworks	4×10^{10}	* Introduction of S52N in heavy chain CDR2	27 (scFv)
	Dyax (2005)	Dyax	Fab	Semisynthetic	Single V _H framework; naïve V _L frameworks	3.5×10^{10} (FAB-310) 1.0×10^{10} (FAB-410) 1.6×10^{10}	- Randomization of selected antigen-contacting residues in heavy chain CDR1 and CDR2 - Diversity of light chain and CDRH3 derived from autoimmune donors	0.22 (Fab) ^c
	HuCAL- GOLD (2008)	MorphoSys	Fab	Synthetic	7 V _H framework; 4 V _κ frameworks; 3 V _λ frameworks	1.6×10^{10}	- Natural amino acid distribution of six CDRs by using trinucleotide mixtures - Elimination of frame-shifted clones by β-lactamase system	0.04 (Fab)
	HuCAL- PLATINUM (2011)	MorphoSys	Fab	Synthetic	7 V _H framework; 3 V _κ frameworks; 3 V _λ frameworks	4.5×10^{10}	- Antibody and pIII linked by disulfide bond - Removal of post-translational modification hot spots - Loop length dependent amino acid distribution in CDRH3	0.002 (Fab) ^d
	Ylanthia (2013)	MorphoSys	Fab	Synthetic	21 V _H /V _κ pairs; 15 V _H /V _λ pairs	1.3×10^{11}	- Optimized sequence for high expression in both prokaryotic and eukaryotic cells - Selected V_H/V_L framework pairs with optimal biophysical properties - CDRH3 length and amino acid composition based on JH4 and JH6 sequences - CDR optimized to be devoid of PTM motifs - Optimized sequence for high expression in both prokaryotic and eukaryotic cells	0.7 (Fab)

50. Once a library is selected, the next stage in the phage-display process is known as “panning,” which at a high level serves to concentrate the bacteriophages that are expressing antibodies that bind the target antigen, while removing the

nonbinding phages. *See* EX2024 at Fig. 1. After panning, the enriched amino acids are sequenced, a process that in the early 2000s took significant time based on the tools available to a POSA (*e.g.*, Sanger sequencing), but by 2017, had become a high-throughput process due to advances in sequencing technology. These next-generation sequencing (NGS) techniques permit researchers to simultaneously sequence thousands to millions of candidate antibodies at a time, and were being used in phage-display experiments to “rapidly obtain[]” a large number of antigen-binding antibodies. *See* EX2025 at 1.

51. All in, phage-display techniques in 2017 were far from the “trial and error” process Dr. McDonnell purports they were. *Contra* EX1002 ¶ 48.

52. Dr. McDonnell asserts that in many cases, antibodies derived from a non-human source must be “humanized” once they have been generated, EX1002 ¶ 49, but he omits that phage display and hybridoma technologies as of 2017 could generate fully human antibodies without the need for humanization. A POSA could use one of the several available fully human antibody libraries to screen for target antibodies, or if using the hybridoma method, they could use one of the several available transgenic animals, such as the XenoMouse®, that generated fully human antibodies in response to immunization with the target antigen. *See* EX2026 at 1–2; Fig. 1, below.

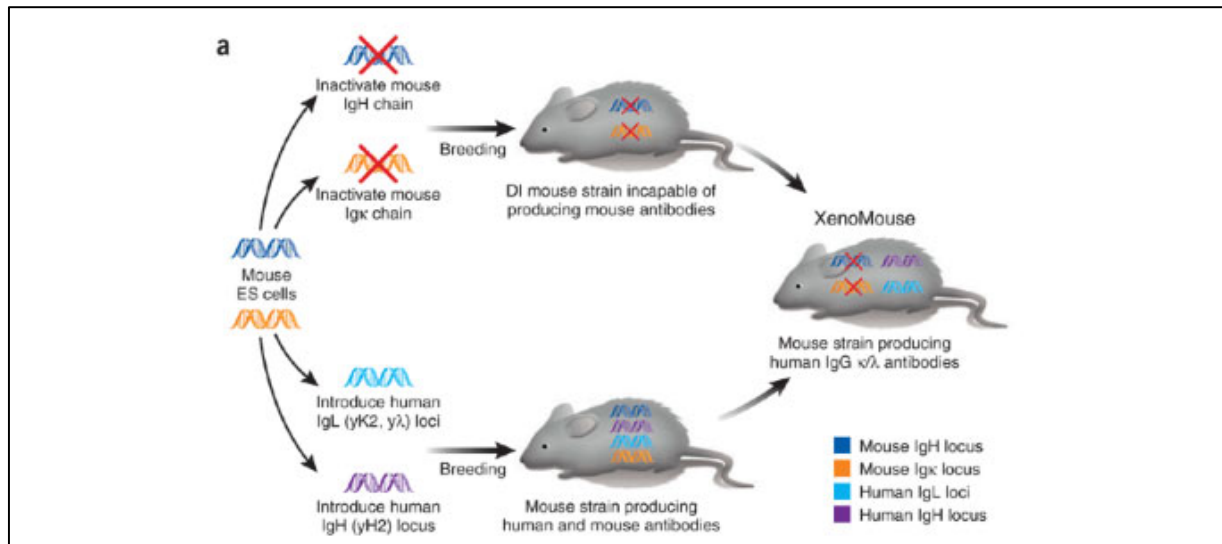


Figure 1: XenoMouse® Platform for Generating Humanized Antibodies (EX2026 at Fig. 1)

53. Even still, by 2017, humanization was commonplace in the field. As Dr. McDonnell’s 2014 reference confirms, “[t]here [we]re several approaches for antibody humanization,” the most common being to graft the complementarity determining regions (“CDRs”) from the non-human antibody onto a humanized scaffold, and introduce back-mutations to preserve antibody specificity. EX1010 at 1; *see also* EX1001 at 15:30–16:16 (describing approaches to humanizing antibodies, including “methods for humanization of the anti-Fzd antibodies disclosed herein”).

54. To summarize, by 2017, antibody engineering was a well-established and mature field, supported by robust tools scientists could use to efficiently and successfully obtain antibodies that bind to a known target antigen such as Fzd or LRP5/6. With improvements in technology between the 2000s and the early 2010s,

by 2017, such antibody engineering did not require undue “trial and error,” as Dr. McDonnell suggests. *Contra* EX1002 ¶¶ 47–48.

55. In any event, Dr. McDonnell vastly overstates the unpredictability of the field. His own cited references highlight the growing role of computer-aided design and predictive technologies in antibody engineering by the early 2010s. A 2011 study by Pedotti et al., for example, assessed the use of “[c]omputational docking, the process of predicting the conformation of a complex from its separated components” as a tool to “predict the binding of two antibodies to the stalk region of influenza hemagglutinin.” EX1064 at 1. Pedotti concluded that computational docking, when paired with experimental validation, “can today achieve excellent results, certainly better than just a few years ago,” and would “only improve with algorithms and computing power.” *Id.* at 21. Another example, a 2012 review by Kuroda et al., surveyed “recent progresses in the field of computer-aided antibody development,” including “several successful examples of *in silico* structure-based antibody designs.” EX1047 at 1.

56. The '278 Patent confirms that by 2017, these predictive tools had continued to advance. It explains that “[d]etermination of the three-dimensional structures of representative polypeptides,” including “variant Fzd binding regions or LRP5/6 binding regions of Wnt surrogate molecules as provided herein,” could be performed using “routine methodologies” such that point mutations could “be virtually modeled

for purposes of determining whether a so derived structural variant retains the space-filling properties of presently disclosed species.” EX1001 at 132:26–35; *see also id.* at 132:36–67 (disclosing several “non-limiting examples of computer algorithms that may be used for these and related embodiments, such as for rational design,” including those that were commercially available).

57. Dr. McDonnell also cites “a study from Xu and Davis” (EX1079 at 2–3) that he purports “reported that differences at just a few amino acid positions in only one of the three heavy chain CDR regions (HCDR3) caused identical antibodies to bind very different antigens.” EX1002 ¶ 41. But the Xu and Davis study did not merely alter “just a few amino acid positions” to find otherwise “identical antibodies” to bind very different antigens. *Contra id.* Instead, the sequences in the article illustrate that each characterized antibody differed *entirely* from the others that bound a different antigen in terms of the amino acid sequence of the “D” (or “diversity”) region of its HCDR3—the region of the antibody that is “the key determinant of specificity in antigen recognition.” EX1079 at 1. Contrary to Dr. McDonnell’s assertions, it was known that slight changes in an antibody’s amino acid sequence in its variable regions often did not alter an antibody’s ability to bind a specific epitope, and that engineered antibodies could therefore tolerate point mutations in their variable regions. *See e.g.*, EX2021 at 107 (ll. 3–9). Dr. McDonnell’s conclusion that “it was virtually impossible to predict with any reliability which antibody sequences

would bind a particular antigen,” EX1002 ¶ 42, therefore does not reflect the state of the art as of 2017. And further, as described above, scientists in the field as of 2017 had developed a wide variety of tools to generate antibodies binding a specific antigen without the need for such prediction. *See* ¶¶ 46–54, above.

58. Dr. McDonnell’s assertion that “[a]s of 2017, a POSA ... 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,” EX1002 ¶ 43; *id.* ¶¶ 41-42 (similar), is irrelevant (because the claims do not require such function as discussed in more detail below) and is a generalized overstatement. For example, there are certain biological pathways where a POSA would understand the features necessary to achieve the desired biological effect. *See e.g.*, EX1001 at 1:54–62 (“Canonical Wnt signals ... involve Low-density lipoprotein (LDL) receptor-related protein 5 (LRP5) or Low-density lipoprotein (LDL) receptor-related protein 6 (LRP6) as co-receptors ..., in addition to Fzds. Accordingly, there is clearly a need in the art for binding moieties that specifically bind to one or more Fzd, LRP5, or LRP6 to modulate Wnt signaling pathways.”). In that context, empirical testing is merely used to confirm a POSA’s expectations based on the antibody’s target receptors—not to explore functionality in the first instance.

59. This exposes a further claim Dr. McDonnell makes as misguided. He purports to describe evaluating candidates for their “ability to affect the biological function of the antigen, if a particular functional property (e.g., antagonism) was desired.” EX 1002 ¶ 50. But the steps he describes were known and such evaluation would have been used to confirm a person of ordinary skill’s expectations. I understand from Dr. Willert that, by 2017, Wnt signaling in particular was supported by a large body of research and well-established analytical tools, such as TOPFlash assays, that provided straightforward and reproducible methods for assessing pathway activation or inhibition. EX2010 ¶¶ 26–31, 56–57; EX1001 at 117:39–118:51 (describing “[v]arious methods” that were “known in the art for measuring the level of canonical Wnt/ β -catenin signaling” as of 2017).

60. Dr. McDonnell cites a study from Gong (EX1027) exploring the effects of anti-LRP6 antibodies—not tetravalent molecules that bind both Fzd and LRP5/6—on Wnt signaling to support his claim 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,” EX1002 ¶ 44, but nothing in Gong suggests that an antibody’s functional dependence on these factors was “unpredictable.” Gong’s results were limited to testing how anti-LRP6 antibodies competed with or complemented Wnt isoforms to activate Wnt signaling. *See* EX1027 at 2. That is, where an anti-LRP6 antibody bound to the LRP6 at a location that blocked the LRP6

molecule's Wnt binding region, the antibody would compete with natural Wnt ligands for the LRP6 binding site, thus inhibiting Wnt signaling. *See id.* at 12–13. By contrast, if the anti-LRP6 antibody bound to an epitope on the LRP6 molecule that did not interfere with natural Wnt binding, downstream signaling would be potentiated. *See id.* Gong's results showed that each antibody tested was capable of potentiating signaling “by the class of Wnt isoforms that bind regions *outside its epitope*,”¹ while the antibodies inhibited signaling “by only the Wnt isoforms *that bind these regions*.” EX1027 at 13. The Gong study thus confirms that mechanistic predictions about the functional effects of various antibodies on Wnt signaling pathways had been formulated and tested as of 2017.

61. In any event, as the Gong study itself explains, it was known as early as 2010 that activation of canonical Wnt signaling pathways requires recruitment of *both* Fzd receptors *and* LRP5/6 coreceptors. *See* EX1027 at 1; *see also* EX1001 at 1:54–59 (“Canonical Wnt signals ... involve Low-density lipoprotein (LDL) receptor-related protein 5 (LRP5) or Low-density lipoprotein (LDL) receptor-related protein 6 (LRP6) as co-receptors ..., in addition to Fzds.”). Thus, a POSA reading Gong would have understood that an antibody that *only* binds Lrp6—as was the case in Gong—may not reliably or effectively agonize Wnt signaling. The '278 Patent

¹ Emphasis in quotations is my own unless otherwise noted.

confirms that understanding. *See e.g.*, EX1001 at Example 4, Figs. 4A–4B (showing the R2M3 IgG molecule, which only binds Fzd and not LRP5/6, “inhibited ... induced reporter signaling” by two exemplary claimed molecules, while a negative control alone “had no impact”).

B. A POSA Could Generate a Wide-Range of Antigen-Binding Fragments Using Known Methods

62. In Paragraphs 51–59, Dr. McDonnell pivots from discussing antibody engineering generally to discussing antibody fragments as purported support for his opinion that the field of antibody engineering was unpredictable. I disagree.

63. As Dr. McDonnell acknowledges, by 2017, researchers were using “laboratory techniques to modify and dissect full-length antibodies to generate various antibody-derived fragments that retain the portions needed for antigen-binding,” and had begun using smaller antibodies such as heavy-chain only antibodies found in other organisms such as camels. EX1002 at ¶ 51. Dr. McDonnell mischaracterizes these structures as an “additional layer of antibody engineering” that “required sophisticated designing strategies and recombination techniques, adding more time and effort to the work needed to make typical, full-length antibodies,” EX1002 at ¶ 51, but their purpose was quite the opposite. By 2017, fragment formats and single-domain antibodies could be generated using established recombinant methods, and were often used to *streamline*, rather than complicate, antibody discovery and characterization. As Dr. McDonnell’s reference confirms,

prior to 2017, the consensus in the field was that “antibody fragments may prove easier and less costly to manufacture due to the lack of glycosylation and relatively small size.” EX1059 at 2. Indeed, the availability of alternative antibody formats reflects the maturity of antibody engineering by 2017 to move beyond full-length antibodies and move toward simpler antibody-derived structures tailored to specific needs.

64. Dr. McDonnell’s statement that “[t]hese fragments may or may not retain the function of a full-length antibody,” EX1002 ¶ 52, mischaracterizes the unpredictability it implies. While antibody fragmentation can alter certain physicochemical properties, it is precisely those altered properties that encouraged scientists to develop them in the first place. For example, as Dr. McDonnell’s cited reference states, “the smaller size of fragments permits penetration into tissues inaccessible to full-size mAbs,” and these fragments are “rapidly degraded in humans and have short circulating half-lives” as a result of their lack of a stabilizing Fc domain capable of binding the FcRn pathway. EX1059 at 2; *see also* EX1002 ¶ 55 (McDonnell: “Compared to full-size antibodies, Fab’ and Fab fragments generally permit more effective tissue penetration but have significantly shorter circulating half-lives.”). Importantly, it was understood that fragmentation does not generally disrupt antigen binding, which is mediated by the variable regions retained in such fragments. *See e.g.*, EX1001 at 13:48–52 (“The Fv fragment includes a non-

covalent $V_H:V_L$ heterodimer including an antigen-binding site which retains much of the antigen recognition and binding capabilities of the native antibody molecule.”). By 2017, the physicochemical differences between antibody fragments and their full-length counterparts were not the source of unpredictability that Dr. McDonnell implies.

65. In Paragraphs 52–59, Dr. McDonnell “briefly discusse[s]” the different types of known antibody fragments. I generally agree with his technical description of the structure for each of these fragments but provide additional context of what was known about each of these fragments by 2017.

66. By 2017, it was known that a $F(ab')_2$ (discussed in McDonnell’s Paragraph 53) could “readily be cleaved” from a full-length antibody by using an enzyme known as pepsin. EX1039 at 59; *see also* EX1001 at 13:40–43. It was also known by 2017 that because $F(ab')_2$ excised the Fc region of the antibody, these fragments retained the same antigen-binding sites as the full-length antibody. *See* EX1001 at 13:40–43 (“The enzyme pepsin is able to cleave IgG molecules to provide several fragments, including the $F(ab')_2$ fragment which comprises both antigen-binding sites.”).

67. Dr. McDonnell also correctly explains that a POSA could generate even smaller fragments that consisted of only a single antigen-binding arm of the molecule. These fragments could either be made by treating a $F(ab')_2$ with a reducing

agent, fragmenting it into two single antigen-binding arms with a small portion of their disulfide bonds remaining attached (known as a Fab' fragment, discussed by Dr. McDonnell in Paragraph 54), or they could be cleaved from a full-length antibody using an enzyme known as papain, leaving single antigen-binding arm fragments without any remaining attached disulfide bonds (known as a Fab fragment, discussed by Dr. McDonnell in Paragraph 55). *See e.g.*, EX1039 at 59; EX1001 at 13:37–40 (“The proteolytic enzyme papain preferentially cleaves IgG molecules to yield several fragments, two of which (the F(ab) fragments) each comprise a covalent heterodimer that includes an intact antigen-binding site.”).

68. Another type of fragment Dr. McDonnell discusses is the Fv fragment, which “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.” EX1002 ¶ 56; EX1001 at 13:48–52. As the '278 Patent explains, “[a]n Fv fragment ... can be produced by preferential proteolytic cleavage of an IgM, and on rare occasions of an IgG or IgA immunoglobulin molecule. Fv fragments are, however, more commonly derived using recombinant techniques known in the art.” EX1001 at 13:43–46. While early iterations of Fv fragments could “rapidly dissociate[,] ... result[ing] in drastically reduced binding affinity,” by 2017, researchers had solved this problem by connecting the V_H and V_L domains using a “flexible peptide linker,” resulting in what was known as an (sc)Fv fragment. EX1013 at 1; EX1001 at 14:7–11. By 2017,

“[a] number of methods ha[d] been described to discern chemical structures for converting the naturally aggregated—but chemically separated—light and heavy polypeptide chains from an antibody V region into an scFv molecule which will fold into a three dimensional structure substantially similar to the structure of an antigen-binding site.” EX1001 at 14:11–19. Alternatively, a POSA could stabilize Fv fragments using an “interdomain disulfide bond,” resulting in a (ds)Fv fragment. EX1013 at 1. Fv structures provided POSAs with even smaller antibody fragments that still retained the antigen-binding properties of their full-length antibody counterparts. Moreover, Fv fragments could be produced using the generation approaches outlined with respect to full-length antibodies above. *See* ¶¶ 46–54, above.

69. Two scFv chains could also be paired together noncovalently to form a diabody with two antigen-binding regions. EX1002 ¶ 58. “Diabodies are multimers of polypeptides, each polypeptide comprising a first domain comprising a binding region of an immunoglobulin light chain and a second domain comprising a binding region of an immunoglobulin heavy chain, the two domains being linked (e.g. by a peptide linker) but unable to associate with each other to form an antigen binding site: antigen binding sites are formed by the association of the first domain of one polypeptide within the multimer with the second domain of another polypeptide

within the multimer.” EX1001 at 14:20–30. As of 2017, diabodies could “be prepared using standard molecular biology techniques.” *Id.* at 13:56–64.

70. By 2017, researchers had also discovered that camelid mammals (such as camels and llamas) naturally produce antibodies “composed only of heavy chains in which the target recognition molecule is composed of a single variable domain.” EX1089 at 1; EX1001 at 15:4–8. Because fragments of the variable domain (known as nanobodies, Nabs, sdAbs, or VHHs) were found to be smaller than even Fv fragments, researchers began generating these fragments and integrating them into human antibody structures using the same generation techniques described above. *See e.g.*, EX1001 at 15:14–21 (“VHH or sdAb are encoded by single genes and are efficiently produced in almost all prokaryotic and eukaryotic hosts e.g. *E. coli* ..., molds ... and yeast.... The production process is scalable and multikilogram quantities of VHH or sdAb have been produced.”).

71. In summary, by 2017, a robust range of antibody fragments were available to a POSA that possessed the same antigen-binding properties as their full-length antibody counterparts. These antibody fragments could be generated using established methods, with little to no further experimentation necessary than that required to generate full-length antibodies.

C. Multivalent, Multispecific Antibodies Could Be Synthesized, But Required Specific Structural Guidance

72. In Paragraphs 60–73 of his report, Dr. McDonnell discusses multivalent antibodies, alleging they presented “heightened demands for more sophisticated empirical evaluation.” EX1002 § VII.D. In my opinion, those characterizations are broad generalizations that do not capture the state of the art as of 2017.

73. As Dr. McDonnell acknowledges, “[b]y 2017, antibody engineers could join antibodies and antigen-binding fragments to create synthetic antibody-like molecules that incorporate multiple antigen-binding regions.” EX1002 ¶ 62. These antibody-like molecules leveraged the fact that antigen-binding fragments could be treated as “modular building blocks” and joined together to create 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.” *Id.*

74. As Dr. McDonnell further explains (EX1002 ¶¶ 60, 65), these antibody-like molecules could be characterized by their valency, specificity, and their stoichiometry. A molecule’s **valency** refers to the number of paratopes (i.e., binding domains) present in the molecule’s structure. A molecule’s **specificity**, on the other hand, refers to the number of epitopes the antibody is capable of binding. Finally, a molecule’s **stoichiometry** refers to the ratio of the number of paratopes on the molecule specific to each epitope or antigen. For example, a molecule with a 2:2 Fzd binding region:LRP5/6 binding region stoichiometry contains two binding domains

that bind one or more Fzd molecules and two binding domains that bind one or more LRP5/6 molecules. As of 2017, a POSA was able to leverage the wide range of antibody fragments available to engineer multivalent, multispecific molecules with varying stoichiometries and using different linkers that, as Dr. McDonnell acknowledges, were known to POSAs in 2017. EX1002 ¶ 66.

75. Dr. McDonnell concludes from his discussion of these parameters that “[g]iven 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.” EX1002 ¶ 67. But a POSA would not approach the design space by undertaking a combinatorial accounting of every possible multispecific and multivalent antibody construct. For example, the claims of the ’278 Patent are directed to tetravalent molecules in a 2:2 stoichiometry, and, of Dr. McDonnell’s 100 cited formats, choosing that narrow structural arrangement would limit a POSA to 32 of those formats. *See* Fig. 2, below.

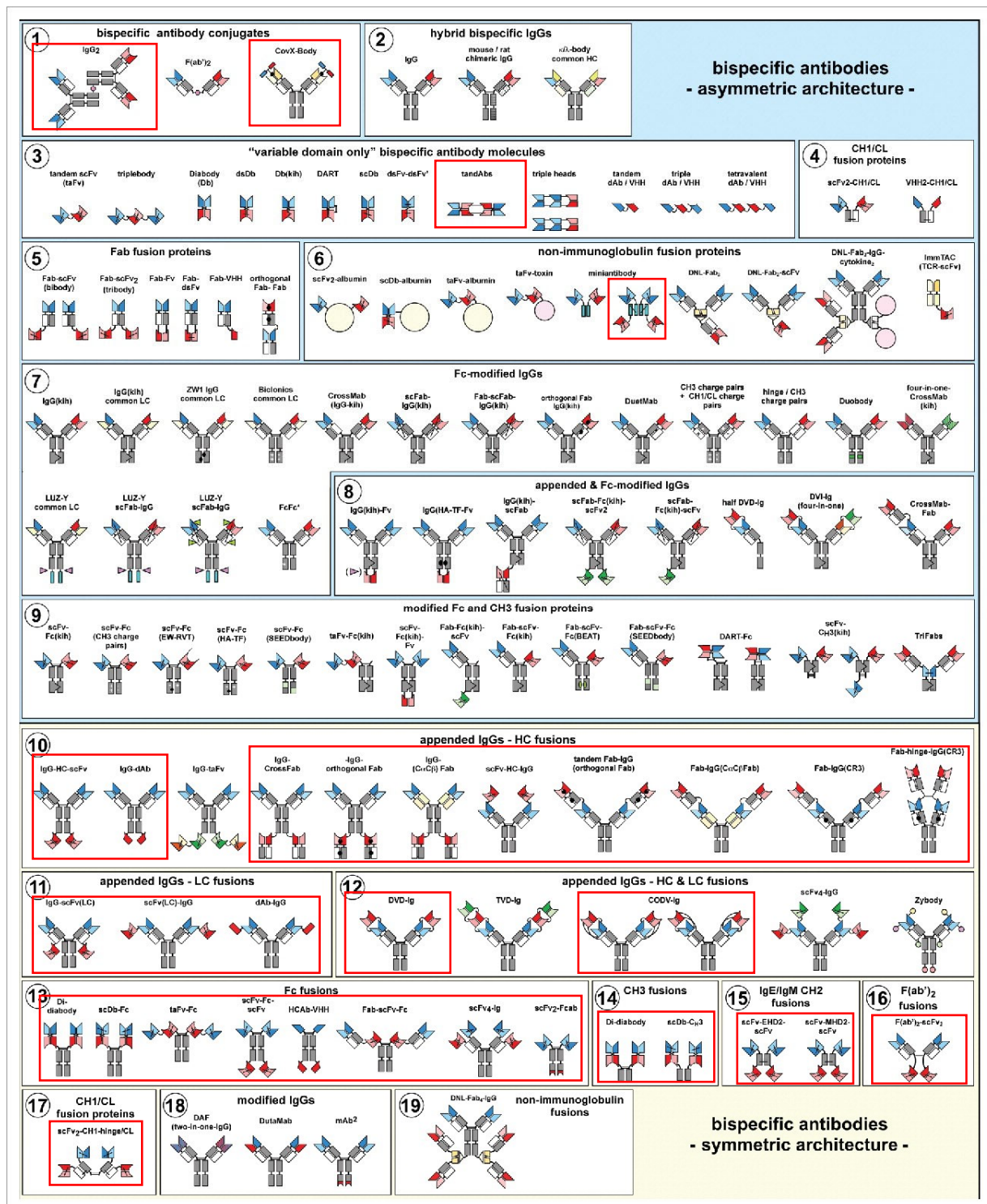


Figure 2: Dr. McDonnell's Fig. 3 (EX1017 at Fig. 2) Annotated to Show Tetravalent, 2:2 Stoichiometry Formats (Red Boxes)

76. A POSA would then select from a set of well-established antibody engineering formats and methods to design candidate molecules. As Dr. McDonnell's reference states, POSAs would be able to use antibody domains and fragments as "partially interchangeable building blocks" and assemble a molecule "in a 'plug and play['] fashion." EX1017 at 18. Indeed, while Dr. McDonnell's cited chart lists 100 different "formats," several of them share common structural features and result from interchanging, adding, or rearranging modular elements. For example, the first molecule in Box 3 depicts "tandem scFv molecules" that "can be buil[t] by connecting two scFvs through a linker (connector)." *Id.* at 4. It was known in 2017 that "[t]he modular nature of this approach allows further extension of tandem scFvs, for instance by adding more scFvs," leading to the second molecular format depicted in Box 3. *Id.* A POSA would thus understand that different "formats" were linked by common structural and mechanistic underpinnings, and would be able to move from one format to others by adding or changing "building blocks."

77. To decide which linker to use, a POSA would have understood as of 2017 that different linker compositions served different purposes, and would be guided by the specific molecular format and intended field of use to determine which linker to use. *See e.g.*, EX1001 at 116:48–52 ("The length of the linker, and therefore the

spacing between the binding domains can be used to modulate the signal strength, and can be selected depending on the desired use of the Wnt surrogate molecule.”).

78. Moreover, it was known as of 2017 that different formats were preferred for different applications. For example, it was known that “[t]he bispecific tandem scFv format has been extensively applied in cancer immunotherapy for the retargeting of T cells to tumor cells or tumor-associated cells of the tumor microenvironment.” EX1017 at 4.

79. In simple terms, Dr. McDonnell’s analysis would be akin to trying to use every tool in an antibody engineer’s toolbox to construct every molecule possible from scratch, whereas in reality a POSA would have been guided by the narrow scope of the claims, the guidance in the ’278 Patent, and the knowledge in the field. In that context, the “extensive and versatile toolbox” available to a POSA as of 2017, EX1017 at 3, was an asset, not a limitation.

80. Dr. McDonnell claims that “[a]s of 2017, ... the structural complexity and functional unpredictability of [multivalent, multispecific] antibody molecules are substantially greater than those of conventional antibodies,” EX1002 ¶ 68, but that is only true to the extent a POSA would be wading through the field without guidance shaping their design choices. As discussed above, if a POSA understood that a tetravalent molecule in a 2:2 stoichiometry that specifically binds Fzd and LRP5/6 was needed for their purposes, and if they were given examples of structures

that worked in functional terms—like those disclosed in the '278 Patent, discussed further below, paragraphs 161–253—they would be able to leverage the “extensive and versatile toolbox” that had been established in the field of antibody engineering to construct such molecules. EX1017 at 3.

81. In purported support for his position that multivalent, multispecific molecules are complex and unpredictable, Dr. McDonnell asserts that “promiscuous pairing” between heavy and light chains means that “co-expression of four different chains in cells ... can theoretically yield 16 different heavy-light chain pairings, of which “only 12.5%”—i.e., two—“are the desired bispecific construct.” EX1002 ¶ 69. But Dr. McDonnell’s theoretical exercise in probabilities entirely ignores that as of 2017, “various strategies ha[d] been develop[ed] and established over the past two decades to solve this problem.” EX1017 at 2; *see also* EX1001 at 18:6–25 (describing known methods as of 2017 to “facilitate binding between two polypeptides); Fig. 3, below.

82. For example, the “knobs-in-holes” (KiH) method involves placing a mutation in the CH3 domain of one heavy chain to create a “knob” and another mutation in the CH3 domain in the other heavy chain to create a “hole.” These mutations “establish intermolecular interactions and promote ... heterodimer formation due to knob/hole pairing.” EX1051 at 3; *see also* EX1001 at 18:9–13 (“Knobs-into-holes amino acid (AA) changes is a rational design strategy developed

in antibody engineering, used for heterodimerization of the heavy chains, in the production of bispecific IgG antibodies.”). The KiH method was found to “yield[] 92% of molecules as heterodimers.” EX1051 at 3. This method could then be supplemented with a “CrossMab” method to prevent mispairing between the heavy chains and light chains. *Id.* “Such bispecific formats clearly reduced ... heavy–light chain mispairing, allowed simultaneous recognition of the two antigens ([e.g.,] VEGF-A and Ang2), retained the affinity and stability profiles of the parent antibodies and exhibited antiangiogenic and antitumor activity *in vivo.*” *Id.* Alternatively, promiscuous pairing could be avoided entirely by relying on scaffolds such as diabodies whose linker structures prevent mispairing within the structure.

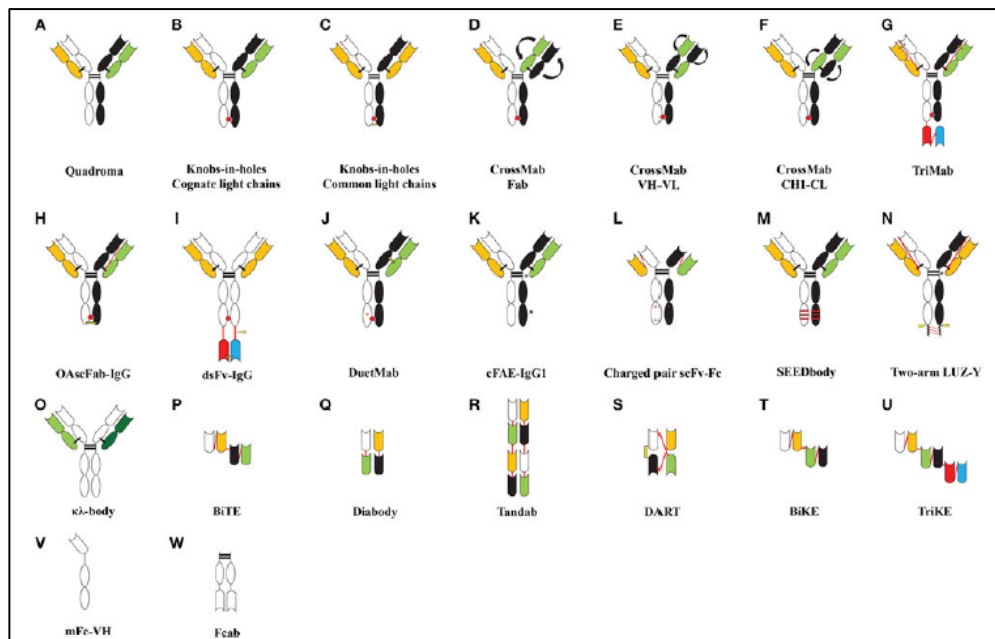


Figure 3: Examples of Known Solutions to Promiscuous Pairing as of 2017 (EX1051 at Fig. 1)

83. Dr. McDonnell similarly opines that “there was no ‘one size fits all’ format capable of achieving ‘the plethora of desired functionalities and applications,’” and from that statement leaps to the conclusion that “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.” EX1002 ¶ 70. But Dr. McDonnell’s assertion rests on the incorrect premise that a POSA was in search of a multivalent, multispecific antibody that could be used in *every* application. To the contrary, a POSA would design a molecule to fit a *specific* application they had in mind, and they would have been able to leverage the specification’s extensive characterization of various multivalent structures, antibody fragments, and linkers, together with their understanding of the target antigens to obtain formats, fragments, and linkers that would best serve their needs. A POSA would thus not need to resort to blind empirical evaluation of every possible multivalent molecule as Dr. McDonnell implies.

84. Dr. McDonnell points out a number of factors, such as antigen density on cell surfaces and “other target-specific properties,” that could influence the valency needed for the molecular structure. EX1002 ¶ 71. These considerations underscore that, in the absence of guidance regarding suitable design parameters, a POSA would be left to resort to empirical testing to identify functional antigen-binding molecules. However, where such guidance was available—in the form of a specified valency

and stoichiometry that worked, and with working examples of representative antibody formats and knowledge in the art, as is the case in the '278 Patent—a POSA could use the knowledge regarding known formats that were shown to work to design additional constructs without needing to engage in indiscriminate, trial-and-error experimentation.

85. Dr. McDonnell also references “[p]harmacokinetic and pharmacodynamic behaviors” as “important factors that were understood to influence the functionality of multivalent, multispecific antibodies,” EX1002 ¶ 72, but by 2017 these factors were well-understood to reflect known tradeoffs associated with different formats, as Dr. McDonnell himself acknowledges. *Id.* (discussing “advantages” of using antigen-binding fragments like “effective tissue penetration”). In any event, these considerations relate to optimization of a molecule’s therapeutic properties, not the ability of a POSA to design functional antigen-binding molecules in the first instance.

86. Dr. McDonnell concludes from his survey of well-known design considerations in the field that “predicting in advance how a particular multivalent, multispecific antibody format would function in vitro, in vivo, and ultimately in humans, was impossible in 2017.” EX1002 ¶ 73. As the preceding discussion shows, Dr. McDonnell’s tremendously broad assertion is entirely unsupported by what was known in the field as of 2017. Using the wealth of knowledge about the “extensive

toolbox” available to engineer multivalent, multispecific molecules, and with sufficient guidance regarding application-specific design considerations and working examples, like those in the ’278 Patent, a POSA would be able to form a working hypothesis of how a particular multivalent, multispecific antibody structure would function without having to first empirically confirm its functionality.

87. Dr. McDonnell also refers to the fact that “there were only two bivalent, bispecific molecules approved by FDA as of 2017,” EX1002 ¶ 73, but it is not clear why that is relevant. Based on my extensive experience working on molecules with pharmaceutical applications, I understand that FDA approval times reflect several factors that have no bearing on a POSA’s ability to design a multivalent, multispecific molecule, including regulatory requirements, pharmaceutical formulation, quality control, adverse event monitoring, and compliance with Good Manufacturing Practices (“GMPs”). That Dr. McDonnell is not “aware of any tetravalent molecules approved by the FDA even today” thus lacks any relevance to his assertion that it was “impossible” to predict any aspect of a multispecific antibody format’s function. *Id.*

88. For all of the reasons above, I disagree with Dr. McDonnell that “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.” *Contra* EX1002 ¶ 73.

D. The Wnt Signaling Pathway Was Well-Characterized and Extensively Studied as of 2017

89. In paragraphs 74–80, Dr. McDonnell characterizes the Wnt signaling pathway as “poorly understood.” As discussed below, I disagree with that conclusion, which overlooks the large body of research that had been completed with respect to Wnt signaling by 2017.

90. Based on my extensive experience in the field, including developing antibodies to modulate cellular signaling pathways, I, like Dr. McDonnell, have a general understanding of the molecular mechanisms and regulation of the Wnt signaling pathway. *See* EX1002 ¶ 74. I have also confirmed my understanding and gained further insights into the relevant mechanisms and principles from my review of Dr. Willert’s declaration and its cited publications. *See* EX2010.

91. As explained in Dr. Willert’s declaration, the Wnt signaling pathway is a foundational cell signaling pathway involved in several biological processes, including the development, homeostasis, and regeneration of many essential organs and tissues. *See* EX2010 ¶ 26 (quoting EX1001 at 1:41–50). The Wnt signaling pathway was first discovered in 1982, and since then, “[d]etails about the mechanisms of Wnt signaling have been revealed, including structural information on the main molecular players.” EX1063 at 1.

92. Contrary to Dr. McDonnell's assertions, by 2017, the main components framing the mechanisms of action in Wnt signaling were well-characterized. Wnt signaling was known to proceed via three main pathways—a “canonical” pathway and two “non-canonical” ones. *See* EX1001 at 119:33–40. It was known by 2017 that the distinguishing feature between canonical and noncanonical Wnt pathways was the role of an intracellular signal transducer protein known as β -catenin. In the canonical pathway, a Wnt ligand binds a complex on the cell surface membrane consisting of a “Frizzled” or “Fzd” receptor and a “Low-density lipoprotein Receptor-related Protein 5 or 6” (LRP5 or LRP6) coreceptor. *See* EX2010 ¶ 29. This triggers a cascade of downstream processes leading to the activation of β -catenin, resulting in downstream changes in the cell's transcription activities. *Id.* ¶ 27; *see also* EX1001 at 119:41–49 (“[A]ctivation of the canonical Wnt signaling pathway results in the inhibition of phosphorylation of the intracellular protein β -catenin, leading to an accumulation of β -catenin in the cytosol and its subsequent translocation to the nucleus where it interacts with transcription factors TCF/LEF, to activate target genes.”). By contrast, it was known as of 2017 that the noncanonical pathways involved recruiting different coreceptors on the cell surface membrane, such as Ryk and Ror, and were generally thought to act in a β -catenin independent manner. *See* EX2010 ¶¶ 28, 33.

93. While Dr. McDonnell claims that “the precise interactions between individual ligands and their corresponding receptors were not yet elucidated,” EX1002 ¶ 78, as Dr. Willert explains, “[t]he ’278 Patent ... provides ... a coherent interaction model for the claimed tetravalent molecules: a 2:2 stoichiometry with two Fzd binding regions and two LRP5/6 binding regions, backed by the support of 90 embodiments tested *in vitro* that all activated the canonical pathway.” EX2010 ¶ 45. Interaction principles between other “individual ligands,” such as natural Wnt molecules, and what was known about them as of 2017 thus “have nothing to do with the claimed tetravalent molecules,” EX2010 ¶ 42, whose ability to interact with Fzd and LRP5/6 receptors is sufficiently described in the ’278 Patent. *See* ¶¶ 161–272, below.

94. Nor was the fact that “[t]he activity of Wnt signaling is influenced ... by cell type, development stage, and other contextual factors,” EX1002 ¶ 77, “poorly understood” as of 2017, as Dr. McDonnell alleges. *Contra* EX1002 ¶ 78. As the ’278 Patent explains, by 2017, “[t]he transcriptional response to Wnt activation ha[d] been characterized in a number of cells and tissues.” EX1001 at 117:48–49. And as Dr. McDonnell’s own cited reference from 2017 explains, it was “unsurprising[]” that the “unique or partially overlapping phenotypes” produced by loss of Wnt genes “correspond to where the Wnts are expressed.” EX1063 at 1; EX1002 ¶ 77. The “different types of cellular responses” Dr. McDonnell cites, “including ‘canonical’

activation ... and alternative ‘noncanonical’ pathways” were also known. *See* EX1001 at 119:23–58 (describing components and mechanisms of canonical and non-canonical Wnt signaling pathways).

95. Dr. McDonnell takes issue with the fact that “no crystallization of the complete Wnt-Fzd-Lrp complex had been reported as of 2017,” and claims that the crystal structures that were known “do not provide a sufficient foundation for designing the full scope of the Wnt surrogate molecules.” EX1002 ¶ 78. I disagree. By 2017, the main Wnt ligand substrates on cell surfaces involved in the canonical signaling pathway had been identified, and scientists understood that “activation of canonical Wnt signaling was primarily a matter of heterodimerizing Fzd and LRP5/6 receptors on the cell surface.” EX2010 ¶ 44. That would have given a POSA more than sufficient mechanistic background to design tetravalent molecules in a 2:2 stoichiometry using the antibody engineering techniques described above in paragraphs 46–54, coupled with the disclosures of the ’278 Patent. As Dr. Willert confirms, a POSA would therefore not have needed “crystallization of the complete Wnt-Fzd-Lrp complex,” EX1002 ¶ 78, to design such molecules. EX2010 ¶ 45.

96. Dr. McDonnell also claims that “[t]he roles of Fzd and Lrp receptors in *noncanonical* Wnt signaling were also poorly characterized,” EX1002 ¶ 79 (emphasis added), but that sidesteps that the roles of Fzd and LRP5/6 in *canonical* pathways were well-characterized and modeled. Because the ’278 Patent’s claimed

invention concerns molecules that bind both Fzd and LRP5/6, a POSA would understand the molecules to concern activation of the *canonical* Wnt signaling pathway, rendering any purported poor characterization of noncanonical pathways irrelevant. *See e.g.*, EX1001 at 16:63–65 (“In particular, the Wnt agonists disclosed herein activate, enhance or increase the canonical Wnt/[β]-catenin signaling pathway.”); EX2010 ¶ 33.

97. Dr. McDonnell further criticizes the assays that were available to researchers in 2017, claiming that “no single assay was universally applicable to all Wnt systems for determining pathway activation,” and that “[o]nly some assays were capable of measuring both canonical and noncanonical responses.” EX1002 ¶ 80. But a POSA would not have required a “universally applicable” assay so long as Wnt signaling activity could be reliably measured. As Dr. McDonnell acknowledges, there were “multiple ways in which WNT signaling [was] read out (such as nuclear β -catenin levels, reporter assays and endogenous gene expression).” EX1002 ¶ 80; *see also* EX1001 at 117:39–40 (“Various methods are known in the art for measuring the level of canonical Wnt/ β -catenin signaling.”). Among these, the TOPFlash reporter assay was widely recognized as a “well-established[,], accurate[,], and reliable” assay for measuring canonical Wnt signaling across a wide variety of cell types. EX2010 ¶ 56; *see also* EX1001 at 117:39–118:36. That assays such as TOPFlash “*might not* capture *all* the important transcriptional changes caused by activated WNT

signaling,” EX1043 at 3, does not diminish their utility in reliably assessing canonical pathway activation. *See* EX2010 ¶ 56.

98. Finally, Dr. McDonnell cites to a study by Mikels and Nusse (EX1056) investigating the effects of the Wnt5a protein on Wnt signaling to allege that “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.” EX1002 ¶ 80. But far from demonstrating any “variability and inconsistency across experimental systems” or a “difficult[y]” in definitively determining changes in Wnt signaling activity, *id.*, that study found, using SuperTopFlash reporter results, that “*[a]lthough Wnt 5a can inhibit canonical Wnt signaling when Ror2^[2] is expressed at detectable levels, Fz 4 and LRP5 coreceptor expression allows Wnt5a to signal in a canonical fashion.*” EX1056 at 11; *see also* EX2010 ¶ 35. Therefore, by 2017, TOPFlash had been used in various receptor contexts to identify “whether a molecule functions as Wnt

² As Dr. Willert explains, Ror2 is a “noncanonical receptor” that mediates a separate Wnt-induced signaling pathway, and therefore lacks relevance to the claimed invention of the ’278 Patent, which interacts with Fzd and LRP5/6 receptors, not Ror2. *See* EX2010 ¶ 35.

agonist, antagonist, both, or neither and under what conditions,” EX1002 ¶ 80, confirming its reliability as a reporter of Wnt signaling activity.

VIII. THE '278 PATENT

A. Disclosures of the '278 Patent

99. The '278 Patent discloses “Wnt pathway agonists and related compositions.” EX1001 at Abstract. More specifically, the specification of the '278 Patent describes a tetravalent, multispecific molecular architecture designed from antibody-derived structures that comprises two Fzd binding regions and two LRP5/6 binding regions. *See e.g., id.* at Figs. 1A–D. As the specification demonstrates, this molecular architecture reliably activates Wnt signaling pathways. *See e.g., id.* at 1:60–61, Examples 2–9, 12–18; *see also* EX2010 ¶¶ 66–134.

100. While the specification notes that “[i]n particular embodiments, the Wnt signaling pathway is a canonical Wnt signaling pathway or a non-canonical Wnt signaling pathway,” it further explains that the “[i]n certain embodiments, the Wnt surrogate molecule increases Wnt signaling, e.g., via the canonical Wnt/[β]-catenin pathway,” and that “[i]n particular, the Wnt agonists disclosed herein activate, enhance or increase the canonical Wnt/[β]-catenin signaling pathway.” EX1001 at 4:49–51, 16:46–48, 16:63–65. The specification thus makes clear that the relevant pathway for purposes of the disclosed invention is the *canonical* Wnt signaling pathway. *See* EX2010 ¶ 27. To that end, the specification discloses “a number of

assays” that can be used to confirm that the disclosed molecules can activate Wnt signaling, including “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.” EX1001 at 117:40–44.

101. Table 1A of the '278 Patent provides amino acid sequences for 448 “antibodies or fragments thereof that bind to one or more Fzd receptor,” along with the specific Fzd receptors each sequence was found to initially bind to. EX1001 at 22:37–38. The table provides examples of sequences binding to each of the ten known Fzd receptors. *See id.* at Table 1A. Further, and contrary to Dr. McDonnell’s inaccurate statement that “[t]he specification does not explain how these clones were made,” United States Provisional Patent Application No. 62/607,877 (“the ’877 Application”), which is incorporated into the specification by reference, EX1001 at 22:29–34, describes the method by which the tested clones were identified:

The Fzd receptor to which each clone was initially identified as binding was determined *by detection of phage-displayed antibody fragments* bound to target antigen immobilized on Nunc Maxisorb microtiter plates (Thermo Fisher Scientific, Waltham, MA) by single-dose or dose-independent ELISA. Detection of bound phage was determined calorimetrically by turnover of TMB substrate (Thermo Fisher Scientific, Waltham, MA) at 415 nm by anti-M13-HRP (GE

Healthcare, Pittsburgh, PA). Clones were identified as binding to a Fzd receptor when the fold OD 450 nm over background was greater than a threshold level.

EX2021 at 97 (ll. 23–31).

102. The inventors then tested 130 clones for confirmed binding, which was “determined by bio-layer interferometry (BLI) using Octet Red 96 (PALL Fortebio, Fremont, CA) instruments at 30°C, 1000 rpm with streptavidin (SA) biosensors.” EX2021 at 97 (ll. 6–10); EX1001 at Table 1B. Notably, of the 130 clones tested, 91 (i.e., more than two-thirds of sequences exhibiting initial binding), demonstrated confirmed binding to at least one Fzd receptor, underscoring the robust and predictive nature of the initial binding methodology. *See id.* Again, contrary to Dr. McDonnell’s inaccurate assertion that “the ’278 Patent does not disclose any parameters reflecting their binding affinity (e.g., K_D),” Table 1B of the ’877 Application provides the K_D thresholds used to determine “confirmed” binding and whether the threshold was met for each sequence with respect to the ten Fzd receptors. As the table shows, all clones listed as exhibiting “confirmed binding” demonstrated a K_D value of 2000 nM or less. *See* EX2021 at Table 1B (reproduced as Table 3, below).

Table 3: Table 1B of '877 Application (EX2021) Showing K_D Ranges for Confirmed Fzd Binding Sequences

Clone ID	HC SID NO	LC SID NO	Confirmed Binding	K _D (nM)									
				Fz1	Fz2	Fz3	Fz4	Fz5	Fz6	Fz7	Fz8	Fz9	Fz10
001S-B01	1	38	Fzd1,2,7,9	**	**	n.b.	n.b.	n.b.	n.b.	**	n.b.	*	n.b.
001S-E02	2	39	Fzd1,2,7	*	**	n.b.	n.b.	n.b.	n.b.	*	n.b.	n.b.	n.b.
001S-G02	3	40	Fzd1,2,7	**	**	n.b.	n.b.	n.b.	n.b.	**	n.b.	n.b.	n.b.
001S-H02	4	41	Fzd1,2,7	**	**	n.b.	n.b.	n.b.	n.b.	**	n.b.	n.b.	n.b.
001S-A03	5	42	Fzd1,2,7,9	*	**	n.b.	n.b.	n.b.	n.b.	**	n.b.	**	n.b.
001S-B03	6	43	Fzd1,2,7	*	*	n.b.	n.b.	n.b.	n.b.	*	n.b.	n.b.	n.b.
004S-G06	7	44	Fzd5					*					
002S-B01	8		Fzd1	*									
002S-C02	9		Fzd1	*									
002S-E02	10		Fzd1	**									
002S-G02	11		Fzd1	**									
002S-F03	12		Fzd1	**									
002S-A04	13		Fzd1	*									
002S-B04	14		Fzd1	**									
002S-D04	15		Fzd1	**									
004S-H04	16	45	Fzd5					**					
001S-A04	17	46	Fzd1,2,5,7,8	*	*	n.b.	n.b.	*	n.b.	*	*	n.b.	n.b.
003S-E07	18	47	Fzd2		**								
003S-D10	19	48	Fzd4	n.b.	n.b.		*	n.b.	n.b.		n.b.	n.b.	n.b.
004S-B08	20	49	Fzd6	n.b.	n.b.		n.b.	n.b.	**		n.b.	n.b.	n.b.
004S-D08	21	50	Fzd6	n.b.	n.b.		n.b.	n.b.	**		n.b.	n.b.	n.b.
004S-C09	22	51	Fzd6	n.b.	n.b.		n.b.	n.b.	**		n.b.	n.b.	n.b.
004S-F10	23	52	Fzd6	n.b.	n.b.		n.b.	n.b.	**		n.b.	n.b.	n.b.
004S-A11	24	53	Fzd6	n.b.	n.b.		n.b.	n.b.	**		n.b.	n.b.	n.b.
004S-A12	25	54	Fzd6	n.b.	n.b.		n.b.	n.b.	**		n.b.	n.b.	n.b.
005S-B07	26	55	Fzd9	n.b.	n.b.		n.b.	n.b.	n.b.		n.b.	**	n.b.
005S-D08	27	56	Fzd9	n.b.	n.b.		n.b.	n.b.	n.b.		n.b.	**	n.b.
005S-E09	28	57	Fzd9	n.b.	n.b.		n.b.	n.b.	n.b.		n.b.	**	n.b.
005S-H10	29	58	Fzd9	n.b.	n.b.		n.b.	n.b.	n.b.		n.b.	**	n.b.
005S-B11	30	59	Fzd9	n.b.	n.b.		n.b.	n.b.	n.b.		n.b.	**	n.b.
005S-D11	31	60	Fzd9	n.b.	n.b.		n.b.	n.b.	n.b.		n.b.	**	n.b.
014S-G02	32	61	Fzd6	n.b.	n.b.		n.b.	n.b.	414		n.b.	n.b.	n.b.
014S-B04	33	62	Fzd8	n.b.	n.b.		n.b.	n.b.	n.b.		**	n.b.	n.b.
014S-B06	34	63	Fzd9	n.b.	n.b.		n.b.	n.b.	n.b.		n.b.	**	n.b.
014S-G06	35	64	Fzd10	n.b.	n.b.		n.b.	n.b.	n.b.		n.b.	n.b.	**
014S-A07	36	65	Fzd10	n.b.	n.b.		n.b.	n.b.	n.b.		n.b.	n.b.	**
017S-B09	37		Fzd8	n.b.	n.b.		n.b.	n.b.	n.b.		*	n.b.	n.b.

* Indicates < 100 nM; ** indicates 100-2000 nM

103. Dr. McDonnell's discussion of the '278 Patent's Table 1B is also incomplete. While he notes that "Table 1B lists the heavy and/or light sequences for only 39 clones," EX1002 ¶ 83, he omits that the table also lists the heavy and light chain CDR sequences for a further 52 clones that exhibited confirmed binding. *See*

EX1001 at Table 1B. In total, Table 1B provides sequence information for 91 clones that exhibited confirmed binding. *See id.*

104. Table 2A discloses the CDR sequences of 211 “antibodies or fragments thereof that bind to LRP5 and/or LRP6,” and indicates whether they exhibit confirmed binding to the LRP5 or LRP6 extracellular domain (“ECD”) using the same Octet BLI method used to characterize the Fzd binding sequences, together with surface plasmon resonance measurements. *See* EX2022 at 94 (l. 26)–95 (l. 17). The table includes both sequences binding to LRP5 and those binding to LRP6, and further includes both sequences binding to the LRP6e1e2 subdomain and those binding to the LRP6e3e4 subdomain. *See* EX1001 at Table 2A. Table 2B provides the heavy chain sequences of 24 clones. *See id.* at Table 2B. While Dr. McDonnell alleges the ’278 Patent provides “no binding affinity data” for those clones, binding affinity ranges for 23 of the 24 clones in Table 2B are presented in U.S. Provisional Patent Application No. 62/607,879 (“the ’879 Application”), which is incorporated by reference. *See* EX2022 at Table 1B; EX1001 at 11:18–24. Dr. McDonnell also alleges that “Table 2B also does not provide any light chain sequences,” but the ’879 Application explains that the illustrative clones in that table “*hav[e] only a heavy chain region.*” EX2022 at 100 (ll. 1–3). Dr. McDonnell thus incorrectly surmises that these fragments comprise an undisclosed light chain.

105. Notably, the '877 and '879 Applications describe experiments conducted by the inventors using alanine-scanning mutagenesis to determine the effect of point mutations in the amino acid sequences of the disclosed CDRs of one anti-Fzd clone and one anti-LRP6 clone. *See* EX2021 at 107 (ll. 4–7); EX2022 at 100 (ll. 17–19). Testing 18 mutants of the anti-Fzd clone and 10 mutants of the anti-LRP6 clone with alanine substitutions at various points in their CDRs, the Applications show that all but one of the tested mutants retained their ability to bind their target antigen. *See* Tables 4–5, below. The Applications thus conclude that the tested antibodies and antigen-binding fragments thereof “can tolerate amino acid modifications within the CDRs,” EX2021 at 107 (ll. 6–9); EX2022 at 100 (l. 19)–101 (l. 2), allowing researchers to generate binding sequences beyond those disclosed in Tables 1A–B and 2A–B of the '278 Patent using point mutations.

Table 4: Table 2 of the '877 Application (EX2021) Showing Alanine-Scanning Mutagenesis Results for 001S-A04, a Confirmed Fzd1 Binder

Clone ID	Kd (nM)	CDRH1	CDRH2	CDRH3	CDRL1	CDRL2	CDRL3
WT	*	YTFTSYGIS	GWISAYNGNTNYA	CASSKEKATYYYGMDVW	GLSSGSVSTNYPS	YTNRSS	CLLYLGRGIWVF
VLL1A	*	YTFTSYGIS	GWISAYNGNTNYA	CASSKEKATYYYGMDVW	GLSSGSVSTNYPS	YTNRSS	CALYLGRGIWVF
VLL2A	*	YTFTSYGIS	GWISAYNGNTNYA	CASSKEKATYYYGMDVW	GLSSGSVSTNYPS	YTNRSS	CLAYLGRGIWVF
VLY3A	*	YTFTSYGIS	GWISAYNGNTNYA	CASSKEKATYYYGMDVW	GLSSGSVSTNYPS	YTNRSS	CLLALGRGIWVF
VLL4A	*	YTFTSYGIS	GWISAYNGNTNYA	CASSKEKATYYYGMDVW	GLSSGSVSTNYPS	YTNRSS	CLLYAGRGIWVF
VLG5A	*	YTFTSYGIS	GWISAYNGNTNYA	CASSKEKATYYYGMDVW	GLSSGSVSTNYPS	YTNRSS	CLLYLARGIWVF
VLR6A	*	YTFTSYGIS	GWISAYNGNTNYA	CASSKEKATYYYGMDVW	GLSSGSVSTNYPS	YTNRSS	CLLYLAGIWIWVF
VLG7A	*	YTFTSYGIS	GWISAYNGNTNYA	CASSKEKATYYYGMDVW	GLSSGSVSTNYPS	YTNRSS	CLLYLGRAIWVF
VLI8A	*	YTFTSYGIS	GWISAYNGNTNYA	CASSKEKATYYYGMDVW	GLSSGSVSTNYPS	YTNRSS	CLLYLGRGIWVF
VLW9A	**	YTFTSYGIS	GWISAYNGNTNYA	CASSKEKATYYYGMDVW	GLSSGSVSTNYPS	YTNRSS	CLLYLGRGIWVF
VLV10A	*	YTFTSYGIS	GWISAYNGNTNYA	CASSKEKATYYYGMDVW	GLSSGSVSTNYPS	YTNRSS	CLLYLGRGIWVF
VHK2A	*	YTFTSYGIS	GWISAYNGNTNYA	CASSKEKATYYYGMDVW	GLSSGSVSTNYPS	YTNRSS	CLLYLGRGIWVF
VHK4A	*	YTFTSYGIS	GWISAYNGNTNYA	CASSKEKATYYYGMDVW	GLSSGSVSTNYPS	YTNRSS	CLLYLGRGIWVF
VHT6A	**	YTFTSYGIS	GWISAYNGNTNYA	CASSKEKATYYYGMDVW	GLSSGSVSTNYPS	YTNRSS	CLLYLGRGIWVF
VHY7A	**	YTFTSYGIS	GWISAYNGNTNYA	CASSKEKATYYYGMDVW	GLSSGSVSTNYPS	YTNRSS	CLLYLGRGIWVF
VHY8A	n.b.	YTFTSYGIS	GWISAYNGNTNYA	CASSKEKATYYYGMDVW	GLSSGSVSTNYPS	YTNRSS	CLLYLGRGIWVF
VHY9A	**	YTFTSYGIS	GWISAYNGNTNYA	CASSKEKATYYYGMDVW	GLSSGSVSTNYPS	YTNRSS	CLLYLGRGIWVF
VHG10A	*	YTFTSYGIS	GWISAYNGNTNYA	CASSKEKATYYYGMDVW	GLSSGSVSTNYPS	YTNRSS	CLLYLGRGIWVF
VHV13A	*	YTFTSYGIS	GWISAYNGNTNYA	CASSKEKATYYYGMDVW	GLSSGSVSTNYPS	YTNRSS	CLLYLGRGIWVF

* Indicates < 100; ** indicates > 100

Table 5: Table 2 of the '879 Application (EX2022) Showing Alanine-Scanning Mutagenesis Results for 009S-E04, a Confirmed LRP6 Binder

Clone ID	Kd (nM)	CDRH1	CDRH2	CDRH3
WT	*	RIFAIYDIA	AMIRPVVTEIDYA	CNAKRPWGSRDEYW
K1A	*	RIFAIYDIA	AMIRPVVTEIDYA	CNAARPWGSRDEYW
R2A	*	RIFAIYDIA	AMIRPVVTEIDYA	CNAKAPWGSRDEYW
P3A	*	RIFAIYDIA	AMIRPVVTEIDYA	CNAKRAWGSRDEYW
W4A	*	RIFAIYDIA	AMIRPVVTEIDYA	CNAKRPAGSRDEYW
G5A	*	RIFAIYDIA	AMIRPVVTEIDYA	CNAKRPWASRDEYW
S6A	*	RIFAIYDIA	AMIRPVVTEIDYA	CNAKRPWGARDEYW
R7A	*	RIFAIYDIA	AMIRPVVTEIDYA	CNAKRPWGSADDEYW
D8A	*	RIFAIYDIA	AMIRPVVTEIDYA	CNAKRPWGSRAEYW
E9A	*	RIFAIYDIA	AMIRPVVTEIDYA	CNAKRPWGSRDAYW
Y10A	*	RIFAIYDIA	AMIRPVVTEIDYA	CNAKRPWGSRDEAW

* Indicates < 100 nM

106. Table 3 of the '278 Patent lists 95 exemplary “Wnt surrogate sequences” that incorporate the antibody and antibody-fragment sequences listed in Tables 1 and 2. See EX1001 at Table 3. Eighty of the molecules listed in Table 3 are tetravalent

and comprise two Fzd binding regions and two LRP5/6 binding regions, while the remaining 15 are bivalent, consisting of a single Fzd binding region and a single LRP5/6 binding region. *See id.* Examples 2–18 of the specification show the results from Wnt signaling reporter assays testing these 95 molecules, in addition to another 10 tetravalent molecules not listed in Table 3. *See id.* at Examples 2–18. Notably, these examples show that ***every single tetravalent molecule tested activated Wnt signaling***, while none of the bivalent surrogate molecules tested were effective in doing so. *See id.*; EX2010 ¶ 73.

107. The examples also disclose the effects of molecular geometry and linker length on Wnt signaling activation. For instance, in Example 9, the inventors conducted a Structure–Activity Relationship (SAR) analysis of IgG–Nab fusions by “rotating the attachment location of the Nab to the different termini of the IgG HC or LC” for three pairs of Ig–Nab fusions. EX1001 at 157:35–37. The ’278 Patent reports TOPFlash results measuring the Wnt signaling activity for each fusion, and notes that all of the tested molecules “activated Wnt signaling to various levels,” concluding that “[t]hese results demonstrate 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.” *Id.* at 157:47–50, Fig. 9. Similarly, Example 14 tests two Fzd–LRP5/6 binder fusions connected via 5, 10, or 15-amino acid linkers, and reports that all fusion proteins “were able to activate Wnt

signaling ... with different linkers.” *Id.* at 159:5–47. The example concludes that “[w]hile all of these scFv formats activated Wnt signaling, potency and overall maximal efficacy may differ depend[ing] on the binder combination, linker length, and relative orientation.” *Id.* at 159:36–39.

108. The specification further demonstrates how various engineering approaches to prevent promiscuous pairing may be used in the Wnt molecules. In Example 15, the specification explains that “[v]arious approaches, such as charge pairing, ‘knobs-in-holes,’ crossover of the heavy and light chains of Fabs, can be employed to ensure proper heavy and light chain pairing.” *Id.* at 159:56–59. Example 15 constructs several molecules using charge pairing and HC-LC crossover approaches, with different linker lengths and binding regions. *See id.* at 159:60–160:21. Some of the examples also demonstrate that “[t]he order of the anti-LRP6 and anti-FZD Fabs could be reversed.” EX1001 at 160:5–8, 17–21. These molecules were then tested for their ability to activate Wnt signaling using TOPFlash reporter assays. *Id.* at 160:5–8, 17–21, Fig. 15A. As the specification explains, “[a]ll fusion molecules activated Wnt signaling while some preference of orientation and linker length was observed.” *Id.* at 160:38–40.

109. Dr. McDonnell’s statement that the ’278 Patent does not “disclose any trispecific or tetraspecific molecules” EX1002 ¶ 85, is wrong and refuted by Table 3, which contains at least 77 examples of molecules that contain cross-reactive anti-

Fzd binding sequences. For instance, the molecules R2M13-3, R2M13-26, and R2M13-36 consist of the 004S-G06 sequence—which Table 1B demonstrates contains binding regions capable of binding the Fzd5 and Fzd8 receptors—and two binding regions, each specific to either LRP5 or LRP6. *See* EX1001 at Table 1B, Table 3. A POSA would thus understand these molecules to be both bispecific, in that they can bind two of the same Fzd receptors and two of the same LRP5/6 receptors, **and** trispecific, in that they can bind two different types of Fzd receptors and the same LRP5/6 receptors, and their ability to activate Wnt signaling is evidenced in Example 17, *see* EX1001 at 161:1–17, Fig. 17C. The specification further discloses that a “LRP5/6 binding region of a Wnt surrogate molecule [can] bind[] to one **or both** of LRP5/6.” *Id.* at 121:44–46. This conveys to a POSA that the inventors were in possession of trispecific **and** tetraspecific molecules.

110. Examples 19–26 report further experiments conducted *in vivo* on the disclosed molecules, including pharmacokinetic and pharmacodynamic characterizations (Example 19), and preclinical results showing the impacts of administration of the molecules on bone mass and liver regeneration after chronic and acute injury (Examples 20–26). EX1001 at 161:35–172:34.

111. Given the extensive disclosures provided in the '278 Patent specification, I disagree with Dr. McDonnell's allegation that “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.” *Contra* EX1002 ¶ 87. In my opinion, the ’278 Patent provides abundant and diverse disclosures, including several helpful and representative working examples that use a vast range of different structures, materials, and engineering methods that provide a POSA with invaluable insights to make and use the claimed tetravalent molecules.

B. Effective Filing Date

112. The ’278 Patent claims priority to three provisional applications, the first of which was filed December 19, 2017. I do not address Dr. McDonnell’s characterizations of what was and was not included in the provisional disclosures, because they are not relevant to my or Dr. McDonnell’s analysis of the ’278 Patent. Dr. McDonnell has assumed an effective filing date of December 19, 2017, EX1002 ¶¶ 88–89, and I likewise use that date in my analysis. I note, however, that my opinions would not change if the effective filing date for the ’278 Patent is any date on or before December 19, 2018.

C. Challenged Claims

113. The ’278 Patent contains five claims, all of which I understand Petitioner has challenged. Claim 1 is the sole independent claim and 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 at cl. 1.

114. Claims 2–5 depend from claim 1 and recite:

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.

EX1001 at cls. 2–5.

D. Prosecution History of the '278 Patent

115. During prosecution of the '278 Patent, the Examiners twice rejected its claims as obvious over Garcia US (EX1011) and Wu. *See* EX1008 at 2973, 3982. Having compared Garcia US with the Garcia reference Dr. McDonnell purports to anticipate claims 1 and 4, I agree that “Garcia US is a publication of the U.S. patent application corresponding to Garcia (EX1004) and is substantively identical to Garcia (EX1004).” EX1002 ¶ 92. The Examiner thus considered Garcia US’s (and therefore Garcia’s) disclosures twice during prosecution and concluded that it did not disclose every limitation of claims 1 and 4.

116. In the first Office Action, the Examiners alleged that while “Garcia [US] teaches that the molecules of the invention are water soluble; bind with high affinity to both (i) frizzled (Fzd) proteins and (ii) Lrp5/6; and directly activate canonical wnt pathway signaling,” it “does not teach dual variable domain (DVD) format of

bispecific antibody,” *Id.* at 2973—an antibody format in which each arm of the antibody includes two variable domains, each variable domain capable of binding a different target. I disagree with Dr. McDonnell’s assertion that the Examiners’ statement somehow evidences that they “narrowly focused on a ‘dual variable domain (DVD) format.’” EX 1002 ¶ 93. Rather, the statement only shows that the Examiners were not able to identify every limitation of the ’278 Patent’s pending claims in Garcia US itself, and thus resorted to identifying the disclosure of a “DVD-Ig format bispecific antibody” in Wu to issue a rejection. *See* EX1008 at 2974.

117. In response to the Examiners’ rejection, Applicant explained that Garcia US “teaches agonists of Wnt pathway signaling that are bivalent and bispecific,” but that those agonists “comprise an LRP binding arm that is a decoy protein based on DKK1”—a fragment not derived from an antibody. *Id.* at 3955. Applicant further pointed out that “Garcia [US] does not suggest a tetravalent, bispecific Wnt agonist with a non-DKK1 LRP binding region, nor is this essential disclosure found in Wu’s reference,” and explained that “the asserted combination of references does not provide one of ordinary skill in the art with the required motivation or any expectation of success in achieving the claimed invention.” *Id.* at 3955–56.

118. In the Examiners’ second Office Action, they reiterated that “Garcia [US] does not teach dual variable domain (DVD) format of bispecific antibody” and again looked to Wu for disclosure of a tetravalent molecular structure. *Id.* at 3982–83. The

Examiners responded to Applicant's arguments by locating an alleged motivation to combine in Wu and by alleging that "one of ordinary skill in the art would not need to replace DKK1 with LRP5/6 binding region of [the] instant invention to arrive at instant claim 1 and dependent claims 17 and 55," and that the "binding domain taught by Garcia [US] is NOT limited only to DKK1." *Id.* at 3985.

119. In response to the Examiners' second Office Action, Applicant explained that "claim 1 is directed to a 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," while the "Wnt surrogates disclosed in Garcia include one Fzd binding region and one LRP binding region, and are bivalent." *Id.* at 4005 (underlining in original). Applicant further explained that (1) the two exemplary Wnt surrogates described in Garcia US "both have the stoichiometry of 1:1" and (2) they both comprised binding region fragments that were not antibody derived. *Id.* Moreover, Applicant explained, "Garcia [US] does not recognize or highlight any requirement for higher valency (meaning having more than one FZD binding domain or having more than one LRP binding domain) as a requirement for Wnt signaling activity." *Id.*

120. Regarding the Examiners' allegation that "one of ordinary skill in the art would not need to replace DKK1 with LRP5/6 binding region of [the] instant invention to arrive at instant claim 1 and dependent claims 17 and 55," Applicant

explained that claim 1 “specifically recites that ‘each of the two LRP5/6 binding regions comprises an antibody or antigen-binding fragment of the antibody.’” *Id.* at 4006. Because “DKK1c is not an antibody or antigen-binding fragment thereof,” Applicant “reiterate[d] that Garcia [US], alone or in combination with Wu, fails to motivate the skilled artisan to modify the Lrp5/6 binding region from DKK1c to an antibody or antigen-binding fragment thereof, as claimed.” *Id.*

121. As for Wu, Applicant explained that “the skilled artisan would appreciate that the teachings of Wu relate to bivalent molecules that allow the simultaneous blockade of multiple targets (e.g., IL-12 and IL-18), which is very different than the claimed molecules, which simultaneously engage two cell surface coeffectors molecules (Fzds and Lrp5/6) required to agonize the canonical Wnt signaling cascade.” *Id.* at 4006 (underlining in original). Thus, Applicant explained, Wu fails to disclose “DVD-IgG molecules that bind to Fzd(s) and Lrp5/6 to initiate Wnt signaling” and therefore did not supply a motivation to combine Garcia US with Wu to arrive at the claimed invention with a reasonable expectation of success. *Id.*

122. Along with its response to the Examiners’ second Office Action, Applicant submitted a declaration authored by named inventor Dr. Yang Li, explaining that “the belief in the art at the time of the claimed invention was the inaccurate notion that bivalent molecules with 1:1 Fzd/Lrp5/6 binding stoichiometry were capable of agonizing a Wnt signaling pathway.” *Id.* at 4007. Dr. Li explained that the finding

that “the claimed tetravalent, multispecific Wnt surrogate molecules ... possess greatly superior activity as compared to those having 1:1 Fzd binder:Lrp5/6 binder stoichiometry, as disclosed by Garcia et al.” was “surprising and unexpected in view of the prior art and understanding of the field.” *Id.* at 4170. Dr. Li further reiterated that Garcia US “only described Wnt surrogate molecules having 1:1 Fzd binder:Lrp5/6 binder stoichiometry, and did not suggest or provide any motivation for a person skilled in the art to design a tetravalent molecule as claimed.” *Id.* at 4168. Indeed, as Dr. Li pointed out, “Garcia’s research group not only continued to teach the original 1:1 Fzd binder:Lrp5/6 binding stoichiometry, but also presented arguments against the superiority of the tetravalent format,” teaching away from the molecules claimed in the ’278 Patent. *Id.* As for Wu, Dr. Li explained that its disclosed DVD-Ig format was used for the “simultaneous blockade of multiple targets,” a POSA would thus not have been motivated to use that format to design the claimed molecules, “which simultaneously engage two cell surface coeffector molecules (Fzd and Lrp5/6) required to agonize the canonical Wnt signaling cascade.” *Id.* (underlining in original).

123. Following Applicant’s submission of its response and Dr. Li’s declaration, the Examiners withdrew their obviousness rejections and allowed the claims on March 25, 2025. *See id.* at 4207–17.

124. Dr. McDonnell expresses purported disagreement with “the characterization of Garcia US by Applicant and Dr. Li,” and cites to two paragraphs in Garcia US/Garcia that allegedly support his opinion that “Garcia US (and Garcia) does disclose a ‘dimer’ molecule consisting of two Fzd binding regions and two Lrp5/6 binding regions.” EX1002 ¶ 97. These paragraphs discuss that the molecules in Garcia US/Garcia may be “dimer[s]” or “multimer[s],” but say nothing about the number of Fzd binding regions and Lrp5/6 binding regions in those molecules. *See* EX1004 at [0056]; *id.* at [0018]. Dr. McDonnell cites to an identical paragraph in a later patent application to claim that “Garcia’s later patent applications continued to disclose Wnt agonist molecules with higher valency.” EX1002 ¶ 97 (quoting EX1014 at [0009]). But because a molecule’s identity as a “dimer” or “multimer” is an entirely distinct concept from and has nothing to do with valency, Dr. McDonnell is incorrect that Applicant and Dr. Li mischaracterized Garcia’s disclosures; it is instead Dr. McDonnell who mischaracterizes them. *See* ¶¶ 356–357, below.

IX. CLAIM CONSTRUCTION

125. Dr. McDonnell opines on the purported meaning of two terms that appear in the ’278 Patent’s claims: (1) “Wnt surrogate molecule” 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.” For the reasons below, in my opinion, a POSA would not understand the preamble term “Wnt surrogate molecule” to be limiting as Dr. McDonnell

alleges. If the preamble is limiting, the term “Wnt surrogate molecule” should have its plain and ordinary meaning. Further, it is my opinion that “wherein each of the two LRP5/6 binding regions is fused to one of the two Fzd binding regions via a linker moiety” should have its plain and ordinary meaning. The meanings Dr. McDonnell imports into these terms are confusing and inconsistent with what a POSA in 2017 would understand those terms to mean in view of the ’278 Patent.

126. For the purposes of my opinions in this declaration, I apply the plain and ordinary meaning of the claims, which, as I explain here, do not include a requirement that the claimed molecules be “biologically active.” See ¶¶ 127–136, below. Where I discuss the claimed molecules’ agonism properties, I do so solely to respond to Dr. McDonnell’s assertions. Regardless, even applying Dr. McDonnell’s constructions, it is my opinion that the claims are supported by adequate written description, enabled, definite, and not anticipated by Garcia, contrary to Dr. McDonnell’s claims.

A. “Wnt Surrogate Molecule”

127. In my opinion, a POSA would understand the term “Wnt surrogate molecule” as used in the ’278 Patent’s claims to state an intended use or purpose for the molecules claimed in the patent. The body of the claims recites a complete structural invention—a molecule comprising “(i) 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; and (ii) two LRP5/6 binding regions that specifically bind to [LRP5/6], 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 at cl. 1. The claims thus use the term “Wnt surrogate molecule” to merely describe the complete invention recited in the claim body. I thus disagree with Dr. McDonnell that this term is necessary to give the claims “life, meaning, and vitality.” *Contra* EX1002 ¶ 104.

128. Even assuming Dr. McDonnell is correct that the term “Wnt surrogate molecule” is a limitation of the claims (which he is not), as I explain below, a POSA reading the patent would not accord the term the meaning Drs. McDonnell and Kahn give it, *i.e.*, 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.” *See* EX1002 ¶ 102; EX1003 ¶ 66. Rather, a POSA would have understood the term “Wnt surrogate molecule” to refer to its plain and ordinary meaning—“a molecule that binds to both (i) Fzd and (ii) LRP5 or LRP6 receptors.”

129. The ’278 Patent’s specification is consistent with this plain and ordinary meaning of “Wnt surrogate molecule.” For example, the specification contains a section titled “Wnt Surrogates,” which begins by explaining that “[t]he disclosure

provides, in certain aspects, Wnt surrogate molecules *that bind both one or more Fzd receptors and one or both of LRP5 and/or LRP6.*” EX1001 at 16:37–39. Similarly, Table 3 of the specification, titled “Wnt Surrogate Sequences,” lists 96 “illustrative Wnt surrogates,” all of which contain at least one Fzd binding domain and one LRP5/6 binding domain.

130. The prosecution history of the ’278 Patent similarly aligns with the specification’s description of “Wnt surrogate molecule.” For example, in response to the Examiner’s second Office Action, Applicant explained that “*the Wnt surrogates* disclosed in Garcia *include one Fzd binding region and one LRP binding region.*” EX1008 at 4005. The declaration of Dr. Yang Li submitted along with Applicant’s response similarly explains that “Garcia et al. only described *Wnt surrogate molecules having 1:1 Fzd binder:Lrp5/6 stoichiometry.*” *Id.* at 4168. Both Applicant and the named inventors thus understood a Wnt surrogate molecule to be a molecule capable of binding both one or more Fzd receptors and one or more LRP5/6 coreceptors.

131. As discussed above, inventor and Applicant repeatedly noted that the claimed molecules’ ability to agonize Wnt signaling pathways stems from their ability to bind both Fzd receptors and LRP5/6 coreceptors in a tetravalent manner. That aspect of the invention is expressly recited in the body of the ’278 Patent’s claims, which require that the molecule contain:

- (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

EX1001 at cl. 1.

132. Dr. McDonnell opines that the inventors defined “Wnt surrogate molecule” to mean “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.” EX1002 ¶¶ 103, 105 (quoting EX1001 at 16:52–56). I disagree. In the same portion of the patent that Dr. McDonnell cites, the specification describes a “Wnt surrogate molecule” as something that “*bind[s] to one or more Fzd receptor[s] and to one or both of LRP5 and/or LRP6.*” EX1001 at 16:52–56. I thus disagree with Drs. McDonnell and Kahn that the inventors clearly declared their intent to depart from the plain and ordinary meaning of the term “Wnt surrogate molecule”—i.e., by requiring that the molecule is “biologically active” or a “Wnt agonist”—by acting as their own lexicographers.

133. Other portions of the specification confirm that Dr. McDonnell’s definition is wrong. For example, Table 3 of the specification, titled “*Wnt Surrogate Sequences*” lists the sequences of 15 bivalent molecules falling outside the scope of the claims that the working examples report were “*ineffective* in activating Wnt signaling.” EX1001 at Table 3, 158:3–6, 28–31, 44–47, 159:44–47. A POSA reading these disclosures would thus understand that the term “Wnt surrogate molecule” was not confined to those molecules that agonized Wnt signaling pathways, let alone gave the claims some threshold requirement of agonistic functionality.

134. The above discussion in the specification is also consistent with how the inventors used the term “Wnt surrogate molecule” during prosecution, *i.e.*, by its binding to one or more Fzd and one or more LRP5/6 receptors, rather than by its agonist or biological activity. For example, in its response to the Examiners’ second Office Action rejecting the claims as obvious over Garcia and Wu, Applicant explained that “the teachings of Wu relate to bivalent molecules that allow the simultaneous blockade of multiple targets ..., which is very different than *the claimed molecules*, which *simultaneously engage two cell surface coeffector molecules (Fzds and Lrp5/6) required to agonize* the canonical Wnt signaling cascade.” EX1008 at 4006 (underlining in original). Applicant likewise used the term “Wnt surrogate molecule” when characterizing Garcia US’s ineffective bivalent molecules. Applicant explained that “*the Wnt surrogates* disclosed in

Garcia [US] *include one Fzd binding region and one LRP binding region*,” noting that “the belief in the art at the time of the claimed invention was the *inaccurate notion* that bivalent molecules with 1:1 Fzd/Lrp5/6 binding stoichiometry were capable of agonizing a Wnt signaling pathway.” *Id.* at 4005, 4007.

135. In other words, the inventors specifically tied the claimed molecules’ ability to agonize Wnt signaling to the Fzd and LRP5/6 binding region claim limitations, not any definition of “Wnt surrogate molecule.” Applicant’s arguments during prosecution evidence the understanding that a molecule that binds both (i) Fzd and (ii) LRP5 or LRP6 receptors need not agonize Wnt signaling to constitute a “Wnt surrogate molecule.”

136. My opinions below apply this plain and ordinary meaning of “Wnt surrogate molecule.” Where I address the claimed molecules’ ability to agonize Wnt signaling—which, in my opinion, is not a limitation of the claims for the reasons above—I do so solely to respond to Dr. McDonnell’s assertions regarding the same.

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

137. Dr. McDonnell also opines that the clause “wherein each of the two LRP5/6 binding regions is fused to one of the two Fzd binding regions via a linker moiety” means “each of the two LRP5/6 binding regions is connected *directly via a linker moiety* to one and only one Fzd binding region.” EX1002 ¶ 108 (original emphasis). In my opinion, Dr. McDonnell’s purported definition of the term imports confusion

and unsupported additional limitations into the claim language. As discussed further below, in my opinion, a POSA would understand the clause to take on its plain and ordinary meaning: “each of the two LRP5/6 binding regions is bound to at least one of the two Fzd binding regions via a linker moiety.”

1. “Fused ... via a Linker Moiety”

138. In my opinion, a POSA would understand the phrase “fused ... via a linker moiety” to simply mean “bound ... via a linker moiety.” In the antibody engineering field, two structures are referred to as “fused” when they are bound or connected to each other through intervening covalent bonds. These structures may be either bound, connected, or “fused” directly through covalent associations between each other, or indirectly through a chain of other covalently bonded structures.

139. The specification’s usage of the term “fused” is consistent with a POSA’s understanding of the term as used to denote a connection between two structures. For example, the specification repeatedly uses “fused” interchangeably with “bound.” *See e.g.*, EX1001 at 17:46–48 (describing molecules comprising multiple “polypeptides, e.g., linked or bound to each other or fused to each other”), 22:23–27 (describing molecules comprising “a Fzd binding region ... fused or bound to a polypeptide that specifically binds to one or more Fzd receptor”), 18:29–31, 156:38–39 (“The Fzd binder, R2M3, was fused to additional LRP6 binders.”). Further, the specification’s embodiments make clear that two structures need not be “directly”

bound to be fused. For example, the specification explains that “[i]n certain embodiments, Wnt surrogate molecules comprise antibody variable domains with the desired binding specificities fused to immunoglobulin constant domain sequences” and that “[i]n particular embodiments, the first heavy-chain constant (C_H1) containing the site necessary for light chain bonding, [is] present in at least one of the fusions.” EX1001 at 124:5–14. And Figure 1C, for example, depicts four tetravalent structures where the Fzd and LRP5/6 binding regions are connected via linker moieties through intervening Fc regions and disulfide bonds. *See* Fig. 4, below.

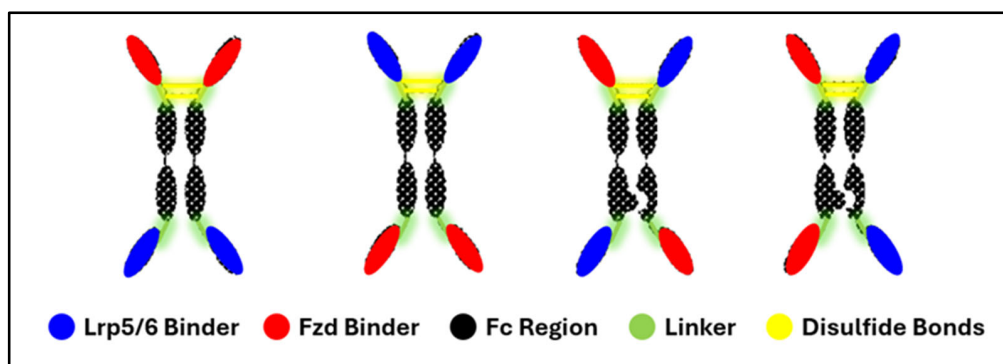


Figure 4: '278 Patent Figure 1C (annotated)

140. Dr. McDonnell nonetheless opines that the phrase “‘fused ... via a linker moiety’ in claim 1 requires being connected directly via the linker moiety,” EX1002 ¶ 109, but the specification itself categorizes fusions via linkers as fusions that are not “direct,” explaining that where “the Wnt surrogate molecules comprise a single polypeptide, ... [t]he binding domains may be directly fused or they may be connected via a linker.” EX1001 at 17:49–54. Further, Dr. McDonnell himself

appears to acknowledge that what he defines as “direct connections” may comprise an intervening constant or Fc domain. For instance, his chart of “possible tetravalent topologies” includes several structures where the LRP5/6 binding regions are fused to one of the two Fzd binding regions via a linker moiety *through an intervening Fc region*. See Fig. 5, below.

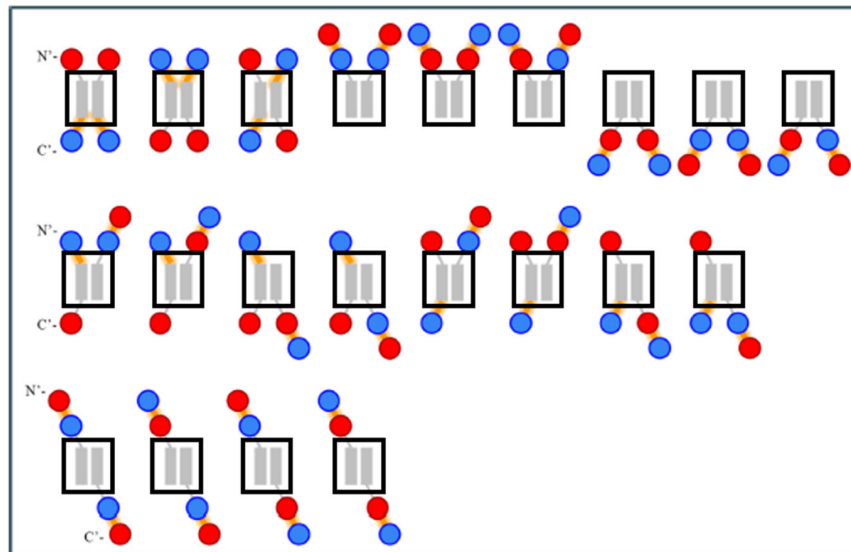


Figure 5: Dr. McDonnell’s Fig. 9, Annotated to Highlight Intervening Fc Regions (Black Boxes)

141. Dr. McDonnell’s discussion of the structures disclosed in the Tao reference similarly acknowledges the claims may encompass indirect connections. For example, Dr. McDonnell alleges 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,” EX1002 ¶ 201, despite the presence of an intervening Fc region between the binding regions. See Fig. 6, below.

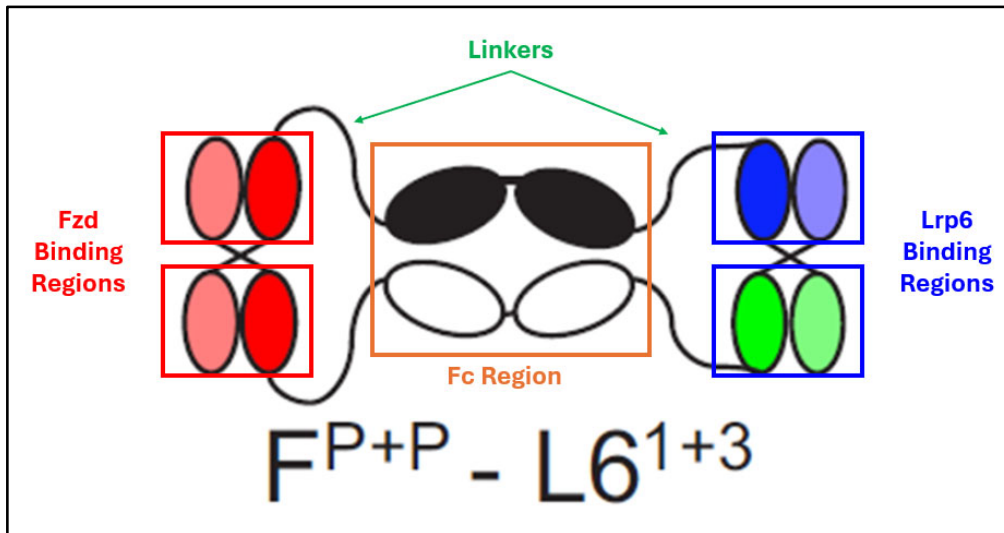


Figure 6: Tao (EX1072) at Fig. 1C (annotated)

142. The sole example Dr. McDonnell provides of “indirect connections” that he alleges the claims do not encompass—“features such as disulfide bonds that are present within or between the polypeptide chains of Wnt surrogate molecules,” EX1002 ¶ 110—only further confuses his definition. A POSA would understand that interchain disulfide bonds—like the intrachain peptide bonds that hold a polypeptide together—are covalent bonds that connect two amino acid residues and play a crucial role in determining the structure of an antibody. Dr. McDonnell thus offers no principled distinction between what he terms a “direct” connection on the one hand, which appears to include the peptide bonds in a linker moiety, and an “indirect” connection on the other, such as interchain disulfide bonds.

143. A POSA would instead understand “indirect” fusions to include both connections through an intervening Fc region and connections through intervening

disulfide bonds. Excluding connections through intervening Fc regions would exclude several embodiments of the claimed invention the '278 Patent discloses, including at least four molecules (26:Fc:17SB9-criss-cross, 26:Fc:17SB9, 17SB9:Fc:26, and 26:Fc:26+17SB9:Fc:17SB9) tested in Example 13 and at least three molecules (18R5:Fc:1115.3, 1115.3:Fc:18R5, and 18R5:Fc:YW211.31.57) tested in Example 14. *See* EX1001 at Examples 13–14, Figs. 13D-13F, 14E-14G.

144. Dr. McDonnell's interpretation of "fused ... via a linker moiety" as excluding disulfide connections is similarly refuted by the specification. Figure 13A, for instance, depicts four different structures formed by combining four Nab regions with an intervening region Fc region. *See* EX1001 at Fig. 13A. The fourth structure in the figure illustrates a molecule where both LRP Nabs are connected via linkers to one Fc heavy chain, and both Fzd binding Nabs are connected to the other. *See* Fig. 7, below. Notably, each LRP5/6 binding region is connected to one of the two Fzd binding regions via a linker moiety ***through the disulfide bonds*** (annotated in orange). A POSA would thus appreciate from this example that the term "fused" can accommodate what Dr. McDonnell terms "indirect connections" when used in the context of claim 1.

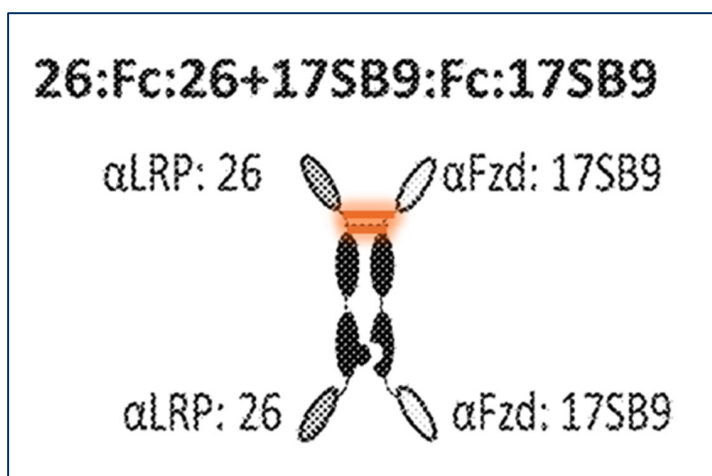


Figure 7: Molecule From '278 Patent Fig. 13A, Annotated to Indicate Disulfide Connections (Orange Lines)

145. In spite of these disclosures, Dr. McDonnell claims that “[t]hroughout the specification, the term ‘fused’ is consistently used to connote direct connections, rather than indirect connections” because the specification “distinguishes the four formats” in Figure 1A “based on how different parts are directly connected to each specific terminus.” EX 1002 ¶ 110. But Dr. McDonnell ignores the context in which specification uses the term “fused” to describe the structures in Figure 1A, which differs materially from the context in which it is used in claim 1’s “linker” limitation.

146. In the field of protein engineering in general and antibody engineering in particular, the phrase “fused to” is not a one-size-fits-all concept, and its meaning varies in relation to the structures being described and the level of specificity provided. For example, a POSA would understand the statement that a Fzd receptor is “fused” to a LRP5/6 receptor—as used in claim 1—to indicate a direct or indirect

covalent association between those structures, without necessarily specifying a particular fusion site. By contrast, and unlike the claim term, the phrases used to describe Figure 1A that Dr. McDonnell cites from the specification convey a specific fusion site to a POSA by using conventional terminology in the field. For example, the phrase “the Nab can be fused to the N-terminus of the IgG light chain,” EX1001 at 150:36–38, identifies both the relevant polypeptide chain (heavy vs. light) and the location on that chain (N-terminus vs. C-terminus) at which the fusion occurs.

147. Dr. McDonnell’s analysis of the structures depicted in Figure 1A does not apply the context-dependent understanding of “fusion” described above. Instead, he claims that if a POSA were to consider so-called “indirect” connections, they would reach the conclusion from the specification’s description of particular attachment sites in Figure 1A that every structure in the molecule is “fused to” every other structure. *See* EX1002 ¶ 111. But that conclusion follows only by divorcing “fused” from the structures in Figure 1A and the language used in that context to describe specific attachment locations on the structures being fused.

148. Dr. McDonnell’s reading of the specification’s discussion of Figure 1B suffers from the same flaws. Dr. McDonnell claims that because the specification explains with reference to Figure 1B that “two HC[s] can be fused together with a linker in between” and the “LCs can be fused and unfused,” EX1001 at 150:64–65, the term “fused” cannot permit “indirect connections” because it would “become

indistinguishable from ‘unfused’ and lose any significance because the LCs would be fused to one another, directly or indirectly, in either case.” EX1002 ¶ 112. But again, Dr. McDonnell’s reading of the term “fused” is untethered from the specific, attachment-location defined context in which it is used to describe Figure 1B.

149. With reference to Figure 1B, the specification first states that “one Fab binder is first reformatted to a full IgG format” and that “[t]he second Fab binder can be fused to the N-terminus of the IgG.” EX1001 at 150:61–64. As with Figure 1A, then, the specification uses conventional terminology in the field to identify a specific end of the IgG molecule (the N-terminus) where the fusion occurs. The N-terminus region of the IgG structure in Figure 1B contains two N-termini—one for the heavy chain and one for the light chain. In that context, the specification further specifies the fusion location of the Fab by explaining that the “two HC can be fused together with a linker in between” while the “LCs can be fused or unfused.” EX1001 at 150:64–65. In my opinion, because “fused” is used in this context to map the specific point of attachment for the Fab–IgG fusion, a POSA would appreciate that the term “unfused” stands in contrast to “fused” *at the specific point of attachment*. Therefore, the term “fused” would not “become indistinguishable from ‘unfused’ and lose any significance,” EX1002 ¶ 112, in this context merely because it can permit indirect connections in others.

150. In my opinion, a POSA would understand that the use of the term “fused” as used in claim 1 differs markedly from its use in the contexts Dr. McDonnell cites. Unlike the specification’s discussion of Figures 1A and 1B, claim 1 does not specify a particular fusion site; instead, the claims require that two structures—each LRP5/6 binding region on the one hand and one of the two Fzd binding regions on the other—be “fused” via a linker moiety. In that context, a POSA would understand the limitation to simply indicate that the two structures (1) must be bound (2) via a linker moiety.

151. To summarize, Dr. McDonnell’s interpretation of “fused... via a linker moiety” rests on a false dichotomy: according to him, either “fusion” is limited to strictly “direct” connections, or it cannot be used to describe attachment locations in any context. A POSA would understand the specification to adopt neither extreme. Instead, it confirms that “fusion” can include indirect connections, including through linkers, constant domains, and disulfide bonds, and that it can also be used to describe specific attachment relationships between identified components.

2. “One of the Two Fzd Binding Regions”

152. Dr. McDonnell alleges that “[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 binding regions.” EX1002 ¶ 114. But again, Dr. McDonnell’s interpretation of the phrase “one of the two” finds no support in the

specification and imports language into the phrase found nowhere in the '278 Patent. In my opinion, a POSA would not understand the term “one of the two Fzd binding regions” to mean “one and only one Fzd binding region.” Instead, a POSA would look at the phrase’s plain and ordinary meaning in view of the '278 Patent’s specification, and understand “one of the two” to set a threshold for the fusion relationships in the molecule: at a minimum, each LRP5/6 binding region must be fused via a linker moiety to at least one of the two Fzd binding regions.

153. To reach his restrictive reading of “one of the two,” Dr. McDonnell characterizes “one of the two” as a “restrictive phrase,” as opposed to “nonrestrictive phrases such as one or both or even a generic ‘a’ or ‘an.’” EX1002 ¶ 115. But Dr. McDonnell provides no explanation as to why “one of the two” is a “restrictive phrase” or is any different from “nonrestrictive phrases such as one or both or even a generic ‘a’ or ‘an.’” To the contrary, the term “one of the two” merely anchors the fusion limitation in the claim language by pointing back specifically to the “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.” EX1001 at cl. 1. The term “one of the two” thus clarifies to a POSA that the fusion limitation must be met as to one of *those* Fzd binding regions, rather than suggesting the presence of other Fzd binding regions in the molecule.

154. A POSA would also not understand the term “one of the two” to be “restrictive” in this context as Dr. McDonnell suggests. Instead, the term makes clear that to identify whether a molecule meets the claim limitations, a POSA must (1) look at each LRP5/6 binding region, and with respect to that binding region, (2) identify a Fzd binding region that it is fused to via a linker moiety. The claim language thus says nothing about what relationship each LRP5/6 binding region has with *the other* Fzd binding region. Indeed, the inventors could have used truly restrictive terminology such as “*only one*” or “*one and only one*” if they had so desired. For example, the ’278 Patent uses precisely such language to explain that “[i]n particular embodiments, *only one* of the Fab of the Fzd binding region or the Fab of the LRP[5/6] binding region is present within the full immunoglobulin (Ig).” EX1001 at 3:55–57. A POSA would thus understand that while the claims require each LRP5/6 binding region to be fused via a linker moiety to one of the two Fzd binding regions, the LRP5/6 binding region may be fused via linker moiety, fused by other means, or entirely unfused from the other. The claims therefore clearly encompass embodiments where one or more LRP5/6 binding regions is linked to two Fzd binding regions via a linker moiety without “effectively mak[ing] the term ‘one of the two’ meaningless” as Dr. McDonnell asserts. EX1002 ¶ 115.

155. Dr. McDonnell claims that “[s]imilar phrases used in other claims also support” his reading, but again, he merely states that “[a] POSA would have

understood that ‘**one** of the light chains’ as recited in claim 5 means **one and only one** light chain,” EX1002 ¶ 116, without providing any reason for that interpretation. For one, claim 5 depends from claim 2, which in turn depends from claim 1, and thus necessarily uses the term “fused” in a narrower context. *Compare* EX1001 at cl. 5, *with id.* at cl. 1. Specifically, unlike claim 1, whose “fusion” limitation merely describes a connection via a linker moiety between two structures, a POSA would have understood the term “light chain” to identify a specific point of attachment on the “full immunoglobulin (IgG)” — “each of the two LRP5/6 binding regions is fused to one of the light chains via a linker moiety.” *Id.* at cl. 5. Moreover, nothing in the language of that claim would indicate to a POSA that “one of the light chains” means “one and only one light chain.” Instead, as with the fusion limitation of claim 1, a POSA would understand that while claim 5 requires each LRP5/6 binding region to be fused via a linker moiety to the IgG molecule with a specific point of attachment on “one of the light chains,” the LRP5/6 binding region may be fused via linker moiety, fused by other means, or entirely unfused from the other.

156. Instead of pointing to anything in the language of claim 5 that supports his interpretation of that claim, and therefore his interpretation of claim 1, Dr. McDonnell resorts to stating, without elaboration, that his interpretation “aligns with the formats shown in Figure 1A.” EX1002 ¶ 116. But Figure 1A illustrates precisely that a LRP5/6 binding region can be fused to **both** light chains, via intervening

disulfide bonds and Fc regions, while one of them *also* serves as a specific attachment point. *See* Fig. 8, below.

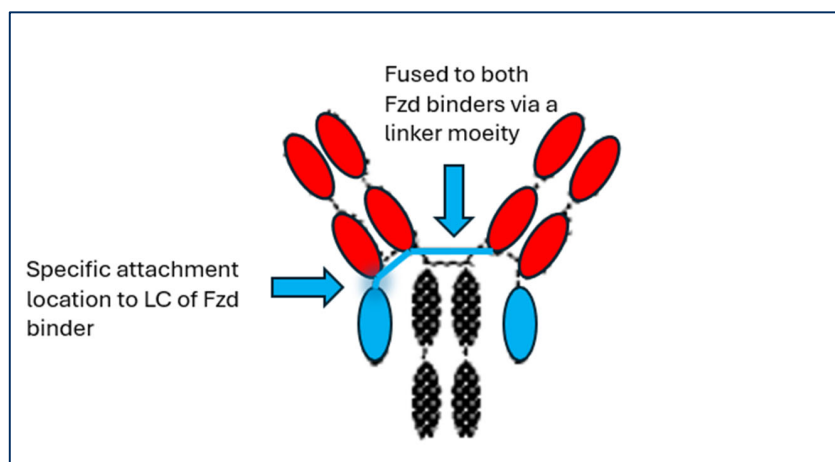


Figure 8: Molecule from '278 Patent Fig. 1A, Annotated to Show Fusions Via Linker Moiety (Blue Line)

157. Dr. McDonnell’s statement that “the ’278 Patent depicts no molecules in which each VHH is connected to both light chains,” EX1002 ¶ 116, does not support his interpretation of “one of the two” for the same reason. As shown above, each VHH in the molecules of Figure 1A *is*, in fact, connected to both light chains via a linker moiety. In any event, Dr. McDonnell ultimately relies on his interpretation of claim 5 to justify his reading of the “one of two” language in *claim 1*. With respect to claim 1, the specification provides multiple examples of molecules in which each LRP5/6 binding region is fused to *both* Fzd binding regions via a linker moiety—indeed, each LRP5/6 binding region is fused to both Fzd binding regions in *every* disclosed embodiment of the claims. *See* Figs. 9–10, below. Dr. McDonnell’s

interpretation of the phrase “one of the two” would thus exclude every embodiment of the claims the '278 Patent describes.

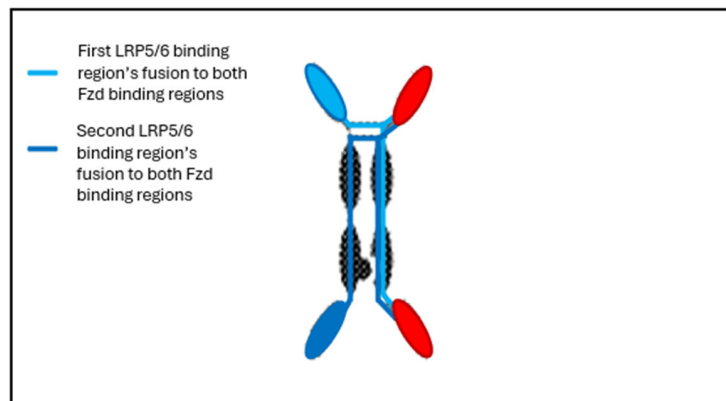


Figure 9: Molecule from Fig. 13A Annotated to Show Fusion of Each LRP5/6 Binding Region to Both Fzd Binding Regions

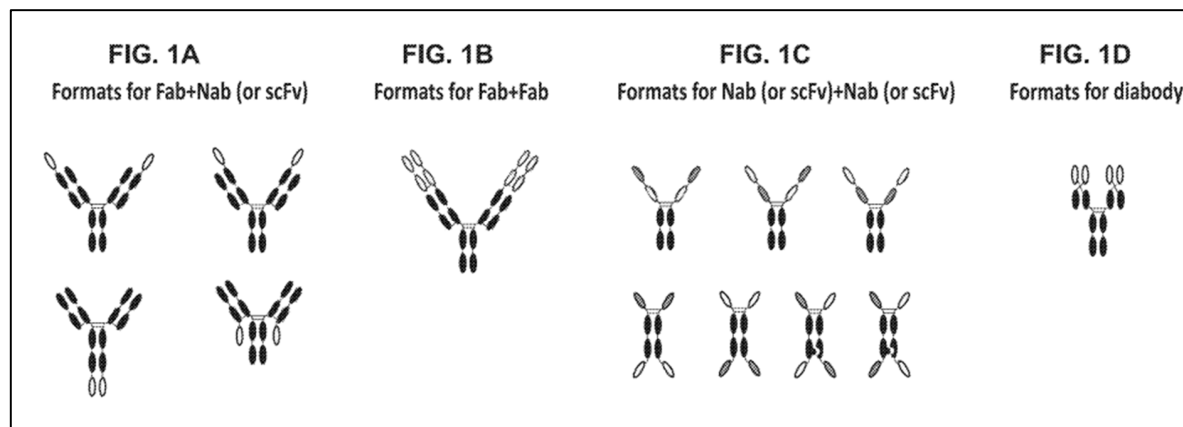


Figure 10: Embodiments in '278 Patent's Fig. 1 Where Each LRP5/6 Binding Region is Fused to Both Fzd Binding Regions via a Linker Moiety

158. Dr. McDonnell finally asserts that the specification reinforces his reading “in two ways,” EX1002 ¶ 117, but none of his cited evidence provides any support. *First*, Dr. McDonnell contrasts the specification’s statement that “one of the binding regions is a VHH or sdAB and the other is an scFv” with its explanation that “any

of these formats may comprise one or more scFvs in place of one or more VHH or sdAb” to claim that “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.” EX1002 ¶ 117. But Dr. McDonnell ignores that the first statement expressly states that “the other” binding region **cannot** be a VHH because “***the other is an scFv.***” See EX1001 at 20:65–67. By contrast, the fusion limitation of claim 1 requires that each LRP5/6 binding region must be fused via a linker moiety to “one of the two” Fzd binding regions, but ***does not impose any requirement as to the fusion relationship with the other.*** Dr. McDonnell’s second quoted sentence, on the other hand, imposes no structural requirements, and permits free interchangeability between scFv and VHH/sdAb binding regions. See EX1001 at 21:36–38. By contrast, the phrase “one of the two” in claim 1 signifies that, at a minimum, each LRP5/6 binding region **must** be fused via a linker moiety to at least one Fzd binding region. Neither of Dr. McDonnell’s quoted sentences from the specification thus support his erroneous conclusion that “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.’” EX1002 ¶ 117.

159. *Second*, Dr. McDonnell asserts that “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” and that “[t]he ’278 Patent does not depict, let alone evaluate, any molecules in which one of the Lrp5/6 binding regions is directly connected to both Fzd binding regions via a linker moiety.” EX1002 ¶¶ 118, 120. But as discussed above, the ’278 Patent depicts multiple examples where each LRP5/6 binding region is fused via a linker moiety to both Fzd binding regions. *See* ¶ 157, above. Dr. McDonnell is thus simply incorrect that the specification’s examples “confirm that ‘one of the two’ means ‘one and only one.’” *Contra* EX1002 ¶ 118. They instead confirm the exact opposite.

160. For at least the reasons discussed above, I disagree that 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 and only one Fzd binding region.” EX1002 ¶ 119. Instead, a POSA would understand from the clause’s plain and ordinary meaning that each LRP5/6 binding region must be bound via a linker moiety to at least one of the Fzd binding regions.

X. CLAIMS 1-5 ARE SUPPORTED BY ADEQUATE WRITTEN DESCRIPTION

A. Claim 1 Is Supported By Adequate Written Description

1. Claim 1’s Breadth Is Bounded By Several Features, and Is Supported By Representative Examples in the Specification

161. In paragraphs 120–150 of his declaration, Dr. McDonnell alleges that a POSA would have considered claim 1 to be “exceedingly broad in scope,” and in

paragraphs 162–185, he alleges that the specification’s working examples are not representative of claim 1’s scope. EX1002 §§ IX.A.1–2, 5–6. For the reasons below, I disagree with both assertions.

162. In my opinion, a POSA would view the ’278 Patent’s description to convey that the inventors were in possession of claim 1’s full scope. The specification contains ample written description supporting claim 1, including, as I explain below and as Dr. Willert explains, hundreds of Fzd and LRP5/6 binding sequences, 90 representative working examples of tetravalent molecules that comprise two Fzd and two LRP5/6 binding regions, each of which activated Wnt signaling, and detailed guidance on how to make the claimed molecules using methods and components that were “known to those of skill in the art.” *See* EX1001 at 79:63–67 (“In other embodiments, the Fzd binding domain comprises a variable region sequence, or the CDRs thereof, from any of a number of frizzled specific antibodies, which are known in the art and are commercially available.”), 116:25–29 (“Antibodies that specifically bind to LRP5 or LRP6 are known in the art and are commercially available.”), 127:20-23 (“The Wnt surrogate polypeptides of this disclosure may be prepared using standard techniques well known to those of skill in the art in combination with the polypeptide and nucleic acid sequences provided herein.”); *see also id.* at 127:54-55 (“Systems for cloning and expression of a polypeptide in a variety of different host cells are well known.”); *see also* ¶¶ 44–88, above; EX2010

¶¶ 66–134. The '278 Patent's wealth of disclosures is therefore more than sufficient to convey to a POSA that the inventors were in possession of the full scope of claim 1.

163. Claim 1 places multiple limitations on the claimed inventions. *First*, claim 1 is directed to **tetravalent** molecules, as evidenced by the fact that the claims specifically recite four binding regions on the molecule. *See* EX1001 at cl. 1. *Second*, the claim identifies the antigen each of the four binding domains must bind to, requiring that the molecule comprise “two Fzd binding regions” and “two LRP5/6 binding regions.” *Id.* *Third*, the claim requires that all four of these binding regions comprise an antibody or fragments thereof which would be familiar to a POSA, such as a “dAb, Fab, Fab', F(ab')², Fv[], single chain (scFv), VHH or sdAb.” *Id.* at 11:31–32; *see also, e.g., id.* at 2:14–17, 49–52. *Fourth*, the claim requires the presence of an intervening linker moiety between each LRP5/6 binding region and one of the two Fzd binding regions. *Id.* at cl. 1.

164. Instead of examining these limitations on claim scope, Dr. McDonnell remarks first that “[c]laim 1 adds no restriction on the specific epitope, binding affinity, or amino acid sequence for any of the Fzd or Lrp5/6 binding regions.” EX1002 ¶ 120; *see also id.* ¶ 144. That assertion, however, conflicts with his own view that properties such as binding affinity and epitope specificity are functional

characteristics that impart no structural constraints on the claimed Wnt surrogate molecules. *See, e.g.*, EX1002 ¶ 160.

165. In any case, claim 1 is not as broad as Dr. McDonnell suggests. Of the four binding regions on the claimed molecules, two binding regions must bind Lrp5 or Lrp6 and the other two must bind a Fzd receptor—thereby restricting possible epitopes to those residing on LRP5/6 and Fzd molecules. *See* EX1001 at cl. 1. Moreover, binding affinity is merely a proxy for assessing a molecule’s ability to bind a specific target substrate, which the claim expressly requires by reciting that binding regions must “specifically bind” their respective targets. *See* ¶¶ 248–250, below; EX1001 cl. 1. And as for amino acid sequences, the claim’s requirements that the binding regions “specifically bind” Fzd and LRP5/6 direct a POSA to a subset of binding sequences including those that were “known in the art and ... commercially available,” and hundreds more of which are disclosed in the ’278 Patent specification. *See* EX1001 at 79:63–80:15, 116:25–39, Tables 1A–B, 2A–B; ¶¶ 101–104, above. Dr. McDonnell is thus incorrect that the claim imposes “no restriction whatsoever” on these characteristics of the claimed molecules.

166. Dr. McDonnell also incorrectly alleges that “[t]he 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 he

complains that it “imposes no meaningful structural limitation for composition, length, or properties.” EX1002 ¶ 121. I disagree. The “linker” limitation imposes constraints on molecular geometry, as Dr. McDonnell himself appears to concede in stating that he “identified 21 possible tetravalent topologies that correspond to the genus of tetravalent molecules recited in claim 1.” EX1002 ¶ 123; Fig. 11, below.

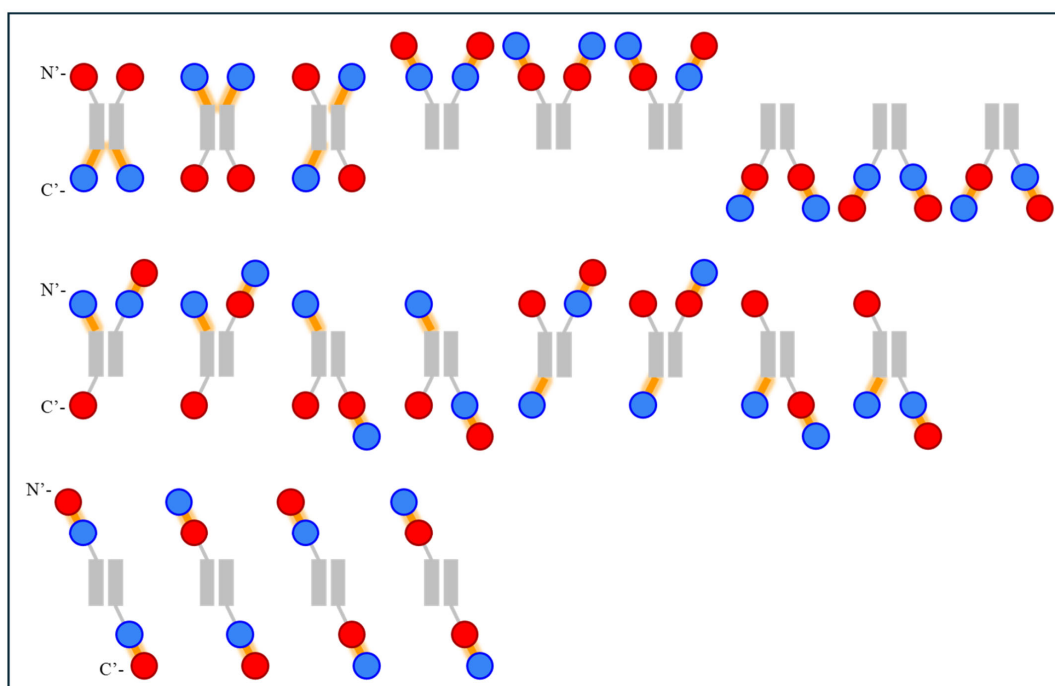


Figure 11: Dr. McDonnell’s Figure 9 Illustrating the Common Structures He Purports Are Encompassed By Claim 1

167. Any other purported “structural limitations” on the linker composition, length, or properties would merely impact the molecule’s signaling potency, not its ability to activate Wnt signaling, and a POSA would understand that linker composition, length, and properties would be guided by the structures intrinsic to the claims and their knowledge of linkers used in the field. *See e.g.*, EX1001 at 116:48–

52 (“The length of the linker, and therefore the spacing between the binding domains can be used to modulate the signal strength, and can be selected depending on the desired use of the Wnt surrogate molecule.”).

168. Because Dr. McDonnell ignores the various “meaningful structural limitations” specified in claim 1, he claims “it is difficult to contemplate fully or articulate the extensive breadth” of the claim. EX1002 ¶ 122. Notwithstanding this purported difficulty, Dr. McDonnell proceeds to make the sweeping assertion that by his “conservative calculation, ... claim 1 encompasses at least **130 million** distinct tetravalent, multispecific formats.” *Id.* A POSA would not find such a combinatorial calculation—premised on highly theoretical assumptions—at all useful or relevant in making the claimed inventions (which is relevant to enablement, as I discuss below in paragraphs 283–319), or for understanding whether the inventors describe a representative number of species in the ’278 Patent, and for those reasons would not view claim 1’s scope in such terms. Instead, a POSA would identify that the claim scope is bounded by a specific (1) valency, (2) stoichiometry of specific binders, (3) set of constituent structures, and (4) linker requirement, and that the inventors disclosed a representative number of examples elucidating these different bounds to the scope of the claims. A POSA would not have concluded that scope to be “exceedingly broad.”

a. The ’278 Patent’s Examples Are Representative Across Topologies

169. Dr. McDonnell begins by identifying 21 “possible tetravalent topologies,” EX 1002 ¶ 123, highlighting both his ability to discern structural commonalities from the claims and the futility of his exercise. As part of his accounting of topologies, Dr. McDonnell “treat[s] connections via N-terminus and connections via C-terminus differently” because the ’278 Patent purportedly recognizes this distinction. *Id.* Dr. McDonnell also “treated arrangements where constant domains are differently located among Fzd and Lrp binding regions as different topologies because the specification does so.” EX1002 ¶ 124. Thus, as Dr. McDonnell’s own listing of topologies shows, the ’278 Patent’s claims and specification provide a limited set of structural configurations the claimed invention may adopt.

170. The ’278 Patent describes working examples and guidance across the range of these topologies. As Dr. McDonnell himself acknowledges, the specification discloses working examples across five different topologies. EX1002 ¶ 165. These topologies include (1) molecules where the Fzd and LRP5/6 binding regions are arranged opposite each other on either side of an intervening Fc region (first two topologies in Dr. McDonnell’s Figure 10), (2) molecules where a Fzd binding region and an LRP binding region are both on the same side of the Fc region but attached to different Fc heavy chains (third topology in Dr. McDonnell’s Figure 10), and (3) molecules where the binding region pairs are oriented on the same side of the Fc region and attached to the same heavy chain (fourth and fifth topologies in Dr.

McDonnell's Figure 10). *See* EX1002 at Fig. 10. Because the specification conveys that molecules in *all* these various arrangements activated canonical Wnt signaling, *see* EX1001 at Examples 2–18, a POSA would understand the claimed invention to be capable of agonizing canonical Wnt signaling across a range of spatial arrangements, including the other 16 topologies, to the extent Dr. McDonnell's (flawed) construction requires such activity.

171. Dr. McDonnell acknowledges he uses the term “topology” as a proxy for the various “spatial arrangement[s]” of Fzd and Lrp5/6 binders the claimed structures can adopt. *See* EX1002 ¶ 122. In that context, the specification's representative examples illustrate that the claimed molecules can agonize Wnt signaling across the full range of spatial arrangements claim 1 encompasses. For instance, as discussed above, Example 9 of the specification undertakes a structure-activity relationship analysis “by rotating the attachment location of the [Lrp5/6 binder] to the different termini of the IgG HC or LC.” EX1001 at 157:35–37; Fig. 12, below. The specification reports that the molecules tested in the analysis “activated Wnt signaling to various levels” and tells POSAs that changing “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 at 157:44–50.

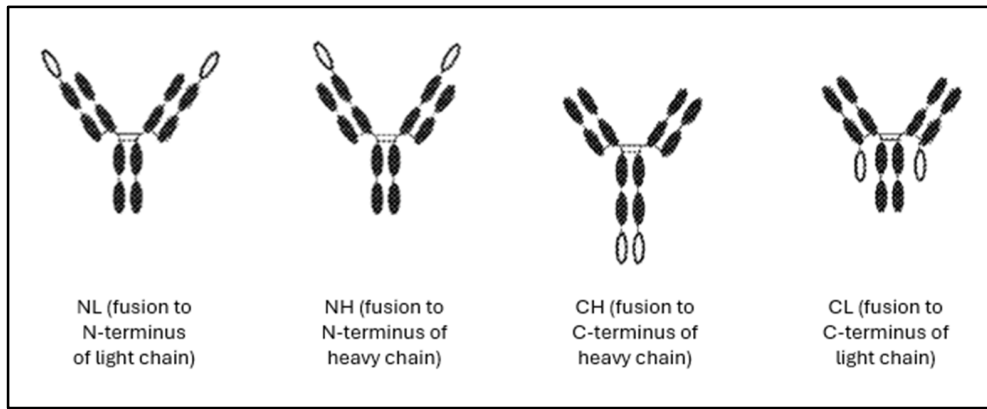


Figure 12: IgG–Nab Formats of '278 Patent Example 9

172. Example 13 similarly tests five structures with LRP5/6 and Fzd binders arranged in various geometries. *See* EX1001 at 158:49–159:3; Fig. 13, below. Again, the specification reports that “these various combinations where [binding regions] 26 and 17SB9 were arranged in different tandem formats or on different ends of the Fc fragment *all* activated Wnt signaling to various levels.” *Id.* at 158:65–159:2. Example 14 likewise tests fifteen tetravalent molecules with varied orientations of the Fzd and LRP6 binders, while also varying the molecules’ linker lengths. *See* EX1001 at 159:5–47. As the example explains, “all of these scFv formats activated Wnt signaling.” EX1001 at 159:36, Figs. 14A–14D; Fig. 14, below. And Example 15 tests thirteen tetravalent molecules, varying whether the Fzd or LRP binder was in the full IgG, the linker length, and the method of HC–LC pairing, the specification reporting again that all molecules “activated Wnt signaling.” EX1001 at 159:54–160:49, Fig. 15; Fig. 15, below. The specification thus makes clear that while POSAs may use different relative spatial orientations of binding regions to tailor signaling

activation for their specific purposes, molecules across various spatial orientations are capable of Wnt signaling. Given these disclosures, a POSA would understand the '278 Patent to provide representative examples concerning the geometry of the claimed molecules.

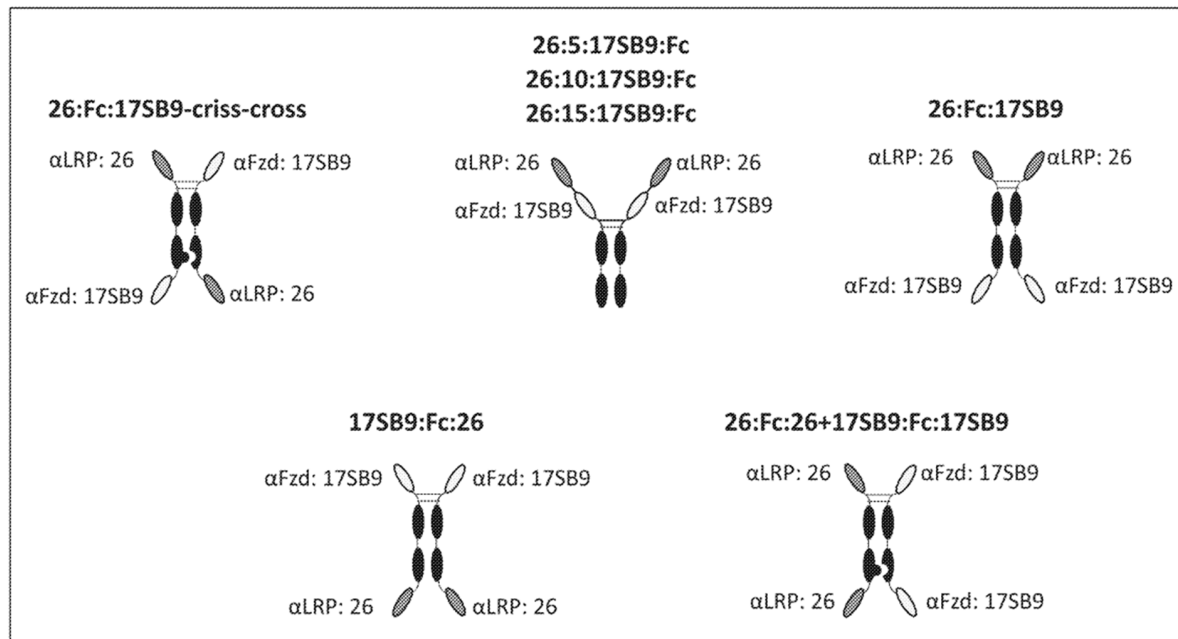


Figure 13: Figure 13D of the '278 Patent

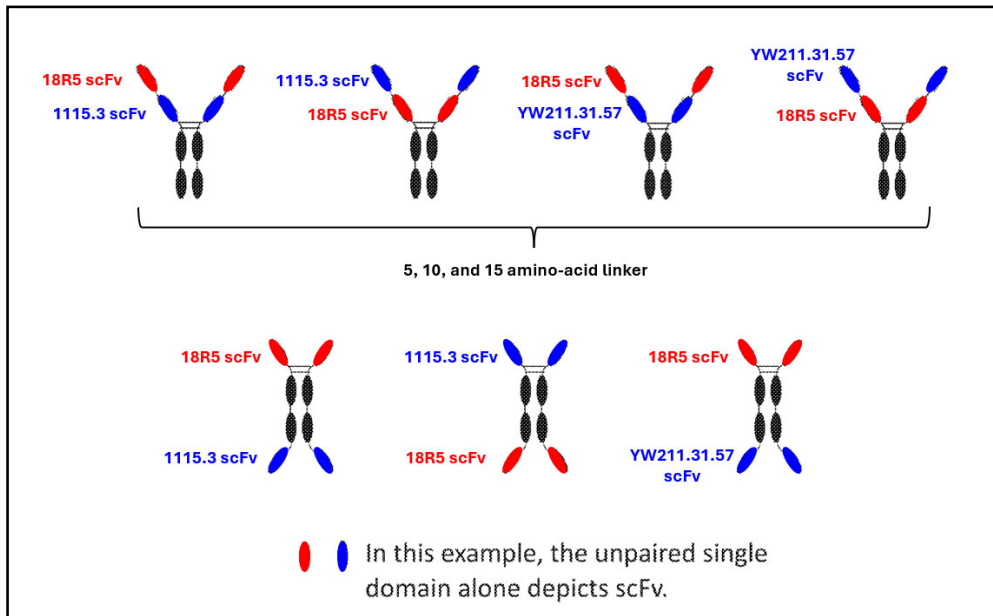


Figure 14: '278 Patent Example 14 Tandem scFv Formats

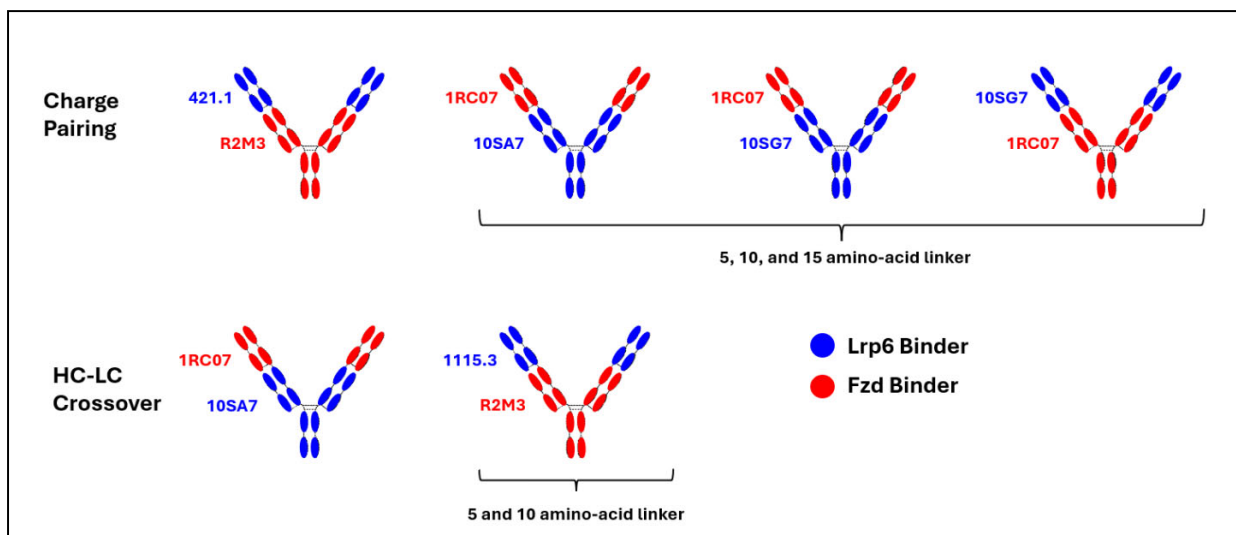


Figure 15: '278 Patent Example 15 Fab-IgG Formats

173. Dr. McDonnell instead purports that “the specification of the '278 Patent discloses only five topologies,” leaving “the remaining 16 topologies” allegedly “untested,” EX1002 ¶ 163. But that ignores the topologically diverse teachings the patent provides, discussed above. *See* ¶¶ 170–172, above. Further, while Dr.

McDonnell claims that “[t]he five tested topologies differ significantly from the 16 undisclosed topologies and therefore cannot be considered representative of unevaluated topologies within the claimed genus,” EX1002 ¶ 164, he provides one “example” of an explanation of the “tested” topologies’ alleged non-representativeness, claiming that four of his “topologies” orient “one set of Fzd and Lrp5/6 binding regions ... opposite to the other set[,] ... providing a greater capacity to engage sparsely distributed Fzd and Lrp5/6 receptors than any of the five topologies evaluated in the ’278 Patent.” *Id.* But as discussed above, three of the five “tested” topologies reflect this arrangement of Fzd and LRP5/6 binding regions. *See* ¶ 170, above. And the ’278 Patent discloses molecular structures and corresponding data showing Wnt signaling agonism for those arrangements. Example 13, for instance, tests one such molecule and demonstrates that it agonized Wnt signaling. EX1001 at 158:49–159:3; Fig. 16, below. Dr. McDonnell’s only exemplary explanation thus fails to demonstrate that the examples disclosed in the ’278 Patent specification are topologically unrepresentative of other disclosed molecules.

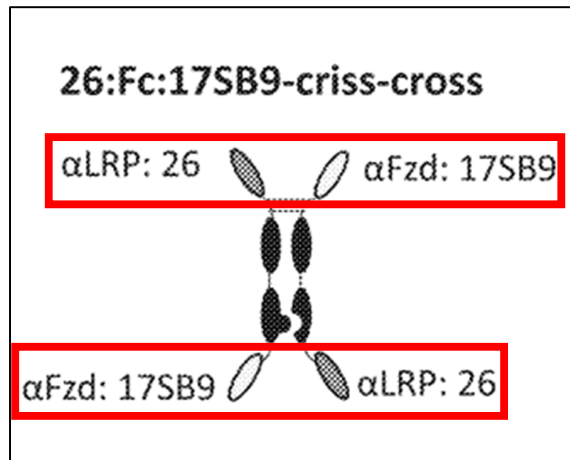


Figure 16: Molecule from Figure 13D of the '278 Patent Annotated to Show Binder Pairs “Oriented Opposite” to Each Other

174. Moreover, Dr. McDonnell explains that the animating reasoning for his ultimately unavailing distinction is the speculative notion that “variations in receptor expression profiles can cause the spatial distance between Fzd and Lrp5/6 receptors to differ substantially across tissues and over time.” EX1002 ¶ 164. But as discussed further below, the '278 Patent demonstrates through experimental results testing—(1) molecules in different cell lines, (2) molecular structures with different linker lengths, and (3) structures with different molecular geometries—that the disclosed molecules were capable of agonizing Wnt signaling in *all* of these settings. See ¶¶ 258–271, below. The purported scientific context behind Dr. McDonnell’s attempt to distinguish what he terms “tested” topologies versus “untested” ones thus only serves to emphasize the representativeness of the specification’s examples.

**b. The '278 Patent's Examples Are Representative
Across Binding Fragments**

175. Dr. McDonnell next multiplies the number of topologies by the number of antibody-derived fragments disclosed in the specification, *see* EX1002 ¶ 125, but his arithmetic operation once again fails to convey any useful information to a POSA as to the breadth of claim 1. Instead, a POSA would appreciate that claim 1 encompasses a set of structurally similar, antibody-derived fragments, and the '278 Patent discloses representative working examples using such fragments.

176. For his mathematical exercise, Dr. McDonnell counts nine different binding region fragments, all of which are highly similar to each other in that they all rely on the antibody's CDRs to bind the target epitope. *See* EX1002 ¶ 126; ¶¶ 62–71, above. Eight of the nine fragments are derived from typical antibodies consisting of a heavy and light chain, *see id.*, and can be grouped into four pairs of the same fragment type—Fab, Fab', scFv, or Fv—that differ only in terms of which of their chains (heavy or light) connects the fragment to the rest of the molecule. *See* Table 6, below. Dr. McDonnell's nine "types of antigen-binding fragments" thus reflect five different types of fragments (Fab, Fab', scFv, Fv, or VHH/Nab) with four of those fragments counted twice based only on attachment location. Because the '278 Patent demonstrates that the claimed molecules activate Wnt signaling across both heavy- and light-chain attachment locations on the fragment (*see e.g.*, Example 9; Fig. 12,

above), a POSA would understand one member of each pair to be representative of the other.

177. A POSA would also understand each of these fragments to be highly structurally similar. For example, a Fab' is identical to a Fab except for the presence of disulfide bonds from the hinge portion of the antibody; a Fv is identical to a Fab except that the Fab includes the C_H1 domain of the antibody; and an scFv is an Fv in which the heavy and light chains are connected by a linker. *See* ¶ 68, above. A POSA would thus understand the '278 Patent's use of one such fragment in a claimed molecule to provide representative teachings for the others. *See e.g.*, EX1001 at 3:49–51 (“In another embodiment, any of the Fzd binding region comprises a Fab or Fv, and the LRP5/6 binding region comprises a Fab or Fv.”). Moreover, the '278 Patent contains working examples and illustrations using each of these five different binding fragments in various combinations, including formats using IgG and diabody structures. *See e.g.*, Table 6, below; EX1001 at 21:39-51, Fig. 1D.

Table 6: Exemplary Representative Molecules for Each of Dr. McDonnell's Listed Antigen-Binding Fragments
(Red Star Represents Point of Attachment to the Rest of the Molecule)

Fragment		Exemplary Representative Molecule
Fab		 <i>E.g., Examples 2, 3, 8–9,15, 17</i>
		
Fv		 <i>E.g., Example 18</i>
		
Fab'		 <i>E.g., Example 16</i>
		

scFv		 <i>E.g., Example 14</i>
VHH/Nab		 <i>E.g., Examples 5–9, 13, 17</i>

178. In all, a POSA would thus understand the '278 Patent to disclose representative examples across the full scope of antibody-derived binding-region fragments that can be used in the claimed molecules.

179. Dr. McDonnell's contrary opinion is wrong. He alleges that "there is limited diversity in the types of antigen-binding fragments" in the patent's working examples because, in each example, "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." EX1002 ¶ 166. But that misleading statement ignores that the patent's working examples use *all five* of the antibody-derived fragment types Dr. McDonnell lists (Fab, Fab', Fv, scFv,

VHH/Nab). *Id.*; see ¶ 177, above. Dr. McDonnell’s allegation that the examples’ Fzd binding regions “comprise the same fragment type with the same connectivity” and that their LRP5/6 binding regions “likewise comprise the same type with the same connectivity” does not detract from the specification’s demonstration that molecules using *each* of these fragment types were capable of agonizing canonical Wnt signaling. See EX1001 at Examples 2–18. Thus, even under Dr. McDonnell’s incorrect construction of the claims, a POSA would expect molecules where the two Fzd binding regions or the two LRP5/6 binding regions comprise different fragment types to activate canonical Wnt signaling based on the specification’s disclosures, and would understand the inventors to be in possession of such molecules.

180. The ’278 Patent also shows that using different antibody fragments reliably activates Wnt signaling when arranged in the claimed 2:2 Fzd:LRP5/6 stoichiometric format (even though I disagree that such activity is a requirement of the claims). Example 2 reports that a molecule comprised of two Fab-based Fzd binding regions (R2M3) and two Nab-based LRP5/6 binding regions (26) “induced reporter activity in a dose dependent manner and was enhanced by the presence of R-spondin similar to a natural Wnt ligand.” EX1001 at 155:12–40. Example 16 used the same R2M3 and 26 binders, except that the R2M3 binding regions in this example were Fab’ fragments instead of Fab fragments. EX1001 at 160:51–67. As

with the Fab-Nab structure in Example 2, the Fab'-Nab structure of Example 16 “was able to activate Wnt signaling.” *Id.*

181. In spite of the clear support in the specification for claim 1’s full scope of antigen-binding fragments, Dr. McDonnell attempts to characterize his opinion as “conservative” by claiming he “limited [his] 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 configurations.’” EX1002 ¶¶ 134–135. These phrases do not feature in the claim language and instead appear to be crop-quotes from the specification’s explanation that the term “antibody” “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.” EX1001 at 11:25–39. Dr. McDonnell’s assertion thus underscores that the ’278 Patent described and contemplated these various design features, conveying the inventors’ possession of these variations to a POSA, and does not detract from the fact that the specification’s

working examples are representative of the full scope of antigen-binding fragments encompassed by claim 1.

c. The '278 Patent Discloses a Representative Number of Linkers

182. Dr. McDonnell tries to bolster his mathematical calculation by alleging that “[t]his number does not yet account for the diversity of the claimed ‘linker moiety,’” which he arbitrarily determines should be 31 options based on the explicit disclosures of different linker moieties in the patent. EX1002 ¶ 129–130. Putting the arbitrariness aside, the patent provides a representative disclosure of linkers for use in the claimed invention.

183. The specification discloses testing on several exemplary molecules dedicated to evaluating the impact of linker length on Wnt signaling activation. For instance, Example 13 evaluates molecules consisting of the 26 LRP5/6 binding region and the 17SB9 Fzd binding region with 5, 10, and 15-mer amino acid linkers, and reports that all three molecules activated Wnt signaling. EX1001 at 158:49–159:3. Likewise, Example 14 tests each of four different sets of binder combinations with 5, 10, and 15-mer linkers, and Example 15 tests four additional sets of binder combinations with the same linker lengths, both examples reporting that their molecules activated Wnt signaling to varying levels. EX1001 at 159:5–160:49. A POSA would thus understand that, in the context of the claimed molecules, the

linkers could be varied while retaining their ability to activate Wnt signaling (even though such activity is not a requirement of the claims).

184. Dr. McDonnell opines otherwise, alleging that “[t]he tetravalent formats evaluated in the specification are also narrow in terms of linkers,” and that “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.” EX1002 ¶ 173. I disagree. For one, the specification expressly states that “[t]he binding regions ... may be separated by ... a polypeptide linker, or a non-peptidic linker,” that this linker may be “rigid” or “flexible,” and that “[t]he length of the linker, and therefore the spacing between the binding domains can be used to modulate the signal strength, and can be selected depending on the desired use of the Wnt surrogate molecule.” EX1001 at 116:46–65. Moreover, a POSA reading the ’278 Patent would understand that linker composition and length impact signaling potency, but that molecules that are structured as claimed (i.e., two Fzd and two LRP5/6 binding regions), and differ only in terms of their linker length and composition, would retain their Wnt signaling agonism functionality. *See* ¶ 183, above. The specification thus conveys the inventors’ possession of the claimed invention across these linkers.

185. Dr. McDonnell incorrectly claims that “[t]he prior art evaluating and comparing different linker types further supports [his] opinion,” EX1002 ¶ 174, but

if anything, Dr. McDonnell's cited prior art underscores the role of linkers in altering the magnitude of, rather than determining, binding functionality. For example, the DiGiammarino study Dr. McDonnell cites explains, with respect to anti-TNF α DVD-IgG formats, that while "affinities for TNF α are generally lower when binding to the inner domain than to the outer domain...[, t]his effect could be mitigated, *to some degree*, by linker design." EX1024 at 1. Likewise, the "'surprising' finding" in DiGiammarino that Dr. McDonnell cites demonstrates only a ">4 fold difference" in binding affinity for TNF α between hinge and G-rich linkers of the same length. EX1024 at 5. Because K_D values are generally measured on a logarithmic scale and can span orders of magnitude, a POSA would understand Dr. McDonnell's "4-fold difference" to reflect a modest change in binding functionality. *See* EX1024 at 4 ("After cleavage, the TNF α affinity of all three cleavable DVD-IgG proteins recovers to a point *only* about 4-fold lower than the reference mAb."). And notably, although DiGiammarino tested molecules containing different linkers, *all* of them were capable of binding TNF α . *See id.* at tbls. 1, 2A.

186. DiGiammarino also provides no support for Dr. McDonnell's conclusion that the "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." *Contra* EX1002 ¶ 174. If anything, a POSA would understand from DiGiammarino that as of 2017,

linker compositions and lengths could be used for different purposes, including to alter the magnitude of molecular functionality.

187. Dr. McDonnell's assertion that a study by van Rosmalen demonstrated purported "unpredictability ... within the subset of G/S linkers," *see* EX1002 ¶ 175, is also incorrect. While Dr. McDonnell selectively quotes van Rosmalen for its observation that "the observed increase in linker stiffness with reduced glycine content is 'much less pronounced than that predicted by a classical model'" that had been used by other researchers in prior studies, *see id.*, he omits that the study set forth a new predictive model based on Gaussian and wormlike analyses of experimental FRET efficiencies. *See* EX1074 at 7. And while Dr. McDonnell claims "van Rosmalen explained that the linker flexibility does not decrease **linearly** as glycine content is reduced," EX1002 ¶ 175, a POSA would understand that the mere lack of a linear relationship between two variables does not render them unpredictable. Rather, van Rosmalen's FRET-based model for evaluating linker flexibility demonstrates that by 2017, linker flexibility was **predictable** based on glycine and serine content in G/S linkers. *See* Fig. 17, below.

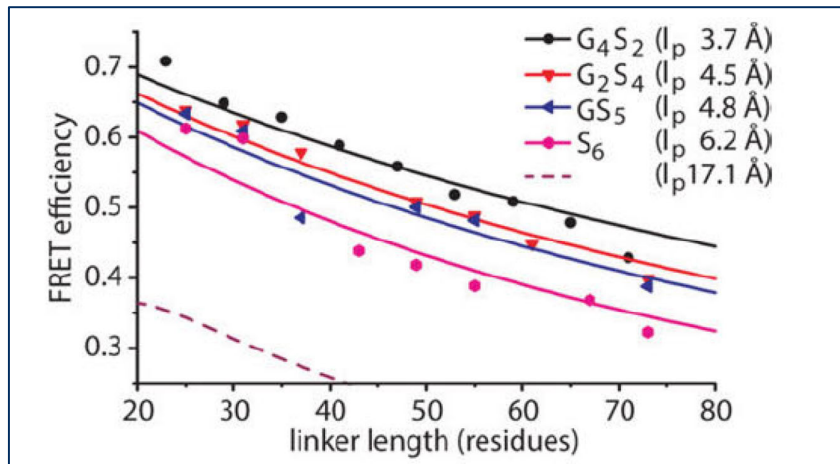


Figure 17: Fig. 4 From Van Rosmalen (EX1074) Showing Predictive Wormlike Chain Model for GS Linkers

(Solid Lines Represent Best Fit Modeled Linker Length Curves, Points Represent Observed Experimental FRET Efficiencies)

188. Dr. McDonnell quotes a general statement from an article stating that “[s]mall format variations, such as minor changes in linker length or composition or ‘switch’ of domains, *can* be crucial determinants of functionality” to support his arguments. EX1002 ¶ 176 (quoting EX1017 at 21). But the specification’s examples demonstrate that the disclosed molecular formats retain their functionality across varying linker lengths and format variations, conveying to a POSA that the disclosed examples are representative across such variations. *See, e.g.*, ¶ 183, above. Dr. McDonnell is thus incorrect that “[i]n 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,” EX1002 ¶ 176; as discussed, a POSA would reach the opposite conclusion.

**d. The '278 Patent's Examples Are Representative
Across Tetravalent Formats**

189. Dr. McDonnell multiplies the numbers he computes for topologies, antibody fragments, and linker moieties to conclude that “claim 1 encompasses at least **132,407,541** possible tetravalent formats” encompassed by claim 1. EX1002 ¶ 131. Based on that figure, he alleges that “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 [by] claim 1 but not evaluated in the specification.” EX1002 ¶ 165. The inflated and meaningless nature of Dr. McDonnell’s assessment of claim 1’s breadth, however, renders his comparison to the specification’s disclosures one of apples to oranges. Unlike Dr. McDonnell’s 130 million estimate—which does not account for qualitative similarities between molecules—the specification’s disclosures and representative working examples together provide a wealth of information permitting a POSA to move beyond the formats disclosed in the examples and convey that the inventors had possession of the full scope of formats encompassed by claim 1. *See* ¶¶ 161–188, above.

190. Dr. McDonnell contends otherwise, setting forth several reasons why he believes the specification’s examples are not representative. His first reason—that there is “limited diversity in the types of antigen-binding fragments” (EX1002 ¶ 166)—is incorrect for the reasons discussed in paragraphs 175–181 above. His assertion that the tested formats are “narrow in terms of linkers” (EX1002 ¶ 173) is

likewise incorrect for the reasons discussed in paragraphs 182–188 above. Dr. McDonnell’s remaining reasons are also unavailing.

191. Dr. McDonnell alleges that “there is limited diversity in the arrangement and order of the antigen-binding regions,” but he again overlooks the import of the working examples read as a whole. EX1002 ¶ 167. For example, Dr. McDonnell contends that “[i]n all but one ... 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.” *Id.* Dr. McDonnell’s assertion appears to be that, in “all but one ... of” the ’278 Patent’s tested formats, both Fzd binding regions and both LRP5/6 binding regions are spatially arranged in the same manner relative to each other and the molecule’s Fc region. But that assertion ignores that the working examples convey that the Fzd and Lrp5/6 binding regions can be arranged in various different orders in the claimed molecules.

192. For example, Example 15 discloses that “[t]he anti-FZD binder, 1 RC07, was ... fused with the anti-LRP binder, 10SG7, either with 1 RC07 in the Fab format fused to the N-terminus of 10SG7 in IgG format, *or in the reverse order* where 10SG7 as Fab fused to the N-terminus of 1 RC07 as IgG with either 5, 10, or 15-mer amino acid linkers.” EX1001 at 159:49–160:49. The specification reports that “[a]ll fusion molecules activated Wnt signaling while some preference of orientation and

linker length was observed.” *Id.* Similarly, as discussed above, Examples 9 and 13 tested the impact of Fzd and LRP5/6 binders in various spatial arrangements (e.g., by varying the attachment point on the N- and C-termini), and reported that *all* tested molecules agonized Wnt signaling to varying levels. EX1001 at 157:31–50, 158:49–159:3.

193. A POSA would have thus understood from the diverse arrangements disclosed in the specification’s working examples that molecules having binder pairs with different orders of connection from each other would also successfully agonize Wnt signaling activity. The specification reinforces this understanding. As McDonnell acknowledges, the specification (in Example 13) discloses a format with different orders of connection between binding region pairs, *see* EX1002 ¶ 167, and the specification reports that the molecule was successfully able to agonize Wnt signaling. *See* EX1001 at 158:65–159:3. Dr. McDonnell also ignores a second format with different orders of connection (the 26:Fc:26+17SB9:Fc:17SB9 molecule tested in Example 13) that the specification reports also successfully agonized Wnt signaling. *See* EX1001 at Figs. 13A, 13C, 158:64–159:3. Accordingly, a POSA would have understood the specification’s disclosed examples to be representative of the different spatial arrangements the disclosed molecular formats can adopt.

194. Dr. McDonnell’s criticism with regard to possible “arrangement[s] and order[s] of the antigen-binding regions,” EX1002 ¶ 167, is also duplicative of his discussion of his “topologies.” Indeed, Dr. McDonnell “use[s] the term ‘topology’ to refer to the spatial arrangement of the claimed components: Lrp5/6 binding regions, Fzd binding regions, and linker moieties,” EX1002 ¶ 122, and several of his 21 “topologies” differ only in terms of the order of the binding regions within the molecule. *See* EX1002 at Fig. 9. Dr. McDonnell’s assertions about the “limited diversity in the arrangement and order of the antigen-binding regions,” EX1002 ¶ 167, are thus unfounded for all the same reasons as discussed above with regard to Dr. McDonnell’s “topologies.” *See* ¶¶ 169–174, above.

195. For example, Dr. McDonnell claims, with reference to Example 9’s structure–activity relationship analysis, that “[t]he ’278 Patent itself demonstrates that arrangement and orientation can profoundly affect the agonistic activity of Wnt surrogate molecules.” *Id.* But that interpretation of Example 9 overreads its statement that “[t]hese results demonstrate 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,” and omits that *every molecule* tested in the example “activated Wnt signaling to various levels.” EX1001 at 157:31–50. A POSA would thus understand this statement from Example 9 to explain that while attachment location and molecular geometry may modulate the

magnitude of Wnt signaling observed, the disclosed molecules retain their ability to agonize Wnt signaling across a range of different spatial binder arrangements. Dr. McDonnell thus fails to provide any support for his belief that the specification's examples offer only "limited diversity in the arrangement and order of the antigen-binding regions." *Contra* EX1002 ¶ 167.

196. Dr. McDonnell also alleges that "all but one ... of the 29 disclosed tetravalent formats are symmetrical, whereas the vast majority of the tetravalent formats encompassed by claim 1 are asymmetrical," EX1002 ¶ 168, but he cites to no evidence, in the specification or otherwise, demonstrating that the claimed molecules somehow lose their functionality in asymmetric formats. Instead, Dr. McDonnell engages in speculation, claiming that "[b]ecause 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." *Id.* But again, these criticisms are duplicative of Dr. McDonnell's discussion of "topologies" and are thus unfounded for the same reasons as discussed above. *See* ¶¶ 169–174, above. Moreover, as Dr. McDonnell concedes, the specification **does** disclose an exemplary asymmetrical molecule, in addition to a second asymmetrical molecule that Dr. McDonnell excludes from his count, and Example 13 demonstrates that both molecules activated Wnt signaling. *See* EX1002 ¶ 168; EX1001 at 158:64–159:3; Fig. 18, below. A POSA would thus

understand that asymmetrical molecules can activate Wnt signaling in the same manner as symmetric structures, and would consider the specification's 90 exemplary molecules as representative of the various symmetric and asymmetric structures the claimed molecules can adopt.

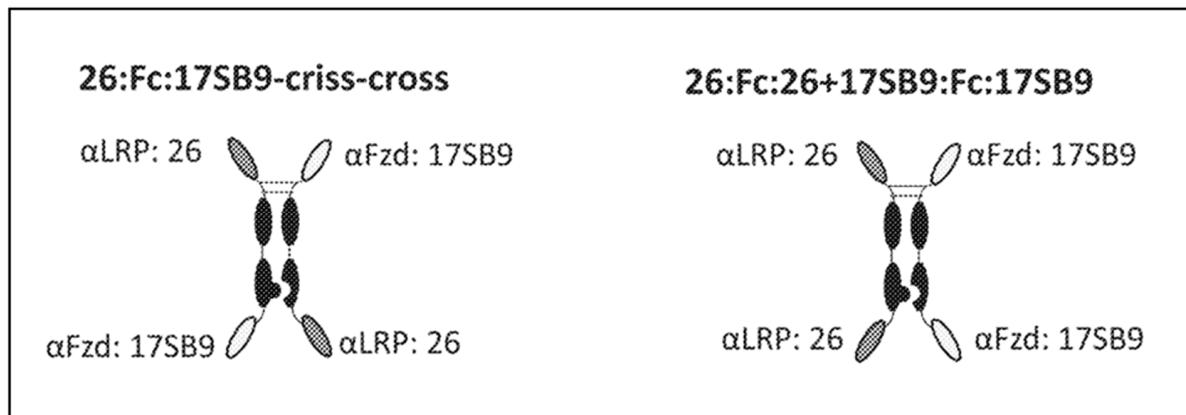


Figure 18: Asymmetric Molecules From Figure 13D of the '278 Patent

197. Dr. McDonnell references Example 9 to allege that “[t]he '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,” EX1002 ¶ 169, but as discussed above, Example 9 supports the exact opposite conclusion, demonstrating that *all* of the tested molecules “activated Wnt signaling to various levels.” EX1001 at 157:44–57; ¶ 171, above. A POSA would thus understand that while attachment location and binder geometry can affect the magnitude of Wnt signaling induced, the disclosed examples are representative across various geometries in terms of their ability to activate Wnt signaling in the first place.

198. In direct conflict with the specification's express disclosure that the tested molecules in Example 9 "activated Wnt signaling to various levels," Dr. McDonnell claims that Figure 9A shows that "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." Ex. 1002 ¶ 169. Dr. McDonnell also claims that a "similar pattern was observed with another sequence pair (18R5-26) in Figure 9C." *Id.* Dr. McDonnell appears to suggest incorrectly that because the lines for the CL formats in Figures 9A and 9C are flatter than those observed for the other formats, a POSA would understand the CL formats to have "failed" to produce a TOPFlash response. *See* Fig. 19, below. That assumption is incorrect. Instead, a POSA would understand that graphical representations such as those in Figures 9A and 9C are limited by their scaling in their ability to depict signaling at a high degree of resolution, and that the scaling of the graph impacts the degree to which such signaling responses are visible. A POSA would thus not understand from Figures 9A and 9C that these formats "failed" to activate signaling, given the specification's express disclosure that the molecules "activated Wnt signaling to various levels." EX1001 at 157:47–50.

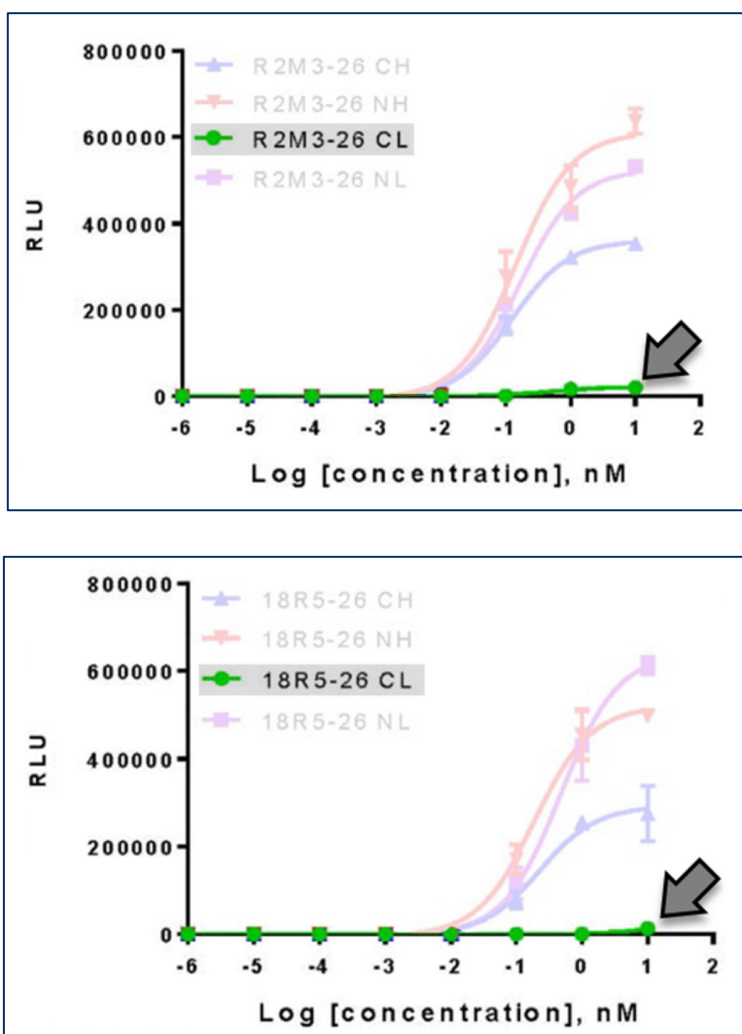


Figure 19: Dr. McDonnell’s Flawed Visual Inspections in His Fig. 12

199. Dr. McDonnell’s discussion of a later-arising patent application by the same inventors (Ex. 1081 or “Li”) illustrates his failure to account for these graphical scaling issues. For example, Dr. McDonnell claims that Figure 11A depicts a “second set of molecules” that he claims “did not” produce a TOPFlash assay response, highlighting the flatter lines on the graph. EX1002 ¶ 172. Figure 10B of Li, however, depicts the activity of the same molecules with a smaller y-axis scale,

revealing that each molecule produced a dose-dependent TOPFlash response characteristic of Wnt signaling activation that is hidden by the scaling of Fig. 11A. See Fig. 20, below. A POSA would be well-versed with the limitations of graphical data representation, and would thus not understand a dose-response curve that appears flat, without more, to constitute a “failure,” as Dr. McDonnell suggests.

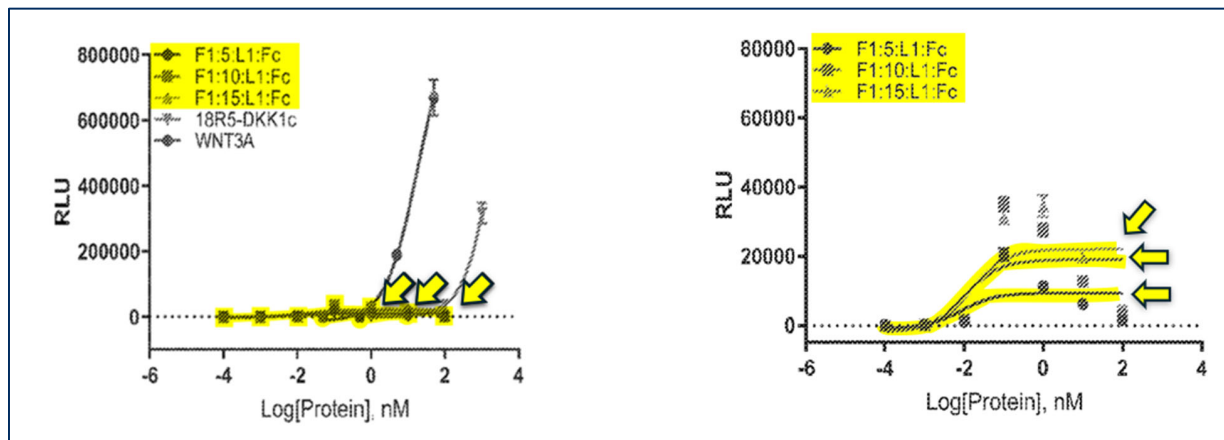


Figure 20: Figures 11A (left) and 10B (right) of Li (EX1081) Depicting Activity Curves for the Same Molecules Using Different y-Axis Scaling

200. For the above reasons, Dr. McDonnell is incorrect that Figures 9A and 9C depict two exemplary tetravalent molecules that “failed” to activate Wnt signaling. To the contrary, a POSA would understand from the specification that these molecules activated Wnt signaling to “varying levels”—given the express disclosures in the ’278 Patent, EX1001 at 157:44–47—and would appreciate that the magnitude of the resultant Wnt signaling activation can be modulated by varying the molecule’s geometry and attachment locations. Thus, a POSA would understand the

disclosed exemplary molecules to be representative of the full range of claimed molecules in terms of their ability to activate Wnt signaling.

201. For the same reasons as above, Dr. McDonnell is incorrect that the molecules disclosed in Li “confirm” his opinion that “the specific tetravalent, multispecific molecules disclosed in the patent are not representative of the full scope of claim 1.” EX1002 ¶ 171. Dr. McDonnell’s assertion is premised on his assumption that “while the first set of molecules produced responses in this assay, the second set of molecules did not.” EX1002 ¶ 172. As discussed above, that assumption is incorrect, as Figure 10B of Li demonstrates that the second set of molecules depicted in Figure 11A also produced a response which was obscured due to the scale of the graph. *See* ¶ 199, above. Figure 11A thus refutes, rather than confirms, Dr. McDonnell’s conclusion, as it demonstrates that three molecules that “are identical except for the relative positioning of the Fzd and Lrp5/6 binding regions,” EX1002 ¶ 172, can all activate Wnt signaling to varying levels. I have therefore modified Dr. McDonnell’s Figure 13, below, by replacing Figure 11A with Figure 10B to graphically depict this. *See* Fig. 21, below.

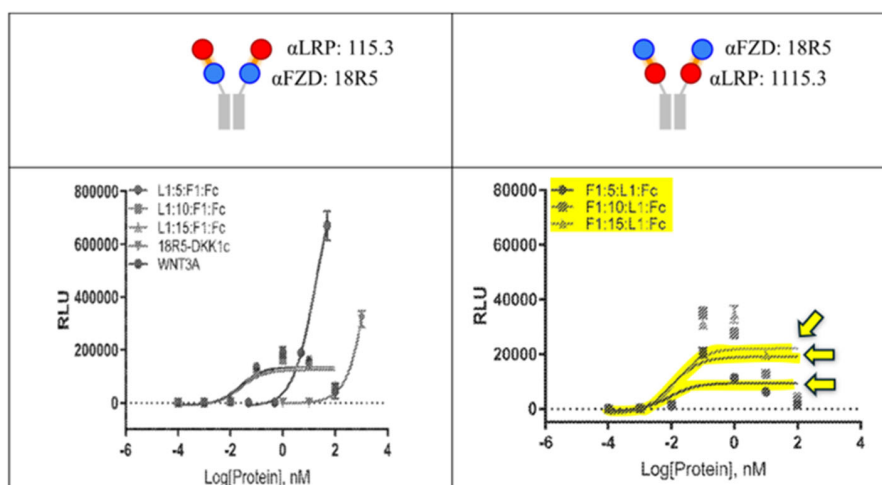


Figure 21: Dr. McDonnell’s Fig. 13 With the Right Panel Replaced to Show y-Axis-Scaled Curves from Fig. 10B of Li (EX1081)

202. Dr. McDonnell also opines that his estimate of more than 130 million formats is “conservative in many ways and therefore significantly underestimates the number of tetravalent formats encompassed by claim 1.” EX1002 ¶ 133. I disagree; instead, Dr. McDonnell’s allegations underscore the representativeness of the ’278 Patent’s examples and the meaningless nature of his mathematical approach.

203. Dr. McDonnell first asserts that his estimates of the number of linker and binding-fragment combinations are “conservative,” *see* EX1002 ¶¶ 134–135. But as I explained above, those assertions are incorrect, as his mathematical exercise in multiplying linker permutations and region types does not reflect how a POSA would approach these design choices. *See* ¶¶ 175–188, above.

204. Dr. McDonnell further alleges that he “did not separately calculate the number of possible constant domains (grey blocks) that are used to hold polypeptide chains together,” EX1002 ¶ 136, but that further underscores the specification’s detailed disclosures rather than reflecting any conservativeness of his unnecessary mathematical exercise. As Dr. McDonnell acknowledges, 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,” and further notes that “[t]he 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.*

205. Indeed, the specification goes into even further detail regarding the various Fc regions that may be used, noting that “[t]he Fc region for the full IgG format may be derived from any of a variety of different Fcs, including but not limited to, a wild-type or modified IgG1, IgG2, IgG3, IgG4 or other isotype, e.g., wild-type or modified human IgG1, human IgG2, human IgG3, human IgG4, human IgG4Pro (comprising a mutation in core hinge region that prevents the formation of IgG4 half molecules), human IgA, human IgE, human IgM, or the modified IgG1 referred to as IgG1 LALAPG.” EX1001 at 19:3–15. And as to heterodimerization strategies, the specification includes working examples demonstrating that the tested molecules

comprising heterodimerized IgG regions using knobs-into-holes and charge-pairing approaches “[a]ll ... activated Wnt signaling.” *See* EX1001 at Example 15.

206. Dr. McDonnell alleges that his calculation of 130 million possible tetravalent formats “does not begin to address the astronomical sequence-level diversity inherent in the individual antigen-binding regions themselves.” EX1002 ¶ 138. But for all of the reasons described above, incorporating the number of sequence-level variations in his calculations would only further inflate his final result rather than providing any insight into claim scope, especially where the specification makes clear that Fzd- and LRP5/6-binding sequences were “known in the art and ... commercially available.” EX1001 at 79:63–67, 116:25–29; *see also* ¶ 165, above. I therefore disagree that “the only possible conclusion that a POSA would have drawn is that the scope of claim 1 is exceedingly broad.” EX1002 ¶ 138. Rather, a POSA would conclude from Dr. McDonnell’s mathematical exercise that his approach is ill-suited in evaluating the breadth of claim 1. To evaluate claim 1’s breadth, a POSA would instead look to the properties expressly recited in the claim to conclude that its scope is bounded by several precise design restrictions, including a specific (1) valency, (2) stoichiometry of specific binders, (3) set of constituent structures, and (4) linker requirement, as described in the claim limitations.

207. For the above reasons, the tetravalent formats disclosed in the specification’s examples are representative of the full range of formats encompassed by claim 1.

**e. The '278 Patent's Examples are Representative
Across Binding Targets**

208. In addition to his flawed combinatorial calculation, in paragraphs 178–185 of his declaration, Dr. McDonnell sets forth several “other” reasons why he believes Claim 1 is “exceedingly broad” in scope, EX1002 ¶ 178, but those reasons, too, overstate the breadth of the claims, which a POSA would understand to be circumscribed by the criteria set forth in the claim, especially in view of what was known in the prior art.

209. Dr. McDonnell first engages in another combinatorial calculation, this time in connection with the number of possible targets the claimed molecules can bind, concluding that “each tetravalent molecule can bind to one of at least 35,721 target combinations,” EX1002 ¶ 142, but once again Dr. McDonnell’s math exercise ignores the patent’s express teachings, including that much of this was known in 2017 and disclosed in the '278 Patent.

210. Instead of engaging in Dr. McDonnell’s flawed combinatorial approach, a POSA would recognize that claim 1 requires binding to two classes of molecules—the Fzd class of receptors and LRP5/6—each of which was known in 2017 to consist of highly similar structures. For example, as of 2017, a POSA would have known that LRP5 and LRP6 contain highly similar extracellular domains consisting of a series of β -propeller regions to which ligands may bind. *See* EX2027 at 1. Similarly, a POSA would have known as of 2017 that the ten Fzd receptors all comprise a

cysteine-rich domain or CRD that is highly conserved across the ten receptors and to which Wnt and other ligands bind. *See* EX2028 at 2. The specification itself illustrates the structural similarity across target binders, demonstrating that several disclosed sequences were cross-reactive with one, two, three, or more Fzd receptors. *See e.g.*, EX1001 at Table 2B, 79:39–41 (“In certain embodiments, the Fzd binding domain comprises the six CDR regions of the *pan specific* frizzled antibody, OMP-18R5.”). A POSA would thus understand from the ’278 Patent itself, and without the need to resort to unnecessarily complicated math exercises, that the target binders of the claimed molecules span a relatively narrow range, and that the disclosed exemplary sequences are representative of target combinations.

211. Dr. McDonnell’s approach, by contrast, proceeds via a purely numerical operation entirely untethered from a POSA’s knowledge and understanding in the field. Following Dr. McDonnell’s approach would imply that a POSA would begin by identifying every single possible antigen target that each binding region could bind and then identify every single possible combination of possible antigen targets across the molecule’s four binding regions before selecting a molecule. That approach gets the process exactly backwards. As the ’278 Patent makes clear, anti-Fzd and anti-LRP5/6 binding regions were “known in the art and ... commercially available,” and the ’278 Patent itself discloses hundreds more that bind to all ten Fzd receptors, LRP5, and LRP6. EX1001 at Tables 1–2, 79:63–67, 116:25–29. A POSA

would already have a target combination of specific Fzd and LRP5/6 molecules in mind based on their specific goals and interests, and would be able to use one of the several known or disclosed anti-Fzd and LRP5/6 binding regions that bind to their specific targets to create their desired tetravalent molecule as claimed.

212. In any event, as Dr. Willert explains, Drs. McDonnell and Kahn's estimate of more than 35,000 possible target combinations is incorrect and the result of "improperly double-counting each cross-reactive binder (*i.e.*, sequences reactive with two or more target Fzd receptors or LRP5/6 coreceptors) as its own binding target." EX2010 ¶ 171. Instead, as Dr. Willert explains, a POSA would understand the number of possible target combinations to be "at most 400." *Id.* ¶ 170. A POSA would thus simply not view claim 1's breadth as a vast landscape of "more than 35,000 possible target combinations," as Dr. McDonnell's contrary approach would suggest. *Contra* EX1002 ¶ 142.

213. Dr. McDonnell's assertion that his calculation of the number of possible target combinations is "conservative" because "each Fzd and Lrp5/6 receptor may present multiple epitopes that the Fzd and Lrp5/6 binding regions can target," EX1002 ¶ 143, is likewise incorrect. As discussed above, Dr. McDonnell misrepresents a POSA's approach to molecular design, and a POSA would view the number of targets in the claims as comprising ten Fzd receptors and LRP5 or LRP6 instead of computing every single possible combination of epitopes the Fzd and

LRP5/6 binding regions can target. *See* ¶ 211; *see also* EX2010 ¶ 44 (explaining a POSA’s understanding as of 2017 that “activation of canonical Wnt signaling was primarily a matter of heterodimerizing Fzd and LRP5/6 receptors expressed on the cell surface, rather than binding particular combinations of epitopes”).

214. In that light, the specification clearly discloses representative examples across the full scope of target specificities. For example, the specification discloses **91** different binding sequences that exhibited confirmed binding to at least one Fzd receptor, including binding sequences for each of the 10 possible Fzd targets, and **211** sequences that exhibited confirmed binding to at least one of LRP5 and LRP6, including binding sequences for both those targets. *See* EX1001 at Tables 1B, 2A. Moreover, the specification discloses more than **300** additional binding sequences that exhibited initial binding to one of the ten Fzd receptors but were not further tested for confirmed binding. *See* EX1001 at Table 1A. Given that more than two-thirds of tested “initial binding” sequences demonstrated confirmed binding, *see* ¶ 102, above, a POSA would be able to obtain hundreds of additional binding sequences from the initial binding list using established methods and with a high degree of success. And as the specification explains, such sequences were also “known in the prior art ... and commercially available.” EX1001 at Tables 1–2, 79:63–67, 116:25–29. Given that binding sequences targeting all 10 known Fzd receptors are disclosed in the ’278 Patent and were known in the prior art, and claim

1 does not claim these binding sequences *themselves* but their specific application in the disclosed tetravalent molecules, a POSA would conclude that the patent provides sufficient representative examples of such binding sequences to support the full scope of the claim 1.

215. Dr. McDonnell reaches the opposite conclusion, but that allegation is premised on a series of unfounded assumptions. *First*, Dr. McDonnell alleges that “every tetravalent molecule evaluated in the specification is limited to bispecific binding.” EX1002 ¶ 179. But as discussed above, that assertion is incorrect. *See* ¶ 109, above. Instead, the specification demonstrates that at least 77 of the tested tetravalent molecules also exhibited trispecificity by virtue of their ability to bind more than one Fzd receptor in addition to at least one LRP5/6 coreceptor. *See* EX1001 at Tables 2B, 3; ¶ 109, above. Dr. McDonnell is thus likewise incorrect that “[t]he ’278 Patent does not present any experimental data” regarding or “meaningful guidance on how to design” trispecific or tetraspecific molecules that could activate Wnt signaling, EX1002 ¶ 179; each of the at least 77 disclosed molecules with cross-reactive Fzd binding regions activated Wnt signaling.

216. In search of support for his conclusory and unsupported allegation that this purported “absence of information,” EX1002 ¶ 179, would be significant to a POSA, Dr. McDonnell confuses the distinct concepts of valency and specificity, only to emphasize the representativeness of the disclosed examples. While specificity refers

to the number of possible antigens or epitopes a molecule may bind, *see e.g.*, EX1001 at 17:11–14, valency refers to the number of **binding domains** on the molecule that bind those antigens. Dr. McDonnell explains that “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.” EX1002 ¶ 179. The specification and claims squarely address these “key determinants,” disclosing that the claimed molecules must comprise **two** Fzd binding regions and **two** LRP5/6 binding regions, permitting them to activate canonical Wnt signaling by simultaneously binding Fzd and LRP5/6. EX1001 at cl. 1; EX1054 at 8. Because, as Dr. Willert explains, the specification discloses **90** tetravalent molecules that meet these requirements, a POSA would understand the specification to be replete with representative examples in terms of the “key determinants” of Wnt signaling activity.

217. Dr. McDonnell next criticizes the ’278 Patent for using “a limited set of anti-Fzd antibody sequences that target only a subset of Fzd receptors,” parsing each multispecific combination of Fzd binding targets to arrive at “63 distinct Fzd combination,” of which he alleges the specification discloses “confirmed binding” sequences for “only 17 of those 63 target options.” EX1002 ¶ 180. As Dr. Willert explains, a POSA would understand there to be **10** possible targets for each anti-Fzd binding region—the ten known Fzd receptors—and that each binding region could

bind only one such target at any given time. *See* EX2010 ¶ 170. A POSA would consider the specification's disclosure of 91 anti-Fzd sequences exhibiting confirmed binding across all 10 Fzd receptors, additional binding sequences known in the prior art, and 90 exemplary tetravalent molecules collectively targeting 7 of the 10 possible Fzd receptors, to be more than sufficiently representative in that regard. *See* ¶¶ 99–111, above.

218. Dr. McDonnell labels the '278 Patent's evaluation of a diverse range of anti-Fzd binding regions as “[p]roblematic[,]” EX1002 ¶ 181, but this erroneous conclusion is again a result of Dr. McDonnell's inflated target binder accounting. Contrary to Dr. McDonnell's assertions, the '278 Patent discloses **90** exemplary tetravalent molecules, together targeting 7 of the 10 known Fzd receptors, *all* of which activated Wnt signaling. *See* EX1001 at Tables 1A–B, 2A–B, 3, Examples 2–18. Given that binding sequences for the Fzd family of receptors were “known in the art and ... commercially available,” EX1001 at 79:63–80:15, 116:25–39, and the patent further discloses additional binding sequences for all ten Fzd receptors, *see id.* at Table 2B, a POSA would be able to design and generate a molecule using methods to target the remaining three Fzd receptors—Fzd3, 6, and 10. And even though the claims do not require Wnt agonist activity, *see* ¶¶ 127–136, above, as Dr. Willert explains, a POSA would understand from the '278 Patent's disclosures and the knowledge of Fzd receptors in the art that the claimed tetravalent molecules

targeting these three Fzd receptors would also activate canonical Wnt signaling. *See* EX2010 ¶ 73.

219. Drs. McDonnell and Kahn also assert that, “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.” EX1002 ¶ 183. This ignores, however, that a POSA would have known in 2017 that the disclosed molecules’ simultaneous binding of both Fzd and LRP5/6 receptors (not just Fzd, or just Lrp5/6) render them applicable to ***canonical*** Wnt signaling. *See* EX2010 ¶ 33. And as Dr. Willert explains, a person of ordinary skill in the art in 2017 would have expected—based on the well-established model of canonical Wnt signaling as involving the binding of both Fzd receptors and LRP5/6 receptors, along with the ’278 Patent’s teaching that every one of the 90 tetravalent molecules tested activated Wnt signaling—that tetravalent molecules binding Fzd3, 6, and 10 (for which binding sequences are disclosed in Table 1B) would also activate canonical Wnt signaling.” *Id.* ¶ 73. Contrary to Dr. McDonnell’s assertions, *see* EX1002 ¶ 183, a POSA would have therefore understood the disclosed molecules and sequences in the ’278 Patent to be representative of the full range of Fzd binding targets.

220. Dr. McDonnell further criticizes the ’278 Patent’s disclosures because in his opinion, “[t]he manner in which tetravalent, multispecific molecules are evaluated

in the specification is also limited.” EX1002 ¶ 182. But for one, Dr. McDonnell’s statement that “the only *in vitro* assay used in the specification is the TOPFlash assay,” *id.*, omits that the specification also provides extensive disclosures of other “[v]arious methods ... known in the art for measuring the level of canonical Wnt/β-catenin signaling,” including the “BioImage β-Catenin Redistribution Assay” and Axin translocation visualization using GFP-Axin fusion proteins. EX1001 at 117:39–118:36. I understand from Dr. Willert, that of these various assays, the TOPFlash assay is a “well-established[,] accurate[,] and reliable indicator of canonical Wnt activity.” EX2010 ¶ 56.

221. As for Dr. McDonnell’s assertion that “the ’278 Patent does not test or demonstrate possession of any tetravalent, multispecific molecules capable of activating *noncanonical* Wnt signaling,” EX1002 ¶ 182, a POSA would understand such testing to be entirely irrelevant given the scope of claim 1. Claim 1 specifically requires that each claimed molecule comprise (1) two Fzd binding regions, and (2) LRP5/6 binding regions. *See* EX1001 at cl. 1. Because a POSA understood as of 2017 that canonical signaling requires recruitment of *both* Fzd and LRP5/6 molecules, it would be clear to a POSA that the claimed invention functions to agonize *canonical* Wnt signaling, even assuming as true Dr. McDonnell’s contention that claim 1 imposes any functional limitations at all (which it does not). *See* EX2010 ¶ 33. This is supported by the ’278 Patent, which unequivocally states

that “[i]n particular, the Wnt agonists disclosed herein activate, enhance or increase the *canonical* Wnt/[β]-catenin signaling pathway.” EX1001 at 16:63–65. A POSA would thus not consider the presence or absence of disclosures regarding *non-canonical* signaling to have any bearing on the representativeness of the specification’s examples in relation to claim 1.

222. Finding no evidence in the specification or prior art for his assertions of non-representativeness, Dr. McDonnell resorts to Li (EX1081), which he claims confirms “[t]he inability to extrapolate across molecules with different Fzd target specificities.” EX1002 ¶ 184. But Li did not state that the 4SC10-3 was incapable of agonizing Wnt signaling—instead, it noted that the 4SC10-3 molecule “was not able to *effectively* activate beta-catenin-dependent signaling ... *in contrast to the positive control molecule R2M3-26*.” EX1081 at 178. Indeed, the molecule’s dose–response curve depicted in Li shows that the molecule produced a TOPFlash response, especially given the y-axis was scaled to 2,500,000 RLU, which is significantly higher than the maximum scaling in other graphs provided in Li. *See* Fig. 22, below; *see also, e.g.*, EX1081 at Fig. 10B (using y-axis scaling to 80,000 RLU). Because the claims of the ’278 Patent do not require a specific level of Wnt signaling activation, and assess a molecule’s Wnt signaling activity in comparison with the “absence of a Wnt agonist,” *not* a positive control, *see* ¶ 335, below, Li’s statement that 4SC10-3’s level of Wnt signaling activation was not “effective” in comparison

with R2M3-26 says nothing about whether 4SC10-3 was able to activate Wnt signaling in the first instance. *See* EX2010 ¶ 61 (“A person of ordinary skill in the art would not need **both** a positive control and a negative control ... to determine whether a given molecule is activating the canonical pathway, because a person of ordinary skill in the art recognizes that Wnt-dependent TOPFlash assays are a highly reliable method of measuring canonical Wnt signaling activity and accepts that any induced reporter activity in a TOPFlash assay with appropriate negative controls indicates activation of canonical Wnt signaling.”). This is especially so given Li’s claims include methods of treating particular diseases by “administering to the subject an **effective** amount of the Wnt surrogate molecule,” EX1081 cl. 48, while the ’278 Patent’s claims do not. A POSA would thus understand that whether 4SC10-3 is effective at signaling such that it can treat a disease has no bearing on whether it activates Wnt signaling in the first place.

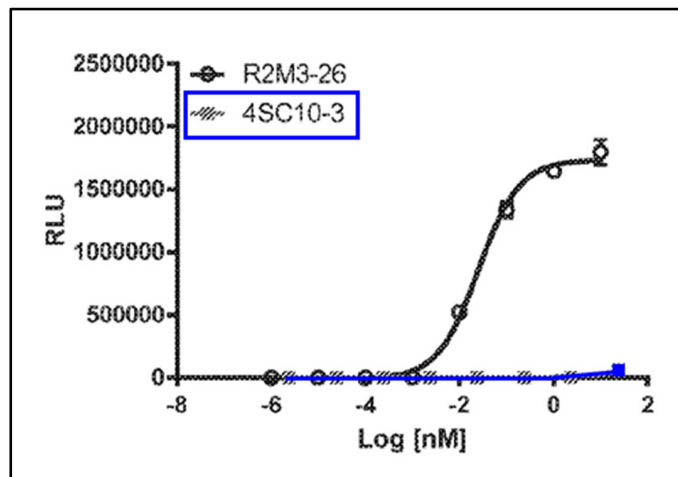


Figure 22: EX1081 Figure 5A (annotated)

223. For the reasons discussed above, the '278 Patent discloses numerous tetravalent, multispecific molecules that are representative of the full scope of claim 1. Dr. McDonnell's contrary conclusion finds no support in the specification, the prior art, or even in the art post-dating the '278 Patent.

f. The '278 Patent's Examples Are Representative Across Anti-Fzd and Anti-LRP5/6 Binding Sequences

224. As discussed above, Dr. McDonnell asserts that his flawed estimate of 130 million formats "underestimates the actual scope of claim 1" because "it does not begin to address the astronomical sequence-level diversity inherent in the individual antigen-binding regions themselves, EX1002 ¶ 138, but that misapprehends the nature of the claimed invention. *See* ¶ 206, above. His discussion of sequence-level diversity in paragraphs 144–150 of his declaration is misguided for the same reasons. The '278 Patent does not purport to claim as its invention every antibody or fragment thereof that binds a Fzd receptor or a LRP5/6 receptor; indeed, the Patent notes that such antibodies were "known in the art and ... commercially available." EX1001 at 79:63–67, 116:25–29. Instead, the '278 Patent uses those two known groups of antibody sequences in a novel, tetravalent molecular structure. Because anti-Fzd and anti-LRP5/6 binding regions were "known in the art ... and commercially available," EX1001 at 79:63–66, 116:25–27, a POSA would be equipped with sequences possessing specific epitopes, binding affinities and amino acid sequences. They

would thus not find the diversity of potential amino acid sequences capable of binding Fzd or LRP5/6 probative in assessing claim 1's breadth.

225. In any event, Table 1A discloses 448 anti-Fzd binding sequences that demonstrated initial binding, and Table 1B discloses 91 of those sequences that demonstrated confirmed binding with a Fzd binding target, with binding examples in both tables for each of the ten known Fzd receptors. *See* EX1001 at Tables 1A–B. Likewise, Table 2A discloses exemplary CDR sequences for 211 binding regions that showed confirmed binding to LRP5 and/or LRP6, and Table 2B provides the full-length heavy-chain sequences for 24 of those binding regions. *See id.* at Tables 2A–B. The '877 and '879 Applications disclose additional clones made using site-specific mutagenesis that also demonstrated binding functionality. *See* EX2021 at Table 2; EX2022 at Table 2. And the '278 Patent specification goes beyond even those hundreds of example sequences to reference the several anti-Fzd and anti-LRP5/6 that were “known in the art ... and commercially available.” *See* EX1001 at 79:63–67, 116:25–29. Additionally, the claimed inventions are tetravalent molecules—not CDR sequences—and the '278 Patent discloses 90 representative examples of the claimed molecules. *See* ¶¶ 161–223, above; EX1001 at Examples 2–18. A POSA would therefore understand the sequences disclosed to be functionally representative of the full range of antibodies and antibody-derived fragments capable of binding Fzd and LRP5/6, as used in those molecules.

226. Dr. McDonnell also misses the point in alleging that “the exemplary CDR amino acid sequences for the Fzd and Lrp5/6 binding regions disclosed in the ’278 Patent are ... not representative of the vast scope of all potential CDR amino acid sequences that confer Fzd and Lrp5/6 binding capabilities.” EX1002 ¶ 149. For one, Dr. McDonnell distills his complaints down to the most granular level—CDR sequence variation—rather than considering the fact that the inventors disclosed anti-Fzd and anti-Lrp5/6 antibodies that bind to every single Fzd and LRP5/6 receptor. *See* ¶ 218, above. But even at that level of granularity, Dr. McDonnell’s assertions are unavailing.

227. Dr. McDonnell faults the ’278 Patent specification for not “explain[ing] how the antibody sequences listed in Table 1A and Table 2A were generated,” alleging this is “problematic because different antibody generation methods can result in sequences that are not representative of one another.” EX1002 ¶ 146. But as his sole supporting “somatic mutation” example shows, that assertion is incorrect. While antibody sequences derived from immunization may undergo somatic mutation, those mutations impact the target antibody’s amino acid sequence *prior* to their isolation, purification, and characterization. Because the final sequences account for such somatic mutations, a POSA would understand that the functional properties of the sequenced antibodies do not depend on the pathway by which they were

generated. Differences in antibody generation methods thus provide no illustration of their purported “lack of representativeness,” as Dr. McDonnell contends. *Id.*

228. In any event, Dr. McDonnell ignores that the '877 and '879 Applications—which are incorporated into the '278 Patent specification by reference—make clear that all the Fzd and LRP5/6 binding sequences in Tables 1 and 2 were transfected, expressed, and characterized using the same method. For instance, as the '877 Application explains:

Antibody Fab, scFv and VHH nanobody fragments disclosed herein were sequenced and sub-cloned into mammalian expression vectors for expression, purification, and characterization of binding affinities to various Fzd receptors.

Soluble recombinant proteins were prepared by transfection of respective expression vectors into Expi293F cells (Thermo Fisher Scientific, Waltham, MA) according to the manufacturer's instructions. Briefly, four days after the transfection, cell culture medium was collected after spin down the cell pellet. The media were incubated with either Protein A resin (REPLIGEN, Waltham, MA) for collecting proteins containing human IgG-Fc portion, or Nickel affinity resin (Roche, Basel, Switzerland) for collecting proteins conjugated with His-tag. Proteins were eluted with 10 mM glycine, pH 3.5 from Protein

A resin, or with 150 mM imidazole, pH 7.4 from Nickel affinity resin, respectively.

EX2021 at 96 (ll. 5–18); *see also* EX2022 at 93 (l. 29)–94 (l. 7).

229. The manner in which the antibodies disclosed in Tables 1 and 2 were first discovered is therefore beside the point. The specification does not rely on uncharacterized screening outputs from various generation methods, but instead discloses concrete antibody sequences that were independently expressed and validated after their initial generation.

230. Dr. McDonnell makes the additional sweeping statement 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,” EX1002 ¶ 147, but I understand that such a showing is not required where, as here, the patent discloses a representative number of species. *See* ¶¶ 161–233, above. Indeed, Dr. McDonnell’s own statements about sequence similarity in fact underscore the representativeness of the disclosed sequences. As the ’877 and ’879 Applications indicate, the CDR sequences of the disclosed antibodies may be capable of tolerating point mutations without compromising binding functionality. *See* ¶105, above; EX2021 at 107 (ll. 6–9); EX2022 at 100 (l. 19)–101 (l. 2). Rather than rely primarily on CDR point mutations which produce variable region sequences with a high degree of identity, Tables 1 and 2 of the ’278 Patent disclose hundreds of diverse,

dissimilar sequences that all bind their target antigens, collectively targeting all ten Fzd receptors, LRP5, and LRP6. *See* EX1001 at Tables 1A–B, 2A–B. Because the claimed invention here is a tetravalent structure combining Fzd- and LRP5/6-binding sequences—not individual anti-Fzd or anti-LRP5/6 antibodies themselves—a POSA would understand these sequences to be representative, in that the Wnt-signaling agonism properties arising from the claimed structures stem not from any specific amino acid sequence, but from the structural and stoichiometric features recited in the claims.

231. Dr. McDonnell draws a different conclusion from the specification’s examples by selectively reading portions of it. He first remarks that “Table 1B of the ’278 Patent discloses only one antibody each for confirmed Fzd2 binding ..., Fzd3 binding ..., and Fzd5 binding.” EX1002 ¶ 149. That sentence is misleading in the first instance because it excludes sequences listed in Table 1B that showed confirmed binding with Fzd2, 3, or 5 *in addition* to being cross-reactive with other Fzd receptors. It does not appear to include, for example, the 001S-H02 sequence, which demonstrated confirmed binding to Fzd1 and Fzd7 in addition to Fzd2. *See* EX1001 at Table 1B. A POSA would see no principled basis to exclude such sequences merely because they are cross-reactive. Counting the sequences Dr. McDonnell arbitrarily excludes, Table 1B contains **16** examples of confirmed Fzd2-binding sequences, **2** examples of confirmed Fzd3-binding sequences, and **15**

examples of confirmed Fzd5-binding sequences. *See* EX1001 at Table 1B. Dr. McDonnell also ignores the additional 28, 14, and 47 exemplary sequences disclosed in Table 1A that were found to initially bind Fzd2, Fzd3, and Fzd5 respectively but were not further tested for confirmed binding, *see* EX1001 at Table 1A, and the fact that more than two-thirds of initially binding sequences tested in the specification demonstrated confirmed binding, *see* ¶ 102, above. In addition, Dr. McDonnell ignores the patent specification's reference to such antibodies that were "known in the art and ... commercially available." *See* EX1001 at 79:63–67, 116:25–29. For example, United States Patent Publication 2014/0105917, which is cited in the patent specification as disclosing known antibodies, characterizes and describes the sequence of the 44R24 antibody, which "was found to specifically bind to human FZD5 and FZD8." EX2029 at [0126].

232. Dr. McDonnell likewise misreads the specification's disclosure of anti-LRP5/6 sequences. While he claims that "Table 2B of the '278 Patent only discloses one antibody ... that showed confirmed binding for LRP5," EX1002 ¶ 149, he ignores that Table 2A discloses the CDR sequences for an additional 9 antibodies that demonstrated confirmed binding to LRP5, and that the specification also describes LRP5-binding antibodies that were "known in the art ... and commercially available," including "Cell Signaling Technology antibody specific for LRP5 (D80F2), catalog number 5731." EX1001 at Table 2A, 116:25–39. Moreover, while

Dr. McDonnell alleges that “each of the antibodies listed in Table 2B has only a heavy chain,” and that therefore “[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,” EX1002 ¶ 149, he omits that Table 2A includes the CDR sequences of **169** binding regions containing both heavy and light chains. *See* EX1001 at Table 2A. Dr. McDonnell is thus incorrect that the specification’s ample disclosure would not have provided representative anti-Fzd or anti-LRP5/6 binding region sequences for the purposes of the claimed invention.

233. To summarize, claim 1 of the ’278 Patent is bounded by specific structural and functional requirements, notwithstanding Dr. McDonnell’s various attempts to inflate that claim’s scope. In addition, the patent specification contains extensive disclosure to support the claim’s scope, including empirical testing of **90** of the claimed molecules. *See* ¶ 106, above; EX1001 at Examples 2–18. In my opinion, the patent’s exemplary molecules, read in light of its numerous other disclosures and the POSA’s knowledge of the prior art, are representative of other molecules that fall within the scope of claim 1 and thus provide adequate written description for the claim, and Dr. McDonnell’s conclusions to the contrary reflect his misunderstandings and misapplications of those disclosures rather than any supposed shortcomings of the specification.

2. The '278 Patent Discloses Its Claimed Structure Reliably Agonizes Wnt Signaling

234. In paragraphs 151–161, Dr. McDonnell alleges that “the '278 Patent fails to address the unpredictability for multivalent, multispecific antibody molecules.” EX1002 § IX.A.3. But that overstatement does not reflect a POSA’s takeaways from the '278 Patent’s disclosures. In my opinion, a POSA would instead view the '278 Patent’s extensive guidance and 90 working examples to show that the inventors were in possession of a wide range of the claimed tetravalent molecules that reliably agonize Wnt signaling (although, again, I disagree that such agonist activity is a requirement of the claims).

235. Dr. McDonnell’s blanket statement that “[a]s of 2017, identifying a multivalent, multispecific molecule capable of modulating a biological pathway of interest required multiple levels of trial-and-error experimentation,” EX1002 ¶ 151, mischaracterizes the state of the art of Wnt signaling. Leveraging what was known in the art—that (1) canonical Wnt signaling is agonized by simultaneously binding Fzd and LRP5/6 receptors, and (2) well-established analytical tools were available to assess such signaling, *see* ¶¶ 89–98, above—the specification discloses that a tetravalent structure consisting of a 2:2 stoichiometry of antibody-derived Fzd and LRP5/6 binding regions reliably agonizes Wnt signaling. *See* EX1001 at Examples 2–18. 90 varied exemplary molecules are provided and tested. *See id.* A POSA reading the '278 Patent’s disclosure would thus not need to engage in “multiple

levels” of trial-and-error experimentation because the ’278 Patent inventors have already done it for them, and this disclosure confirms to a POSA that the inventors were in possession of the claimed invention. *Contra* EX1002 ¶ 151.

236. Dr. McDonnell’s statement that a POSA would have understood that “no single format [was] suitable for all, or even most of, the desired applications” provides no support for his conclusion that “identifying functional multivalent, multispecific molecules required empirical trial-and-error investigation.” *See* EX1002 ¶ 151. Instead, as the ’278 Patent shows, every disclosed tetravalent molecule with two Fzd and two LRP5/6 binding regions agonized canonical Wnt signaling to varying degrees, and POSAs could leverage the examples disclosed in the specification to make molecules for specific needs. *See* ¶ 106, above.

237. Dr. McDonnell’s “one size fits all” approach also imports into the claims the unfounded requirement that *each* claimed molecule agonize Wnt signaling to *every* possible level in *every* application. A POSA would understand that requirement is unsupported by the claim language or the specification (even under Dr. McDonnell’s construction), not necessary for the claimed molecules to achieve their claimed purpose of specifically binding to both Fzd and LRP5/6, and an unreasonable approach to assessing claim 1’s support in the specification that is untethered from understandings in the field.

238. Dr. McDonnell next claims that the Wnt signaling pathway is “particularly complex, involving multiple ligands and receptors interacting simultaneously,” EX1002 ¶ 152, but the Wnt pathway is not “particularly complex” in this regard. Moreover, as I understand from Dr. Willert, the pathway’s mechanism of action was not “poorly understood” by 2017. Rather, Wnt signaling pathways had been studied for more than 35 years, their key components had been identified and characterized, and three separate canonical and noncanonical pathways had been classified—so much so, that by 2017, researchers began to examine how the Wnt pathway could be modulated using synthetic molecules. *See* EX2010 ¶¶ 26–30. The ’278 Patent added to the field of knowledge, demonstrating that where 1:1 stoichiometries of the past failed to agonize Wnt signaling, the inventors’ 2:2 Fzd:LRP5/6 stoichiometry tetravalent molecules were capable of reliably doing so. *See* EX1008 at 4006; EX1001 at Examples 2–18. Dr. McDonnell is therefore incorrect 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 ... tetravalent formats would yield a functional Wnt surrogate molecule.” EX1002 ¶ 152.

239. Continuing, Dr. McDonnell, relying in turn on Dr. Kahn, asserts that “the mechanism by which each Wnt and non-Wnt ligand engaged specific Fzd and Lrp5/6 molecules to trigger Wnt signaling was poorly understood.” EX1002 ¶ 153. That assertion is irrelevant to the patent claims, which do not say anything about the

mechanism by which Wnt ligands engage the Fzd and LRP5/6 molecules. Moreover, as I understand from Dr. Willert, by 2017, it was understood that canonical Wnt signaling pathways are agonized by binding one or more Fzd receptors and one or more Lrp5/6 coreceptors. EX2010 ¶ 33.

240. In addition, by 2017, researchers had developed several analytical tools such as the TOPFlash assay to report Wnt signaling activity. EX2010 ¶¶ 51–65; EX1001 at 117:39-44. Several aspects of Wnt signaling had also been characterized by this time. For example, researchers had found that the Fzd receptor family contained highly conserved sequences, particularly in their cysteine-rich domains, which form the binding site for Wnt ligands, obtained expression profiles of different Fzd and LRP5/6 receptors on the surfaces of various types of cells, and had found specific Fzd receptors to be implicated in specific medical conditions. *See* ¶¶ 91, 210 above; EX1001 at 144:1–145:16; EX2010 ¶ 48. Dr. McDonnell’s characterization of Wnt signaling as “poorly understood” thus overlooks the decades of intensive research conducted in the field.

241. In spite of the specification’s abundant disclosures, Drs. McDonnell and Kahn claim that, “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.” EX1002 ¶ 153. Dr. McDonnell goes on to argue that “[n]either 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.” EX1002 ¶ 154.

242. Putting aside that the claims do not require any sort of Wnt signaling activation, I disagree with the premise of Dr. McDonnell’s assertion. As explained above, the ’278 Patent discloses **90** exemplary tetravalent molecules, which collectively bind 7 of the 10 target Fzd receptors, and LRP5 and LRP6, and provides additional sequences that demonstrated confirmed binding to each Fzd receptor and LRP5/6. *See* EX1001 at Tables 1A–B, 2A–B, 3, Examples 2–18. The patent thus teaches a POSA that if he has anti-Fzd and anti-LRP5/6 antibodies that have confirmed binding to their desired Fzd and LRP5/6 receptors (which POSAs knew how to find and test), and they are then formatted as a tetravalent molecule in a 2:2 stoichiometric ratio (which was well within a POSA’s wheelhouse to do in 2017, *see* ¶¶ 44–88, above), it will agonize Wnt signaling (which a POSA could confirm using assays that were commonplace in 2017).

243. Dr. McDonnell’s “five possible stoichiometric combinations” theory, EX1002 ¶ 154, likewise does not show any unpredictability in the ’278 Patent’s disclosures. His argument assumes that each theoretical receptor-engagement configuration must be treated as a separate molecule-specific design choice that a POSA would need to test one by one. But that framing is wrong. Signaling pathway

activation is not assessed by isolating a single molecule and asking which receptor-engagement configuration it happens to adopt. It is assessed across a *population* of molecules at the tested concentration. For any given construct, a POSA would expect such a population of molecules to collectively engage cell-surface Fzd and LRP5/6 receptors in *all five* “stoichiometric combinations.” Those possible combinations would therefore not preclude the construct from achieving its Wnt signaling agonism function (which is again not required by the claims), and Dr. McDonnell is incorrect that “a POSA would need to test each possibility empirically.” *Contra* EX1002 ¶ 154.

244. Dr. McDonnell attempts to further question the '278 Patent's disclosures by speculating that “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.” EX1002 ¶ 155. But Dr. McDonnell cites no study demonstrating that variations in molecular “flexibility” or “reach” would prevent such molecules from activating Wnt signaling altogether. A POSA would instead understand that factors such as cell line type and expressed receptor/coreceptor density may influence the *magnitude* of Wnt signaling observed, not whether a molecule can activate the Wnt signaling pathway, period.

245. In that context, Dr. McDonnell is incorrect that “[t]he specification provides no guidance to account for the variability and unpredictability of Wnt agonist activity arising from different expression profiles of Fzd and Lrp5/6.” EX1002 ¶ 156. To the contrary, the specification provides ample description and guidance on this issue in at least three different ways. *First*, Example 5 reports experimental results measuring the Wnt signaling of the same exemplary molecules across different cell lines, including “293, Huh7, A375, and BNL.CL2.” EX1001 at 156:34–52. Despite the fact that these cell lines express Fzd and Lrp5/6 at varying levels, the specification reports that the tested molecules “activated Wnt signaling to various levels.” *Id.*

246. *Second*, Examples 13 and 15 test several molecules that differ only in terms of their linker length, in effect varying their “reach,” to use Dr. McDonnell’s terms. Again, the specification reports that the tested molecules all agonized Wnt signaling to varying degrees. EX1001 at 158:49–159:3, 159:49–160:49. *Third*, Example 9 of the specification conducts a “SAR” or “structure–activity relationship” analysis on several tetravalent molecules by investigating the impact of binder attachment locations on Wnt signaling activity. *Id.* at 157:31–50. Because changing the attachment location alters the relative distance between Fzd and LRP5/6 binding regions, the tested molecules in Example 9 also differed in terms of their “reach.” Nonetheless, the specification explains that the tested molecules “activated Wnt

signaling to various levels.” *Id.* at 157:44–47. The specification is thus clear that regardless of the disclosed molecules’ “reach” or “flexibility,” they were all capable of agonizing Wnt signaling in the first instance.

247. Dr. McDonnell’s contrary conclusions about the specification’s disclosures stem from his misguided view that the specification was required to provide “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.” EX1002 ¶ 156. The expression levels are entirely irrelevant to whether the molecules activated Wnt signaling—they did, regardless of whether there were low levels of the Fzd and Lrp5/6 receptors, or high levels.

248. Dr. McDonnell also asserts that “[a]lthough the specification states that the ‘distance between binding domains’ must be ‘enforced,’ ... there is no meaningful guidance in the specification on how to achieve that requirement,” EX1002 ¶ 156, but his selective quotes of the specification distort its meaning. The specification explains that “[t]he length of the linker, and therefore the spacing between the binding domains can be used to modulate the signal strength, and can be selected depending on the desired use of the Wnt surrogate molecule,” and refers to the spacing between binding domains resulting from linker length as the “enforced distance between binding domains.” *See* EX1001 at 116:48–64. As discussed above, varying linker lengths and flexibilities in molecular structures was well within a

POSA's capabilities as of 2017. *See* ¶¶ 77, 187, above. Dr. McDonnell's crop-quoted sentence thus underscores what the specification's examples demonstrate—while all examples of the disclosed molecules demonstrated the ability to agonize Wnt molecules, the level of activity can be tailored for specific applications. For all of these reasons, Dr. McDonnell is incorrect that “a POSA would ... have to rely on extensive trial-and-error experimentation to identify functional Wnt surrogate molecules capable of accommodating varying levels and types of Fzd and Lrp5/6 expression.” EX1002 ¶ 157. Instead, the specification contains abundant disclosure demonstrating that its disclosed molecules are precisely “capable of accommodating varying levels and types of Fzd and Lrp5/6 expression.” *Contra* EX1002 ¶ 157.

249. Dr. McDonnell alludes to two “other Wnt signaling variables” that purportedly compromise the '278 Patent's disclosures, but they, too, fail to support his sweeping conclusion that “the '278 Patent lacks any meaningful guidance for a POSA to avoid trial-and-error experimentation.” EX1002 ¶ 159. *First*, Dr. McDonnell claims that “a POSA reading the '278 Patent would not be able to obtain any insight on which epitope to target for a given Wnt system.” But a POSA would understand that the relevant frame of reference for the claimed invention is not the specific epitopes each binding region targets, but instead their specific *antigens*. As the specification explains, “[i]n particular embodiments, Wnt surrogate molecules disclosed herein are multivalent, e.g., they comprise two or more regions that bind

to *an epitope* within one or more Fzd receptor and/or two or more regions that bind to an epitope within LRP5 and/or LRP6.” EX1001 at 17:15–20. The identity of the specific epitope is thus less important than binding the Fzd and LRP5/6 themselves. *See also* EX2010 ¶ 44 (explaining a POSA’s understanding as of 2017 that “activation of canonical Wnt signaling was primarily a matter of heterodimerizing Fzd and LRP5/6 receptors expressed on the cell surface, rather than binding particular combinations of epitopes”). This would align with a POSA’s understanding that canonical Wnt signaling requires binding both Fzd and LRP5/6 to initiate downstream signaling cascades. *See* ¶ 219, above.

250. *Second*, Dr. McDonnell claims that “[t]he specification is similarly deficient with respect to binding affinity,” but it is his criticisms that are similarly deficient. EX1002 ¶ 160. At the outset, as Dr. McDonnell acknowledges, binding affinity data was available for Fzd antibodies and Lrp5/6 antibodies known in the prior art, such as 18R5, which is used as a Fzd binding region in several of the exemplary molecules tested. *See* Table 7, below; EX1001 at Examples 6–7, 9, 14. Dr. McDonnell also overlooks that the ’877 and ’879 Applications, incorporated into the ’278 Patent by reference, provide K_D ranges for several of their disclosed sequences. *See* EX2021 at Tables 1B, 2; EX2022 at Tables 1B, 2. But Dr. McDonnell’s more fundamental mistake is that he assumes a binding affinity or K_D value is necessary to determine whether a particular molecule is a binder. As the specification explains, however,

“[t]he strength, or affinity of immunological binding interactions *can be expressed* in terms of the dissociation constant (K_d) of the interaction,” EX1001 at 121:55–57, but it was not a necessary step to determining binding in the first instance. Indeed, a POSA would understand that a molecule’s K_D is not an absolute or context-independent property, but instead reflects a binding interaction measured under *specific experimental conditions*. As a result, K_D values are most appropriately used for relative comparisons within a given assay, not as universal thresholds to determine what is considered a “binder,” as Dr. McDonnell suggests.

**Table 7: Table 5 of U.S. Patent Publication 2014/0105917 (EX2029)
Referenced in the '278 Patent**

Affinity of 18R8 and 18R5 IgG antibodies		
FZD	18R8 K_D (nM)	18R5 K_D (nM)
1	15.6	4.6
2	6.2	3.3
5	4.2	1.9
7	5.2	1.8
8	29.3	5.8

251. Instead of relying simply on a K_D value, the specification provides ample disclosure of how binding was determined for its disclosed sequences. For instance, the '877 Application explains:

Binding kinetics of antibody fragments to a variety of Fzd cysteine rich domain (CRD) protein targets (Fzd1, Fzd2, Fzd3, Fzd4, Fzd5, Fzd6, Fzd7, Fzd8, Fzd9 and/or Fzd10 CRDs) was determined by bio-layer

interferometry (BLI) using Octet Red 96 (PALL ForteBio, Fremont, CA) instruments at 30° C, 1000 rpm with streptavidin (SA) biosensors. C-terminal biotinylated Fzd CRD recombinant protein was diluted to 20 nM in the running buffer (PBS, 0.05 Tween-20, 0.5% BSA, pH 7.2) and captured to the SA biosensor until coupling length reached 0.2 nm. Following capture of the Fzd CRD, the SA biosensor with captured biotinylated-Fzd CRD was dipped into wells containing the relevant antibody fragment at 7 different concentrations (0, 1.37, 4.12, 12.4, 37, 111.1, 333.3, 1000 nM) in running buffer, plus a well with only running buffer as a reference channel. K_D was determined by global fitting, 1:1 binding model according to manufacturer recommended settings.

EX2021 at 97 (ll. 6–18).

252. Using this Octet BLI method, the specification discloses exemplary sensorgrams obtained from this methodology. For example, Figure 2C of the '278 Patent provides a BLI Octet sensorgram for binding interactions between the R2M3-26 molecule and Fzd1. *See* Fig. 23, below.

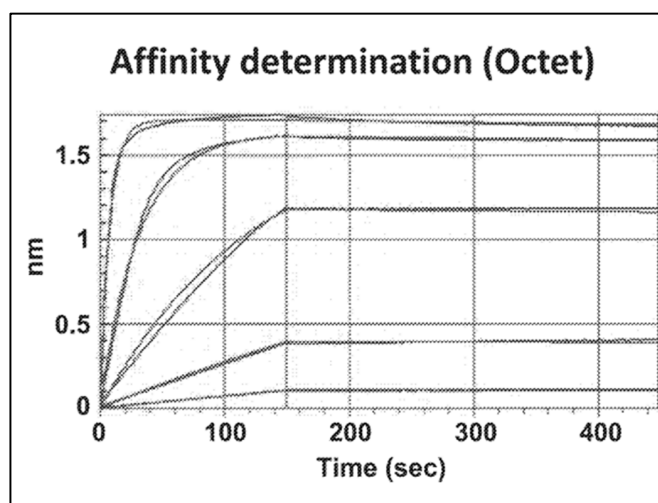


Figure 23: Fig. 2C of the '278 Patent

A POSA would be able to qualitatively determine from this Octet BLI output that R2M3-26 can bind Fzd1, without needing to first calculate a K_D value for the interaction. Specifically, a POSA would observe from the sensorgram that (1) the interaction creates an association signal above baseline that (2) produces a larger association signal with higher concentrations of the ligand before plateauing to conclude that the R2M3-26 binds Fzd1. *See* Fig. 1, above. A POSA would have understood that this Octet BLI process was used to confirm binding for each of the binding sequences disclosed in Tables 1B and 2A–B. *See* EX2021 at 97; EX2022 at 94. Dr. McDonnell’s criticism regarding the purported lack of disclosure of K_D is thus irrelevant to the '278 Patent’s disclosures.

253. Dr. McDonnell next claims that “[b]inding 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.” EX1002 ¶ 160. True, but it has a positive effect. As Dr. McDonnell’s reference confirms, functional affinity may be *enhanced* by multivalent “avidity” effects—cooperative binding interactions that substantially enhance effective target engagement—rather than diminishing binding functionality as Dr. McDonnell implies. *See* EX1020 at 2. The patent’s Examples 2 and 3 support as much, observing that “the fusion of the LRP6 binding arm” to each of those molecules “did not affect” the Fzd binding regions’ interaction with their Fzd targets. *See* EX1001 at 155:38–40, 156:12–14.

254. To summarize, Dr. McDonnell’s sweeping assertions about the ’278 Patent’s purported lack of disclosure and the state of the art do not reflect a POSA’s understanding. Dr. McDonnell claims that “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,” EX1002 ¶ 161, but his qualms regarding the ’278 Patent’s disclosures are either incorrect or demand that the specification should have done further downstream characterization that a POSA would deem unnecessary. The inventors’ goal was to determine a molecular structure that reliably agonizes Wnt signaling (although such agonism is not required by the claims, which are to the molecular structure itself). In my opinion, the ’278 Patent specification demonstrates that research assignment was completed.

3. The '278 Patent Discloses Structural Features Common to the Full Scope of Claim 1

255. I understand that a patent need not demonstrate a correlation between common structural features and function to satisfy the written description requirement where it discloses a representative number of examples sufficient to convey possession of the claimed invention. *See* ¶ 30, above. Dr. McDonnell's allegation that "the '278 Patent fails to disclose a common structural feature correlating to Wnt signaling activation," EX1002 § IX.A.5, thus does not change my opinion that the '278 Patent's ample representative examples are sufficient to convey the inventors' possession of claim 1's invention to a POSA. Nonetheless, for completeness, here I address Dr. McDonnell's discussion of common structural features in paragraphs 186–196 of his declaration. As I discuss below, Dr. McDonnell misreads the specification's disclosures, which provide no support for his conclusion that "the '278 Patent itself demonstrates the absence of any correlation" between the claimed molecules' structure and their ability to agonize Wnt signaling. *Contra* EX1002 ¶ 186.

256. Dr. McDonnell contends that "[t]he 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." EX1002 ¶ 186. But as discussed above, first, that assertion relies on an untenable interpretation of the claim's final "wherein" clause that lacks any support in the specification, and second, Dr. McDonnell ignores

the features in addition to the claim's "linker" limitation that structurally bound claim 1, including the presence of four antibody-derived binding regions that all share several structural features (*e.g.*, the presence of CDRs that harbor each binding region's binding functionality) recited in the claim. *See* EX1001 at cl. 1; ¶¶ 137–160, 163, above.

257. The specification makes clear that binding regions were "known in the art and ... commercially available" that met claim 1's Fzd- and LRP5/6-functional binding requirements. *See* EX1001 at 79:63–67, 116:25–29. The invention recited in claim 1 is thus a structural one that arranges these binding regions into a tetravalent, antibody-derived, and linker-mediated scaffold, as evidenced by the claim limitations. *See* EX1001 at cl. 1. The '278 Patent discloses that all the molecules that adopted its claimed tetravalent structure activated canonical Wnt signaling. *See* EX1001 at Examples 2–18. By contrast, the '278 Patent tests several molecules that do **not** conform with the claimed tetravalent structure (*i.e.*, those molecules had one Fzd and one LRP5/6 binding region), *see* Fig. 24, below, and were "ineffective" in agonizing canonical Wnt signaling. *See* EX1001 at 158:3–6, 44–47, 159:44–47. A POSA would thus discern that the common structural features running through claim 1 correlate with the molecules' demonstrated Wnt signaling activity.

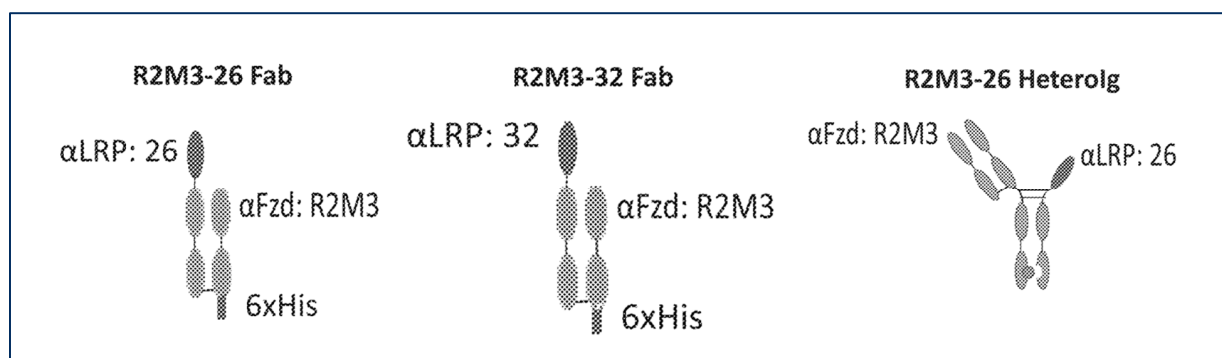


Figure 24: Examples of Molecules Tested in the '278 Patent That Did Not Conform to Claim 1's Structure

258. Dr. McDonnell claims that the '278 Patent fails to disclose a structure–function correlation because, according to him “several molecules ... failed to produce responses in the absence of R-spondin in a TOPFlash assay.” EX1002 ¶ 187. I disagree. *First*, Dr. McDonnell relies on the alleged flat lines on the molecules’ dose–response curves to suggest they “failed to produce responses ... in a TOPFlash assay.” *See* ¶ 198, above. But as discussed above, a POSA would recognize that the flat appearance of the molecules’ dose–response curves could be the result of the scale presented on the graphs rather than any indication of inactivity. *Id.*

259. The specification confirms these allegedly “inactive” molecules were, in fact, active. Example 2 of the specification explains that the R2M3-26 molecule Dr. McDonnell claims is inactive in the absence of R-spondin “induced reporter activity in a dose dependent manner and was *enhanced* by the presence of R-spondin similar to a natural Wnt ligand,” indicating that the molecule produced a response even in

R-spondin's absence. EX1001 at 155:12–40. Example 3 says the same regarding R2M3-32—another one of Dr. McDonnell's purportedly “inactive” molecules. *Id.* at 155:42–156:14. Figure 5 of the patent further demonstrates the activity of these molecules, using *y*-axis scaling that clearly shows a measurable increase in STF reporter activity for these molecules in the absence of R-spondin. *Compare* EX1001 at Figs. 2D (*y*-axis scaled from 0 to 3,500,000 RLU), 3D (*y*-axis scaled from 0 to 2,500,000 RLU), *with id.* at Fig. 5A (*y*-axis scaled from 0 to 25,000 RLU) (reproduced as Fig. 25, below³); *see also* EX2010 ¶ 83.

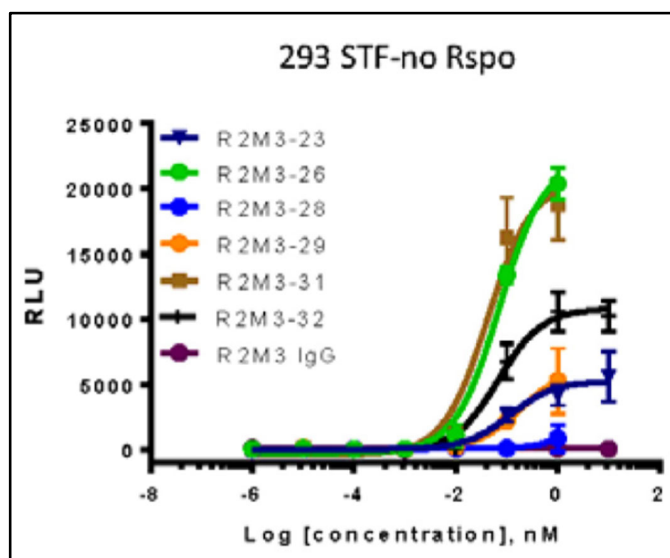


Figure 25: '278 Patent Figure 5A (EX1005 at 42)

³ The figure here is the color version of the '278 Patent's Figure 5A, included in Provisional Application No. 62/607,875 to which the '278 Patent claims priority.

260. Likewise, Example 6 explains that the molecules tested in that example, including the 18R5-28 molecule Dr. McDonnell alleges to be inactive, “demonstrated ability to activate Wnt signaling.” *Id.* at 156:54–67. And Example 13 observes that its various binder combinations, including the allegedly inactive 26-17SB9 molecule, “induced canonical Wnt signaling” in the presence of R-spondin. *Id.* at 158:49–159:3; *see also* EX2010 ¶ 146 (“A person of ordinary skill ... understands that a molecule which activates canonical Wnt signaling in the presence of R-spondin is a Wnt agonist.”), A POSA would thus understand Dr. McDonnell’s purported evidence to indicate an outcome of the scales used in displaying the data rather than an indication of inactivity.

261. The activity of Dr. McDonnell’s purportedly inactive molecules is further confirmed by the fact that as of 2017, it was known that R-spondin cannot on its own **activate** Wnt signaling, but can only **amplify** an existing pathway signal. *See* EX2010 ¶ 146; *see also* EX1001 at 155:29–36, 62–64 (explaining that the Wnt signaling activity of the R2M3-26 and R2M3-32 molecules was **enhanced** in the presence of R-spondin). A POSA would thus understand that “a molecule which activates canonical Wnt signaling in the presence of R-spondin is a Wnt agonist.” *See* EX2010 ¶ 146. And they would therefore understand Dr. McDonnell’s purportedly inactive molecules to activate Wnt signaling at a level masked by the y-axis scale used in the specification’s graphs. *See id.*

262. Because Drs. McDonnell and Kahn wrongly conclude that certain disclosed molecules failed to activate Wnt signaling in the absence of R-spondin, they incorrectly claim that “the inability of these molecules to do so raises serious questions as to whether they can properly be characterized as Wnt ‘surrogates.’” EX1002 ¶ 187. Putting aside that the ability to activate Wnt signaling is not a requirement of the claims, as discussed above, these criticisms are unwarranted because nothing in the specification would convey to a POSA that these molecules were inactive (*see* ¶¶ 200–201, above), and indeed, the presence of a more potent response in the presence of R-spondin indicates the opposite. Dr. McDonnell’s own reference confirms that R-spondin may potently and significantly amplify Wnt signaling induced by endogenous Wnt ligands. *See* Fig. 26, below; EX1093 (Fig. 3). The specification thus creates no “confusion as to what is required to be a Wnt surrogate molecule,” as Drs. McDonnell and Kahn suggest. *Contra* EX1002 ¶ 187.

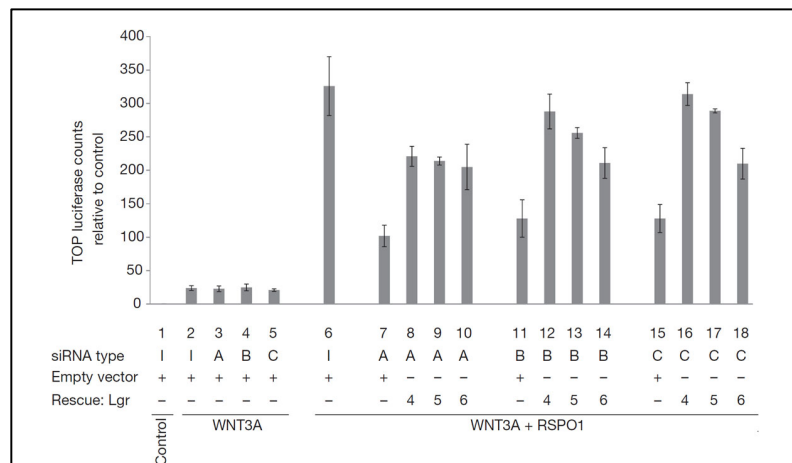


Figure 26: Figure 3 of De Lau (EX1093) Showing Wnt3A Activity in the Presence and Absence of R-Spondin

263. Dr. McDonnell points to what he claims are three additional molecules (R2M3-25, R2M3-27, 1RG05-26) that “failed to activate Wnt signaling.” EX1002 ¶ 188, but again, these conclusions are refuted by the specification’s express statements. Example 5, for instance, discloses that its tested molecules, which include R2M3-25 and R2M3-27, “activated Wnt signaling to various levels,” and Example 8 likewise concludes that its disclosed molecules, including 1RG05-26, “were able to activate Wnt signaling.” EX1001 at 156:32–52, 157:14–29. A POSA would thus rely on those express statements in the specification to conclude that the three molecules activated Wnt signaling without engaging in Dr. McDonnell’s imprecise and speculative visual inspection of dose–response curves.

264. Dr. McDonnell repeats the same error by conducting yet another set of visual dose–response curve inspections, this time on Example 9’s tested molecules. Based on the erroneous premise that the “CL” format of the tested molecules “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),” Dr. McDonnell concludes that “[t]he ’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.” EX1002 ¶ 189. But as discussed above, the specification expressly observes that its tested molecules, which include *all three* tested “CL” formats, “activated Wnt signaling to

various levels.” *See* ¶ 198, above. What Dr. McDonnell calls “unpredictability” in Wnt activity is nothing more than expected variability in the precise level of activity, which says nothing about the claimed molecules’ ability to agonize Wnt signaling in the first instance. *Contra* EX1002 ¶ 189.

265. In sum, Dr. McDonnell fails to demonstrate any “unpredictable variability” demonstrating that a molecule’s ability to activate Wnt signaling “depends on structural features that are neither recited in the claims nor adequately disclosed in the specification.” *Contra* EX1002 ¶ 190. Instead, the specification demonstrates that each of the **90** tested exemplary molecules meeting claim 1’s requirements activated Wnt signaling to various levels. *See* ¶ 106, above.

266. Dr. McDonnell makes much of the specification’s teaching 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 at 157:47–50, equating this statement to an “acknowledgment ... 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,” EX1002 ¶ 190, but that entirely contorts the meaning of the cited sentence. Instead, as discussed above, a POSA would understand from Dr. McDonnell’s purported “acknowledgment” that the *level* of

Wnt signaling induced by the claimed molecules can be altered by modifying attachment location and geometry. *See* ¶ 264, above. And because every single molecule adhering to claim 1’s requirements activated Wnt signaling to some degree, a POSA would understand that claim 1 is unified by a common underlying structure that correlates with its embodiments’ ability to agonize Wnt signaling.

267. Dr. McDonnell points to two other purportedly “confounding factors that affect how each molecule activates [the] Wnt signaling pathway,” but neither factor complicates the structure–function relationship between claim 1 and the specification’s disclosures. *First*, Dr. McDonnell claims that “[t]he specification ... does not teach any common structural feature that confers the ability to ‘simultaneously engage two cell surface coeffector molecules’ (*i.e.*, Fzd and Lrp5/6), EX1002 ¶ 191, but that is precisely what the two Fzd binding regions and two LRP5/6 binding regions recited in claim 1 confer. *See* EX1001 at cl. 1. Dr. McDonnell’s only support for his assertion is his claim that the R2M3-26, R2M3-32, 18R5-23, and 26-17SB9 molecules “failed to produce TOPFlash responses in the absence of R-spondin in a TOPFlash assay,” and that the R2M3-25, R2M3-27, and 1R-G05-26 molecules “failed to produce TOPFlash responses even in the presence of R-spondin,” EX1002 ¶ 191; which is incorrect for the reasons explained above. *See* ¶¶ 259–262, above.

268. *Second*, Dr. McDonnell claims that a “a POSA would not have known how to account for a ‘hook’ effect,” or a relative decrease in signaling at high concentrations of the tetravalent molecule, EX1002 ¶ 192, but a POSA would understand that the “hook” effect is entirely irrelevant to whether a molecule is capable of activating Wnt signaling in the first instance, as the hook effect relates to the concentration-dependent modulation of signaling.

269. Moreover, the figures from the '278 Patent demonstrate that the disclosed molecules not only produced dose-dependent activation at lower concentrations, but also continued to activate Wnt signaling even *after* the hook effect came into play at higher concentrations. *See* Fig. 27, below. Because the '278 patent's claims do not require agonism functionality at any specific concentration under even Dr. McDonnell's “biologically active” construction (or, for that matter, any level of signaling activity), the “hook” effect has no bearing on whether a molecule could function as a Wnt agonist in the first place, and it provides no basis for Dr. McDonnell's conclusion “other, unidentified elements [beyond claim 1's limitations] are required for, and therefore correlated with, ... Wnt agonist functionality.” *Contra* EX1002 ¶ 194.

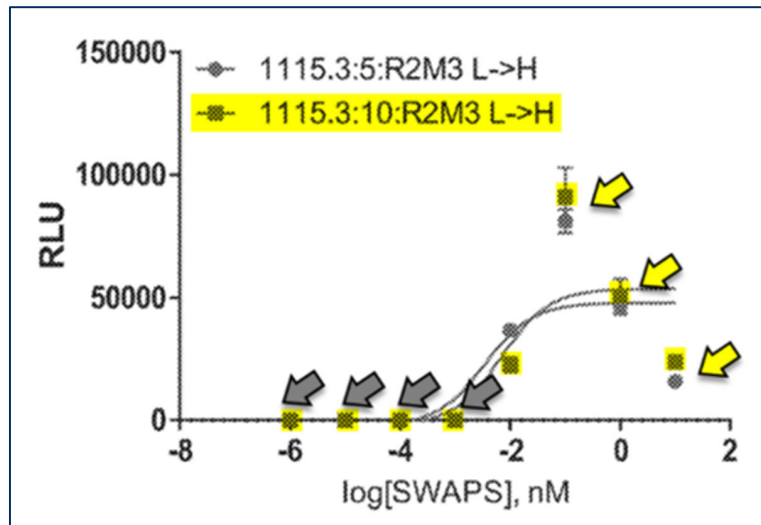


Figure 27: Right Panel of Dr. McDonnell’s Fig. 18, Showing Molecule’s Wnt Signaling Activity Even With the “Hook” Effect

270. *Third*, Dr. McDonnell alleges that “[t]he 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,” but Dr. McDonnell merely refers back to the same figures from Li that he alleges show various inactive molecules. EX1002 ¶ 195.

271. As discussed above, Li demonstrates that Dr. McDonnell’s assertions of inactivity stems from his misinterpretation of a graphical scaling issue rather than any actual demonstration of inactivity. *See* ¶¶ 199, 201, above. Further, as for the molecule 4SC10-3, Li explains only that it was “not able to *effectively* activate beta-catenin-dependent signaling ... *in contrast to the positive control molecule R2M3-26*,” which a POSA would have understood said nothing about whether 4SC10-3 was able to activate Wnt signaling in the first instance. *See* EX1081 at 178; ¶ 222,

above. This factor, too, is neither “confounding” nor provides any confirmation “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.” EX1002 ¶ 194.

272. To summarize, Dr. McDonnell is incorrect that “the ’278 Patent fails to disclose a common structural feature that correlates with” Wnt signaling functionality. *Contra* EX1002 ¶ 186. Rather, assuming Dr. McDonnell is correct that Wnt signaling activity is required by the claims (which I disagree with), claim 1 provides an underlying structural scaffold—a tetravalent molecule with two Fzd and two LRP5/6 binding regions—and the specification demonstrates exhibited signaling activity when applied in **90** different exemplary molecules. A POSA would have understood from this that the structure described in claim 1 is capable of reliably and predictably activating canonical Wnt signaling pathways.

4. Dr. McDonnell’s “Other Reasons” Are Duplicative and Do Not Render the ’278 Patent Deficient

273. In addition to his “other confounding factors,” Dr. McDonnell raises two “other reasons” why he believes the ’278 Patent’s disclosures to be deficient, but they merely restate his prior opinions and are incorrect for the same reasons.

274. *First*, Dr. McDonnell alleges that the specification of the ’278 Patent does not provide adequate written description for the Fzd and Lrp5/6 binding regions recited in claim 1. EX1002 ¶ 197. I disagree. As discussed above, the specification

discloses hundreds of sequences for such binding regions and further explains that such sequences were “known in the art and ... commercially available.” See EX1001 at 79:63–80:15, 116:25–39; ¶¶ 99–111, above.

275. *Second*, Dr. McDonnell claims that “the specification of the ’278 Patent disclose[s] only 17 of th[e] 63 target options as having ‘confirmed binding’ activities.” EX1002 ¶ 198. I disagree with that too, at least because Dr. McDonnell’s “63 target options” unnecessarily complicates matters. There is no question that the specification discloses a representative number of anti-Fzd and anti-LRP5/6 antibodies that bind to *all 10* Fzd receptors and *both* LRP5/6 receptors, in addition to pointing a POSA to those that were “known in the art and ... commercially available.” EX1001 at 79:63–80:15, 116:25–39; ¶¶ 99–111, above.

276. In sum, neither of Dr. McDonnell’s other reasons support his conclusion that claim 1 of the ’278 Patent lacks adequate written description.

5. The Presence of Purportedly Later-Arising Formats Does Not Change My Written Description Opinions

277. As an alternative, Dr. McDonnell contends that if Surrozen disagrees with his proposed construction of the last “wherein clause,” that would “exacerbate the written description problem” by “significantly broaden[ing] 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.” EX1002 ¶ 201. I disagree.

278. The only purported examples Dr. McDonnell identifies—those disclosed in Tao (EX1072)—are supported by the '278 Patent specification. The structures disclosed in Tao are tetravalent molecules consisting of two Fzd binding regions and two LRP6 binding regions. *See* EX1072 at 2. Specifically, two diabodies are connected to either side of a Fc dimer, with one diabody containing both Fzd binders and the other containing both LRP5/6 binders. *See id.* The '278 Patent expressly contemplates that “[i]n certain embodiments, an antibody as described herein is in the form of a diabody,” and also provides an illustrative format of a tetravalent molecule comprising two diabodies fused to a Fc dimer. *See* EX1001 at 14:20–21, Fig. 1D. A POSA would have therefore understood the '278 Patent inventors to be in possession of tetravalent molecules using diabodies, like those described in Tao.

279. Dr. McDonnell alleges that 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,” but as discussed above, a POSA would not understand two binding regions to be “directly connected” if the connection is interceded by a Fc region. *See* ¶ 143, above. Likewise, a POSA would not understand two binding regions to be connected if interceded by a third binding region, and Dr. McDonnell is thus incorrect that the formats in Tao directly link each of the two LRP5/6 binding regions to both Fzd binding regions. Even if Dr. McDonnell were correct, however, the '278 Patent is replete with exemplary embodiments where each of the two

LRP5/6 binding regions is fused via a linker moiety to both Fzd binding regions. *See* ¶ 157, above. A POSA would thus understand the '278 Patent to expressly disclose the same “mode of connection” as that described in Tao.

B. Claims 2–5 Are Supported By Adequate Written Description

1. Claims 2, 3, and 5

280. Claims 2, 3, and 5 recite additional limitations that narrow the scope of claim 1. For example, claim 2 requires 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 at cl. 2. Claim 3 depends from claim 2 and further specifies that the LRP5/6 binding region be “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.” *Id.* at cl. 3. Claim 5 also depends from claim 2 and recites that each of the two LRP5/6 binding regions must be “fused to one of the light chains via a linker moiety.” *Id.* at cl. 5. Because these limitations narrow the scope of claims, while the specification’s abundant disclosures convey possession of the full scope bounded by each of these additional structural limitations, in my opinion, each of these claims is also supported by adequate written description.

281. Dr. McDonnell opines otherwise by restating his criticisms of claim 1, but his assertions are unfounded for the same reasons as discussed with respect to claim 1. For example, Dr. McDonnell alleges that “each of these claims encompasses

trispecific and tetraspecific molecules, whereas all molecules evaluated in the specification are bispecific,” EX1002 ¶ 205, but that assertion is wrong. *See* ¶ 109, above. Likewise, Dr. McDonnell’s assertion that “the disclosed species are limited to only a subset of ... Fzd receptors and combinations,” EX1002 ¶ 205, is incorrect, as the specification discloses Fzd binding regions targeting all ten Fzd receptors, which a POSA would understand to be representative of the full scope of Fzd targets. *See* ¶¶ 208–223, above. And similarly, Dr. McDonnell’s contention that the disclosed linkers are not representative, *see* EX1002 ¶ 205, is undermined by the specification’s disclosures and the prior art. *See* ¶ 230, above.

282. Dr. McDonnell also alleges that the specification “fails to disclose any common structural feature that correlates to the claimed function of Wnt signaling activation,” EX1002 ¶ 206, but he again ignores that *all* exemplary molecules in the specification encompassed by each of the claims activated canonical Wnt signaling. *See* ¶ 106, above. Dr. McDonnell’s assertions again rely on his flawed visual inspection of the dose–response curves of the same allegedly “inactive” molecules that he evaluated with respect to claim 1, which is expressly refuted by the specification’s disclosures, as I discussed above. *See* ¶¶ 198, 258–264, above. Dr. McDonnell is thus incorrect that these molecules “confirm the lack of correlation between the additional features recited in these claims” and the claimed molecules’ Wnt agonist functionality. *Contra* EX1002 ¶ 208.

283. For the above reasons, in my opinion, claims 2, 3, and 5 are supported by adequate written description.

2. Claim 4

284. Claim 4 depends from claim 1 and recites a “pharmaceutical composition comprising a physiologically acceptable excipient, diluent, or carrier, and the Wnt surrogate molecule according to claim 1.” EX1001 at cl. 4. While Dr. McDonnell opines this claim is also invalid, he alleges no other reasons beyond those he sets forth for claim 1 to explain why claim 4 is unsupported by the ’278 Patent’s description. Because Dr. McDonnell has failed to show that claim 1 lacks adequate written description, in my opinion, he likewise fails to demonstrate that claim 4 lacks written description. And because claim 4’s additional limitations beyond claim 1 consist of components of pharmaceutical formulations, such as excipients, diluents, and carriers, expressly discussed in the specification, EX1001 at 133:1–136:38, in my opinion, claim 4 is also supported by adequate written description.

XI. CLAIMS 1-5 ARE ENABLED

A. Claim 1 Is Enabled

285. In paragraphs 211–235 of his declaration, Dr. McDonnell alleges that all five claims of the ’278 Patent are not enabled. For the reasons below, I disagree.

1. Claim 1 Is Structurally and Functionally Bounded in Scope

286. As discussed above in connection with written description, Dr. McDonnell mischaracterizes claim 1 as “exceedingly broad” because it is purportedly “defined

almost entirely by [its] functions of binding to Fzd and LRP5/6 receptor combinations and activating the Wnt signaling pathway.” EX1002 ¶ 4; *id.* ¶ 211. But as I have explained, claim 1 is bounded by several meaningful structural and functional features, including a specific (1) valency, (2) stoichiometry of specific binders, (3) set of structurally similar antibody-derived constituents, and (4) linker requirement. *See* ¶ 163, above. Dr. McDonnell’s characterization of the claims as purely “functional” is thus incorrect. In my opinion, the same limitations that bound the scope of claim 1 for purposes of written description—which are both structural and functional in nature—likewise bound its scope for purposes of enablement.

287. Moreover, as I have explained, Dr. McDonnell’s assertion that “each of the four [Fzd and Lrp5/6] binding regions is defined solely by function, with no limitations on structural features” ignores the claim’s requirement that each binding region comprise “an antibody or antigen binding fragment of the antibody,” EX1002 ¶ 211—structural entities with well-understood and common architectural features, including CDR loops, variable domains, and framework regions. *See* ¶¶ 62–71, 163, 175–181, above; EX1001 at 12:24–13:13. A POSA would thus understand claim 1 to be structurally and functionally bounded, not the open-ended functional genus Dr. McDonnell portrays.

288. Dr. McDonnell’s enablement opinions also reraise his allegations that “there is no structural limitation on the linker moiety itself” in service of his opinion that

claim 1 is “exceedingly broad,” EX1002 ¶ 212, but as discussed above, Dr. McDonnell’s own references confirm that linker moieties of various lengths and compositions were known and incorporated into molecular structures as of 2017, and the patent itself provides numerous examples wherein the linker length was varied. *See* ¶¶ 182–188, above. A POSA would thus not view the diversity of linker compositions and lengths as significantly broadening the scope of claim 1.

289. In addition, Dr. McDonnell repeats his assertion that claim 1 encompasses “over 35,000 target combinations and more than 130 million formats.” EX1002 ¶ 213. But as discussed above, these combinatorial calculations are irrelevant. *See* ¶¶ 161–233, above. A POSA would not evaluate the breadth of claim 1 by exhaustively enumerating every theoretical permutation of binding regions, linker lengths, and topologies; rather, a POSA would recognize that the claim scope is bounded by the specific valency, stoichiometry, and structural constraints recited in the claim. *See* ¶ 163, above. Dr. McDonnell’s inflated estimate thus provides no meaningful measure of claim 1’s breadth, or the amount of experimentation a POSA would need to undertake to practice the invention.

290. Dr. McDonnell reiterates yet another incorrect assertion from his written description opinions in contending that each Fzd and Lrp5/6 binding region featured in claim 1 is “defined solely by function” and that therefore the “total number of Wnt surrogate molecules potentially falling within the scope of the claim is far

greater, and likely indefinite.” EX1002 ¶¶ 211, 213. As discussed at length above with respect to written description, however, the specification makes clear that Fzd and LRP5/6 binding regions were “known in the art and ... commercially available,” and the ’278 Patent itself discloses hundreds of exemplary sequences. *See* ¶¶ 101–105, above; EX1001 at 79:63–66, 116:25–27. Because the claimed invention is a tetravalent molecular structure using these known binding regions—not the binding regions themselves—the diversity of possible antibody sequences does not expand the breadth of claim 1 in the manner Dr. McDonnell suggests. Instead, a POSA would understand claim 1 is to a specific application of two known types of binding regions—two Fzd and two LRP5/6 binding regions—*i.e.*, a tetravalent molecule. *See* ¶¶ 214, 224–232, above.

2. The Specification Provides Ample Working Examples and Guidance

291. As I discussed above in paragraphs 161–278, and as Dr. Willert explains, EX2010 ¶¶ 66–134, the ’278 Patent provides numerous working examples of the claimed molecules across the scope of claim 1. And although not required for purposes of these claims, these examples are no doubt representative of the claimed Wnt surrogate molecules’ ability to activate Wnt signaling, as Dr. McDonnell claims is required. *See id.* Indeed, as I have explained, all 90 molecules in the tetravalent format that were tested by the inventors activated Wnt signaling. *See* ¶ 106, above.

292. Dr. McDonnell nonetheless contends that “compared to the expansive scope of claim 1, the disclosure of the ’278 Patent is simply too narrow,” alleging that “the specification evaluated only 5 of 21 possible topologies and 29 of more than 130 million tetravalent formats.” EX1002 ¶ 214. But as discussed above, these characterizations—premised on a highly inflated and artificial estimate of the number of formats—fundamentally misstate the specification’s disclosures. *See* ¶¶ 161–206, above. The specification tested 90 exemplary tetravalent molecules, and every single one activated Wnt signaling. *See* ¶ 106, above. These working examples span multiple topologies, multiple Fzd and LRP5/6 binding regions, and multiple linker lengths, providing extensive guidance to a POSA on how to make and use the claimed invention. *See* ¶¶ 161–233, above.

293. Dr. McDonnell further asserts that “[a]ll 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.” EX1002 ¶ 214. But as discussed above, each of these assertions is either incorrect or irrelevant. *See* ¶¶ 109, 182–188, 208–223, above. The specification discloses exemplary molecules using all five types of antibody-derived fragments (Fab, Fab’, Fv, scFv, VHH/Nab), targeting 7 of the 10 known Fzd receptors, and employing linkers of varying lengths (5, 10, and 15 amino acids)—and again, in every example, the molecules activated Wnt signaling (which is not required by the claims). *See* ¶¶ 106, 161–233, above.

The specification thus provides ample working examples and guidance across the relevant dimensions of the claimed invention.

294. A POSA would have found the specification's guidance especially valuable in light of the knowledge in the prior art. As I explained above, by 2017, linkers of various lengths, compositions, and flexibilities were standard components of engineered molecules, and in particular, antibody based molecules (as Dr. McDonnell's own references confirm), ¶¶ 182–188, above; binding sequences for targeting Fzd receptors and LRP5/6 “[we]re known in the art and ... commercially available” (and the '278 Patent specification discloses hundreds more), *see* EX1001 at 79:63–66, 116:25–27, Tables 1A–B, 2A–B; and antibody-derived fragments were well characterized and could be interchanged in molecular design. *See* ¶¶ 62–71, 175–181, above. A POSA would thus be able to use the substantial guidance of the '278 Patent, together with the wealth of knowledge in the prior art, to alter the specification's disclosed examples and generate the claimed molecules beyond those disclosed without undue experimentation. That is all the claims require. Even under Dr. McDonnell's view of the claims, a POSA, based on the teachings in the '278 Patent, would have the expectation that these molecules would successfully activate Wnt signaling so long as they adhered to claim 1's requirements. *See* ¶¶ 255–272, above.

295. Dr. McDonnell also incorrectly alleges that “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.” EX1002 ¶ 215. But valency and specificity are at the heart of the claimed invention and the specification’s disclosures. Indeed, claim 1 specifies a valency that all claimed molecules must possess (tetravalence), and also specifies that the claimed molecules must exhibit specificity with one or more Fzd receptors and one or more LRP5/6 coreceptors. *See* EX1001 at cl. 1. And that is precisely what the inventors tested in their examples.

296. As for Dr. McDonnell’s discussion of “flexibility”—which is entirely premised on his speculation that different Fzd and Lrp5/6 expression profiles on different cell types “*may* require a functional Wnt surrogate molecule to have greater flexibility and extended reach to interact effectively with both Fzd and Lrp5/6,” EX1002 ¶ 155—Example 5 of the specification makes clear that the claimed molecules exhibit functionality across cell lines with different expression profiles, obviating the need for a specific “flexibility” to activate Wnt signaling in the first instance. EX1002 ¶ 155. And Examples 9, 13, 14, and 15, among others, demonstrate that the disclosed molecular structures retain their Wnt signaling agonism “to various levels” across variations in binder attachment location, molecular geometry, and linker length. *See* ¶¶ 171–172, above. Dr. McDonnell is thus incorrect that the

specification “provides no indication of which attachment location or geometry for each Fzd and Lrp5/6 pair would confer activation capability,” EX1002 ¶ 215; to the contrary, the specification demonstrates that the claimed molecules are capable of activating Wnt signaling across a range of geometries and attachment locations, and that such considerations may impact signaling potency, not whether they can activate signaling in the first instance. A POSA reading these examples would thus understand how to vary these parameters while retaining Wnt signaling functionality (although such functionality is not required by the claims), without resorting to indiscriminate trial-and-error experimentation.

297. Dr. McDonnell engages in further mischaracterization by claiming that the specification “speculates” that what Dr. McDonnell purports is “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 molecule[])) may impact activation of Wnt signaling.” EX1002 ¶ 216. Dr. McDonnell labels these disclosures as “open-ended suggestions” that are “largely meaningless,” but this characterization does not follow from his perceived breadth of the disclosures. *Id.* To the contrary, a POSA would understand the claimed molecules can span a variety of inter-binder distances,

binding affinities, specific Fzd–Lrp5/6 combinations bound while retaining their Wnt signaling functionality.

298. Indeed, as I explained above, a POSA would not find any of Dr. McDonnell’s cited examples “exceedingly broad.” By 2017, a POSA would have understood that linker length impacts signaling potency, not its ability to activate signaling in the first instance, as evidenced by the disclosures in the ’278 Patent. *See* ¶¶ 182–188, above; EX1001 Example 14 (“While all of these scFv formats activated Wnt signaling, potency and overall maximal efficacy may differ depends on the ... linker length[.]”). Likewise, they would understand “a K_D of 50 μ M or lower” to be a reasonable range for binding affinity by virtue of avidity effects arising from the claimed molecules’ multivalence. *See* ¶ 253, above. And a POSA would appreciate from the specification that any combination of binders targeting the ten Fzd receptors and LRP5/6 in the claimed molecules would activate canonical Wnt signaling, so long as the molecule conformed to the claim’s requirement of two Fzd and two LRP5/6 binding regions. *See* ¶¶ 208–254, above.

299. In light of claim 1’s bounded nature and the state of the prior art, a POSA would thus not find the ’278 Patent’s disclosures to be “simply too narrow,” as Dr. McDonnell suggests. *Contra* EX1002 ¶ 214. Instead, a POSA would recognize the specification provides ample guidance for a POSA to make and use molecules beyond those disclosed in the working examples without undue experimentation.

3. The Relevant Art Was Mature

300. Dr. McDonnell asserts that “the field of multivalent, multispecific antibodies was both nascent and unpredictable in 2017,” and that “the field of Wnt signaling regulation was also nascent and unpredictable.” EX1002 ¶¶ 217–218. But as I have discussed at length above, both of these characterizations are inaccurate. *See* ¶¶ 44–98, above. By 2017, antibody engineering was a mature field with over four decades of research, a robust “toolbox” of well-characterized fragments, linkers, and formats, and routine methods for generating antibodies to particular antigens. *See* ¶¶ 44–88, above. Likewise, the Wnt signaling pathways had been studied for more than 35 years, the receptors, ligands, and messenger molecules involved in these pathways had been identified and characterized, and three separate canonical and noncanonical pathways had been classified. *See* ¶¶ 89–98, above; EX2010 ¶¶ 26–31.

301. Dr. McDonnell points to the fact that “no molecule specifically designed to activate Wnt signaling had received FDA approval by 2017” and that no tetravalent antibody has been approved “even today,” EX1002 ¶¶ 214, 217, but as I discussed above in paragraph 87, no POSA would use FDA approval as a measure for the field’s maturity and predictability.

302. In support of his assertion that “the field of Wnt signaling regulation was ... nascent and unpredictable as of 2017,” Dr. McDonnell claims that “[c]ontemporary review articles characterized the Wnt signaling pathway as exceptionally complex,”

EX1002 ¶ 218, but that language does not appear in any article he cites. For good reason. For instance, it was understood that canonical Wnt signaling is agonized by binding both Fzd and LRP5/6 receptors, EX2010 ¶ 33, which is precisely the mechanism the claimed molecules exploit. *See* EX1001 at cl. 1. By 2017, the sequences of several anti-Fzd and anti-LRP5/6 antibodies and fragments thereof “[we]re known in the art ... and commercially available.” EX1001 at 79:63–66, 116:25–27.

303. While Dr. McDonnell alleges that “cellular context and local environmental conditions could substantially alter the *outcomes* of Wnt signaling,” EX1002 ¶ 218, that purported uncertainty lacks relevance to the claimed molecules, which the inventors showed are able to effectively and reliably *activate* Wnt signaling. *See* ¶¶ 106, 234–271, above; EX1001 at Examples 2–18. And while Dr. McDonnell alleges that “[c]ritical mechanistic questions also remained unanswered,” his sole example of such a “[c]ritical mechanistic question”—“the stoichiometry of the proposed Wnt–FZD–LRP5/6 signaling complex,” EX1002 ¶ 218—does not concern the claimed molecules’ ability to activate Wnt signaling. A POSA therefore would not understand Dr. McDonnell’s purportedly “critical” question to create uncertainty about the ’278 Patent’s claimed invention, whose 2:2 Fzd binder:LRP5/6 binder stoichiometry the inventors repeatedly demonstrated activated Wnt signaling. *See* ¶¶ 106, 234–272, above.

304. Dr. McDonnell also raises a purported “practical limitation[.]”—namely that “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 truly functioned as a Wnt agonist.” EX1002 ¶ 219. But as Dr. Willert has described, and as the patent explains, various different assays existed as of 2017 to measure Wnt signaling. *See* EX2010 ¶¶ 51–65; EX1001 at 117:39-44 (“Various methods are known in the art for measuring the level of canonical Wnt/ β -catenin signaling,” including “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”). In any case, as of 2017, as Dr. Willert explains, the TOPFlash assay, which the inventors used in their examples, was a “well-established[,], accurate[,], and reliable” choice for reliably measuring canonical signaling across a variety of conditions, both *in vivo* and *in vitro*. *See* EX2010 ¶ 56; *see* EX1001 at Examples 2–18. Dr. McDonnell is thus incorrect that this “practical limitation[.]” compounded his purported “scientific uncertainties.” *Contra* EX1002 ¶ 219.

305. Given the wealth of knowledge in and the maturity of the field, a POSA would be able to use the ample guidance of the specification to move beyond the specification’s disclosed examples and practice claim 1’s full scope without the need for trial-and-error experimentation.

4. The Level of Skill in the Art Was High

306. While Dr. McDonnell makes no mention of this factor in his enablement analysis, he asserts that a POSA would at least “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.” EX1002 ¶ 21. Dr. McDonnell also asserts that a POSA “may also have had access to other POSAs with complementary experience in antibody engineering.” *Id.* The level of skill in the art was thus undisputedly high. A POSA would have been familiar with the extensive literature in antibody engineering, under both my definition and Dr. McDonnell’s, and would have been able to apply known antibody-engineering techniques to the field of Wnt signaling pathways.

5. The Amount of Experimentation Required Was Not Undue

307. Given the knowledge in the field and the extensive disclosures in the ’278 Patent, I disagree with Dr. McDonnell that it would have required “undue” experimentation to make and use the full scope of claim 1. EX1002 ¶ 221. A POSA would use the guidance provided in the specification—together with the extensive knowledge available in the art—to design functional tetravalent molecules without resorting to exhaustive trial-and-error experimentation. Therefore, in my opinion, the amount of experimentation required would have in fact been far from undue.

308. Dr. McDonnell contends that “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.” EX1002 ¶ 222. But as I have explained, anti-Fzd and anti-LRP5/6 binding sequences were “known in the art and ... commercially available” as of 2017, *see* EX1001 at 79:63–66, 116:25–27, and the ’278 Patent itself discloses hundreds of such sequences with confirmed binding to their respective targets. *See* ¶¶ 101–105, above. A POSA would thus not need to generate binding sequences *de novo*; rather they could use known binding sequences disclosed in the specification and in the prior art, whether on their own or as starting points. Indeed, because claim 1 does not claim anti-Fzd and anti-LRP5/6 antibodies *themselves*, but rather incorporates them into a specific structure (i.e., a tetravalent molecule), and because anti-Fzd and anti-LRP5/6 binding regions were already well known and commercially available, undertaking to find them all would in essence be tangential to the focus of the claimed invention.

309. Moreover, generating antibodies to particular targets was well within a POSA’s capabilities in 2017, as the ’278 Patent itself makes clear. *See* EX1001 at 13:55–64, 14:42–47, 126:11–127:15; ¶¶ 46–54, above. Dr. McDonnell’s observation that this process was “both time and resource intensive,” EX1002 ¶ 222, was rapidly becoming a thing of the past. With the advent and widespread commercial availability of next generation sequencing (NGS) sequencing antibodies

in the 2010s, the throughput of antibody screening methods increased exponentially. By 2017, a POSA could thus screen *tens of billions* of antibodies at the same time to identify those that bound a target antigen, and then simultaneously sequence them in the millions using NGS to identify their amino acid sequences. *See* ¶¶ 49–50, above. A “reliable method for predicting, from amino acid sequence alone, whether an antibody would bind a desired target antigen” was thus not necessary in 2017 to identify antibodies that successfully bound a target antigen in a short amount of time. *Contra* EX1002 ¶ 222. Dr. McDonnell is thus incorrect that “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.” *Contra* EX1002 ¶ 224.

310. Dr. McDonnell alleges that “[t]he ’278 Patent illustrates the iterative nature of this process,” pointing to two of the **448** sequences listed in Table 1A that showed initial binding but did not show confirmed binding. EX1002 ¶ 225. But he ignores that more than two-thirds of tested initial binding antibodies also exhibited confirmed binding, underscoring the high degree of success a POSA would have experienced in 2017. As for his assertion that this process would need to be extended “across the more than 35,000 distinct Lrp-Fzd target combinations encompassed by claim 1,” *id.* that represents a vast double-counting of targets that would need to be screened at the antibody binder stage. *See* ¶ 212, above. For example, a POSA identifying an anti-Fzd2 binder to be used in combination with an anti-Fzd3 binder

and two anti-LRP5 binders would not need to follow a separate generation process than if they were identifying an anti-Fzd2 binder to be used in combination with another anti-Fzd2 binder and two anti-LRP5 binders, but Dr. McDonnell’s 35,000 estimate counts these as separate “target combinations.”

311. In any event, as explained above, this antibody generation exercise—which Dr. McDonnell perceives to be a “substantial amount of work,” EX1002 ¶ 226—would be akin to extra credit in the context of the ’278 Patent’s invention, which combines two groups of antibodies that were “known in the art and ... commercially available” as of 2017 in a specific, tetravalent application. EX1001 at 79:63–66, 116:25–27. Dr. McDonnell thus proceeds to identify other purported difficulties in generating tetravalent, multispecific formats, which he claims “would have been a particularly difficult task as of 2017” owing to challenges such as chain mispairing. EX1002 ¶ 226. But as I discussed above, by 2017, well-established strategies for addressing these challenges were available, including “knob[s]-in-holes” methods for promoting heavy-chain heterodimerization and “CrossMab” methods for addressing light-chain mispairing. *See* ¶¶ 81–82, above; EX1001 at 18:6–25. Alternatively, scaffolds such as diabodies were available that inherently prevented mispairing. *See* ¶¶ 81–82. None of this would have been undue experimentation to a POSA. Indeed, the specification itself demonstrates the successful assembly of 90

tetravalent molecules, further confirming that a POSA would be capable of assembling such molecules without undue experimentation.

312. Dr. McDonnell presses two assertions that he claims support his contention that mispairing was an issue in 2017, but both mischaracterize the reference they cite as support. *First*, Dr. McDonnell claims that “light-chain mispairing ... remained a persistent and significant problem” and cites to a review article by Brinkmann et al. for that proposition. EX1002 ¶ 227. But nowhere does Brinkmann state that light-chain mispairing was a “persistent or significant” problem. Instead, the article summarizes at least seven different methods that had been developed by 2017 to **prevent** light-chain mispairing, including CrossMab, TCR CαCβ, and MUT4 strategies. *See* EX1017 at 12. *Second*, Dr. McDonnell alleges, with reference to a review by Spiess et al., that “[a]ddressing these issues often required ‘sophisticated upfront engineering,’ and even then the assembly of tetravalent, multispecific formats was ‘not invariably successful.’” EX1002 ¶ 227. But Dr. McDonnell selectively quotes descriptions Spiess provided of **two specific strategies** to avoid mispairing issues—DutaMabs and “two-in-one” antibodies. EX1069 at 5. Speaking more generally about light chain-pairing issues, Spiess explains that “[s]everal **robust strategies have been developed to overcome the BsIgG heavy ... and light chain ... pairing problems,**” and that light chain mispairing “can be **obviated**” using these strategies. *Id.* And in any event, a POSA would not demand “invariabl[e]

success[],” even as to those strategies that required “sophisticated upfront engineering,” as Dr. McDonnell suggests. *Contra* EX1002 ¶ 227.

313. Dr. McDonnell is thus incorrect that “producing sufficient quantities of even a single correctly assembled molecule for testing was challenging,” EX1002 ¶ 227; to the contrary, by 2017, several strategies were available and part of the “extensive and versatile toolbox” at an antibody engineer’s disposal to make and use various molecular structures. EX1017 at 3; ¶¶ 72–88, above. This is further evidenced by the 90 exemplary molecules the inventors of the ’278 Patent were able to produce, test, and disclose in the patent’s specification. *See* EX1001 at Examples 2–18.

314. To try and maximize the degree of experimentation needed, Dr. McDonnell claims that “[s]caling 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.” EX1002 ¶ 227. But that erroneously presumes a POSA would need to make and use *every single* possible embodiment of the claimed invention.

315. Dr. McDonnell proceeds to shift to various perceived criticisms with TOPFlash assays, none of which raises the level of experimentation required to make and use the claimed invention. *First*, Dr. McDonnell claims that because the TOPFlash assay only measures canonical Wnt signaling, “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.” EX1002 ¶ 228. But as I explained above, a POSA would understand the claimed molecules to possess functionality in activating *canonical* Wnt signaling, and therefore the level of experimentation needed to further characterize the claimed molecules for their ability to activate *non*-canonical signaling has no bearing on the level of experimentation needed to use the claimed invention. See ¶ 96, above.

316. *Second*, Drs. McDonnell and Kahn take issue with the fact that a candidate molecule could purportedly “produce inconsistent responses depending on the assay and experimental conditions, making the determination of Wnt signaling activation even more difficult,” which allegedly “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.” EX1002 ¶ 229. But those assertions focus on factors that influence the magnitude of the signaling response, not whether the disclosed molecules are capable of activating Wnt signaling. Differences in a molecule’s magnitude of induced Wnt signaling in different cell types, at different concentrations, and in the presence or absence of potentiators would all be downstream considerations to whether activation occurs in the first instance, and would thus have no relevance to the ’278 patent’s claims under even Dr. McDonnell’s “biologically active” construction. Moreover, Drs. McDonnell and Kahn ignore that these considerations would be guided by a POSA’s specific design

interests and goals, rather than forcing a POSA to blindly test the claimed molecules across every cell type, molecular concentration, and potentiator context. *See* ¶ 211, above.

317. Dr. McDonnell concludes by speculating that practicing the full scope of claim 1 would require “more than 26,000 years’ worth of work.” EX1002 ¶ 230. But as Dr. Willert explains, that estimate is based on the unreasonable and flawed assumption that *one* person would need to test *every single one* of the purported 130 million different tetravalent formats encompassed by claim 1 in an iterative fashion (i.e., by running a single assay consecutively week after week) to make and use *any one* molecule falling within the claims. *See* EX2010 ¶¶ 163–166. A POSA would not proceed using this unnatural, exhaustive methodology that tests every conceivable format, nor would they run single assays back-to-back (which is where Dr. McDonnell gets his “26,000 years’ worth of work” metric). Instead, armed with the specification’s guidance, the prior art, and their own expertise, a POSA would design molecules guided by the structural and functional parameters disclosed in the specification—*e.g.*, valency, stoichiometry, binding region identity, and linker design—and would rely on the specification’s demonstration that the claimed tetravalent scaffold reliably agonizes Wnt signaling. And even if a POSA set out to make and test hundreds or thousands of molecules, they would not do so one-by-

one, but would rather run multiple, high-throughput assays simultaneously. Dr. McDonnell's suggestion otherwise ignores laboratory basics.

318. For at least the above reasons, Dr. McDonnell's opinion that "practicing the full scope of the claimed tetravalent, multispecific Wnt surrogate molecules would have required undue experimentation," EX1002 ¶ 231, is incorrect and notable for its theoretical and combinatorial assumptions, which strip away the practical considerations that govern how a POSA would design and evaluate such molecules. Given the nature of molecular design and the wealth of knowledge in the '278 Patent's specification and the prior art, a POSA would be able to make and use any molecule falling within the scope of the claims without undue experimentation.

6. The Presence of Purportedly Later-Arising Formats Does Not Change My Enablement Opinions

319. Dr. McDonnell also argues that a broader construction of the last "wherein" clause would "further exacerbate the enablement problem" because it would "cover Wnt surrogate molecules with tetravalent formats that were unknown to a POSA in 2017." EX1002 § X.A.5, ¶ 232. But as discussed above, the formats Dr. McDonnell alleges were "unknown to a POSA in 2017," EX1002 ¶ 232, are supported by the description of the '278 Patent. *See* ¶¶ 277–279, above. Dr. McDonnell's contention that any construction other than his own would "exacerbate" any perceived "enablement defect" is thus incorrect, as demonstrated by my discussion above of

the ample guidance in the specification that would permit a POSA to practice the full scope of claim 1 without undue experimentation.

B. Claims 2–5 Are Enabled

320. Dr. McDonnell alleges that claims 2–5 are also not enabled, *see* EX1002 ¶¶ 233–234, but his arguments merely restate those he advanced with respect to claim 1. As discussed above, claims 2, 3, and 5 recite additional limitations that narrow the scope of claim 1, and claim 4 adds pharmaceutical formulation components. *See* ¶¶ 280, 284, above. Because Dr. McDonnell has failed to demonstrate that claim 1 lacks enablement, he likewise fails to demonstrate that these dependent claims are not enabled. Moreover, Dr. McDonnell’s specific assertion that multiple molecules satisfying the additional limitations of claims 2, 3, and 5 “failed to produce TOPFlash responses,” EX1002 ¶ 234, is, as discussed above, based on his flawed visual inspection of dose–response curves and is refuted by the specification’s express statements. *See* ¶¶ 198, 258–264, above.

321. Claim 4 recites a pharmaceutical composition comprising “a physiologically acceptable excipient, diluent, or carrier” and the Wnt surrogate molecule according to claim 1. EX1001 at cl. 4. As with written description, Dr. McDonnell alleges no other reasons beyond those he sets forth for claim 1 to explain why claim 4 is not enabled. Because Dr. McDonnell has failed to show that claim 1 is not enabled, he likewise fails to demonstrate that claim 4 is not enabled. Moreover, the additional

limitations of claim 4—excipients, diluents, and carriers—are components of pharmaceutical formulations whose preparation is disclosed in the '278 Patent. *See* ¶ 284, above; EX1001 at 133:1–136:38. In my opinion, claims 2–5 are therefore enabled.

XII. CLAIMS 1-5 ARE DEFINITE

A. “Wnt Surrogate Molecule” Has Reasonable Certainty

322. Dr. McDonnell opines that the term “Wnt surrogate molecule” as used in claims 1–5 renders the claims indefinite because it “fails to provide a POSA with reasonable certainty” on how to determine whether “a candidate molecule is [a] ‘Wnt surrogate molecule’ *that is ‘biologically active ... in activation of Wnt signaling, i.e., the Wnt surrogate molecule is a Wnt agonist.’*” EX1002 ¶ 236. But as I explained above, that purported problem is one of Dr. McDonnell’s own making, not the inventors’, as Dr. McDonnell improperly imports a requirement that a “Wnt surrogate molecule” be “biologically active” where neither the claims nor the specification support that reading. *See* ¶¶ 127–136, above.

323. In any event, even assuming Dr. McDonnell’s interpretation of the term Wnt surrogate molecule is correct (which it is not), Dr. McDonnell’s assertion that “biological activity in activation of Wnt signaling can depend on a range of factors,” EX1002 ¶ 236, does not support his claim that a POSA would not understand the meaning of “biological activity” in the first place. And Dr. McDonnell’s allegations

that “there was no standard assay to determine biological activity in activating Wnt signaling” and that the specification purportedly discloses “multiple conflicting assays and assay conditions that lead to different results,” EX1002 ¶ 236, are both inaccurate and ignore the specification’s detailed guidance about measuring Wnt agonist activity. I therefore disagree with Dr. McDonnell’s opinion that claims 1–5 are indefinite.

324. In my opinion, even assuming the term “Wnt surrogate molecule” requires that the molecule be biologically active (a premise that, again, I disagree with), the specification clearly explains how to determine if a molecule is “biologically active.” In the same portion of the specification that Dr. McDonnell cites as allegedly supporting his construction of Wnt surrogate molecule, the ’278 Patent explains that “the Wnt agonists disclosed herein activate, enhance, or increase the canonical Wnt/[β]-catenin signaling pathway,” and then defines “enhances” as “a measurable increase in the level of Wnt/[β]-catenin signaling compared with the level in the absence of a Wnt, e.g., a Wnt surrogate molecule disclosed herein.” EX1001 at 16:64–17:2. This is further reinforced by the specification’s evaluation of enhancement of canonical Wnt pathway signaling by comparison to “a neutral substance or negative control.” EX1001 at 118:37–44. A POSA would thus understand a given molecule to be “biologically active” if it effects “a measurable

increase in the level of Wnt/[β]-catenin signaling” in comparison with the level of canonical signaling in the molecule’s absence.

325. To that end, the specification provides several ways to measure canonical signaling:

Various methods are known in the art for measuring the level of canonical Wnt/ β -catenin signaling. These include, but are not limited to assays that measure: 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. The canonical Wnt/[β]-catenin signaling pathway ultimately leads to changes in gene expression through the transcription factors TCF7, TCF7L1, TCF7L2 (a.k.a. TCF4), and LEF. The transcriptional response to Wnt activation has been characterized in a number of cells and tissues. As such, global transcriptional profiling by methods well known in the art can be used to assess Wnt β -catenin signaling activation or inhibition.

EX1001 at 117:39–52.

326. Of these methods, the specification uses the TOPFlash assay to measure Wnt signaling activation in its working examples. I understand from Dr. Willert that as of 2017, TOPFlash was a well-established, accurate, and reliable choice for

measuring canonical Wnt signaling activation, and was capable of doing so both *in vivo* and *in vitro*. See EX2010 ¶ 56. The specification provides detailed background on the TOPFlash assay:

Changes in Wnt-responsive gene expression are generally mediated by TCF and LEF transcription factors[.] A TCF reporter assay assesses changes in the transcription of TCF/LEF controlled genes to determine the level of Wnt/ β -catenin signaling. A TCF reporter assay was first described by Korinek, V et al. 1997. Also known as TOP/FOP this method involves the use of three copies of the optimal TCF motif CCTTTGATC, or three copies of the mutant motif CCTTTGGCC, upstream of minimal c-Fos promoter driving luciferase expression (pTOPFI_ASH and PFOPI_ASH, respectively) to determine the transactivational activity of endogenous [β]-catenin/TCF4. A higher ratio of these two reporter activities (TOP/FOP) indicates higher β -catenin/TCF4 activity, whereas a lower ratio of these two reporter activities indicates lower β -catenin/TCF4 activity.

EX1001 at 117:53–67.

327. Given the extensive disclosure in the specification on canonical Wnt signaling measurement methods, a POSA would understand that the “biological activity” of a molecule could be determined using a TOPFlash assay to detect a

measurable increase in the level of canonical Wnt signaling in the presence of the molecule as compared to the level of canonical Wnt signaling in its absence.

328. Drs. McDonnell and Kahn allege that “the Wnt signaling pathway is complex, involving multiple ligands and receptors that interact simultaneously,” and that “the identity, receptor specificity, and concentration of potential Wnt agonists could affect their biological activity in activation of Wnt signaling.” EX1002 ¶ 237. But those assertions provide no explanation why a POSA would be incapable of determining whether a Wnt surrogate molecule is “biologically active” in the first place. Indeed, even assuming Drs. McDonnell and Kahn are correct that “Wnt and non-Wnt ligands could exert different effects depending on tissue, cell type, and development stage,” it does not follow that a POSA would be unable to determine whether the claimed molecules are biologically active when applied to a *specific* “tissue, cell type, and development stage.” To the contrary, the specification provides several different methods of evaluating Wnt signaling activity, and extensively illustrates the use of what was known in 2017 as a “well-established[,] accurate[,] and reliable indicator of canonical Wnt activity”—the TOPFlash assay, EX2010 ¶ 56—across different cell lines derived from different tissues in its working examples. *See* EX1001 at Examples 2–18, Figs. 2–18.

329. Drs. McDonnell and Kahn’s assertion that “no single assay was universally applicable to all Wnt systems for determining pathway activation,” EX1002 ¶ 238,

fails to support their indefiniteness allegations for the same reasons. The fact that “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,’” *id.*, does not negate the fact that as of 2017, these methods could be used in any given biological context to determine whether a given Wnt surrogate is biologically active.

330. Drs. McDonnell and Kahn criticize the TOPFlash assay and other canonical assays for not measuring “the activation of *noncanonical* signaling.” *See e.g.*, EX1002 ¶ 238. But a POSA would understand from the specification that the claimed molecules were designed to agonize *canonical*, rather than noncanonical, signaling. For example, the specification begins by explaining that “[*c*]/*anonical Wnt signals* ... involve Low-density lipoprotein (LDL) receptor-related protein 5 (LRP5) or Low-density lipoprotein (LDL) receptor-related protein 6 (LRP6) as co-receptors ... in addition to Fzds,” and a POSA would recognize that the claimed molecules accordingly comprise binding regions for both Fzd and LRP5/6. EX1001 at 1:54–59. Moreover, the specification expressly notes that “the Wnt surrogate molecules of the invention enhance the *canonical* Wnt/ β -catenin signaling pathway.” *Id.* at 117:33–35. The ability of canonical assays to measure noncanonical activity and vice versa thus has no bearing on whether a POSA would be able to determine

whether the claimed molecules are biologically active in agonizing *canonical* Wnt signaling.

331. Drs. McDonnell and Kahn also reference a study involving Wnt5 (Mikels, EX1056) that they purport demonstrate 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,” EX1002 ¶ 238, but that reading of Mikels is misleading. Mikels was not concerned with, nor did it show, any purported variability in Wnt signaling reporting *depending on the assay* deployed to measure it; instead, the study explained that “one Wnt ligand can function in *two discrete pathways* based on receptor availability”—one, the canonical Wnt signaling pathway involving dimerization of Fzd4 and LRP5, which agonized Wnt signaling, and the other, a wholly distinct pathway mediated by Ror2 instead of Fzd and LRP dimerization, which decreased the level of Wnt signaling observed by Wnt3a activation of the canonical pathway. EX1056 at 11; Fig. 28, below.

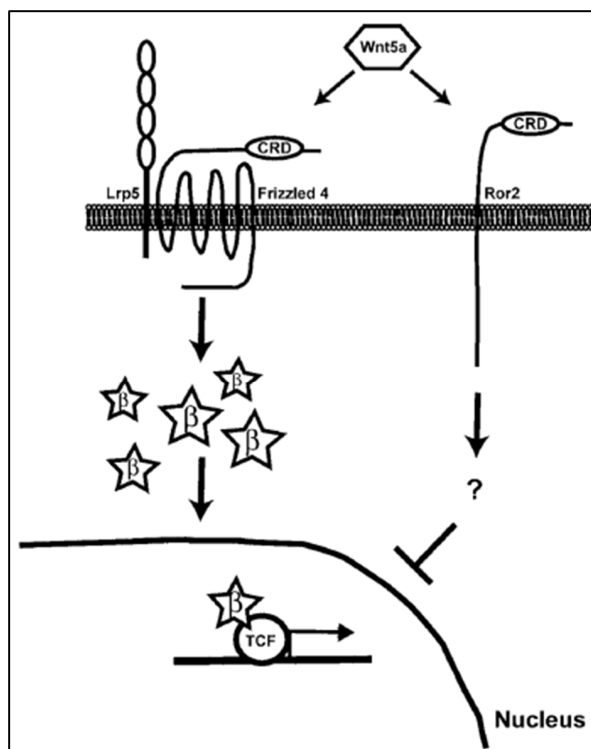


Figure 28: Figure 7 from Mikels (Ex. 1056) Showing that Wnt5a’s Inhibitory Activity Is Mediated by Ror2, Not Fzd and LRP5/6

332. Given Mikels’s findings, Drs. McDonnell and Kahn are incorrect that the study illustrated that a molecule’s biological activity depends “entirely on the assay and assay conditions used, rather than on any inherent property of the molecule itself.” EX1002 ¶ 238. For one, a POSA would understand that the Ror2-mediated pathway that inhibits Wnt signaling is entirely irrelevant to the claimed invention, which does not require binding regions that are capable of binding Ror2. *See* EX2010 ¶ 35. In fact, a POSA would understand that it is precisely Wnt5a’s ability to engage receptors involved in both pathways that confers its ability to act as both an agonist and an inhibitor in different receptor contexts, underscoring, contrary to

Dr. McDonnell, that these properties *are* “inherent ... [to] the molecule itself.” *Contra* EX1002 ¶ 238. Moreover, a POSA would not understand Wnt5a’s behavior to have somehow arisen from the assay used rather than Wnt5a’s molecular properties, much less reflect any shortcomings about Wnt signaling measurement methods. If Drs. McDonnell and Kahn were correct that the signaling activity described in Mikels arose “entirely [from] the assay and assay conditions,” EX1002 ¶ 239, Mikels would not have been able to reach any conclusion about Wnt5a’s behavior in different receptor contexts. Given Mikels’s conclusion from their TOPFlash studies that “we show one ligand can function in two discr[ete] pathways based on receptor availability,” EX1056 at 11, a POSA would understand Drs. McDonnell and Kahn’s conclusion to be inaccurate.

333. Mikels, in fact, uses precisely the same assay as disclosed in the ’278 Patent. For example, Figure 4B of Mikels used the STF (SuperTopFlash) method to report changes in STF reporter levels caused by Wnt5a in cells expressing only Fzd4 in comparison with those co-expressing Fzd4 with LRP5. *See* Fig. 29, below. The figure makes clear that when LRP5 was coexpressed, the presence of Wnt5a measurably increased STF reporter levels as compared to in its absence. Based on that data, the study concluded that “*Wnt5a treatment activates the STF reporter when LRP5 is coexpressed.*” EX1056 at 7. Mikels thus underscores that a POSA had a clear way to determine from a TOPFlash assay whether a ligand activates Wnt

signaling—*i.e.*, by identifying “a measurable increase in the level of Wnt/[β]-catenin signaling compared with the level in the absence of a Wnt agonist.” EX1001 at 117:35–39.

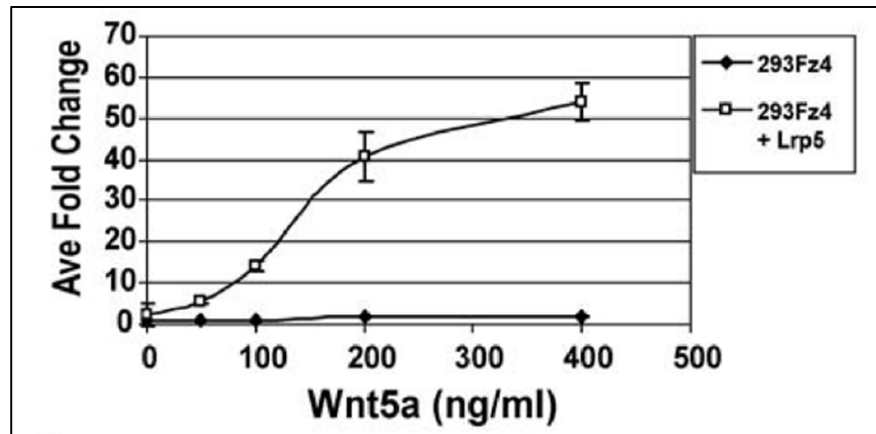


Figure 29: Figure 4B from Mikels (EX1056) Using STF Assay to Measure Wnt5a’s Ability to Activate Canonical Wnt Signaling

334. Drs. McDonnell and Kahn nonetheless allege that the specification “compounds” the purported ambiguity regarding Wnt signaling activation assays in two ways—first, by allegedly “defining the Wnt signaling pathway as either ‘a canonical Wnt signaling pathway *or* a non-canonical signaling pathway,’” and, second, by “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.*” EX1002 ¶ 239. Neither is accurate. *First*, as discussed above, the specification expressly notes that “the Wnt surrogate molecules of the invention enhance the *canonical* Wnt/ β -catenin signaling pathway,” obviating any purported confusion as to the pertinent signaling pathway to measure. EX1001 at 117:33–35.

Second, while the specification describes a number of possible assays that were known in the art and could be used to measure Wnt signaling activity, it directs POSAs to use the TOPFlash assay by using it to measure the activity of each of its 90 disclosed exemplary molecules. *See* EX1001 at Examples 2–18, Figs. 2–18. Drs. McDonnell and Kahn’s inaccurate assertions that “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” thus does not detract from the fact that the specification provides a clear method for determining whether a given molecule is “biologically active” under Dr. McDonnell’s view of the claims. EX1002 ¶ 239. In any event, Dr. McDonnell’s only support for this allegation draws from statements made by Dr. Kahn, *see id.* (quoting EX1003 ¶¶ 19, 121, 144–55), which, as Dr. Willert explains, fail to provide any evidence of “inconsistent results.” *See* EX2010 ¶¶ 135–151.

335. Dr. McDonnell himself acknowledges that “the ’278 Patent employed a TOPFlash assay most frequently,” but criticizes the results disclosed in the patent for not including “a biologically relevant positive control, such as a Wnt protein.” EX1002 ¶ 240. Given his position that it is impossible to determine with certainty whether a molecule is “biologically active,” it is unclear how Dr. McDonnell would have a POSA determine what constitutes a “biologically relevant positive control.” Moreover, Dr. McDonnell’s criticism assumes that a POSA would not know if a

given molecule is a Wnt agonist without comparing its activity to that of, e.g., a natural “Wnt protein,” *id.*, but, as Dr. Willert explains, that assumption is supported nowhere in the ’278 Patent. *See* EX2010 ¶¶ 136–142. The ’278 Patent instead sets forth an altogether different reference point to evaluate whether a molecule is a Wnt agonist—by comparing its activity to that “in the absence of a Wnt agonist.” EX1001 at 16:65–17:2; EX2010 ¶ 137. A POSA would thus understand a positive control or threshold to be unnecessary in determining whether a given molecule is “biologically active,” which as discussed, provides a clear benchmark for biological activity.

336. In that context, the ’278 Patent’s TOPFlash assay results contain sufficient information for a POSA to determine whether a given molecule is “biologically active.” For instance, Example 5 of the specification uses three control molecules that did not contain **both** Fzd and LRP5/6 binding regions—R2M3-24 and R2M3-34, which comprise “non-LRP6 binder Nabs” and R2M3 IgG, which is an IgG with only anti-Fzd binding regions. *See* EX1001 at 155:34–36, 156:45–47. The specification reports that these control molecules “displayed no activity in Wnt dependent 293 reporter assay,” while the exemplary tetravalent molecules—those with two Fzd and two LRP5/6 binding regions—“activated Wnt signaling to various levels.” *Id.* at 156:43–45, 47–48. The specification is thus clear that the disclosed exemplary claimed molecules displayed a “measurable increase,” *i.e.*, via the

TOPFlash assay, “in the level of Wnt/ β -catenin signaling compared with the level in the absence of a Wnt surrogate molecule of the invention.” *See* EX1001 at 117:35–38.

337. Notwithstanding the '278 Patent's express disclosures, Dr. McDonnell alleges that a “lack of certainty is evident in the candidate molecule ‘18R5:Fc:111.3,’” which he alleges produced a “minuscule” TOPFlash reporter response. EX1002 ¶ 241. But Dr. McDonnell's characterization of the molecule's response as “minuscule” does not support his conclusion that the '278 Patent—whose claims do not specify a threshold minimum level of activity—“fails to provide a POSA with reasonable certainty as to whether this response satisfies the requirement for a ‘biologically active’ Wnt surrogate molecule.” *Id.* To the contrary, as Dr. McDonnell acknowledges, the specification expressly “describes this molecule as ‘activat[ing] Wnt signaling,’” *id.*, unequivocally indicating that it produced a measurable increase in Wnt signaling activity, as measured using the TOPFlash method, as compared to the lack of activity displayed by the non-agonists tested. A POSA would thus experience no uncertainty in concluding that the 18R5:Fc:1115.3 activated Wnt signaling based on the specification's express disclosures.

338. Drs. McDonnell and Kahn opine further that the specification's characterization, purportedly “based solely on the positive responses observed in the

presence of R-spondin,” that the tested exemplary molecules “induc[ed] canonical Wnt signaling” creates ambiguity as to whether these molecules qualify as ‘Wnt surrogate molecules.’ EX1002 ¶ 242. Those assertions suffer from the same defects discussed above. *First*, these assertions again rest on the unfounded assumption that a molecule is not biologically active if it behaves “unlike natural Wnt and non-Wnt ligands,” EX1002 ¶ 242—a requirement which, as discussed above, is unsupported by the specification. *See* ¶ 335, above. *Second*, Drs. McDonnell and Kahn’s opinions are also premised on their similarly unsupported allegation that “several candidate molecules disclosed in the specification (R2M3-26, R2M3-32, 26-17SB9) failed to produce responses in the absence of R-spondin.” EX1002 ¶ 242. As I explained above, Drs. McDonnell and Kahn engage in a flawed visual inspection of dose–response curves that ignores that the specification expressly states that these molecules activated Wnt signaling “to various levels,” even in the absence of R-spondin, and a POSA would thus not understand these molecules to have “failed.” *See* ¶¶ 198, 258–262, above. This is especially so because Drs. McDonnell and Kahn omit that R-spondin can only *amplify* already existing activity; it cannot activate Wnt signaling on its own. *See* ¶ 261, above. A POSA would thus understand that the presence of R-spondin in the specification’s testing of R2M3-26, R2M3-32, and 26-17SB9 only increased the amplitude of these molecules’ Wnt signaling activity and

thus confirms that the claimed molecules exhibited Wnt signaling activity in the first instance. *See* EX2010 ¶¶ 143–147.

339. Drs. McDonnell and Kahn next seek support for their opinions by claiming that “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 Fz/Lrp molecules expressed in the tissue of interest,” EX1002 ¶ 243, but they again rely solely on a visual inspection of the ’278 Patent’s figures showing differences in the activity levels between cell lines while ignoring the specification’s express disclosure that the molecules tested in those figures “demonstrated ability to activate Wnt signaling.” *See* EX1001 at 156:64–67. In any event, the ’278 Patent’s claims do not require that their recited molecules activate Wnt signaling at all, let alone in *every* circumstance, or for that matter, in *any particular* circumstance. *See* EX1001 at cl. 1. A POSA would thus understand that a Wnt molecule’s ability to activate Wnt signaling in any single context suffices to demonstrate that the molecule is a Wnt surrogate molecule under Dr. McDonnell’s view of the claims.

340. Dr. McDonnell’s opinion that “assay outcomes depend on concentration and can behave unpredictably rather than in a consistent dose-dependent manner,” EX1002 ¶ 244, is unsupported for the same reason. For one, Dr. McDonnell’s speculation that “assay outcomes ... *can* behave unpredictably rather than in a consistent dose-dependent manner,” *id.*, lacks any support in the specification. To

the contrary, Examples 2 and 3 of the patent, for instance explain that their respective tested molecules “induced reporter activity *in a dose dependent manner.*” EX1001 at 155:12–156:14. But in any event, because the claims do not demand Wnt signaling activation at *every* concentration, or for that matter at *any given* concentration, a POSA would understand that a molecule qualifies as a Wnt surrogate so long as it activates Wnt signaling at any single concentration or range of concentrations. And while Dr. McDonnell contends that “[t]he 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,’” EX1002 ¶ 244, that is irrelevant because it would impose no uncertainty on a POSA in determining whether a molecule is “biologically active” or what the term “biologically active” means in the first place.

341. For the same reason, Dr. McDonnell’s discussion of “hook” effects, EX1002 ¶ 245, likewise has no bearing on whether a POSA could determine whether a given molecule is “biologically active.” *First*, as discussed above, Dr. McDonnell’s characterization of the “hook” effect as a phenomenon that causes molecules to “unpredictably lose agonistic activity at higher concentrations” is incorrect because the specification itself demonstrates that molecules were capable of agonizing Wnt signaling even after any “hook” effect came into play. *See* ¶¶ 268–269, above. *Second*, Dr. McDonnell’s implication that molecules that exhibit a “hook” effect “do

not behave in a dose-dependent manner” is incorrect because, as Dr. McDonnell himself concedes, the “hook” effect is directly tied to the concentration of the tetravalent molecule introduced into the system. *See* EX1002 ¶ 192. *Third*, and as with Dr. McDonnell’s other criticisms, because the ’278 Patent’s claims do not require their claimed molecules to be “biologically active” at every possible concentration, a POSA would not need an “explanation for how such effects should be interpreted or accounted for” to determine whether a particular molecule is “biologically active” at any single concentration or range of concentrations. *Contra* EX1002 ¶ 245.

342. To summarize, to the extent Drs. McDonnell and Kahn claim that the term “Wnt surrogate molecule” requires showing that the claimed molecule is “biologically active” (which, in my opinion, it does not), the ’278 Patent clearly explains how a POSA may determine with reasonable certainty whether a given molecule is “biologically active.” Drs. McDonnell and Kahn attempt to show the contrary, but ultimately fail to do so because their assertions merely catalog the various ways in which biological activity may differ in different experimental contexts instead of demonstrating that a POSA would somehow be unable to determine whether a given molecule is biologically active in the first place. It is therefore my opinion that claims 1–5 of the ’278 Patent are definite.

B. My Construction of the “Linker” Limitation Does Not Make the Claims Incomprehensible

343. As I explained above, in my opinion, Dr. McDonnell is incorrect that 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* ¶¶ 137–160, above. Instead, a POSA would adopt the limitation’s plain and ordinary meaning, which (1) allows for both “direct” and “indirect” connections between binding regions, and (2) permits each LRP5/6 binding region to be connected to more than one Fzd binding region. *See id.* This natural reading of the claims clearly delimits them and does not render them “incomprehensible and indefinite” as Dr. McDonnell claims. *Contra* EX1002 ¶ 247.

344. Dr. McDonnell advances three reasons why, in his opinion, a “broader” construction of the “linker” limitation than his own “would render all claims of the ’278 Patent incomprehensible and indefinite.” EX1002 ¶ 247. *First*, Dr. McDonnell alleges that such a construction “would make the specification’s characterization of different molecular formats incomprehensible” because, according to him, permitting fused to encompass “indirect” connections would allegedly “collapse” the specification’s distinction, with respect to Figure 1A, between fusions to “the C-terminus of HC” and those to “the C-terminus of LC.” EX1002 ¶ 249. But as explained above, that conclusion relies on an unnaturally rigid interpretation for the

word “fused” that does not take into the account the context in which it is used in different parts of the specification. *See* ¶¶ 145–149, above.

345. As used in the claims, the term “fused” requires only a connection between “each of the two LRP5/6 binding regions” and “one of the two Fzd binding regions via a linker moiety.” EX1001 at cl. 1. In that context, the term thus simply denotes a connection—either direct or indirect through, e.g., intervening Fc regions—between each LRP5/6 binding region on the one hand and one of the two Fzd binding regions on the other. By contrast, as used with reference to Figure 1A, the term “fused” is used in a narrower context, specifying *where* on the Fzd binding region the LRP5/6 binding region is fused. A POSA would have no trouble using the context in which “fused” is used in discerning meaning from the specification’s discussion of Figure 1A while also appreciating that the term has a broader meaning in the context of claim 1. *See* ¶¶ 145–147, above.

346. Dr. McDonnell’s assertion that claims 3 and 5 would be rendered “incomprehensible” under a “broader construction,” EX1002 § XI.B, fails for the same reasons. Unlike claim 1, both claims 3 and 5 use the term “fused” to specify attachment locations within their binding regions—“the N-terminus or the C-terminus of the heavy chain or ... the N-terminus or the C-terminus of the light chain” in claim 3, and the “one of the light chains” in claim 5. *See* EX1001 at cls. 3, 5. A POSA would thus understand the context in which “fused” is used in these

claims to be narrower than that used in claim 1, which, as discussed above, simply denotes a connection between the LRP5/6 and Fzd binding regions via a linker moiety. This understanding also aligns with the fact that claims 3 and 5 depend from claim 1, and thus necessarily use the term “fused” in a narrower context as compared to claim 1. *See* ¶¶ 152–157, above. Nor would the words “each” and “one” in claim 5 be rendered “meaningless” under a broader construction, as Dr. McDonnell purports. *See* EX1002 ¶ 252. Rather, a POSA would understand those terms to specify a relationship between “each” of the two LRP5/6 binding regions and “one of the light chains,” without precluding each LRP5/6 binding region from also being fused to the other light chain, in the same way “each” and “one” are used in the “linker” limitation of claim 1. *See* ¶¶ 152–160, above. Dr. McDonnell’s purported “defect[s]” in any “broader construction” than his own thus fail to demonstrate that such a construction would render claims 3 and 5 “incomprehensible.”

347. *Second*, Dr. McDonnell alleges that “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.” EX1002 ¶ 250. Dr. McDonnell’s only example in support of this assertion is again two molecules from Figure 1A, for which he claims a POSA would understand under a broader “linker” limitation construction where a binding region within the IgG “begin[s] and end[s].” *Id.* But

Dr. McDonnell ignores that the specification expressly explains that “[i]n various embodiments, *including but not limited to those depicted in Fig. 1A*, a Wnt surrogate molecule comprises one or more Fab or antigen-binding fragment thereof and one or more VHH or sdAb or antigen-binding fragment thereof,” and that further, with respect to the two molecules Dr. McDonnell cites as examples, that “the Fab is present in a full IgG format.” EX1001 at 18:48–52, 62. A POSA would thus understand that the “binding regions” of the two molecules Dr. McDonnell cites are two Fab fragments “in a full IgG format” and two Nabs, and would not need to resort to speculating whether the binding region “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,” as Dr. McDonnell suggests. *See Fig. 30*, below.

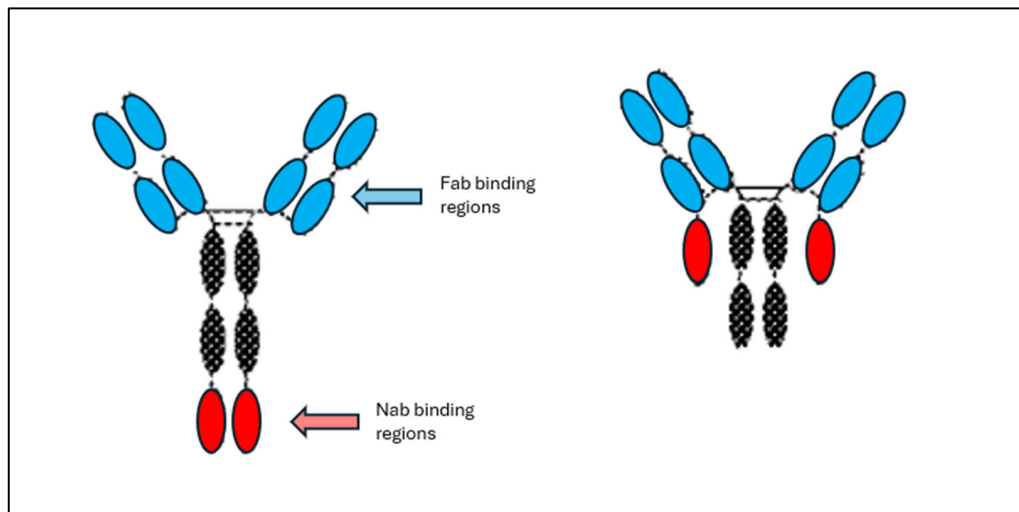


Figure 30: Two Molecules from Fig. 1A, Annotated to Show Binding Regions as Delimited by the '278 Patent Specification

348. *Third*, Dr. McDonnell alleges that “if ‘fused’ in claim 1 allows for indirect connections, the claim would become internally inconsistent and therefore impossible to practice” because “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 fuse to both Fzd binding regions via indirect connections, creating an irreconcilable contradiction.” EX1002 ¶ 251. But that presumes Dr. McDonnell is correct that the claims mandate that the “each of the two Lrp5/6 binding regions would be required to be fused to only ‘one of the two Fzd binding regions,’” which, as I have explained above, he is not. *See* ¶¶ 152–159, above. Instead, as discussed above, the phrase “each of the two LRP5/6 binding regions is fused to one of the two Fzd binding regions via a linker moiety” sets a threshold requirement that must be met between each of the two LRP5/6 binding regions and “one of the two” Fzd binding regions but places no restrictions on the fusion relationship between each LRP5/6 binding region *and the other* Fzd binding region. *See* ¶ 158, above. Dr. McDonnell’s “irreconcilable contradiction” thus arises from his own construction of the “linker” limitation, not any purported indefiniteness of any other construction, underscoring the incompatibility of his interpretation of the limitation with the patent’s claims and disclosures.

XIII. CLAIMS 1 AND 4 ARE NOT ANTICIPATED BY GARCIA

349. Dr. McDonnell opines that claims 1 and 4 of the '278 Patent “are additionally invalid because they are anticipated by Garcia,” EX1002 ¶ 253, but as explained below, Garcia does not disclose each and every limitation of claim 1 and claim 4. It is therefore my opinion that Dr. McDonnell is incorrect, and Garcia does not anticipate either claim.

A. Garcia Does Not Anticipate Claim 1

1. Garcia Does Not Disclose “a Soluble Tetravalent, Multispecific Wnt Surrogate Molecule” Comprising “Two Fzd Binding Regions” and “Two LRP5/6 Binding Regions”

350. As I explained above, during prosecution of the '278 Patent's claims, the Examiners, Applicant, and Dr. Yang Li all recognized that Garcia US, which is substantively identical to Garcia, *see* EX1002 ¶ 92, does *not* disclose every limitation of the then-pending claims. For example, the Examiners noted twice that Garcia US “does not teach dual variable domain (DVD) format of bispecific antibody”—a particular tetravalent format—and looked to a second reference, Wu, to supply the missing tetravalence limitation, before withdrawing their rejections based on Garcia US and allowing the claims. *See* ¶¶ 115–123, above. Likewise, Applicant explained in response to the Examiners' second office action that Garcia US disclosed only “bivalent, bispecific molecules comprised of a single polypeptide and having a stoichiometry of 1:1 Fzd binder:LRP5/6 binder.” EX1008 at 4005 (underlining in original). And Dr. Li observed in his declaration that “Garcia et al.

only described Wnt surrogate molecules having 1:1 Fzd binder:Lrp5/6 binder stoichiometry, and did not suggest or provide any motivation for a person skilled in the art to design a tetravalent molecule as claimed.” EX1008 at 4168.

351. Dr. McDonnell expresses disagreement with these statements, claiming that “the reference *does* disclose this ‘tetravalent, multispecific’ limitation,” EX1002 ¶ 255, but that contention rests on a conflation between the number of polypeptide chains a molecule may contain and the number of binding domains it comprises (i.e., the molecule’s valency), and also misinterprets Garcia’s disclosures. In my opinion, the Examiners, Applicant, and Dr. Li all correctly noted that Garcia US, and therefore Garcia, does **not** disclose this “tetravalent multispecific” limitation.

352. Dr. McDonnell first alleges that “Garcia ... discloses soluble Wnt surrogate molecules” because it explains that “those compositions are ‘water soluble’ and ‘directly activate canonical wnt pathway signaling,’” EX1002 ¶ 256, but that says nothing of whether this activity amounts to “biological[] activ[ity],” as is required under Dr. McDonnell’s construction. *See* EX1002 ¶ 102. Indeed, nowhere in his declaration does Dr. McDonnell show that Garcia discloses a “biologically active” Wnt surrogate molecule, despite requiring such biological activity for the ’278 Patent claims throughout the remainder of his declaration.

353. Moreover, Dr. McDonnell’s approach to Garcia—which takes its statement that its molecules “directly activate canonical wnt pathway signaling” at face

value—is at odds with his various purported criticisms of the '278 Patent's disclosures. The '278 Patent's examples repeatedly state that their tested molecules “activated Wnt signaling to various levels,” but Dr. McDonnell ignores those express statements and instead points to perceived flaws in their dose–response curves to conclude that they “failed” to do so. *Compare, e.g.*, EX1001 at 157:44 – 47 (noting the molecules in Example 9 “activated Wnt signaling to various levels”), *with* EX1002 (alleging the CL format in Example 9 “failed”); EX1001 at 155:32, 62, 158:61–63 (explaining that the R2M3-26 and R2M-32 molecules “induced reporter activity,” and the 26-17SB9 molecule “induced canonical Wnt signaling”), *with* EX1002 ¶ 187 (alleging the same molecules “failed to produce responses in the absence of R-spondin); EX1001 at 156:45 (explaining that the molecules tested in Example 5 “activated Wnt signaling to various levels”), *with* EX1002 ¶ 188 (alleging that three molecules tested in Example 5 “failed to produce responses in a TOPFlash assay).

354. Indeed, Garcia presents many of the same alleged flaws Dr. McDonnell criticizes in the '278 Patent's disclosures. For instance, Garcia discloses that its two exemplary tested bivalent molecules exhibited varying levels of Wnt signaling activity in different cell lines; measures their activity using the same SuperTopFlash assay that Drs. McDonnell and Kahn allege “could produce inconsistent responses depending on the assay conditions,” EX1002 ¶ 229; includes graphical depictions of

Wnt signaling activity in which the activity of the exemplary molecules in the absence of R-spondin appears almost flat compared to the level of activity in the presence of R-spondin without adjusting for scale; and presents data showing that one of the exemplary molecules demonstrated what Dr. McDonnell would call a “minuscule” increase relative to a natural Wnt ligand, EX1002 ¶ 241. *See* Figs. 31–33, below. If, under Dr. McDonnell’s interpretation, the ’278 Patent fails to show its exemplary molecules are “biologically active,” so does Garcia.

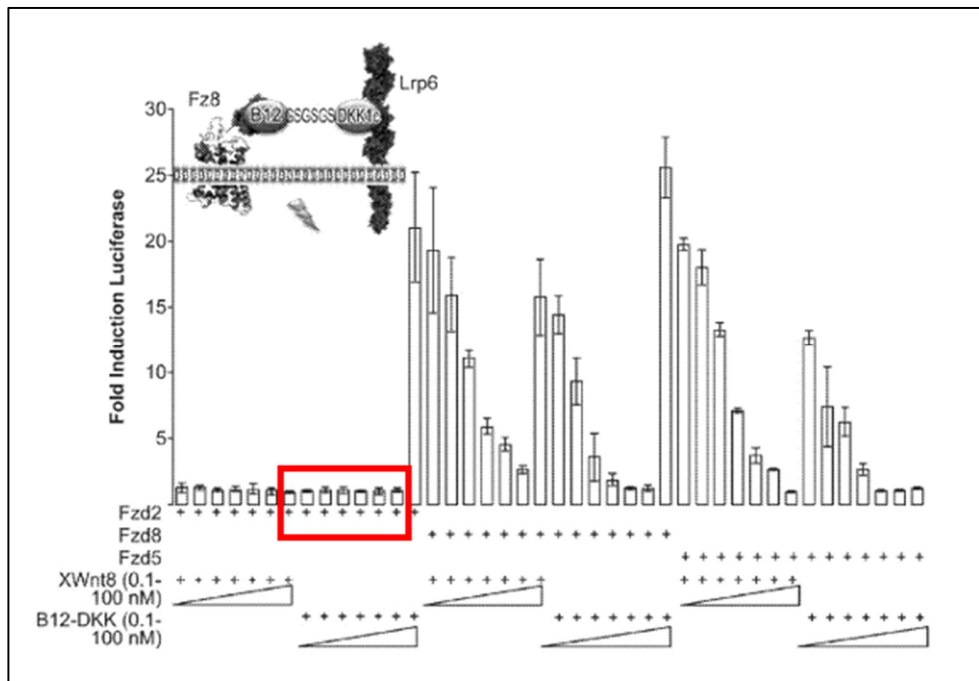


Figure 31: Figure 4 of Garcia (Ex. 1004), Annotated to Show What Appears to Be Low Activity of the Disclosed Working Example B12-DKK in Cells Expressing Fzd2

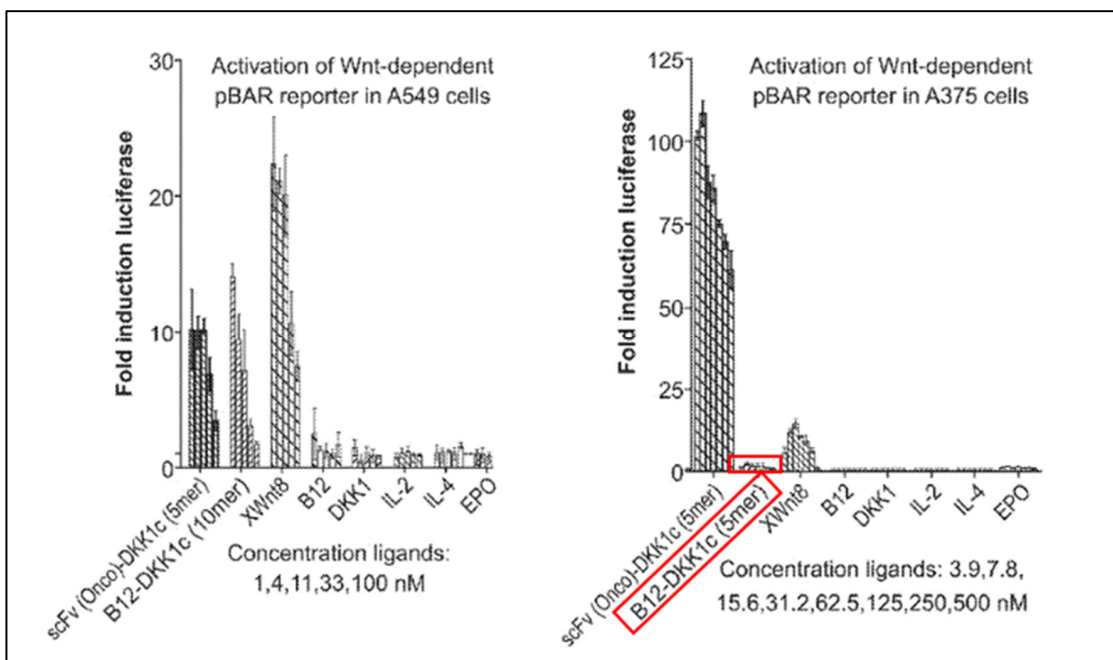


Figure 32: Figures 8A and 8B of Garcia (Ex. 1004), Annotated to Show Variation in Wnt Signaling Activity of the Disclosed Working Example B12-DKK1c in Different Cell Lines

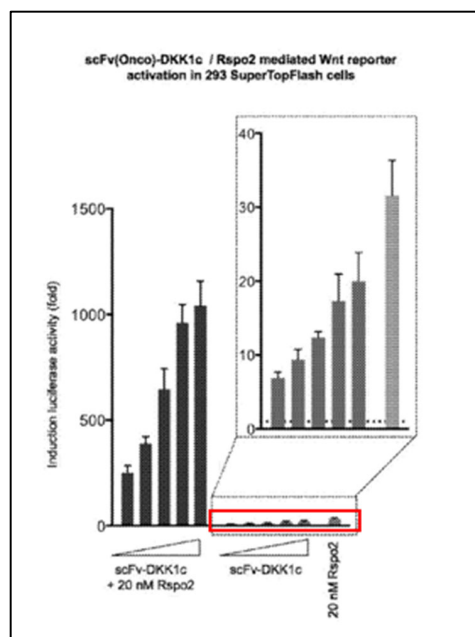


Figure 33: Figure 15 of Garcia, Showing What Appears to Be Little to No Activity of the Working Example scFv-DKK1c Without y-Axis Scaling in the Absence of R-Spondin

355. Moreover, Dr. McDonnell’s opinion that Garcia discloses a “tetravalent, multispecific Wnt surrogate molecule,” as he interprets that phrase, contradicts his own purported understanding of the state of the art as of 2017. Indeed, even assuming Garcia disclosed a tetravalent molecule comprising two Fzd binding regions and two LRP5/6 binding regions as Dr. McDonnell claims (it does not, as I explain below), Garcia does not report any testing results for such a molecule demonstrating its ability to activate Wnt signaling. Instead, it only reports testing results for two *bivalent* molecules each comprising a *single* Fzd binding region and a *single* LRP5/6 binding region. See EX1004 at Figs. 4–15. Given Dr. McDonnell’s written description position that “predicting in advance how a particular multivalent, multispecific antibody format would function in vitro, in vivo, and ultimately in humans was *impossible* in 2017,” and that “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,” EX1002 ¶ 73, it follows from his opinions regarding the ’278 Patent’s disclosures that Garcia does *not* disclose a “tetravalent, multispecific Wnt surrogate molecule” under his construction.

356. Dr. McDonnell instead inconsistently argues that Garcia discloses a tetravalent Wnt surrogate molecule based on a single sentence in the reference

explaining that its disclosed “polypeptide wnt surrogate may be a single chain, *dimer*, or higher order multimer”—in other words, the molecule can consist of one, two, or more polypeptide chains. *See* EX1002 ¶ 257 (quoting EX1004 at [0056]). But that says nothing about the polypeptide’s *valency*, or the number of binding domains on the molecule, because any given polypeptide chain in a molecule can contain none, one, or more binding domains, and several different polypeptide chains may fold together to form a single binding domain. Garcia itself illustrates this point. For example, Garcia explains that “[i]ntact antibody *tetramers* are comprised of two heavy chain-light chain *dimers*.” EX1004 at [0096]. Yet, “[w]hen natural antibodies fold ..., the heavy and light chains are brought together in three-dimensional space so that they create a *single* hypervariable antigen binding site.” *Id.* In other words, Garcia itself describes a *dimer* structure—each heavy chain–light chain pairing in a natural antibody—that is *monovalent*. A POSA would thus understand Dr. McDonnell’s quoted sentence to say nothing about *the valency* of Garcia’s disclosed polypeptides.

357. Dr. McDonnell nonetheless asserts that his quoted sentence discloses a tetravalent molecule because “each polypeptide, as disclosed by Garcia, comprises a binding region for Fzd and a binding region for Lrp5/6,” and thus “a dimer formed from two such polypeptides contains two binding regions for Fzd and two binding regions for Lrp5/6.” EX1002 ¶ 257. But that misreads Garcia’s general statement

permitting latitude in the number of polypeptide chains comprising its *bivalent* structure. As the immediately preceding sentence in Garcia explains, “[a] wnt surrogate can be *a* polypeptide, where *a* binding region domain for Fzd is joined to *a* binding domain for Lrp5/6,” and this polypeptide comprising *a* Fzd binding region and *a* Lrp5/6 binding region “may be a single chain, dimer, or higher order multimer.” EX1004 at [0056]. Dr. McDonnell’s quoted sentence thus confirms that regardless of the number of polypeptide chains the disclosed molecules contain, they are all *bivalent* and comprise a *1:1* Fzd binder:LRP5/6 binder stoichiometry. Contrary to Dr. McDonnell’s assertions, Garcia thus does *not* disclose a tetravalent molecule with a 2:2 Fzd binder:LRP5/6 binder stoichiometry.

358. Despite the express statement in Dr. Li’s declaration that “Garcia et al. *only* described Wnt surrogate molecule having 1:1 Fzd binder:Lrp5/6 binder stoichiometry, and did *not* suggest or provide any motivation for a person skilled in the art to design a tetravalent molecule as claimed,” EX1008 at 4168, Dr. McDonnell incorrectly alleges that the declaration supports his opinion. *See* EX1002 ¶ 259. This conclusion is based on the misleading premise that “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.” *Id.* But Dr. McDonnell’s crop quotes Dr. Li’s full statement—that he synthesized a molecule in the “tandem scFv format *in the 1:1 configuration* (with a

single scFv binding linked to a single scFv Lrp5/6 binding domain) *described by Garcia et al.*” EX1008 at 4170.

359. Dr. McDonnell also selectively quotes Dr. Li’s declaration in alleging that “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.’” EX1002 ¶ 259. In fact, the full sentence from Dr. Li’s statement reads, “the aggregation of two *or three* monomeric tandem scFv molecules,” corresponding to “two *or more* binding domains for FZD and two *or more* binding domains for LRP in one molecule,” was “associated with Wnt activity.” EX1008 at 4171. Dr. Li’s declaration thus provides no “confirm[ation]” that Garcia disclosed the claimed tetravalent molecules in the claimed stoichiometry. *Contra* EX1002 ¶ 259. Instead, the declaration explains that the molecule aggregated *in various higher-order* combinations that were not necessarily tetravalent nor necessarily in a 2:2 Fzd binder:Lrp5/6 binder stoichiometry, and those aggregations were able to activate Wnt signaling. Indeed, Dr. Li described these higher-order aggregations as “contamination,” indicating that the aggregation may have been a result of the specific synthesis pathway Dr. Li used to generate his tested molecules. *See* EX1008 at 4170. Dr. McDonnell fails to cite any evidence showing that a *tetravalent, 2:2 Fzd binder:LRP5/6 binder* molecule results from any disclosure in Garcia, much

less necessarily does so. Instead, as discussed above, his sole quoted sentence from Garcia only confirms that Garcia only disclosed **bivalent** molecules in a **1:1** Fzd binder:LRP5/6 binder stoichiometry, as the Examiner, Applicant, and Dr. Li all recognized. See ¶¶ 116–122, above. Garcia does not disclose this limitation and, therefore, does not anticipate.

2. Garcia Does Not Disclose “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”

360. Dr. McDonnell alleges that “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,” EX1002 ¶ 260, but for the reasons discussed above, Dr. McDonnell is incorrect that Garcia discloses a “dimeric Wnt surrogate molecule” containing **two** Fzd binding regions. See ¶¶ 351–359, above. Instead, Dr. McDonnell’s own quoted sentences from Garcia confirm that it only discloses molecules with a **single** Fzd binding region. For example, the specification explains that “[i]n polypeptide embodiments, **the Fzd binding domain** [singular] may be selected from any domain that binds Fzd at high affinity.” See EX1004 at [0011]. Thus, regardless of whether Garcia’s “polypeptide embodiments” are single chains, dimers, or higher-order multimers, Garcia is clear that they all contain only **one** Fzd binding domain. Garcia therefore does not disclose this limitation.

3. **Garcia Does Not Disclose “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**

361. Dr. McDonnell’s allegation that Garcia discloses this limitation is incorrect for all the same reasons discussed above—Garcia states that its disclosed polypeptides contain a *single* LRP5/6 binding domain, regardless of whether the polypeptide is a single chain, dimer, or higher order multimer, instead of the two LRP5/6 binding regions specified in this limitation. *See* ¶¶ 351–359, above. For example, as with its molecules’ Fzd binding region, Garcia explains that “[i]n polypeptide embodiments, *the Lrp5/6 binding domain or element* [singular] may be selected from any domain that binds Lrp5/6 at high affinity,” confirming that Garcia’s polypeptide embodiments—including those that are dimers—only comprise a *single* LRP5/6 binding region. *See* EX1004 at [0013].

362. In addition, under his construction of “Wnt surrogate molecule,” which requires a molecule to be “biologically active,” EX1002 ¶ 102, Dr. McDonnell’s opinion that this limitation is disclosed is at odds with his own opinions on the purported lack of maturity in the art as of 2017. There, Dr. McDonnell purports that different antigen-binding fragments “may or may not retain the function of a full-length antibody,” so much so, that he multiplies his combinatorial estimate of the number of possible “formats” by a scale of **6,531** to account for this variation. *See* EX1002 ¶ 52. But Garcia does not disclose a *single* molecule comprising an

antibody-derived LRP5/6 binding arm; instead, both its tested working examples used DKK1c, a non-antibody-derived binding fragment. *See* EX1004 at [00197]–[00198]. Dr. McDonnell’s assertion that Garcia’s listing of various possible antibody fragments that can be used in its invention disclose this limitation, *see* EX1002 ¶ 261, thus conflicts with his opinion that a POSA would not be able to make the ’278 Patent’s claimed embodiments without undue experimentation. Dr. McDonnell therefore fails to prove that Garcia discloses this limitation, under his own interpretations of the ’278 Patent claims and the relevant art or otherwise.

4. Garcia Does Not Disclose That “Each of the Two LRP5/6 Binding Regions Is Fused to One of the Two Fzd Binding Regions via a Linker Moiety”

363. Dr. McDonnell alleges that “[t]he tetravalent dimeric Wnt surrogate molecule disclosed in Garcia satisfies this limitation,” EX1002 ¶ 262, but as discussed above, Garcia discloses no such molecule, as its disclosed polypeptides consist of one Fzd binding region and one LRP5/6 binding region, and are thus bivalent. *See* ¶ 351–359, above. Nor does Dr. McDonnell provide any explanation as to how “each LRP5/6 binding region” in his purported “tetravalent dimeric Wnt surrogate molecule” is “connected *directly* to *one and only one*” Fzd binding region as his erroneous interpretation of the limitation requires. *See* EX1002 ¶ 108. Garcia thus fails to disclose this limitation, and Dr. McDonnell fails to show otherwise.

364. To summarize, Garcia does not disclose every limitation of claim 1, and Dr. McDonnell fails to show otherwise. Garcia thus does not anticipate claim 1.

B. Garcia Does Not Anticipate Claim 4

365. Dr. McDonnell alleges that Garcia also anticipates claim 4, which recites a “pharmaceutical composition comprising a physiologically acceptable excipient, diluent, or carrier, and the Wnt surrogate molecule according to claim 1.” But claim 4 depends from claim 1, and as explained above, Garcia does not disclose each and every limitation of that claim. *See* ¶¶ 351–364, above. Moreover, while Dr. McDonnell points to a general statement in Garcia explaining that “[c]ompositions of interest include, without limitation, an effective dose of a wnt signaling agonist in a pharmaceutically acceptable excipient,” EX1004 at [0019]; EX1002 ¶ 264, he points to no disclosure combining Garcia’s purported “tetravalent dimeric Wnt surrogate molecule” in such a composition. Indeed, Garcia does not disclose a pharmaceutical composition as recited in claim 4 because it does not disclose a molecule comprising two Fzd binding regions and two LRP5/6 binding regions as the ’278 Patent claims. *See* ¶¶ 351–359, above. Garcia thus does not disclose each and every limitation of claim 4, and therefore does not anticipate the claim.

XIV. CONCLUSION

366. 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: 5/26/2026

Jeffrey Ravetch

Dr. Jeffrey Ravetch

APPENDIX A

DR. JEFFREY RAVETCH MATERIALS CONSIDERED

In offering the opinions set forth in my Declaration, I considered all materials cited therein along with all materials listed in this Appendix.

Case Documents

- Declaration of Dr. Karl Willert (Ex. 2010), and all materials cited therein
- Declaration of Dr. Michael Kahn, Ph. D (Feb. 10, 2026) (Ex. 1003), and all materials cited therein
- Declaration of James McDonnell, Ph.D. (Feb. 11, 2026) (Ex. 1002), and all materials cited therein
- Merck Sharp & Dohme LLC's Petition for Post-Grant Review (Feb. 12, 2026)

Patent Materials

- File History of U.S. Patent No. 12,297,278 (Ex. 1008)
- International Patent Publication WO 2016/040985 (Ex. 1004)
- International Patent Publication WO 2020/010308 (Ex. 1081)
- International Patent Publication WO 2020/018445 (Ex. 1014)
- U.S. Patent Appl. Publication No. 2014/0105917 (Ex. 2029)
- U.S. Patent Appl. Publication No. 2017/0306029 (Ex. 1011)
- U.S. Patent No. 12,297,278 (Ex. 1001)
- U.S. Provisional Patent Appl. No. 62/607,875 (Ex. 1005)
- U.S. Provisional Patent Appl. No. 62/607,877 (Ex. 2021)
- U.S. Provisional Patent Appl. No. 64/607,879 (Ex. 2022)

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