Paper No. 1
Filed: February 12, 2026

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

MERCK SHARP & DOHME LLC,
Petitioner,

v.

SURROZEN OPERATING, INC.,
Patent Owner.

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

PETITION FOR POST-GRANT REVIEW

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GLOSSARY

Patent or ’278 Patent	U.S. Patent No. 12,297,278
Bold and italicized	Emphasis added unless otherwise indicated
Garcia	International Patent Publication No. WO 2016/040895 A1
POSA	Person of ordinary skill in the art

TABLE OF EXHIBITS

Exhibit	Description
1001	U.S. Patent No. 12,297,278
1002	Declaration of James McDonnell, Ph.D.
1003	Declaration of Michael Kahn, Ph.D.
1004	International Patent Publication No. WO 2016/040895 A1
1005	U.S. Provisional Application No. 62/607,875
1006	U.S. Provisional Application No. 62/641,217
1007	U.S. Provisional Application No. 62/680,522
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1011	U.S. Publication No. 2017/0306029 A1 ("Garcia US")
1012	Chengbin Wu, et al., *Simultaneous targeting of multiple disease mediators by a dual-variable-domain immunoglobulin*, 25 NAT. BIOTECH. 1290-1297 (2007).
1013	Tapan K. Bera, et al., *A bivalent disulfide-stabilized Fv with improved antigen binding to erbB2*, 281 J. MOL. BIOL. 475-483 (1998).
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1030	Alex Gregorieff, et al., *Expression pattern of Wnt signaling components in adult intestine*, 129 GASTROENTEROLOGY 626-638 (2005).
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1090	*FDA approves emicizumab-kxwh for prevention and reduction of bleeding in patients with hemophilia A with factor VIII inhibitors*, (c. Nov. 16, 2017) U.S. FDA,

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	https://www.fda.gov/drugs/resources-information-approved-drugs/fda-approves-emicizumab-kxwh-prevention-and-reduction-bleeding-patients-hemophilia-factor-viii (Retrieved on Feb. 9, 2026).
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1093	Wim de Lau, et al., *Lgr5 homologues associate with Wnt receptors and mediate R-spondin signalling*, 476 NATURE 293-298 (2011).

I. INTRODUCTION

Petitioner Merck Sharp & Dohme LLC ("Petitioner") request post-grant review of U.S. Patent No. 12,297,278 (Ex. 1001; the "Patent" or "'278 Patent"), assigned to Patent Owner Surrozen Operating, Inc., and cancellation of claims 1-5.

Wnt signaling is involved in a vast array of biological processes, and known to be notoriously complex as it involves multiple, simultaneously interacting ligands and receptors and further varies by cell type and other factors. Notwithstanding the extreme complexity and nascent state of art, the '278 Patent claims an extremely broad genus of tetravalent, multispecific "Wnt surrogate" molecules defined by the function of activating Wnt signaling, rather than specific structures such as amino acid sequences. Each claimed molecule comprises two Fzd binding regions (each independently binding any or all of Fzd1-10) and two Lrp binding regions (each independently binding Lrp5 and/or 6), again claimed solely by function. As discussed below, the topology (spatial arrangement) and format (types of antibody-derived segments and linkers as arranged) of these Fzd and Lrp binding regions is essentially undefined, except that "each of the two LRP5/6 binding regions is fused to one of the two Fzd binding regions via a linker moiety." But this adds no meaningful constraints, as the linkers encompass peptidic and non-peptidic linker moieties regardless of composition, sequence, rigidity, or length.

These claims are unpatentable on four independent grounds: three grounds under Section 112, which the Examiner failed to raise during prosecution, and the last ground under Section 102, which Patent Owner avoided during prosecution by mischaracterizing cited prior art.

First, the challenged claims fail to satisfy the written description requirement. These claims are exceedingly broad. Claim 1, for example, encompasses molecules with more than ***130 million*** different tetravalent ***formats***, binding to over ***35,000*** different ***target combinations***, made of essentially ***unknowable*** numbers of Fzd and Lrp5/6 binding region ***sequences***. In contrast, the specification discloses only a small group of substantially similar molecules embodying at most ***29 formats***, binding to a ***handful*** of target combinations, made of a ***small*** group of sequences. Regardless of how it is evaluated—whether based on format, target combinations, or sequence, the challenged claims are unpatentable. *See Juno Therapeutics, Inc. v. Kite Pharma Inc.*, 10 F.4th 1330, 1340-42 (Fed. Cir. 2021). Indeed, none of the disclosed molecules—and nothing in the specification—describes a common structural feature shared among all tetravalent formats that correlates with the claimed function of activating Wnt signaling. The data in the specification confirms that no such correlation exists. The patent's meager disclosure cannot "bear the weight of the vast scope of these generic claims." *Ariad Pharms., Inc. v. Eli Lilly & Co.*, 598 F.3d 1336, 1358 (Fed. Cir. 2010) (en banc).

Second, the challenged claims fail to satisfy the enablement requirement. The breadth of the claims is vast and lacks structural integrity. The relevant field was both nascent and unpredictable with complex Wnt signaling pathways involving numerous ligands and receptors. Because the specification offers only minimal guidance as to what may or may not work as a Wnt surrogate molecule with all the possible variables—tetravalent format and linker options to name just a few—a POSA would be "forced to engage in painstaking experimentation to see what works." *Amgen Inc. v. Sanofi*, 598 U.S. 594, 614 (2023) (citation omitted). A conservative estimate indicates that it would take more than ***26,000 years*** to cursorily survey candidate molecules that may fall within the claim scope. As the Supreme Court stated, "[t]hat is not enablement. More nearly, it is a hunting license." *Id*. (citation omitted).

Third, the challenged claims are indefinite. As demonstrated in the specification and the prior art, the determination as to whether a given molecule activates Wnt signaling varies by assay, cell-type, and molecule concentration. But the specification provides no standard or means to interpret conflicting results. As such, a POSA would not be able to ascertain, with reasonable certainty, the metes and bounds of the challenged claims. *Akamai Techs., Inc. v. MediaPointe, Inc*., 159 F.4th 1370, 1379 (Fed. Cir. 2025) ("[W]hen multiple methods for determining

whether a claim limitation is met lead to different results without guidance as to which method should be used, the claim is indefinite.") (citation omitted).

Fourth, claims 1 and 4 are anticipated. During prosecution, Patent Owner overcame a prior art rejection based on Garcia (EX1004), arguing that Garcia does not teach or suggest a "tetravalent" Wnt surrogate molecule. Not so. Garcia discloses a "dimer" of ***bivalent*** Wnt surrogate molecules binding to Fzd and Lrp5/6, thereby teaching each and every limitation of claims 1 and 4. Even the named inventor's sworn statement submitted during prosecution confirms that Garcia "described" this "dimer" embodiment.

As further explained in the accompanying declarations of Dr. James McDonnell (EX1002) and Dr. Michael Kahn (EX1003), experts in the field of antibody engineering and Wnt biology, trial should be instituted, and the challenged claims canceled. EX1002, ¶¶12-16; EX1003, ¶¶11-15.

II. TECHNICAL BACKGROUND

A. Wnt Signaling Is Complex and Poorly Understood

1. Ligands and Receptors

Although the first member of the Wnt family of proteins was discovered in the early 1980s, "a number of factors [had] thwarted progress in this field" as of 2017, including that "the WNT signalling cascade is bewilderingly complex." EX1043, 1; EX1063, 1; EX1003, ¶¶2, 76-100; EX1002, ¶¶74-75.

As of 2017, more than fifteen receptors and co-receptors were believed to be involved in Wnt signaling and nineteen Wnt ligands were known. EX1043, 1. Among those receptors and co-receptors are ten Frizzled (Fzd) receptors, Fzd1-10, and two low-density lipoprotein receptor-related proteins (Lrp), Lrp5 and Lrp6. EX1063, 1, 3; EX1003, ¶¶80-82; EX1002, ¶76. Secreted proteins such as R-spondin were also known to potentiate Wnt signaling. EX1063, 5; EX1003, ¶88. Wnt and non-Wnt ligands (such as Norrin that are unrelated to Wnts but bind to their receptors) were further understood to play tissue-specific roles. EX1043, 3, 9; EX1044, 1-2; EX1063, 1; EX1003, ¶¶98-100; EX1002, ¶¶76-77.

Wnt and non-Wnt ligands were also known to elicit different types of cellular responses, including "canonical" activation of the β-catenin and T-cell factor ("TCF") transcription complex and alternative, "noncanonical" responses that did not involve this transcription complex. EX1063, 1; EX1003, ¶¶90-92; EX1002, ¶¶77-79. This distinction, however, was not absolute as they shared common biological players such as Fzds and Lrps. EX1028, 4; EX1029, 1; EX1043, 1, 3; EX1045, 2; EX1060, 2-5; EX1066, 1, 5-6; EX1003, ¶¶90-97. How each ligand interacted with its corresponding receptors was not even fully elucidated, precluding general design principles for Wnt mimicking molecules. EX1003, ¶¶80-89; EX1002, ¶¶76-79; *see* EX1038, 2; EX1044, 2-4; EX1053, 3; EX1046, 2.

2. Assays for Measuring Wnt Signaling Pathway

Adding to this complexity, experimentally determining whether and to what degree Wnt signaling is activated was challenging and unresolved. EX1003, ¶¶3, 101-12; EX1002, ¶80. No assay was universally applicable to all Wnt systems and each assay type had fundamental limitations, including being "highly cell-type dependent." EX1043, 11; EX1086, 1; EX1003, ¶¶101-11. The "TOPFlash" reporter assay, for example, did not "capture all the important transcriptional changes caused by activated WNT signalling." EX1043, 3, 11; EX1055, 1; EX1034, 1; EX1070, 3-5, 7; EX1003, ¶¶108-11.

This is in part because Wnt activation is not "intrinsic[]" to Wnt ligands but depends on other external factors. *See* EX1056, 1. For example, the Wnt5a ligand was found to both ***inhibit*** and ***induce*** the activation of canonical Wnt signaling in TOPFlash assays depending on the cell type tested. *Id.*, 2-5. This ability "to toggle between two considerably diverse forms of signaling" illustrates that Wnt activity is condition dependent. *Id*., 11; EX1087, 9; EX1003, ¶¶101-12; EX1002, ¶80.

B. Multivalent, Multispecific Antibody Engineering Was Unpredictable

As a baseline, making an antibody against a biological target was unpredictable as of 2017. EX1002, ¶¶40-50. One could not predict whether a particular antibody would bind to a given target without making and testing it. EX1064, 2; EX1047, 12-13; EX1079, 2-3; EX1002, ¶¶40-42. Even if able to bind a

particular target, one typically could not predict whether the antibody would antagonize (inhibit), agonize (enhance), or have no effect. EX1027, 2-3, 7; EX1002, ¶¶43-44. That is certainly the case in the context of Wnt signaling targets. EX1002, ¶¶43-44.

Making and using antibodies and their fragments to simultaneously target two or more biological targets—like Fzds and Lrp5/6 in this case—multiplied unpredictability and complexity. EX1002, ¶¶60-73. Multivalent, multispecific formats—only a fraction of which had ever been constructed as of 2017—required empirical evaluation because their activity unpredictably depended on a range of factors, including their specific antibody sequences and the arrangement of those sequences. EX1017, 1-2; EX1024, 6; EX1002, ¶¶70-73.

1. Antibodies and Antibody Fragments

A naturally-occurring IgG antibody typically contains two identical longer ("heavy") amino acid chains and two identical shorter ("light") amino acid chains. EX1039, 56-57; EX1002, ¶¶33-35. As depicted below, these chains come together via disulfide bonds to form a "Y" shaped molecule. EX1039, 56; EX1002, ¶¶33-35. The variable domains of the heavy and light chains (shown in red below) bind to a biological target ("antigen"). EX1039, 57; EX1002, ¶¶36-39. A conventional IgG antibody is "bivalent" (having *two* binding regions) and "monospecific" (each binding region binding to the *same* site in the antigen). EX1002, ¶61.

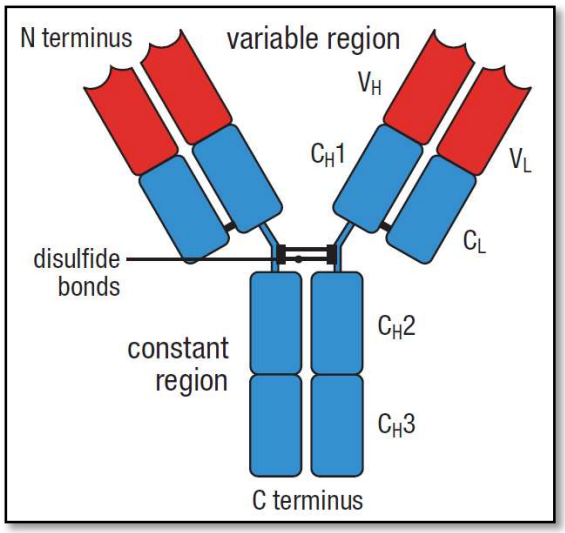


Figure 1. IgG Antibody (EX1039, 56)

By 2017, many types of modified antibody binding regions had been reported. EX1002, ¶¶51-59. For example:

- A "Fab" contains one arm of the "Y" molecule, i.e., a light chain paired with a partial heavy chain (EX1039, 59);
- A single-chain Fv ("scFv") contains the heavy and light chain variable domains linked via a peptide linker (EX1059, 3; EX1009, 2-3; EX1013, 1-2); and
- A "VHH" contains a single heavy chain variable domain (and is derived from species that have heavy chain only antibodies such as llamas, alpacas, and camels) (EX1059, 4; EX1078, 2), and its recombinant version was called a "single-domain antibody" or "nanobody" ("Nab") (EX1089, 2).

EX1002, ¶¶53-59.

2. Multivalent, Multispecific Antibody Formats

By 2017, researchers had engineered various antibody formats that are "multivalent" (*two or more* binding regions in the engineered antibody-like format)[1] and "multispecific" (binding to *two or more* different sites in the antigen(s) targeted by the format) using antibodies and antibody fragments as building blocks. EX1017, 1; EX1002, ¶¶60-62. But only about 100 different experimental formats had been made and tested at this time. EX1017, 1, Fig. 2.

That literature recognized, however, that the variety of possible multivalent, multispecific formats was much broader. EX1017, Fig. 1; EX1051, 2-3; EX1002, ¶¶63-67. For each format, each binding region could be chosen from a multitude of different antibody and antibody fragment types, arranged in different orientations. EX1017, Fig. 1; EX1002, ¶¶63-65. There was also an incredible variety for each "linker" that connected the parts of these molecules, as they could vary in length, composition, sequence, and flexibility. EX1017, Fig. 1; EX1051, 8-9; EX1002, ¶66. Because many external factors impacted function, including the spatial

[1] A format with four binding regions that collectively target *two different* sites is "tetravalent, *bi*specific." A format with four binding regions that collectively targets *three or four different sites* is respectively "tetravalent, *tri*specific," and "tetravalent, *tetra*specific." EX1002, ¶¶60 & n.2.

"arrangement or size of the different target antigens" as well as "the target densities on cell surfaces," empirical evaluation was required for each different format and molecule for each biological system. EX1017, 21; EX1002, ¶¶70-73.

III. THE '278 PATENT

The '278 Patent claims priority to three provisional applications, the earliest filed December 19, 2017. EX1001, item (60); EX1005; EX1006; EX1007. Although none of these applications adequately describe or enable the challenged claims, for purposes of this Petition, December 19, 2017 is used as the effective filing date. EX1002, ¶¶88-89; EX1003, ¶63. Given the § 112 defects in the non-provisional specification, the challenged claims of the '278 patent are unpatentable even if December 19, 2018 (the first non-provisional filing date) is used as the effective filing date. EX1002, ¶89; EX1003, ¶63.

A. Person of Ordinary Skill in the Art ("POSA")

A POSA would have 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, ¶¶19-21; EX1003, ¶¶63-65. A POSA may also have had access to other POSAs with complementary experience in antibody engineering or Wnt signaling. EX1002, ¶21; EX1003, ¶65.

B. Challenged Claims

The ’278 Patent contains one independent claim and four dependent claims, each of which encompasses a potentially unlimited number of soluble, tetravalent multispecific Wnt surrogate molecules. EX1002, ¶¶90-91; EX1003, ¶¶46-50. Claim 1 is representative:

> 1. A soluble, tetravalent, multispecific Wnt surrogate molecule, wherein the Wnt surrogate molecule comprises:
>
> (i) two Fzd binding regions that specifically bind to two Frizzled (Fzd) receptors, wherein each of the two Fzd binding regions comprises an antibody or antigen-binding fragment of the antibody; and
>
> (ii) two LRP5/6 binding regions that specifically bind to a Low-density lipoprotein (LDL) receptor-related protein 5 (LRP5) and/or a Low-density lipoprotein (LDL) receptor-related protein 6 (LRP6), wherein each of the two LRP5/6 binding regions comprises an antibody or antigen-binding fragment of the antibody, and
>
> wherein each of the two LRP5/6 binding regions is fused to one of the two Fzd binding regions via a linker moiety.

EX1001, cl. 1. The dependent claims recite that the Fzd binding regions comprise a full IgG and the Lrp5/6 binding regions comprise a VHH (claim 2), fusion locations (claims 3 and 5), or pharmaceutical compositions (claim 4).

None of the claims specify the amino acid sequences of the claimed Wnt surrogate molecules, or even the Fzd or Lrp5/6 binding regions within the molecules. EX1002, ¶91. The claims encompass binding to any of Fzds 1-10 and any of Lrp5 and/or Lrp6. EX1003, ¶¶49-50; EX1002, ¶91. In addition, the claims do not specify how to determine the claimed "Wnt surrogate" function. EX1003, ¶48.

C. Disclosures of the '278 Patent

The '278 Patent purports to disclose "Wnt pathway agonists and related compositions." EX1001, Abstract. The Patent states that "Wnt surrogate molecules of the present invention are ***biologically active*** in binding to one or more Fzd receptor and to one or more of LRP5 and LRP6, and ***in activation of Wnt signaling***, i.e., the Wnt surrogate molecule is a Wnt agonist." *Id*., 16:52-56. The Patent further states that "Wnt agonists typically initiate a reaction or activity that is similar to or the same as that initiated by the receptor's natural ligand." *Id*., 16:61-64; EX1002, ¶81; EX1003, ¶¶18-19.

The Patent states that "the Wnt signaling pathway is a canonical Wnt signaling pathway or a non-canonical Wnt signaling pathway," and that the "ability of the Wnt surrogate molecules and other Wnt agonists disclosed herein to mimic the activity of Wnt can be confirmed by a number of assays." EX1001, 4:49-51, 16:58-61, 117:39-44; EX1002, ¶82; EX1003, ¶19.

Table 1A of the Patent lists "antibodies or fragments thereof that bind to one or more Fzd receptor." EX1001, 22:37-38. Although Table 1A lists about 450 clones by name, the Fzd binding information for each is admittedly preliminary ("Initial Binding"). *Id.*, Table 1A. Many of these clones have only heavy chain CDRs, i.e., no light chain CDRs. *Id*. Table 1B lists a subset of these clones further evaluated for binding ("Confirmed Binding"). *Id*., Table 1B. Many of these clones are marked with "n.b." or "n.s," suggesting that they did not bind to any Fzd or were not studied, and the Patent does not disclose the binding strength (e.g., K_D) of the other clones. *Id*. Table 1B lists the heavy and/or light sequences for only 39 clones. *Id*.; EX1002, ¶83.

Table 2A of the Patent lists "antibodies or fragments thereof that bind to LRP5 and/or LRP6." EX1001, 80:42-43. Table 2A lists about 250 clones by name and identifies whether Lrp5 or Lrp6 is bound ("Confirmed Binding"). *Id.*, Table 2A. Many of these clones lack light chain CDRs, and no binding affinity data is disclosed for any clone. *Id*. Table 2B identifies the heavy chain sequences of 24 clones. No light chain sequences are provided, and only one clone is reported to bind Lrp5. *Id*., Table 2B; EX1002, ¶84. Notably, the Patent does not explain how the clones in Table 1A and Table 2A were made. *See generally* EX1001; EX1002, ¶¶83-84.

Table 3 of the Patent lists 104 potential "Wnt surrogate" molecules. EX1001, Table 3. 96 of those were tested, including 88 tetravalent, bispecific molecules and

8 bivalent, bispecific molecules. *Id.* Although encompassed by the claims, ***no*** trispecific or tetraspecific molecules are listed in Table 3. *See id*.; EX1002, ¶85.

The Patent includes Examples 1-26. Example 1 discloses "illustrative Wnt surrogate molecule formats." EX1001, cols. 150-155; EX1002, ¶85. Examples 2-18 evaluate potential Wnt surrogate molecules using the TOPFlash assay. EX1001, cols. 155-161. Two of those molecules were further tested for binding to the extracellular domain of Fzd1, although the specification does not identify the epitopes bound by those molecules. *Id.*, cols. 155-156; EX1002, ¶86; EX1003, ¶¶20-36. Examples 19-26 evaluate three of those molecules and a prior-art Wnt agonist in mice. EX1001, cols. 161-172; EX1003, ¶¶37-45. As discussed below, the examples in the Patent illustrate the unpredictability in making and identifying Wnt surrogate molecules. *See infra* §§ V.A.4, VII.A; EX1002, ¶¶ 87, 186-96, 239-46; EX1003, ¶¶144-54.

D. Prosecution History of the '278 Patent

U.S. Patent No. 11,773,171 (EX1091) is a parent of the '278 Patent, and issued with claims that define the Fzd and Lrp5/6 binding regions by specific CDR sequences. EX1091, cl. 1.

In contrast, the claims examined by the Office in this case are substantively similar to the issued claims, encompassing any Fzd and Lrp5/6 binding regions, solely defined by function. EX1008, 274, 1396. The Examiner issued two Office

Actions, in which the Examiner rejected the then-pending claims as obvious over Garcia US[2] (EX1011) in view of Wu (EX1012). EX1008, 2973-75, 3982-84; EX1002, ¶¶92-95; EX1003, ¶¶51-52.

In response, Applicant argued that, unlike the claimed "tetravalent, multispecific Wnt surrogate molecule," "the Wnt surrogates disclosed in Garcia [US] include one Fzd binding region and one LRP binding region, and are bivalent, bispecific molecules comprised of a single polypeptide and having a stoichiometry of 1:1 Fzd binder:LRP5/6 binder." EX1008, 4005 (emphasis in original). Further, "Garcia [US] does not disclose or contemplate any other stoichiometry between Fzd binding regions and LRP5/6 binding regions." *Id.* Applicant also submitted a declaration from named-inventor Dr. Li, who similarly asserted that "Garcia [US] ***only*** described Wnt surrogate molecules having 1:1 Fzd binder:Lrp5/6 binder stoichiometry" and that "Garcia's research group not only continued to teach the original 1:1 Fzd binder:Lrp5/6 binder stoichiometry, but also presented arguments ***against*** the superiority of the tetravalent format." *Id.*, 4168 (citing EX1014); EX1002, ¶96.

[2] Garcia US is a U.S. publication of the national phase entry of Garcia (EX1004), and substantively identical to it.

But contrary to Applicant and Dr. Li's characterization, Garcia discloses a "dimer" consisting of two Fzd binding regions and two Lrp5/6 binding regions. *E.g.*, EX1004, [0056]; EX1002, ¶¶97, 254-59; *see infra* § VIII.A. Moreover, Dr. Garcia's research group continued advocating for a Wnt agonist "multimerized" through, e.g., "an Fc domain." *E.g.*, EX1014, [0009]; EX1002, ¶97.

With respect to Wu, both Applicant and Dr. Li asserted that "the teachings of Wu relate to bivalent molecules that allowed the simultaneous blockade of multiple targets," which is "very different than the claimed molecules" that "agonize the canonical Wnt signaling cascade." EX1008, 4006, 4168 (emphasis in original); EX1002, ¶98; EX1003, ¶¶53-55.

The Examiner allowed the claims without providing reasons for allowance. EX1008, 4212-14; EX1002, ¶99; EX1003, ¶55. During examination of the '278 Patent, the Examiner did not raise an anticipation rejection, a rejection under 35 U.S.C. § 112(a), or a rejection under 35 U.S.C. § 112(b)—the grounds at issue in this Petition. *See infra* §§ V, VI, VII, VIII.

E. Claim Construction

Petitioner proposes construing the following two terms. EX1002, ¶¶100-19; EX1003, ¶¶66-75.

1. "Wnt Surrogate Molecule"

"Wnt surrogate molecule," a preamble term, should be construed as limiting and 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, ¶¶102-107; EX1003, ¶¶5-6, 66-75.

The Patent expressly defines "***Wnt surrogate molecules of the present invention***" as molecules that "are biologically active in binding to one or more Fzd receptor and to one or more of LRP5 and LRP6, and in activation of Wnt signaling, i.e., the Wnt surrogate molecule is a ***Wnt agonist***." EX1001, 16:52-56. By referring to molecules with these functional properties as their "invention," the named inventors acted as lexicographers. *Trading Techs., Int'l, Inc. v. eSpeed, Inc*., 595 F.3d 1340, 1353-54 (Fed. Cir. 2010); *Honeywell Int'l, Inc. v. ITT Indus., Inc.*, 452 F.3d 1312, 1318 (Fed. Cir. 2006); EX1002, ¶¶102-103; EX1003, ¶¶67-68.

Additional intrinsic evidence also indicates that the "Wnt surrogate molecule" preamble is "necessary to give life, meaning, and vitality to the claim" and thus limiting. *Catalina Mktg. Int'l, Inc. v. Coolsavings.com, Inc.*, 289 F.3d 801, 808 (Fed. Cir. 2002) (citation omitted).

The Patent defines its alleged "invention" as a "Wnt agonist" and repeatedly emphasizes being directed to "Wnt signaling pathway ***agonists***." *E.g.*, EX1001, Abstract; *see also id*., 1:34-35 (the "present invention relates generally to Wnt

signaling pathway ***agonists***"); 16:52-56 ("the Wnt surrogate molecule ***is a Wnt agonist***"). Further, every example that tested candidate molecules evaluated whether they activated Wnt signaling. *E.g.*, EX1001, cols. 156-161 (Examples 6-18: "activate" Wnt signaling). The Patent thus "underscores the importance of [the preamble] as a limitation of the claimed invention." *Deere & Co. v. Bush Hog, LLC*., 703 F.3d 1349, 1357-58 (Fed. Cir. 2012); EX1002, ¶¶104-05; EX1003, ¶¶69-72.

In addition, Patent Owner relied on the preamble to overcome a prior art rejection, thereby "transform[ing] the preamble into a claim limitation." *Catalina*, 289 F.3d at 808. Specifically, with respect to the Wu prior-art reference, Applicant argued that the claimed molecules "agonize the canonical Wnt signaling cascade," which is "an important biological distinction" from Wu that focused on "blockade of multiple targets." EX1008, 4006 (emphases in original); *id*. (the alleged invention is a "Wnt agonist molecule capable of agonizing a Wnt signaling pathway in cells") (emphasis in original). Inventor Li reinforced this in a sworn declaration, stating that the claimed molecules "agonize" Wnt signaling. *Id.*, 4168 (emphasis in original); EX1002, ¶106; EX1003, ¶¶73-74.

In view of Patent Owner's repeated reliance on the preamble term to both characterize its alleged invention and overcome the prior art, the term "Wnt surrogate molecule" should be construed as limiting and given its express definition of a "molecule that is biologically active in binding to one or more Fzd receptor and

to one or more of LRP5 and LRP6, and in activation of Wnt signaling, i.e., the molecule is a Wnt agonist." EX1002, ¶¶102-107; EX1003, ¶¶66-75.

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

The last clause of claim 1, "wherein each of the two LRP5/6 binding regions is ***fused to*** one of the two Fzd binding regions ***via a linker moiety***," should be construed to mean "wherein each of the two LRP5/6 binding regions is ***connected directly via a linker moiety*** to one and only one Fzd binding region." EX1002, ¶¶108-19.

A POSA would have understood that one Lrp5/6 binding region being "fused . . . via a linker moiety" to one Fzd binding region requires being connected *directly* via the linker moiety. *Id.*, ¶¶109-13. The Patent repeatedly uses "fused" to refer to direct connections, distinct from indirect connections among and within polypeptide chains (e.g., through disulfide bonds). *Id.*, ¶110. For example, in discussing the tetravalent formats depicted in Figure 1A (reproduced and annotated below), the Patent explains that "the Nab binder can be ***fused*** to any of the 4 available termini of the IgG," and then illustrates each distinct fusion as a direct connection to a specific terminus, i.e., "the Nab binder can be ***fused*** to the N-terminus of the IgG light chain" (upper left), the "N-terminus of the IgG heavy chain" (upper right), the C-terminus of the heavy chain (lower left), and the C-terminus of the light chain (lower right). EX1001, 150:37-44.

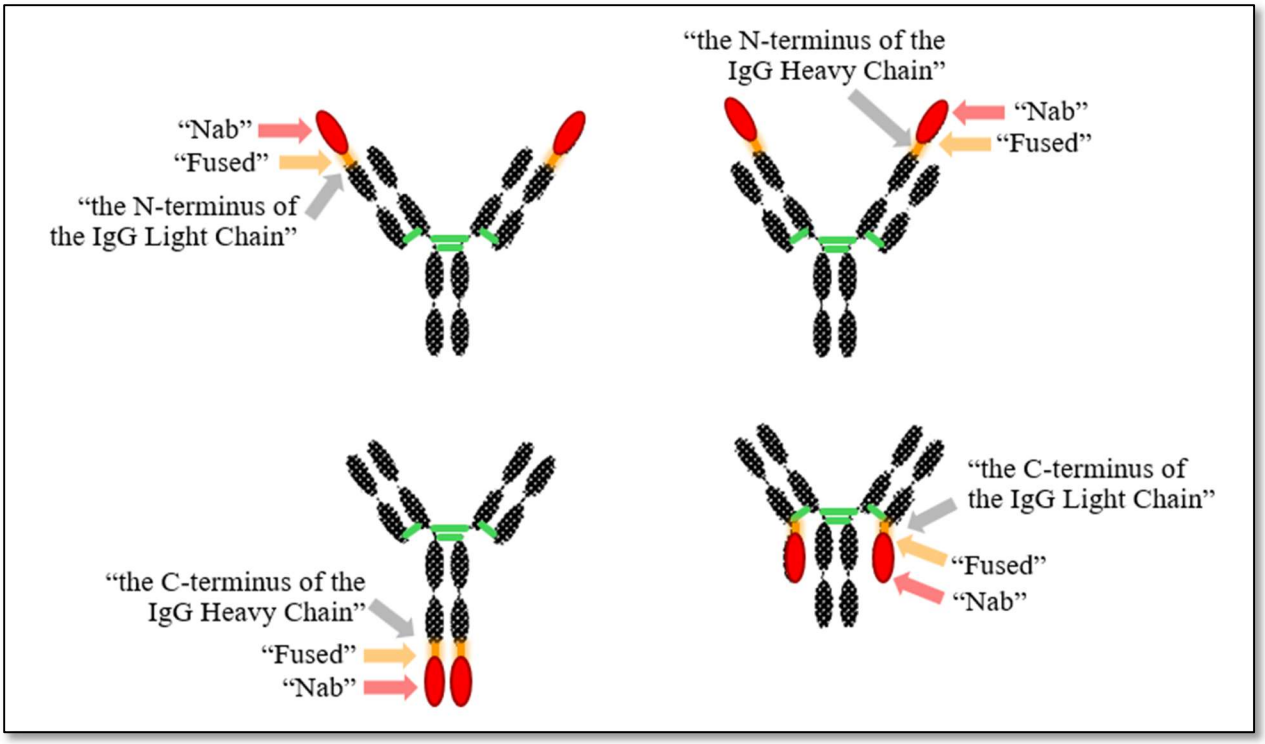


Figure 2. Annotated Patent Figure 1A

If the term "fused . . . via a linker moiety" were interpreted to encompass indirect connections (such as through interchain disulfide bonds in green), Patent Owner's characterization and distinguishing of these different formats would become incomprehensible. For example, the "Nab" in each of these depictions is *indirectly* connected to (i) both the IgG heavy and light chains (ii) at both the C-terminal and N-terminal ends. EX1002, ¶111. Distinguishing one as "fused" to a specific terminus would not be possible if the term included these indirect connections. *See also infra* § VII.B.

Petitioner's construction also follows from the specification's discussion of Figure 1B, reproduced below with annotations. EX1002, ¶112. The specification

states that "one Fab binder is first reformatted to a full IgG format" (shown in black and blue) while the "second Fab binder" (shown in white and red) "can be ***fused*** to the N-terminus of the IgG." EX1001, 150:62-64. The specification explains that the "two HC can be ***fused together with a linker*** in between" but the "LCs can be ***fused or unfused***." *Id.*, 150:64-65. If the term "fused" allowed indirect connections, the term would cease to have meaning because the LCs would be fused to one another regardless. EX1002, ¶112.

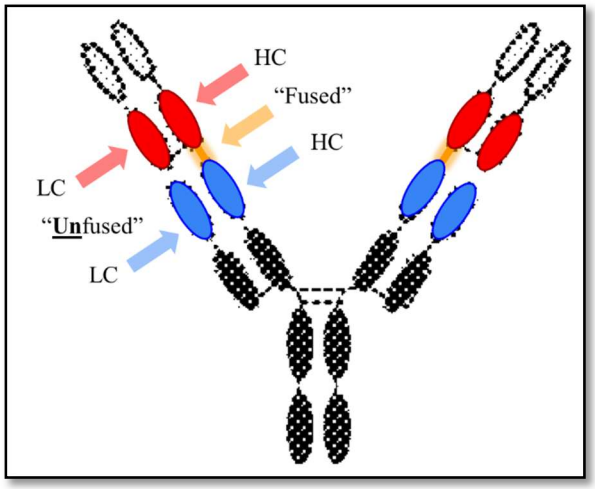


Figure 3. Annotated Patent Figure 1B

By specifying that "each of the two LRP5/6 binding regions is fused to ***one of the two*** Fzd binding regions via a linker moiety," claim 1 clarifies that each of the two LRP5/6 binding regions is connected directly via a linker moiety to ***one and only one*** Fzd binding region, not both Fzd binding regions. EX1002, ¶¶114-18. Indeed, Patent Owner consciously used specific, numerical words (e.g., "one" of the "two" Fzd binding regions) in this context while using open-ended words in other

contexts (e.g., "a" Lrp5 and/or "a" Lrp6), manifesting its intent to be limited to a singular, i.e., "one and only one," Fzd binding region. *See also WMS Gaming, Inc. v. Int'l Game Tech*., 184 F.3d 1339, 1349-50 (Fed. Cir. 1999) (construing "one of said . . . numbers" to mean "a single number, not a combination of numbers"). EX1002, ¶115.

This is consistent with how other claims of the Patent use a similar phrase. *Id.*, ¶116. Claim 2 recites that "the Fzd binding regions comprise a full immunoglobulin G (IgG), comprising two light chains and two heavy chains" and "the LRP5/6 binding regions comprise a VHH." EX1001, cl. 2. Claim 5, which depends from claim 2, recites that "each of the two LRP5/6 binding regions is fused to ***one of the light chains*** via a linker moiety." *Id.*, cl. 5. Clearly, "***one*** of the light chains" in claim 5 meant ***one and only one*** light chain to align with the formats depicted in Figure 1A, as opposed to undisclosed formats where each VHH is connected to both arms of the full-length IgG antibody. EX1002, ¶116.

Similarly, the specification distinguishes between phrases such as "one of the" and "one or more," only the latter referring to multiple options. *Compare* EX1001, 20:65-67 ("one of the binding regions is a VHH or sdAb and the other is an scFv"), *with id*., 21:36-38 ("any of these formats may comprise one or more scFvs in place of one or more VHH or sdAb"). EX1002, ¶117. Moreover, the tetravalent, multispecific molecules evaluated in the specification further support this "one and

only one" construction because no molecule tested in the Examples or depicted in Figure 1 directly connects one of the two Lrp5/6 binding regions to two Fzd binding regions via a linker moiety. Similarly, all of the molecules tested in the Examples and depicted in Figure 1 contain a linear, peptide linker that directly connects one binding region to another binding region. *Id.*, ¶118. Allowing a Lrp5/6 binding region to be directly connected to two Fzd binding regions would render the phrase "one of the two" meaningless. *Id.*, ¶¶116-18.

A contrary construction that allows for indirect connections or binding to one or both of Fzd binding regions would significantly broaden claim scope, magnifying their unpatentability. *See infra* §§ V.A.7, VI.A.4, VII.B.

For at least these reasons, the "wherein" clause should be construed to mean "wherein each of the two LRP5/6 binding regions is connected directly via a linker moiety to one and only one Fzd binding region." EX1002, ¶¶108-19.

IV. STATEMENT OF PRECISE RELIEF REQUESTED

Petitioner requests cancellation of claims 1-5 on the following grounds.

Ground	Basis	Claims
1	Lack of written description under 35 U.S.C. § 112(a)	1-5
2	Lack of enablement under 35 U.S.C. § 112(a)	1-5
3	Indefiniteness under 35 U.S.C. § 112(b)	1-5
4	Anticipation by Garcia, International Patent Publication No. WO 2016/040895 A1 under 35 U.S.C. § 102(a)(1)	1, 4

V. GROUND 1: CLAIMS 1-5 LACK WRITTEN DESCRIPTION

To satisfy the written description requirement for a genus, the specification must disclose: (1) a representative number of species falling within the scope of the genus; or (2) structural features common to the members of the genus, such that a POSA can visualize or recognize the members of the genus. *Ariad*, 598 F.3d at 1350. The Patent discloses neither.

The challenged claims are exceedingly broad, encompassing more than ***130 million*** possible tetravalent formats and an astronomical number of potential amino acid sequences. *See infra* § V.A.1. By contrast, especially given the nascent and unpredictable state of the art (*infra* § V.A.2), the Patent's extremely narrow disclosure—evaluating at most ***29*** substantially similar, tetravalent formats—is not representative of other, untested but claimed molecules (*infra* § V.A.3). The Patent itself demonstrates that a POSA could not visualize or recognize the members of the "Wnt surrogate molecule" genus or derive common structural features because numerous unspecified features—including antibody format, sequence, and orientation—unpredictably affect biological function. *See infra* § V.A.4. As further discussed below, the challenged claims are unpatentable for lack of written description support.

A. Claim 1 Lacks Written Description

1. The Scope of Claim 1 Is Exceedingly Broad

The "purpose of the written description requirement is to ensure that the scope of the right to exclude, as set forth in the claims, does not overreach the scope of the inventor's contribution to the field of art as described in the patent specification." *Ariad*, 598 F.3d at 1353-54 (citation omitted). Here, the disparity is staggering between the "scope of the right to exclude" set forth in claim 1 versus the limited "scope of the inventor's contribution" disclosed in the specification.

Claim 1 encompasses a genus of tetravalent, multispecific Wnt surrogate molecules comprising two Fzd binding regions and two Lrp5/6 binding regions without any limitation on their four sequences. It broadly allows each to comprise "an antibody or antigen binding fragment of the antibody" without limitation to, for example, target epitope, binding strength, and importantly, amino acid sequence. EX1002, ¶¶3, 120.

Claim 1 imposes only one pseudo-structural limitation, i.e., "each of the two LRP5/6 binding regions is fused to one of the two Fzd binding regions via a linker moiety." *Id.*, ¶121. As also reflected in the specification, however, the claimed linker moieties lack any structural constraints at all—such as with respect to type, composition, sequence, length, or flexibility—encompassing "but not limited to"

polypeptide and non-peptidic linkers, rigid and flexible linkers, and any length without limitation. *See* EX1001, 17:49-54, 116:40-65.

Any way considered, the scope of claim 1 is exceedingly broad. As Dr. McDonnell explains, even without considering sequence variability, claim 1 encompasses an incredible diversity of tetravalent, multispecific formats—conservatively at least ***130 million***. EX1002, ¶¶122-38.

As illustrated below, the claimed genus encompasses twenty-one possible tetravalent topologies, i.e., different arrangements among claimed components of Lrp5/6 binding regions (red), Fzd binding regions (blue), and linker moieties (orange) each directly connecting one Lrp binding region to one Fzd binding region. Each topology is shown in the orientation of the N- to C-terminus. *Id.*, ¶123. For simplicity, the grey blocks are used to illustrate constant domains that the specification explains are "necessary" to hold different polypeptide chains together. *See* EX1001, 124:5-13, 17:55-18:25; EX1002, ¶124. These constant domains can be located at the end of both Fzd and Lrp binding regions (as in the six topologies shown in the top right corner in **Figure 4** below) or between the Fzd and/or Lrp binding regions (as in the three topologies shown in the top left corner in **Figure 4** below), which the specification distinguishes as different arrangements. *Compare* EX1001, 18:48-67, *with id*., 20:62-21:37; EX1002, ¶124.

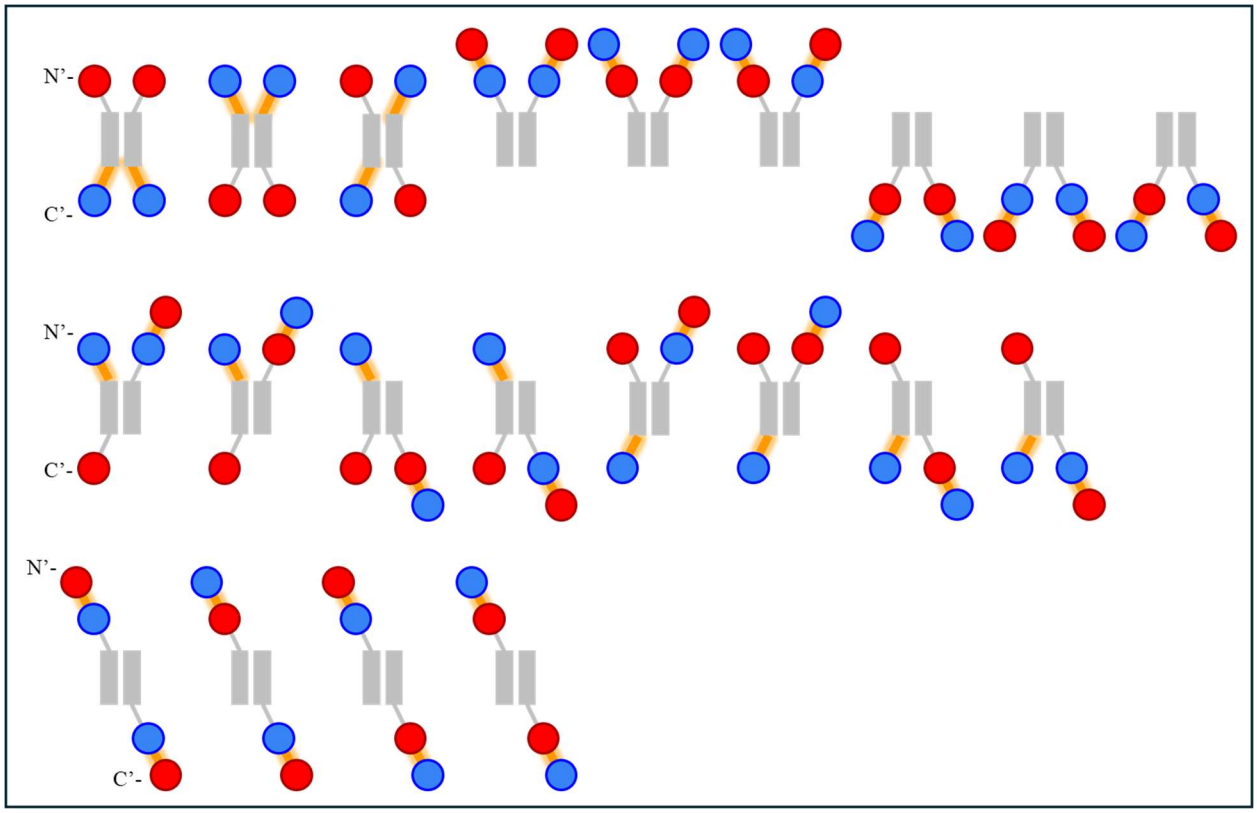


Figure 4. Possible Tetravalent Topologies (EX1002, ¶¶123-24)

In each topology, there are four binding regions, two directed to Fzd and the other two directed to Lrp5/6. EX1002, ¶125. And claim 1 allows each of these binding regions to "comprise[] an antibody or antigen-binding fragment of the antibody." EX1001, cl. 1. The specification in turn defines an "antibody" open-endedly, encompassing numerous antigen-binding fragment types, including Fab, Fab', Fv, scFv, VHH, and "any other modified configuration of the immunoglobulin molecule that comprises an antigen-binding site or fragment." *Id.*, 11:25-38. Moreover, when any of the four claimed binding *regions* comprises two binding *domains* (as in 4 of the 5 binding region types listed—Fab, Fab', Fv, scFv), binding

region can be "fused … via a linker moiety" through either its heavy chain or light chain. EX1002, ¶¶125-26. The specification expressly distinguishes these as different structural options. *See, e.g.*, EX1001, 150:32-44 (a Nab binder is connected to "the N-terminus of the IgG light chain" ("NL") versus the "N-terminus of the IgG heavy chain" ("NH")).

Accounting for these different connectivity options, the five different fragment types of Fab, Fab', Fv, scFv, and VHH result in nine different structural options for each claimed binding region. Collectively, this leads to ***6,531*** different binding region type combinations for four claimed binding regions. EX1002, ¶127. Combined with the 21 topologies within the scope of claim 1, this leads to at least ***137,781 possible different tetravalent formats***. *Id.*, ¶128.

But this does not yet account for different linker options encompassed by the claimed genus. Claim 1 encompasses two linker moieties, each linking one Lpr5/6 binding region to one Fzd binding region. *Id.*, ¶129. While there is no limitation in the claim on these linker moieties, the specification broadly distinguishes between two formats: "a polypeptide linker, or a non-peptidic linker." EX1001, 116:46-48. And while there is also no limitation in the claims for length, the specification states that the peptide linker may be from "***about 1***" to "***30 or more***" amino acids in length and every individual length options in between. *Id.*, 116:58-64. With a conservative estimate of 30 different peptide linker length options and one non-peptidic linker

option for each of the two required linker moieties, claim 1 encompasses ***132,407,541 possible different tetravalent formats***. EX1002, ¶¶130-32.

This, of course, is still an exceedingly conservative estimate. *Id.*, ¶¶133-37. According to the Patent, the "antibody or antibody-binding fragment" for each of the four binding regions are not limited to the types used in the calculations above, but instead can be things like "***synthetic variants thereof***," "***fusion proteins***," and "***any other modified configuration***." EX1001, 11:25-38. Because each of these categories encompasses essentially any possible binding fragments, the possible number of formats encompassed by claim 1 becomes essentially incalculable. EX1002, ¶135.

The conservative estimate also does not account for other elements encompassed by claim 1, including different types of constant regions and other moieties used to hold the various polypeptide chains together. *Id.*, ¶136. As noted above, the specification recognizes that constant regions, which are part of "antibody or antigen-binding fragment," are "necessary" for light or heavy chain pairing. *See* EX1001, 124:5-13; 11:25-38 ("antibody" includes "any other modified configuration of the immunoglobulin molecule"). The specification discusses different types of constant regions, including those derived from "different classes of antibodies including IgA (which includes subclasses IgA1 and IgA2), IgD, IgE, IgG (which includes subclasses IgG1, IgG2, IgG3, and IgG4), and IgM." *Id.*,

122:13-19. The specification also states that whole or partial constant regions from each class can be used and further modified to "facilitate binding between two polypeptides." *Id*., 18:2-25. In reality, the possible number of formats encompassed by claim 1 is astronomical. EX1002, ¶¶136-37.

But format breadth is only part of the problem. Target variety and unlimited potential sequence variability further compound the exceedingly broad claim scope. *Id.*, ¶¶139-43; EX1003, ¶¶113-23. Claim 1 allows each Fzd binding region to bind any Fzd. The '278 Patent states that each Fzd binding region can cross-react with "one or more" or "two or more" of Fzds 1-10, or 8 different combinations of three or more Fzds, amounting to 63 different Fzd binding options.[3] EX1001, 2:31-46. Claim 1 also allows each Lrp5/6 binding region to bind Lrp5, Lrp6, or both. Collectively, there are over ***35,000*** different Fzd/Lrp combinations that each claimed tetravalent molecule can bind. EX1002, ¶¶4, 140-43; EX1003, ¶¶4, 7, 113-23.

[3] For example, a tetravalent molecule comprising two Fzd binding regions, each of which cross-reacts with Fzd1, Fzd2, and Fzd7, would bind to two Fzd molecules, each selected from Fzd1, Fzd2, and Fzd7. In contrast, if the Fzd binding region reacts with Fzd1 only, the tetravalent molecule would still bind to two Fzd molecules, but both would be Fzd1. EX1002, ¶141; EX1003, ¶115.

Moreover, claim 1 defines each of the four binding regions solely by their functions (binding to Fzd or Lrp5/6), not by their amino acid sequences. EX1002, ¶¶144-49. As Dr. McDonnell explains, while the Patent lists a variety of Fzd and Lrp 5/6 sequences, it fails to identify common sequences or structures that confer binding to Fzd and Lrp 5/6 as well as Wnt surrogate activity (and further, discloses only a small fraction of antibodies with these functions). *Id.*, ¶¶144-48; EX1001, Tables 1A & 2A. Because of the fundamental unpredictability in antibody activity, the total number of antibody sequences capable of binding to Fzd or Lrp5/6 remains unknowable and potentially unbounded. EX1002, ¶¶40-42, 144-49; EX1049, 7; EX1079, 2-3. As such, even if claim 1 is limited to a single tetravalent format, which is not the case, the number of tetravalent, multispecific molecules that fall within the claim scope is exceedingly large, potentially impossible to calculate. EX1002, ¶¶4, 144-50.

2. The '278 Patent Fails to Address Recognized Unpredictability

Finding a multivalent, multispecific molecule that could modulate a particular biological pathway of interest was a trial-and-error endeavor as of 2017, even for relatively simple and well-characterized targets. EX1002, ¶¶60-73, 151; EX1017, 21; *see supra* § II.B. Here, the level of unpredictability was much greater given the complexity, variability, and limited knowledge of the many and variable Wnt systems. EX1002, ¶152; EX1003, ¶¶76-112, 124; *see supra* § II.A. A POSA could

not have deduced from the Patent any useful "design parameters" to predict which of the more than 130 million possible tetravalent formats within the claim scope could lead to a surrogate molecule capable of agonizing Wnt activity. EX1002, ¶¶152-61; EX1003, ¶¶124-35; EX1017, 21. Because the Patent fails to address, much less overcome, this art recognized unpredictability, its functionally defined claim 1 is "inherently vulnerable to invalidity challenge for lack of written description support." *See AbbVie Deutschland GmbH & Co. v. Janssen Biotech, Inc*., 759 F.3d 1285, 1301 (Fed. Cir. 2014).

Components and Stoichiometries: While it was postulated in 2017 that "Wnt proteins bind to a receptor complex of two molecules, FZD (FZD) and LRP5/6" (EX1063, 3), how each Wnt or non-Wnt ligand interacted with specific Fzd(s) and Lrp5/6 to trigger signaling was both poorly understood and significantly varied from one ligand to another. EX1053, 3; EX1033, 6; EX1082, 1; EX1002, ¶153; EX1003, ¶¶76-89, 125. Moreover, there was no consensus as to "the stoichiometry of the putative Wnt-FZD-LRP6 (or LRP5) complex." EX1054, 8; EX1016, Fig. 5; EX1022, Fig. 7; EX1033, Fig. 8; EX1002, ¶154; EX1003, ¶¶85, 128-29.

The Patent does not provide this information for any—much less all—of the numerous Wnt systems covered by the claimed "Wnt surrogate molecule" genus. EX1002, ¶153; EX1003, ¶¶117-20, 126-27. For example, the specification indiscriminately suggests targeting one or both of Lrp5 and Lrp6 and one or more of

Fzd1-10. EX1001, 2:2-5, 2:31-46. As discussed above, expressly contemplated binding combinations alone amount to over 35,000 different Fzd/Lrp target combinations (*see supra* § V.A.1), but the specification is silent on how a POSA could recognize those that lead to Wnt signaling activation from those that do not—other than via trial-and-error experimentation. *See PureCircle USA Inc. v. SweeGen, Inc.*, No. 2022-1946, 2024 WL 20567, at *3 (Fed. Cir. Jan. 2, 2024) ("In general the need for extensive trial and error testing argues against a finding of adequate written description.").

Likewise, the specification lacks critical detail on the stoichiometry among Fzd and Lrp molecules required for activating Wnt signaling. EX1002, ¶154; EX1003, ¶130. Yet, claim 1 of the Patent encompasses tetravalent, "multispecific" molecules, where (i) two Fzd binding regions bind to two Fzd receptors (i.e., each must bind to a different Fzd molecule); but (ii) each LRP5/6 binding region can bind to the same or different sites. EX1002, ¶154; EX1003, ¶130. As Dr. McDonnell and Dr. Kahn explain, the stoichiometry of Fzd and Lrp5/6 molecules that could be bound by each claimed tetravalent molecule encompasses five possible options: (1) two different Fzds and one Lrp5; (2) two different Fzds and two different Lrp5s; (3) two different Fzds and one Lrp6; (4) two different Fzds and two different Lrp6s; and (5) two different Fzds, one Lrp5, and one Lrp6. EX1002, ¶154; EX1003, ¶130. Because neither the prior art nor the Patent teaches the appropriate stoichiometry, it

is improperly left to others to determine for each given Wnt system which stoichiometry could lead to a functional Wnt surrogate molecule. *See Ariad*, 598 F.3d at 1353 ("research hypotheses do not qualify for patent protection"). Of course, even this assumes that one had already identified appropriate Fzd and Lrp binding sequences and formats, all of which are structurally undefined. EX1002, ¶¶120-38.

Structures and Expression Profiles: Complicating matters further, different tissues at different developmental stages expressed different amounts and types of Fzd and Lrp5/6 receptors, indicating that the distance between these targets significantly varies from one tissue to another and one timeframe to another. *Id.*, ¶155; EX1003, ¶¶98-99, 131-32; EX1030, 1-2; EX1077, 11. Consequently, the requisite flexibility and reach that tetravalent, multispecific molecules must have over their targets needs to be determined case-by-case: for example, sparse Fzd and Lrp5/6 concentrations may require high flexibility and extended reach while dense Fzd and Lrp5/6 concentrations conversely may require a compact format. EX1002, ¶¶71, 155; EX1003, ¶¶131-32.

The specification does not overcome the variability and unpredictability in Wnt agonist activity. EX1002, ¶¶156-57; EX1003, ¶133. For instance, the specification acknowledges that "the spacing between the binding domains can . . . modulate the signal strength" and the "distance between binding domains" therefore must be "enforced." EX1001, 116:48-56. Rather than providing guidance on what

that "distance" may be and how that "distance" can be "enforced," the specification leaves it to a POSA to "select[]" the appropriate distance "depending on the desired use." *Id*. But the specification allows for any linker ("not limited to those disclosed herein") and only speculates that any types of linkers or distances between those binding regions could potentially work, e.g., peptidic or non-peptidic linkers of "less than about 100 angstroms" that can alternately be "rigid" or "flexible." *Id.*, 17:52-54, 116:46-58; EX1002, ¶156; EX1003, ¶133. Even more broadly, claim 1 allows for any "linker moiety" linking the Lrp5/6 binding regions and Fzd binding regions. EX1001, cl. 1; EX1002, ¶157. Otherwise, claim 1 does not require any structural constraints for how the two binding regions to Fzd or Lrp 5/6 are joined to one another. EX1001, cl. 1; EX1002, ¶157. As such, a POSA is again left to extensive trial-and-error experimentation, further exacerbating the inadequacy of the written description. EX1002, ¶¶155-57; EX1003, ¶133; *see PureCircle*, 2024 WL 20567, at *3.

Other Variables: In 2017, it was known that different Wnt and non-Wnt ligands interact with their corresponding receptors with ***different*** strengths and at ***different*** sites. EX1003, ¶¶82-84, 134; EX1025, Table 1 (different binding kinetics between Wnt3, 4, 5 and Fzd1, 2, 4, 5, 7, 8); EX1054, 7 (different sites in Lrp6 bound by Wnt1 and Wnt3); EX1016, 1, 3. As such, it was recognized that "differences in affinities of different Wnt and Frizzleds and their local concentrations . . . would

determine to which signaling branch a particular Wnt couples," and that "the analysis of a particular Wnt ligand or Frizzled receptor in a certain biological context always requires an investigation of how the Wnt signal is transduced." EX1065, 4.

Nothing in the specification addresses this significant variability from one Wnt system to another. EX1002, ¶¶158-59; EX1003, ¶135. While recognizing that the molecules bind to "two or more different epitopes, e.g., one or more Fzd receptor, and LRP5 and/or LRP6" (EX1001, 17:11-14), the specification does not teach which epitopes within Fzd and Lrp5/6 are appropriate for activating Wnt signaling. EX1002, ¶159; EX1003, ¶135. In fact, the specification does not even disclose specific epitopes bound by tested putative Wnt surrogate molecules. *See* EX1001, Table 3; EX1002, ¶159. The prior art also provides no meaningful guidance on this point, and in fact the binding sites in Fzd and Lrp for many Wnt ligands had not been characterized. EX1003, ¶¶80-86.

With respect to binding strengths, the specification acknowledges that a Wnt surrogate molecule must "specifically" bind Fzd and Lrp5/6. EX1001, 2:1-9. While it defines "specific binding" to mean "more frequently, more rapidly, [and] with greater duration and/or with greater affinity," the specification fails to teach which frequency, rapidity, duration, or affinity correlates with Wnt signaling activation. EX1001, 120:66-121:3. Nor does the specification disclose relevant information, e.g., affinity, for the tested Wnt surrogate molecules. *See id.*, Table 3; EX1002, ¶160;

EX1003, ¶135; EX1020, 2. At most, the specification offers an exceedingly broad range of affinities (e.g., "a K_D of 50 μM or lower"), which, as Dr. McDonnell explain, is no guidance at all. EX1001, 4:39-44; EX1002, ¶160.

Inconsistent with the specification's scant guidance, claim 1 is open to any Fzd binding region and any Lrp5/6 binding region, regardless of which Fzds and Lrp5/6 they bind, the specific epitopes bound by the Fzds and Lrp5/6 binding regions, and how strongly they bind to Fzds 1-10 and Lrp5/6. EX1002, ¶¶158-60; EX1003, ¶¶134-35. This again renders the written description inadequate.

* * *

In sum, Wnt biology in December 2017 was unpredictable, and there was very little information that a POSA could rely on to find suitable tetravalent formats. Because the '278 Patent fails to bridge this chasm, a POSA would need to empirically evaluate each potential tetravalent format, with each potential Fzd and Lrp5/6 binding region, hoping that the resulting molecules would bind to appropriate Fzds and Lrp5/6 at appropriate sites with appropriate strength to activate a Wnt signaling pathway. EX1002, ¶¶151-61; EX1003, ¶¶124-35. The Patent at most represents "a wish list of properties" that a Wnt surrogate molecule must have, which is not enough to satisfy the written description requirement. *Centocor Ortho Biotech, Inc. v. Abbott Lab'ys*, 636 F.3d 1341, 1351 (Fed. Cir. 2011).

3. The ’278 Patent Fails to Disclose a Representative Number of Species Across the Scope of Claim 1

Contrary to the expansive scope of tetravalent, multispecific molecules encompassed by claim 1, the named inventors explored only a very small corner of the claimed genus in terms of both format and biological target. *See AbbVie*, 759 F.3d at 1299-300. In other words, the ’278 Patent fails to disclose a representative number of species. EX1002, ¶¶5-6, 162-85.

First, as discussed above, Dr. McDonnell identified at least twenty-one tetravalent topologies, conservatively leading to at least ***130 million*** tetravalent formats for the Wnt surrogate molecules of claim 1. *See supra* § V.A.1; EX1002, ¶¶120-38. In contrast, the topologies and formats evaluated in the Patent are exceedingly narrow, and not representative of other, unexplored topologies and formats.

As annotated below, among twenty-one different tetravalent topologies, the specification evaluated only five (red box), leaving sixteen entirely untested. EX1002, ¶163; EX1001, Table 3. As Dr. McDonnell explains, these unevaluated topologies are materially different from those tested. EX1002, ¶164.

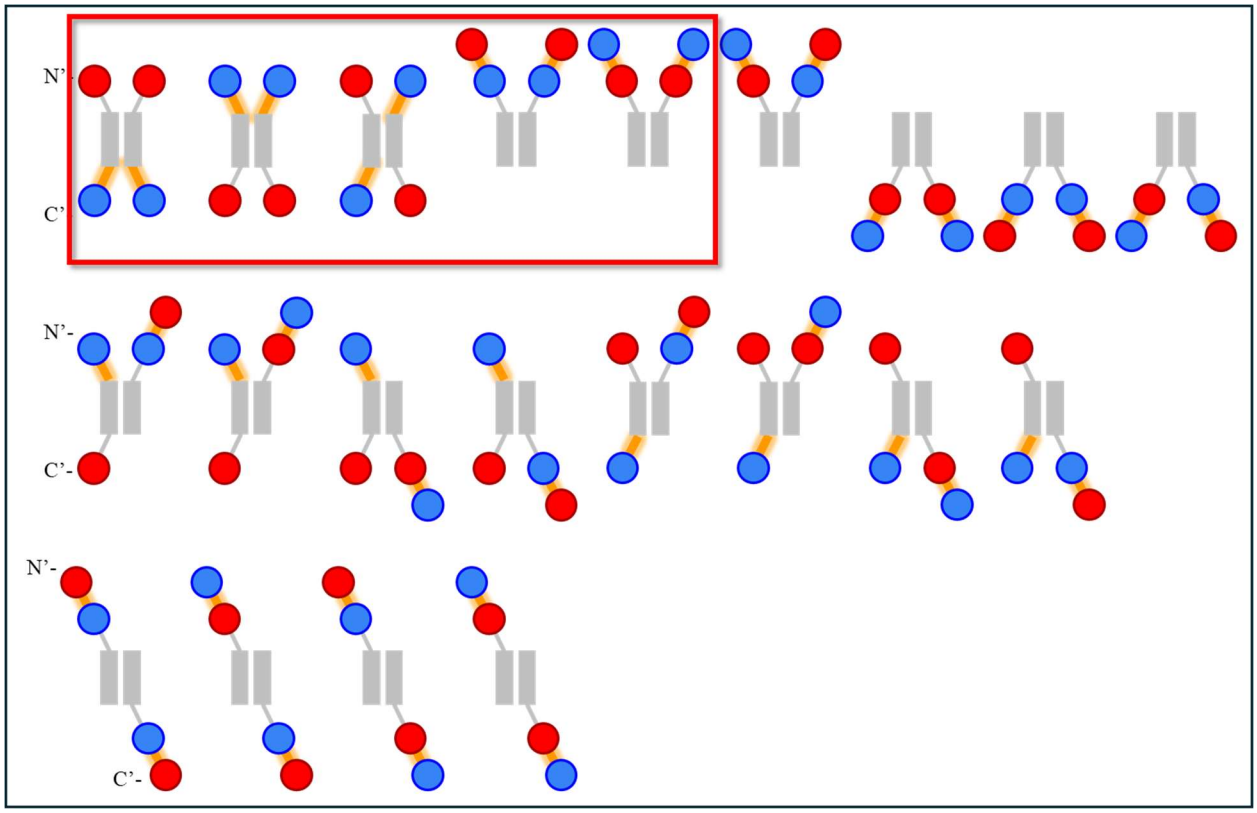


Figure 5. Possible Versus Tested (Red Box) Topologies (EX1002, ¶163)

For example, topologies in which the two binding regions are oriented in the opposite direction from their counterpart binding regions (as shown in the bottom row) confer greater reach than any of the tested topologies. This can unpredictably impact activity, particularly if the binding partners need to be simultaneously engaged to trigger agonist activity. EX1002, ¶164. A POSA would have concluded that the limited tested topologies are not representative of other untested topologies, for example, those that are capable of extending further with greater flexibility. *Id.*, ¶164.

Second, the specific formats tested in the specification are also not representative of the full scope of claim 1. *Id.*, ¶¶165-77. As reproduced below, the specification evaluated just ***29*** of ***over 130 million*** possible tetravalent formats. *Id.*, ¶165. As Dr. McDonnell explains, the limited number of formats tested in the specification is not representative of other formats using different antibody fragment types, arrangements, and orientations, all of which impact how the claimed molecules interact with Fzds and Lrp5/6. *Id.*, ¶¶166-68.

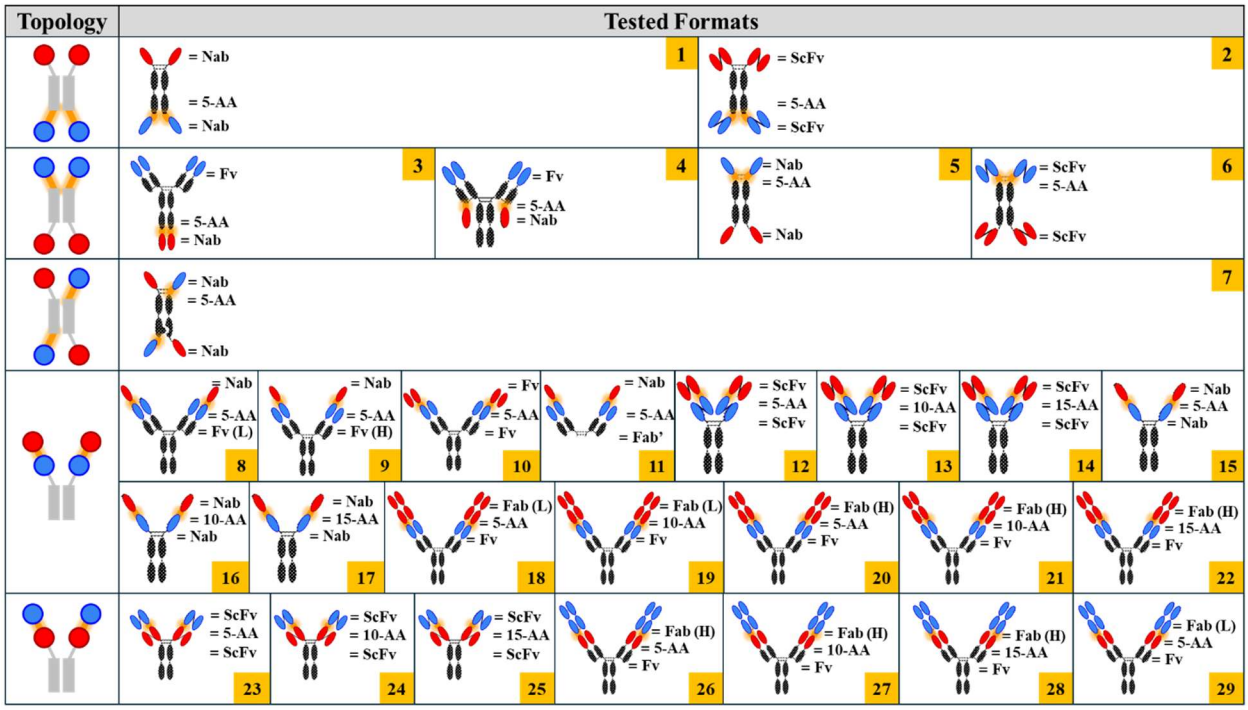


Figure 6. Tested Formats in the Patent (EX1002, ¶165)

The Patent itself illustrates that one format is not representative of another format for any given pair of specific Fzd and Lrp5/6 binding region sequences. *Id.*, ¶¶169-70. As summarized in **Figure 7** below, the Patent evaluated four formats

using the TOPFlash assay as a proxy for Wnt signaling activation.[4] For the same pair of Fzd and Lrp5/6 binding region sequences (18R5 paired with 26), three formats (NL, NH, CH) produced responses in this assay, while the remaining one (CL) failed to do so. EX1001, Figs. 9C; EX1002, ¶169. The same phenomenon was seen with another pair of Fzd and Lrp5/6 binding region sequences (R2M3-26). EX1001, Figs. 9A; EX1002, ¶169. From this, a POSA would have understood that the chance of activating Wnt signaling for any given pairing of Fzd and Lrp5/6 binding region sequences unpredictably varies format-to-format, i.e., one is not representative of another. EX1002, ¶170.

[4] As discussed below, the assay used in the specification suffers from various defects, obscuring the interpretation of results. *See infra* § VII.A.

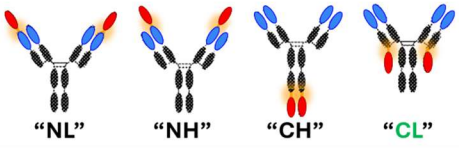
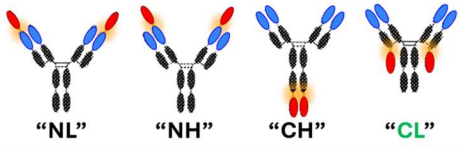
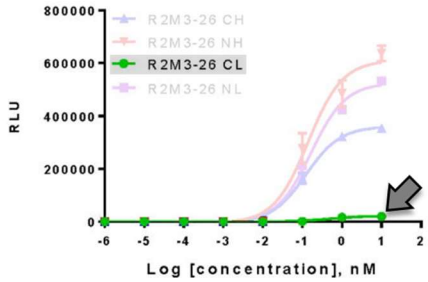
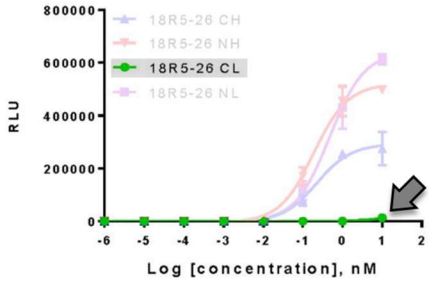
	Figure 9A	Figure 9C
Common Sequence Pairing	Fzd: R2M3 Lrp5/6: 26	Fzd: 18R5 Lrp5/6: 26
Formats		
Result		

Figure 7. Tetravalent, Multispecific Molecules

(Annotated Patent Figures 9A and 9C)[5]

Tetravalent, multispecific molecules made and tested since the priority date of the Patent confirm the lack of representative species. *Id.*, ¶¶171-72; *Amgen Inc. v. Sanofi*, 872 F.3d 1367, 1374-75 (Fed. Cir. 2017) (post-priority date evidence can be used to illustrate lack of written description). Named co-inventor Yang Li filed a patent application, EX1081 ("Li"), after the '278 Patent. Li's Figure 11 compares molecules comprising a pair of specific anti-Fzd and anti-Lrp5/6 antibody sequences (18R5 and 1115.3, respectively). EX1081, Table 6A, Fig. 11A. As shown below,

[5] Instead of the black-and-white figures in the Patent, Petitioner reproduced corresponding color figures from one of the provisional applications (EX1007).

these otherwise identical molecules flip the relative positioning of the Fzd and Lrp5/6 binding regions. *Id.*, 187. One set of molecules was active in a TOPFlash assay ("L1:5:F1:Fc," "L1:10:F1:Fc," "L1:15:F1:Fc"). The other set was not ("F1:5:L1:Fc," "F1:10:L1:Fc," "F1:15:L1:Fc"). EX1002, ¶172. Ultimately, "suitable formats must be identified by generating and comparing the functionalities of different formats." EX1017, 21; EX1002, ¶172.

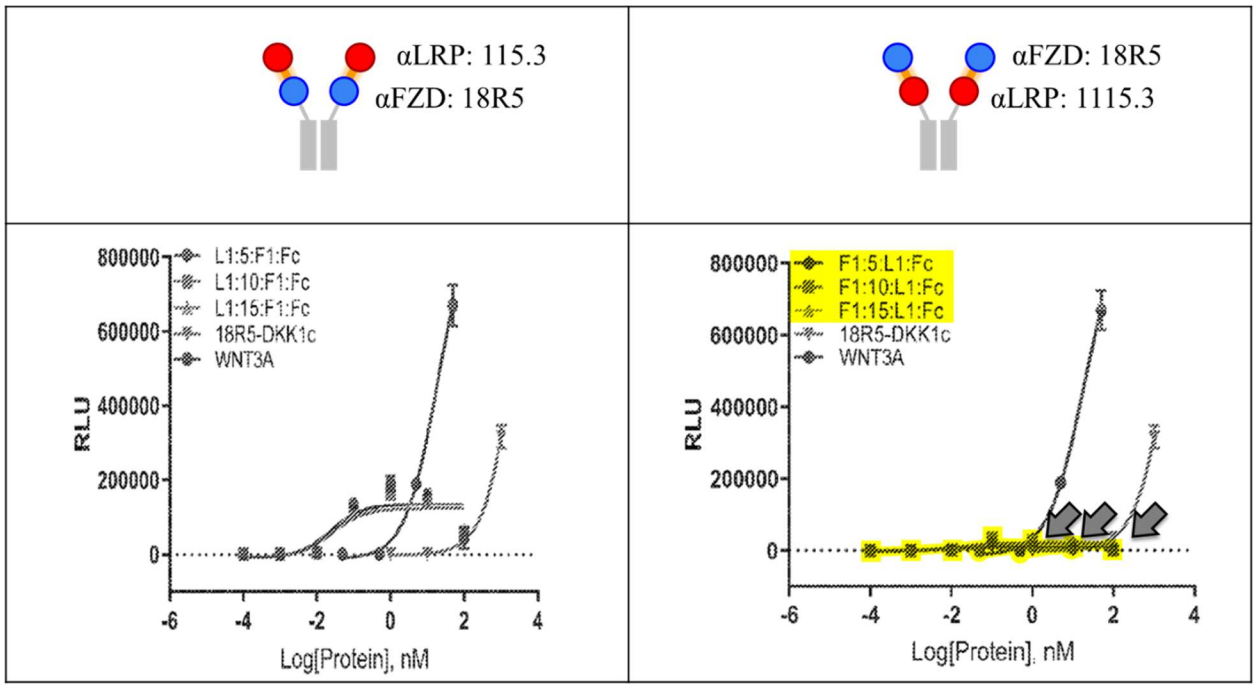


Figure 8. Tetravalent, Multispecific Molecules (Annotated Li (EX1081) Figure 11A; WNT3A and 18R5-DKK1c Are Positive Controls)

Even for the limited formats tested, the specification narrowly relies on the same type of linkers—peptide linkers of 5, 10, or 15 amino acids made exclusively of glycine (G) and serine (S) residues. EX1001, Table 3A, Fig. 19; EX1002, ¶173. As Dr. McDonnell explains, molecules with flexible, G/S-rich linkers of 5-15 amino

acids are not representative of molecules with non-peptidic, rigid, or peptidic linkers of substantially different lengths. EX1002, ¶¶173-76. Indeed, the unpredictable effects of different linkers were acknowledged in the specification. EX1001, 116:48-52 ("the spacing between the binding domains can . . . modulate the signal strength" and is selected based on the "desired use").

The field of tetravalent molecules similarly recognized this unpredictability. For example, DiGiammarino compared various linker types and lengths, including G-rich linkers and those made of other amino acids. EX1024, Table 1. DiGiammarino reported that tetravalent formats with a "hinge" linker or a G-rich linker "have nearly identical linker lengths, but show >4-fold difference" in target binding affinity. *Id*., 5; EX1002, ¶174. Even among G-rich linkers, linker length and glycine content could unpredictably affect flexibility and therefore activity. EX1002, ¶175; *see also* EX1074, 7-8. A POSA reading the '278 Patent would have known that, as reported in the prior art, even "minor changes in linker length" "can be crucial determinants for functionality" of tetravalent formats. EX1017, 21. The linkers evaluated in the specification are too similar to represent the full spectrum of other claimed but untested linkers. EX1002, ¶¶173-76.

The tested molecules also are not representative of the full scope of claimed molecules because all of them are bispecific (i.e., each Fzd and each Lrp binding region binds to the same site, respectively), while claim 1 encompasses trispecific

and tetraspecific molecules binding multiple different sites in Fzd and/or Lrp5/6. *See* EX1001, Table 3A; EX1002, ¶¶178-79. Indeed, the '278 Patent provides ***no evidence*** that trispecific and tetraspecific molecules can activate Wnt signaling. *See generally* EX1001. Nor does it provide any guidance on designing trispecific and tetraspecific molecules that function as Wnt surrogate molecules, even though these molecules constitute the majority of possible candidates. *See id*. A POSA would have understood that this missing information was essential. EX1002, ¶179; EX1017, 21 (factors determining functionality in a tetravalent, multispecific molecule include "bivalent, trivalent or multivalent binding to one or both antigens in a simultaneous or mutually exclusive manner").

Additionally, the molecules evaluated in the '278 Patent include a limited number of anti-Fzd antibody sequences directed to a subset of Fzd receptors, whereas claim 1 encompasses molecules binding to any one or more Fzd receptor type. EX1002, ¶¶180-81; EX1003, ¶¶117-20. Specifically, the specification identified at least 63 different Fzd combinations to which each Fzd binding region can bind. *See supra* § V.A.1. But only fourteen anti-Fzd antibody sequences were evaluated, which, according to the Patent, bind only 8 different Fzd combinations. EX1001, Tables 1B & 3; EX1002, ¶181; EX1003, ¶¶119-20. This leaves 55 expressly recognized Fzd combinations, such as Fzd3, 6, and 10, where the Patent

lacks any example or evidence showing they can function as part of a Wnt surrogate molecule. EX1002, ¶181; EX1003, ¶¶7, 36, 119-20.

In addition, the only *in vitro* activity assay used in the specification is a TOPFlash assay, which measures only the canonical Wnt signaling pathway. EX1002, ¶182; EX1003, ¶¶19, 72, 121; EX1001, Examples 2-18. The Patent thus fails to have tested or shown possession of any species that activates noncanonical signaling (even *in vitro*). EX1002, ¶182; EX1003, ¶¶19, 72, 121.

This limited disclosure is insufficient to support the full scope of claim 1. By December 2017, different Fzds were known to function differently, some activating the canonical Wnt signaling pathway, some activating the noncanonical one, and some both. EX1003, ¶¶94-95; EX1077, 4-6. A molecule that binds to one specific Fzd or Fzd combination and activates the canonical Wnt signaling pathway would not have been deemed representative of others that bind to other Fzds or Fzd combinations. EX1002, ¶183; EX1003, ¶¶113-21, 125-35.

The inability to extrapolate from one molecule to another with different Fzd specificity is confirmed by Li. EX1081; EX1002, ¶184. In Figure 5A, Li compared two molecules with the same tetravalent format, a "R2M3-26" molecule that engages Fzd1, 2, 5, 7, and 8 and a "4SC10-3" molecule that engages Fzd6. EX1081, 178. Notwithstanding having the same tetravalent format, "R2M3-26" produced

responses in a TOPFlash assay while the 4SC10-3 molecule "was ***not*** able to effectively activate beta-catenin-dependent signaling in 293STF reporter cells." *Id*.

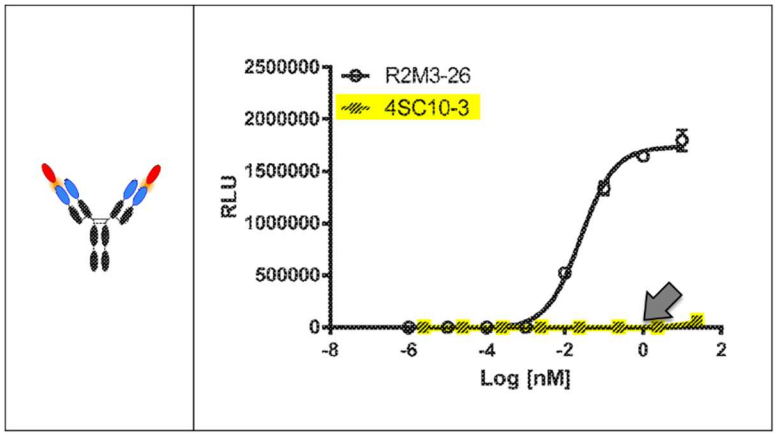


Figure 9. Tetravalent, Multispecific Molecules

(Annotated Li (EX1081) Figure 5A)

For at least these reasons, the species disclosed in the '278 Patent are limited in both quantity and quality and are not representative across the vast scope of claim 1. EX1002, ¶¶162-85; EX1003, ¶¶113-21, 125-35.

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

The claimed molecules are a composite of multiple functionally-defined elements, i.e., tetravalent, multispecific Wnt surrogate molecules comprising two Fzd binding regions and two Lrp5/6 binding regions. EX1002, ¶¶120, 186. The only arguable "structural" feature is that each of the two Lrp5/6 binding region is connected directly to one and only one Fzd binding region via a "linker moiety." EX1001, claim 1; EX1002, ¶¶121, 186. However, a POSA would have understood

that this is insufficient to provide the claimed "Wnt surrogate" function. EX1002, ¶¶155-57, 186; EX1003, ¶¶122, 131-33. The '278 Patent itself demonstrates this lack of correlation. EX1002, ¶¶5-6, 187-96.

First, as reproduced below, several molecules that share this claimed structural feature did ***not*** produce responses in a TOPFlash assay in the absence of R-spondin (a biological potentiator). EX1001, Figs. 2D, 3D, 6A, 13B[6]; EX1002, ¶187; EX1003, ¶¶148-49. As Dr. Kahn explains, these molecules would not ordinarily be considered Wnt "surrogates" because they required R-spondin to be active. EX1003, ¶¶36, 88; EX1063, 5; EX1060, 9-11; EX1053, 4-5; EX1093, 1-3. The Patent fails to comment on the lack of response in the absence of R-spondin, and moreover characterizes these molecules as "activ[e]" based on positive responses observed in the presence of R-spondin. *E.g.*, EX1001, 155:13-40; 156:54-67. In any event, the Patent fails to establish whether any of these molecules would be "biologically active." *Id.*, 16:52-56; *see supra* § III.E.1.

[6] In the Patent, Figure 13B is a duplicate of Figure 13E. Figure 13B of the underlying provisional (EX1007) appears to match the description of the figure in the specification.

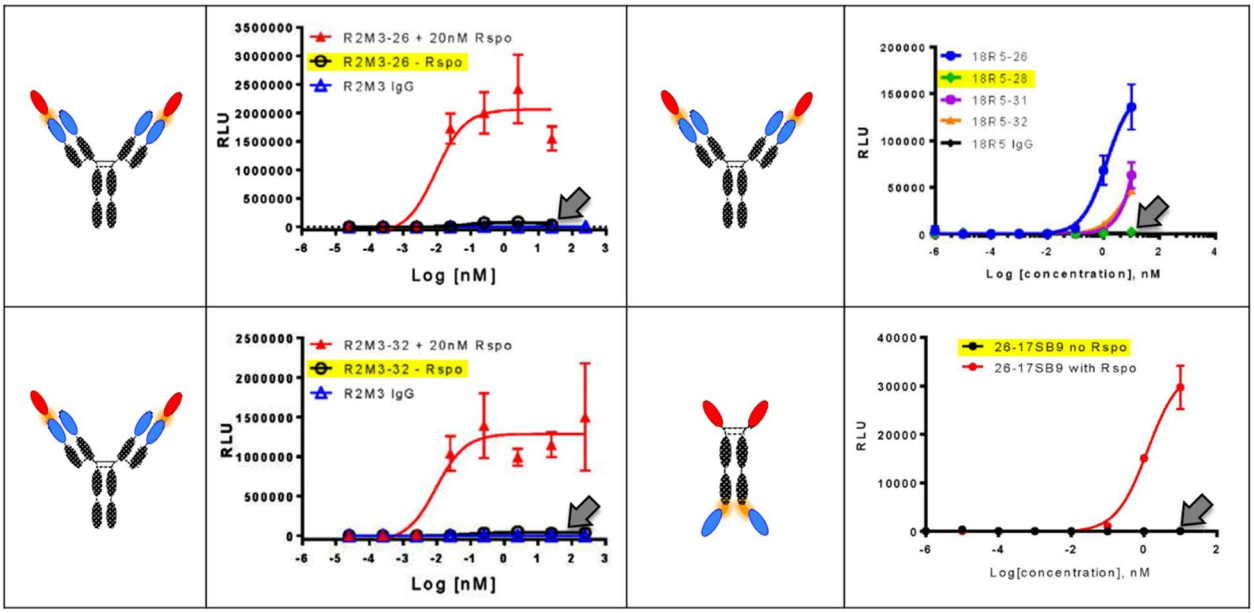


Figure 10. Tetravalent, Multispecific Molecules

(Annotated Patent Figures 2D, 6A, 3D, and 13B)

Second, despite having two Lrp5/6 binding regions each connected directly to one and only one Fzd binding region via a linker moiety, multiple molecules still did ***not*** produce responses in a TOPFlash assay even in the presence of R-spondin, as reproduced below. EX1001, Figs. 5B, 8B; EX1002, ¶188. Several other molecules produced miniscule responses in those assays, which Dr. Kahn explains lack a positive control, and would not be understood as "biologically active." EX1003, ¶¶144-47; EX1001, Fig. 14E. The specification fails to address these inactive molecules or explain how a POSA could distinguish active tetravalent, multispecific molecules from those that are not active, other than by empirically making and testing them. *See* EX1001, 156:32-52, 157:14-29; EX1002, ¶188.

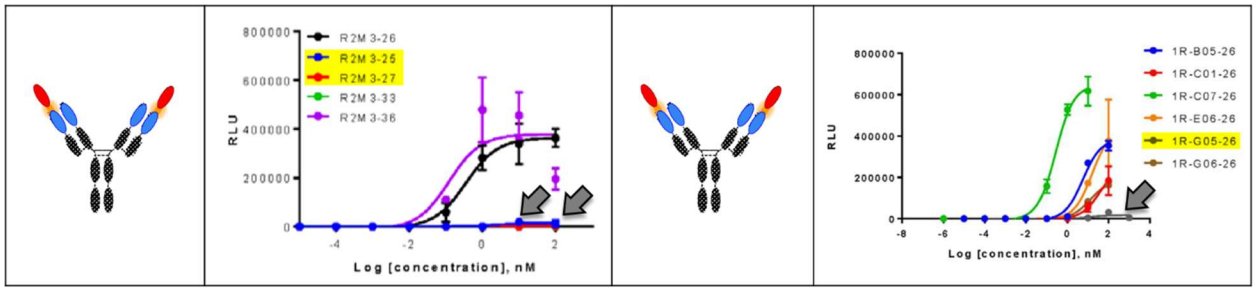


Figure 11. Tetravalent, Multispecific Molecules

(Annotated Patent Figures 5B and 8B)

Third, even with the same tetravalent format, the activity of molecules unpredictably depends on which antibody fragments are used. EX1002, ¶¶189-90; EX1003, ¶122. Figure 9, reproduced below, is illustrative. In Figure 9, four tetravalent formats were evaluated, labeled "NL," "NH," "CH," and "CL." EX1001, Fig. 9. Notably, the "CL" format was active only with a particular pair of specific anti-Fzd and anti-Lrp5/6 antibody sequences (R2M3 and 32, respectively) even though other pairs (R2M3 and 26 or 18R5 and 26) were active in the other tested formats.

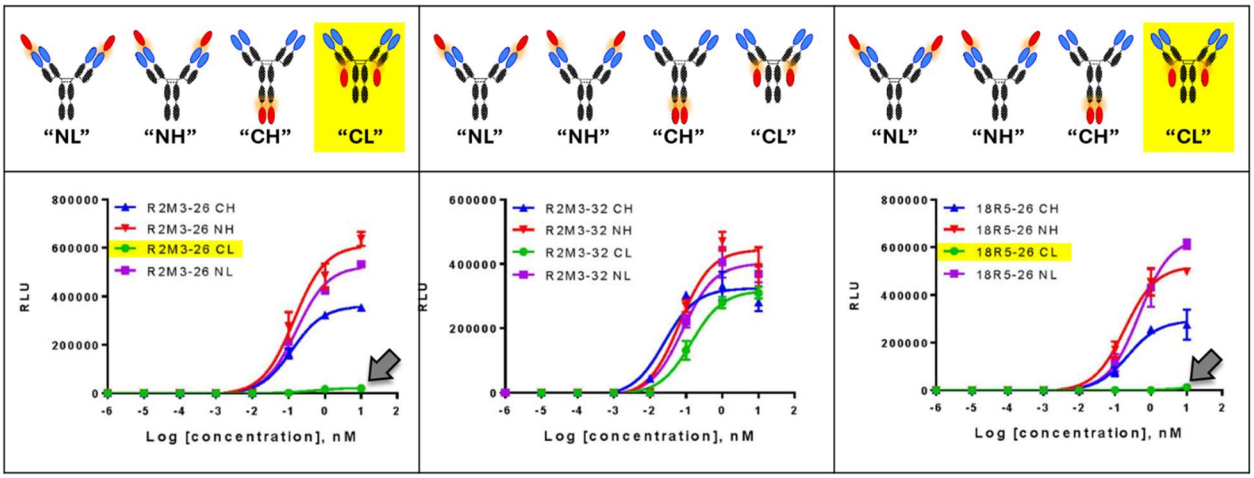


Figure 12. Tetravalent, Multispecific Molecules (Annotated Patent Figures 9A-C)

As Dr. McDonnell explains, this unpredictable variation illustrates that the claimed "Wnt surrogate" activity depends on structural features that are ***not*** enumerated in the claims or specification, e.g., which specific amino acid sequences are used and how those sequences are arranged. EX1002, ¶190. Indeed, in discussing Figure 9, the '278 Patent expressly acknowledges that additional structural features control Wnt activation: "the attachment location of the fusion and the geometry between the Fzd and LRP binding domains play roles in the ability of the Wnt surrogates to activate Wnt signaling." EX1001, 157:47-50. In other words, the '278 Patent admits that "attachment location" and "geometry" need to be empirically evaluated. EX1002, ¶190.

Fourth, during prosecution, both Applicant and its declarant argued that the claimed molecules "***simultaneously engage*** two cell surface coeffector molecules (Fzds and Lrp5/6) required to agonize the canonical Wnt signaling cascade."

EX1008, 4006; *see also id.*, 4168 (inventor Li asserting the same). But the specification fails to teach a common structural feature that accomplishes this simultaneous binding. EX1002, ¶¶191-94. As reproduced below, several candidate molecules produced responses in a TOPFlash assay at intermediate concentrations, but their effects tapered off at higher concentrations. EX1001, Figs. 14A, 15G; EX1002, ¶¶192-93; EX1003, ¶¶152-53.

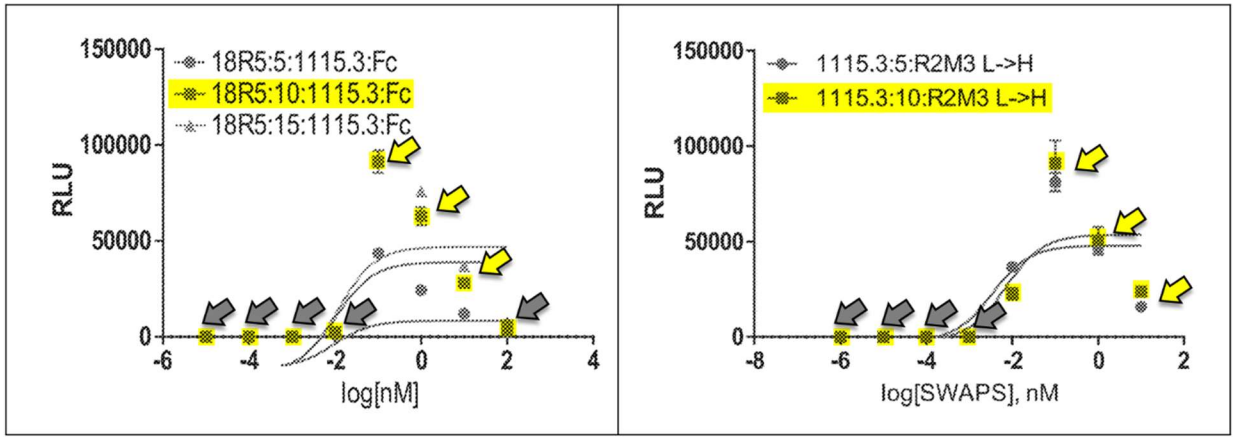


Figure 13. Annotated Patent Figures 14A and 15G

As Dr. McDonnell explains, this "hook" effect indicates that some molecules at higher concentrations are no longer able to engage Fzd and Lrp5/6 simultaneously as the molecules begin to bind just Fzd or Lrp5/6 separately. EX1002, ¶¶192-93. The specification does not explain how to account for this unpredictability, let alone why some, but not all, candidate molecules experience a hook effect. *Id.*, ¶194. This again confirms that being a "Wnt surrogate" as claimed depends on extrinsic factors. *Id.* Stated differently, factors other than being "tetravalent," "multispecific" or

having Fzd and Lrp5/6 regions "fused via a linker" affect the claimed function of Wnt agonism. *Id.*

Tetravalent, multispecific molecules made and tested after the Patent further confirm that the Patent fails to disclose a structure-function correlation. *Id.*, ¶195. As discussed above, Li reported several inactive tetravalent, multispecific molecules despite having one Lrp5/6 binding region directly connected to one Fzd binding region via a linker moiety. EX1081, 178, 187, Figs. 5A, 11A; EX1002, ¶¶171-72, 184. As stated in Li, the "effects of orientation on the reporter activity" appears to be due to "the geometry of the receptors assembled by the surrogate molecules." EX1081, 187. Li confirms that features beyond the functional and limited structural features of the Patent—such as orientation and geometry—unpredictably impact activity. EX1002, ¶195.

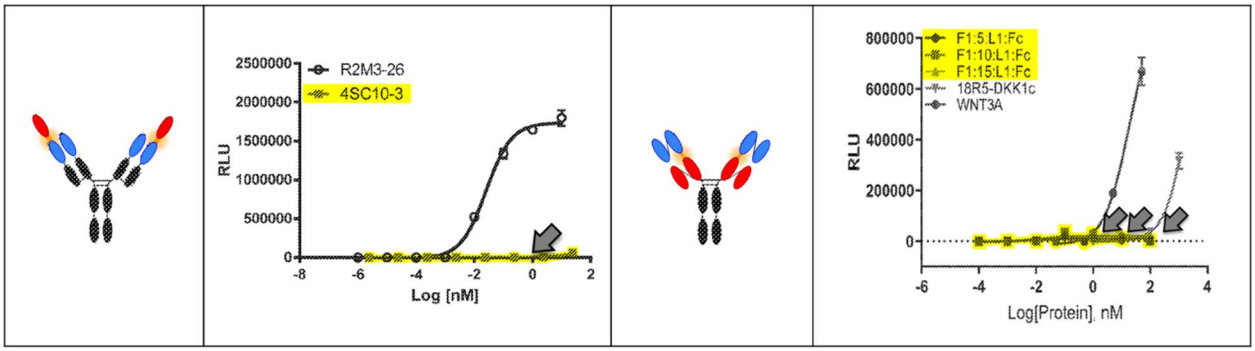


Figure 14. Tetravalent, Multispecific Molecules

(Annotated Li (EX1081) Figures 5A and 11A)

In sum, the Patent both demonstrates and acknowledges that unclaimed structural features may unpredictably control how a given tetravalent, multispecific

molecule behaves. Yet, it fails to teach a POSA how to address this unpredictability other than by making and testing each molecule under a wide variety of conditions. EX1001, 157:47-50; EX1002, ¶¶186-96; EX1003, ¶¶122-35. The numerous inactive molecules disclosed in the '278 Patent and reported thereafter further confirm that no adequate structure-function correlation is disclosed. EX1002, ¶¶187-95; EX1003, ¶¶148-49, 152-53. The '278 Patent therefore fails to disclose a common structural feature correlating to the claimed "Wnt surrogate" function. *Ariad*, 598 F.3d at 1350.

5. The '278 Patent Fails to Satisfy the Written Description Requirement for Additional Reasons

The tetravalent, multispecific molecules of claim 1 comprise multiple functional elements: two Lrp5/6 binding regions and two Fzd binding regions. *See supra* § V.A.1. The specification further fails to adequately describe these functional elements. *See Boston Sci. Corp. v. Johnson & Johnson*, 647 F.3d 1353, 1365 (Fed. Cir. 2011) ("the test for written description is the same whether the claim is to a novel compound or a novel combination of known elements").

As discussed above, both claim 1 and the specification encompass Fzd binding regions that bind to "one" or "two" of Fzds 1-10 as well as 8 different specified combinations of three or more Fzds, amounting to 63 different Fzd binding options. EX1001, 2:31-46; EX1002, ¶¶141, 180, 197-98; EX1003, ¶¶113-15. In contrast, Table 1B "confirmed binding" to only 17 of those 63 target options.

EX1001, Table 1B; EX1002, ¶¶180, 198; *see supra* § V.A.3. The specification *does not* disclose even a single example for the other 46 of 63 specifically identified Fzd targets and *does not* teach how a POSA could identify binding regions for them other than the brute force making and testing. EX1002, ¶¶180, 198-99. Especially given the absence of any binding regions directed to the majority of the identified Fzd binding targets, a POSA reading the specification would have understood that the inventors were *not* in possession of the full scope of claimed Fzd binding regions. *Univ. of Rochester v. G.D. Searle & Co*., 358 F.3d 916, 926-27 (Fed. Cir. 2004) (the specification disclosing "nothing more than a hoped-for function for an as-yet-to-be-discovered compound," i.e., "a research plan" is inadequate).

6. Federal Circuit Precedent Supports Lack of Written Description

The inadequacy of claim 1 is also confirmed by Federal Circuit precedent invalidating even less overbroad functionally-defined genus claims for lacking sufficient written description support.

In *Juno*, for example, the Federal Circuit invalidated claims directed to CD19 binding scFvs because while "scFvs in general were well-known," "the realm of possible CD19-specific scFvs was vast and the number of known CD19-specific scFvs was small." 10 F.4th at 1339-42. That same reasoning applies here. Although various components of the claimed molecules, *e.g.*, Fzd binding regions, Lrp5/6 binding regions, and linkers linking these regions, had been reported in the art, the

"realm" of possible tetravalent, multispecific molecules that could activate a Wnt signaling pathway is exceedingly vast while the specification's disclosures are extremely limited. *See supra* §§ V.A.1-5. Indeed, despite claiming broadly, the specification fails to disclose essential information—either a structure-function correlation or a representative number of species—that could "reasonably convey[] to [a POSA] that the inventor[s] had possession of the claimed subject matter as of the filing date." *Juno*, 10 F.4th at 1341-42 (citing *Ariad*, 598 F.3d at 1351); *see supra* §§ V.A.1-5.

Patent Owner may argue that the novel feature of claim 1 is not the specific components (e.g., Fzd or Lrp5/6 binding regions) of the claimed Wnt surrogate molecules, but their combination as tetravalent, multispecific molecules. An analogous argument was considered and rejected in *Juno*, where the patentee argued that the invention is not a CD19 binding scFv, but a "backbone," which combines the scFv and other cellular components, and therefore does not need to describe more than the backbone itself. *See Juno*, 10 F.4th at 1341. The Federal Circuit disagreed, noting that the claims at issue are "not limited to just the claimed backbone; they also include the functional scFv for binding the target." *Id*. As with the invalidated claims in *Juno*, claim 1 is not just about piecing components together but also achieving "Wnt surrogate" functionality. As the Federal Circuit explained, the test for written description "is the same whether the claim is to a novel compound or a

novel combination of known elements." *Id*. (citing *Boston Sci.*, 647 F.3d at 1365). As discussed above, claim 1 fails the written description test for its purported "novel" feature. *See supra* §§ V.A.1-5.

AbbVie is also instructive. There, the Federal Circuit determined that the disclosure of "about 300 antibodies" was not sufficient to support claims directed to any and all anti-IL-12 antibodies because the disclosed species were highly similar to one another, thereby "only abid[ing] in a corner of the [claimed] genus." *AbbVie*, 759 F.3d at 1291, 1299-300. Like the 300 antibodies in *AbbVie*, the tetravalent, multispecific molecules disclosed in the '278 Patent are substantially similar—having a small group of similar formats, bispecific binding, closely related peptidic linkers of similar lengths, and directed to a subset of the claimed Fzd receptors. *See supra* § V.A.3. Claim 1 nevertheless attempts to claim every tetravalent, multispecific molecule that would achieve the desired function. *See AbbVie*, 759 F.3d at 1301. The claim therefore lacks written description.

Another fundamental problem with the '278 Patent was addressed in *Idenix Pharmaceuticals LLC v. Gilead Sciences Inc.*, 941 F.3d 1149 (Fed. Cir. 2019). The '278 Patent lacks written description support because it "provides lists or examples of supposedly effective [tetravalent, multispecific molecules], but do[es] not explain what makes them effective, or why." *Id.* at 1164; *see supra* § V.A.4. "As a result, a POSA is deprived of any meaningful guidance into what compounds

beyond the examples and formulas, if any, would provide the same result." *Idenix*, 941 F.3d at 1164. The "written description requirement specifically defends against such attempts to 'cover any compound later actually invented and determined to fall within the claim's functional boundaries.'" *Id.* at 1164-65 (citing *Ariad*, 598 F.3d at 1353).

For all these same reasons, the Board should find that claim 1 of the '278 Patent is unpatentable.

7. Rejecting Petitioner's Construction Would Further Exacerbate the Written Description Problem

As discussed above, Petitioner proposes construing the last "wherein" clause as "wherein each of the two LRP5/6 binding regions is ***connected directly via a linker moiety*** to ***one and only one*** Fzd binding region." *See supra* § III.E.2. To the extent that Patent Owner disagrees and argues for a broader construction, it would exacerbate the lack of written description support for claim 1 because the broader construction would sweep in tetravalent formats that were unknown to a POSA in December 2017 and are materially different from those evaluated in the specification. EX1002, ¶¶200-03; EX1072.

Idenix is instructive. There, the patentee contended that the specification described a claimed genus of nucleosides, including those having specific modifications and chemical orientations, even though it was undisputed that the specification disclosed no such nucleosides. *Idenix*, 941 F.3d at 1163-64. Under

those facts, the Federal Circuit concluded that the patent lacked adequate written description because it "fails to provide sufficient blaze marks to direct a POSA to the specific subset" of nucleotides that possessed the claimed function. *Id*. at 1164. As in *Idenix*, the challenged Patent discloses formats that are substantially similar to one another but materially different from those arising later. EX1002, ¶¶200-03; EX1072. To the extent that Patent Owner contends that claim 1 is broad enough to encompass formats in which each of two Lrp5/6 binding regions is ***not*** connected directly via a linker moiety to one and only one Fzd binding region, claim 1 is further invalid for failing to provide sufficient blaze marks to direct a POSA to those undescribed formats.

B. Claims 2-5 also Lack Written Description

1. Claims 2, 3, and 5

Claim 2 recites that "the Fzd binding regions comprise a full immunoglobulin G (IgG), comprising two light chains and two heavy chains, and the LRP5/6 binding regions comprise a VHH." EX1001, cl. 2. Each of claims 3 and 5 depends from claim 2, and recites that the "LRP5/6 binding region is fused to the N-terminus or the C-terminus of the heavy chain or is fused to the N-terminus or the C-terminus of the light chain" (claim 3) or that "each of the two LRP5/6 binding regions is fused to one of the light chains via a linker moiety" (claim 5). *Id*., cls. 3, 5. These additional features do not save these claims. EX1002, ¶¶204-09.

For the reasons set forth above for claim 1, and as additionally elaborated here, the specification fails to disclose a representative number of species falling within the scope of these claims. *See supra* § V.A.3; EX1002, ¶¶162-85, 205. The claims encompass trispecific and tetraspecific molecules, whereas all of the molecules evaluated in the specification are bispecific. EX1002, ¶¶85, 179, 205. The claims encompass molecules binding to any of ten Fzds, whereas the disclosed species are limited to only a subset of Fzds. *Id.*, ¶¶140-43, 180-81, 205. The claims encompass the use of essentially any peptidic or non-peptidic linkers, but the disclosed species falling with the scope of claims 2, 3, and 5 use only two highly-similar peptidic linkers of the same length (GSGGS or GSGSG). EX1001, Table 3, Fig. 19; EX1002, ¶¶129-30, 173-76, 205.

Many of the molecules illustrating the lack of structure-function correlation for claim 1 share the features additionally recited in claims 2, 3, and 5. *See supra* § V.A.4; EX1002, ¶¶186-96, 206-08. These molecules confirm that the additional recited features do not correlate with the claimed Wnt surrogate function, as other features, such as the specific amino acid sequences tested, appear determinative. EX1002, ¶¶187-88, 206-08.

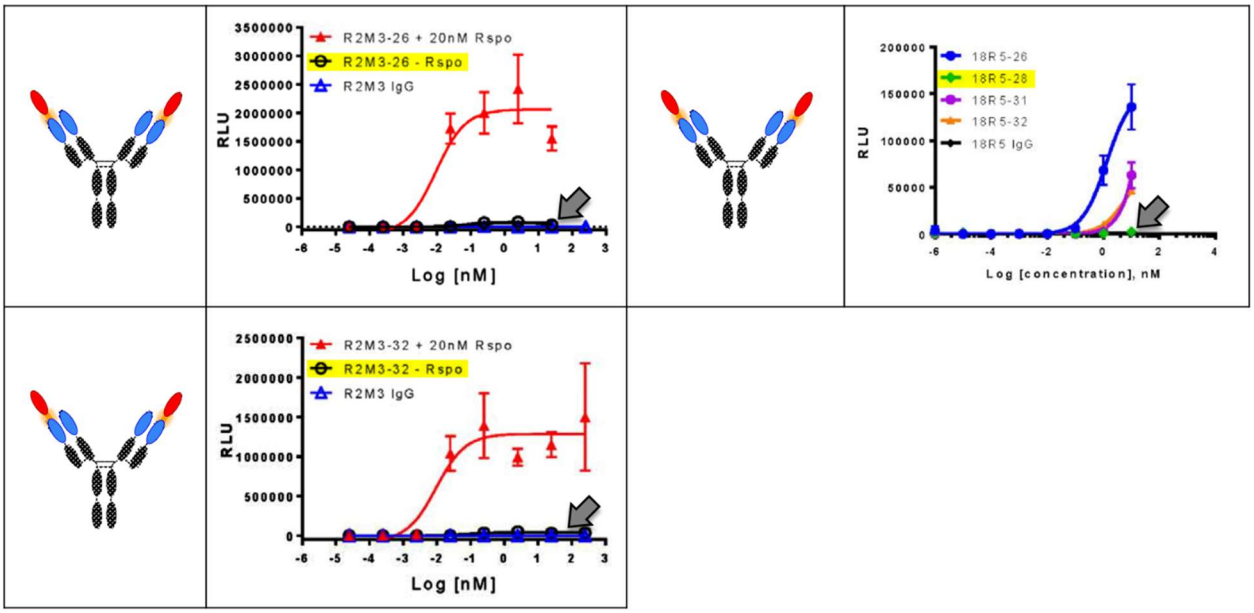


Figure 15. Molecules in the Absence of R-spondin

(Annotated Patent Figures 2D, 6A, and 3D)

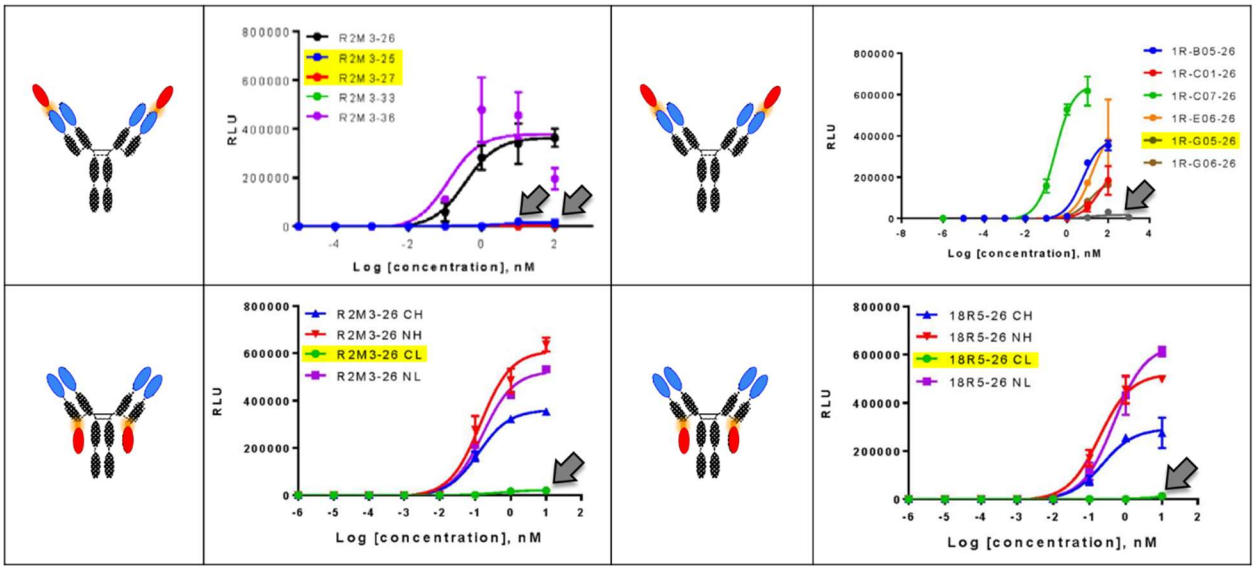


Figure 16. Molecules in the Presence of R-spondin

(Annotated Patent Figures 5B, 8B, 9A, and 9C)

Thus, claims 2, 3, and 5 are invalid for lack written description. *Id.*, ¶¶204-09.

2. Claim 4

Claim 4 recites a "pharmaceutical composition comprising a physiologically acceptable excipient, diluent, or carrier, and the Wnt surrogate molecule according to claim 1." EX1001, cl. 4. Claim 4 does not narrow the incredibly broad scope of the tetravalent, multispecific Wnt surrogate molecules recited in claim 1, and is therefore invalid for the same reasons. EX1002, ¶210.

VI. GROUND 2: CLAIMS 1-5 LACK ENABLEMENT

A. Claim 1 Is Not Enabled

A claim is not enabled when making and using its full scope would require undue experimentation. *See Amgen*, 598 U.S. at 612. Each of the *Wands* factors indicates that the challenged claims are not enabled. *See In re Wands*, 858 F.2d 731, 737 (Fed. Cir. 1988). The breadth of the claims is vast, unbound by any meaningful structural limitation. *See infra* § VI.A.1. The specification lacks sufficient guidance or working examples to allow a POSA to distinguish tetravalent, multispecific molecules that activate Wnt signaling from those that do not. *See infra* § VI.A.2. The relevant art was nascent and unpredictable, requiring a POSA to engage in trial-and-error experimentation to find other undisclosed tetravalent, multispecific Wnt surrogate molecules. *See infra* § VI.A.3. Because making and testing even a single candidate molecule would have been challenging, making and testing functionally defined candidate molecules within the more than 130 million different tetravalent

formats would have required an unreasonable amount of experimentation. *See infra* § VI.A.4.

1. Breadth and Nature of Claim 1

Claim 1 lacks meaningful structural limitations. EX1002, ¶¶120-50, 211-13; *see supra* § V.A.1. Claim 1 is directed to tetravalent, multispecific Wnt surrogate molecules comprising two Fzd binding regions and two Lrp5/6 binding regions. Each binding region is defined solely by function, rather than by structure. EX1002, ¶¶120, 211. The claim recites that "each of the two LRP5/6 binding regions is fused to one of the two Fzd binding regions via a linker moiety." EX1001, cl. 1. But the specification fails to place any limit on the structure for this "linker moiety"—instead, it can be polypeptide or non-peptidic, rigid or flexible, and of any length or sequence. *See* EX1001, 116:40-65; EX1002, ¶¶121, 212.

The breadth of claim 1 is therefore exceedingly broad. EX1002, ¶¶120-50, 211-13; *see supra* § V.A.1. Claim 1 encompasses over ***35,000*** target combinations and more than ***130 million*** tetravalent formats, and the number of Wnt surrogate molecules that potentially fall within the scope of this claim is astronomical because the amino acid sequences of the Fzd and Lrp5/6 binding regions are undefined. EX1002, ¶¶120-50, 213; EX1003, ¶¶113-23; *see supra* § V.A.1. Claim 1 is indisputably vast in scope.

2. Limited Working Examples and Guidance in the Specification

"[T]he more a party claims, the broader the monopoly it demands, the more it must enable." *Amgen*, 598 U.S. at 613. Here, the narrow disclosure of the '278 Patent fails to enable the incredible breadth of claim 1. EX1002, ¶¶9, 214-16. As discussed, the specification evaluated just ***29*** of more than ***130 million*** tetravalent formats. The evaluated molecules are all bispecific, contain only one kind of linker (G/S flexible linkers), and bind to only a subset of Fzds and Fzd combinations. *Id.*, ¶¶162-85, 214; *see supra* § V.A.3. These limited working examples do not teach or suggest whether and how other untested formats, target combinations, and binding region sequences would function as a Wnt surrogate. EX1002, ¶¶162-85, 214; *see supra* § V.A.3. Moreover, all of the working examples evaluated in *in vitro* activity assays lack a positive control, preventing a POSA from determining whether these are even "biologically active" as claimed. EX1003, ¶¶36, 145-47.

The rest of the specification fails to remedy these deficiencies. EX1002, ¶¶151-61, 186-96, 215-16; EX1003, ¶¶124-43; *see supra* §§ V.A.2, V.A.4. While recognizing that properties such as flexibility, valency, and specificity are critical for Wnt agonism, the specification fails to teach how to identify appropriate flexibility, valency, and specificity for each candidate molecule—other than through trial-and-error experimentation. EX1002, ¶¶151-61, 215-16; EX1003, ¶¶124-43; *see supra* § V.A.2. Indeed, the specification merely speculates that a wide range of

"enforced" distances (e.g., "less than about 100 angstroms"), specificities (e.g., "a K_D of 50 μM or lower"), and valencies (e.g., all possible combinations of one or two Fzd molecules and one or two Lrp5/6 molecules) can impact Wnt agonism. EX1002, ¶¶151-61, 215-16; EX1003, ¶¶124-43; *see supra* § V.A.2. Further, while the specification admits 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," it is silent on ***which*** 'attachment location" and ***which*** "geometry" for each pair of Fzd and Lrp5/6 binding region sequences actually confer Wnt agonism. *See* EX1001, 157:47-50; *see supra* §§ V.A.2, V.A.4.

Because the specification provides no meaningful guidance such as "a quality common to every functional embodiment," a POSA would be "forced to engage in painstaking experimentation to see what works." *Amgen*, 598 U.S. at 614 (citation omitted).

3. State of the Art, Level of Ordinary Skill in the Art, and Unpredictability in the Art

The relevant art—both nascent and unpredictable—would not have helped a POSA avoid trial-and-error experimentation. EX1002, ¶¶8, 40-50, 60-80, 151-61, 217-20; EX1003, ¶¶76-100, 124-43; *see supra* §§ II, V.A.2. As discussed, the literature discussing multivalent, multispecific formats recognized that there was no "one best format" that worked for all possible biological applications. EX1017, 21. Instead, "suitable formats must be identified by generating and comparing the

functionalities of different formats." *Id.*; EX1002, ¶¶70-73, 151, 217. Reflecting the nascent state of the field, there were only two bivalent, bispecific molecules approved by FDA as of 2017, neither of which was directed to Fzd or Lrp5/6. EX1017, Table 3; EX1090. Further, at that time, no trispecific or tetraspecific molecule had been approved by FDA (for any targets), and even as of today no tetravalent molecule has been approved by FDA. EX1002, ¶¶73, 217.

The field of Wnt modulators was particularly nascent and unpredictable. EX1043, 15 ("Targeting the WNT signalling pathway in the clinic using small-molecule therapeutics or even biologics is still in its infancy."). The Wnt signaling cascade was recognized as "bewilderingly complex." *Id.*, 1. Numerous Wnt and non-Wnt ligands were known to interact with multiple different receptors with different strengths and at different sites. EX1003, ¶¶82-84, 134; *see supra* §§ II.A.1, V.A.2. In 2017, "the stoichiometry of the putative Wnt-FZD-LRP6 (or LRP5) complex" was unresolved. EX1054, 8. Factors such as local cellular conditions were also known to influence Wnt signaling. EX1065, 4-5; EX1002, ¶218; EX1003, ¶¶83-86, 98-100. On top, researchers struggled to adequately characterize the Wnt agonistic activity of a candidate molecule because then-existing assays suffered from various shortcomings such as cell-type dependency and lack of comprehensiveness. EX1043, 10-11; EX1003, ¶¶101-12, 136. Tellingly, there was no FDA-approved

molecule specifically developed to activate Wnt signaling in 2017. *See* EX1043, 11, Table 1. There is no such molecule to date. EX1002, ¶219; EX1003, ¶89.

A POSA could not have derived any general rule or set of parameters for making tetravalent, multispecific molecules for activating Wnt signaling because of the complexity and unknowns of Wnt biology. EX1002, ¶¶60-73, 151-61, 217-20; EX1003, ¶¶76-100, 124-43; *see supra* §§ II, V.A.2. As such, a POSA would have to make and test each candidate molecule. EX1002, ¶¶151-61, 217-20; EX1003, ¶¶124-43.

4. Amount of Experimentation Required

The amount of experimentation required to make and use the full scope of claim 1 would have been undue. EX1002, ¶¶2, 9, 221-31; EX1003, ¶¶4, 8, 124-43. As a starting point, a POSA would need to make and test candidate antibodies that bind to each or both of Lrp5/6 as well as those that bind one or more of Fzds 1-10. EX1002, ¶ 222; *see* EX1001, 2:31-46. In 2017, there was no reliable way to predict which amino acid sequence could bind an intended target. EX1002, ¶¶40-44; EX1047, 12-13. As such, a POSA would need to make and test each candidate antibody in an appropriate binding assay, which was a time-consuming and resource-intensive process. EX1002, ¶¶45-50. Moreover, the Patent illustrates that multiple rounds of binding testing may be required to identify antibodies capable of binding to intended targets. *Compare* EX1001, Table 1A (reporting "initial binding" of

"004S-C12" and "004C-D12" to Fzd6), *with id*., Table 1B (reporting "n.b" for both clones); EX1002, ¶225; EX1010, 4.

There were additional complications unique to Wnt signaling. As Dr. Khan explained, it was known that different Wnt and non-Wnt ligands interact with their corresponding receptors at different sites, meaning that there was no one Fzd or Lrp5/6 epitope on which a POSA could focus on in making binding sequences. EX1002, ¶223; EX1003, ¶¶82-84; *see supr*a §§ II.A, V.A.1. Making and testing candidate antibodies that bind to any epitopes in the over 35,000 different Lrp/Fzd target combinations (and many possible binding sites within each Fzd and Lrp5/6) within the claim scope would have required undue experimentation, as the Supreme Court held in *Amgen* in invalidating claims directed to all antibodies binding to a single target epitope. *See Amgen*, 598 U.S. at 612-15.

But making functional Fzd and Lrp5/6 binding regions is only the beginning. EX1002, ¶226. Here, a POSA would then need to take those tested binding regions and transform them into tetravalent, multispecific formats, which would have been a significant challenge in 2017. *Id.*, ¶¶60-73, 226-27. Each tetravalent, multispecific format is made of multiple different heavy chains and/or multiple different light chains. *Id.*, ¶¶68-69. Upon production from cells, these chains are prone to mispair with unintended chains, significantly lowering the overall yield of correctly paired, tetravalent, multispecific molecules. *See* EX1017, 2. Further, while

heterodimerization modules potentially reduced mispairing between two heavy chains, they did not prevent mispairing between light chains. *Id*., 11. As such, "sophisticated upfront engineering" was often required to address production complications, and even then, it was "not invariably successful" because in many cases, mispairing among various chains was impossible to avoid. *See* EX1069, 5-6; EX1002, ¶227. In sum, getting enough material for testing a single molecule was a "sophisticated upfront engineering" challenge, and doing so for molecules with more than ***130 million*** different tetravalent, multispecific formats—together with the astronomical set of potential binding regions—would have required an unreasonable amount of experimentation. EX1002, ¶¶222-27.

Testing those candidate molecules would have also required an unreasonable amount of experimentation. *Id.*, ¶¶228-31; EX1003, ¶¶136-43. In 2017, evaluating a candidate molecule for Wnt agonism was not a straightforward task. EX1003, ¶¶101-12. As discussed, the TOPFlash assay, which is the most used *in vitro* assay in the '278 Patent, only measured canonical Wnt signaling. *See supra* §§ II.A.2, V.A.3; EX1003, ¶¶19, 121. A POSA interested in identifying a Wnt surrogate molecule that could activate noncanonical Wnt signaling would need to test each candidate molecule in an assay nowhere identified in the specification. *See* EX1001, 117:26-118:36 (listing assays used for "measuring the level of canonical Wnt/β-catenin signaling" only); EX1003, ¶¶19, 121.

Adding to the challenge, the ***same candidate molecule*** could produce inconsistent responses depending on the choice of assays and assay conditions. *See infra* § VII.A; EX1003, ¶¶110-11, 144-54. For example, even with the TOPFlash assay, both the prior art and the specification demonstrate that the same molecule could agonize Wnt signaling, antagonize Wnt signaling, or show no activity depending on which cells were used, which Fzd and Lrp5/6 were expressed in those cells, whether a potentiator like R-spondin was used, and what concentrations were tested. *See* EX1056, 11 (reporting that Wnt5a can inhibit or activate Wnt signaling in the TOPFlash assay depending on whether 293 cells express Fzd4); EX1001, Fig. 2D ("R2M3-26" showing activity only in the presence of R-spondin); *id.*, Figs. 6A and 6B ("18R5-28" showing no activity in 293 cells without R-spondin but showing activity in A375 cells without R-spondin); *id.*, Fig. 14A (three candidate molecules showing activity at 0.1 nM but no activity at 100 nM); EX1003, ¶¶110-11, 144-54; *see infra* § VII.A. This extreme variability from one assay condition to another would have required a POSA to test each candidate molecule in multiple cell types, multiple concentrations, and with or without R-spondin. EX1003, ¶¶136-39.

As Dr. Kahn explains, a TOPFlash assay in 2017 typically took about a week, from growing cells to reading output signals. *Id.*, ¶¶108, 140-42. Even assuming that (i) a POSA tested one candidate molecule per target combination in only two cell types at two concentrations with R-spondin (*e.g.*, 4 reactions per candidate

molecule) and (ii) each assay is run weekly in a high throughput manner (e.g., 384 reactions per run), testing candidate molecules with over 35,000 target combinations for Wnt agonism would require running nearly 400 assays, amounting to more than 7 years of work. *Id.*, ¶¶140-41. Likewise, testing just one candidate molecule for each tetravalent format for Wnt agonism would require testing 130 million different tetravalent, multispecific formats, involving nearly ***1.4 million*** assays and more than ***26,000 years*** of work. *Id.*, ¶142. This conservative estimate does not account for the time and effort required to make those candidate molecules, and ignores the uncertainty of negative assay results given the variability and unpredictability associated with different assay conditions. EX1002, ¶¶229-30; EX1003, ¶¶141-42. Making and using the full scope of claimed tetravalent, multispecific Wnt surrogate molecules would have required undue experimentation. EX1002, ¶¶221-31; EX1003, ¶¶139-43.

Of course, a broader construction of the "wherein" clause would further exacerbate the enablement problem. *See supra* §§ III.E.2, V.A.7. A broader construction would encompass formats that had not been made for any targets as of 2017. *See supra* § V.A.7. This would require extensive additional experimentation, all without any meaningful guidance or working examples in the specification. *See supra* § VI.A.2. In sum, regardless of whether Petitioner's construction is adopted or not, claim 1 is not enabled. EX1002, ¶¶7, 232.

5. Supreme Court and Federal Circuit Precedents Support Lack of Enablement

Claim 1 is indistinguishable from claims invalidated in recent cases such as *Amgen*, *Seagen*, *Baxalta*, and *Idenix*, except that it is in many ways ***more complex*** and ***less predictable*** than the technology in those cases. Mirroring the expansive scope of the invalidated claims in those cases, claim 1 encompasses molecules of more than ***130 million*** tetravalent formats, with each functionally defined binding region encompassing an unknowable number of possible sequences. *See supra* § VI.A.1; *Amgen*, 598 U.S. at 613 ("millions of candidates"); *Seagen Inc. v. Daiichi Sankyo Co*., 160 F.4th 1322, 1329 (Fed. Cir. 2025) ("over 47 million different tetrapeptide units"); *Baxalta Inc. v. Genentech, Inc*., 81 F.4th 1362, 1366 (Fec. Cir. 2023) ("millions of potential candidate antibodies"); *Idenix*, 941 F.3d at 1159 ("at least many, many thousands"). Like the disclosures in those cases, the specification of the '278 Patent fails to provide "a quality common to every functional embodiment" that would allow a POSA to distinguish tetravalent, multispecific molecules that activate Wnt signaling from those that do not. *Amgen*, 598 U.S. at 614; *Seagen*, 160 F.4th at 1333; *Baxalta*, 81 F.4th at 1366-67; *Idenix*, 941 F.3d at 1160-61. *See supra* §§ V.A.4, VI.A.2.

Thus, the only way for a POSA to find other, undisclosed Wnt surrogate molecules would be to engage in trial-and-error experimentation, i.e., making and testing each candidate molecule. *See supra* §§ VI.A.2, VI.A.3. As the Supreme

Court and Federal Circuit has repeatedly held, the requirement for such trial-and-error experimentation is the hallmark of nonenablement. *See Amgen*, 598 U.S. at 615 (disclosure offering a POSA "little more than advice to engage in trial and error" is not enabling) (citation omitted); *Seagen*, 160 F.4th at 1333 ("ADC science was so unpredictable that a skilled artisan would be required to use an assay to test whether any given ADC with a given drug moiety meets that functional limitation"); *Baxalta*, 81 F.4th at 1367 (disclosure that require a POSA to "make candidate antibodies and screen them to determine which ones perform the claimed functions" is not enabling); *Idenix*, 941 F.3d at 1162 ("The immense breadth of screening required to determine which [candidate molecules] are effective . . . can only be described as undue experimentation."). The same reasoning applies here.

The law does not necessarily require making and testing every possible format, target combination, and binding sequence being claimed. *See Amgen*, 598 U.S. at 610-11. But as both Dr. McDonnell and Dr. Kahn explain, the problem here is that it is impossible to predict ***which*** format, ***which*** target combination, and ***which*** binding sequence will have the requisite biological activity, necessitating trial-and-error experimentation for determining "***which***" candidate molecules fall within the scope of claim 1. *See Idenix*, 941 F.3d at 1160. That complexity is further compounded by the lack of a reliable assay to assess Wnt agonism and the blurred

metes and bounds of the claim. For at least these reasons, the Board should find that claim 1 of the '278 Patent is unpatentable.

B. Claims 2-5 Are Not Enabled

1. Claims 2, 3, and 5

Claim 2 recites that "the Fzd binding regions comprise a full immunoglobulin G (IgG), comprising two light chains and two heavy chains, and the LRP5/6 binding regions comprise a VHH." EX1001, cl. 2. Each of claims 3 and 5 depends from claim 2 and recites that the "LRP5/6 binding region is fused to the N-terminus or C-terminus of the heavy chain or is fused to the N-terminus or C-terminus of the light chain" (claim 3) or that "each of the two LRP5/6 binding regions is fused to one of the light chains via a linker moiety" (claim 5). *Id*., cls. 3, 5.

None of these claims is enabled. As discussed, multiple tetravalent, multispecific molecules with the features recited in these claims did not activate Wnt signaling in the presence or absence of R-spondin. *See supra* § V.B.1; EX1002, ¶¶187-88, 233-34. The specification provides no meaningful guidance on how to distinguish molecules with the features recited in these claims that activate Wnt signaling from those that do not. *See supra* § VI.A; EX1002, ¶234. Just like claim 1, these claims demand trial-and-error experimentation, and therefore are not enabled for the reasons discussed above. *See supra* § VI.A; EX1002, ¶234.

2. Claim 4

Claim 4 recites a "pharmaceutical composition" comprising "the Wnt surrogate molecule according to claim 1." EX1001, cl. 4. Claim 4 does not narrow the scope of the tetravalent, multispecific Wnt surrogate molecules recited in claim 1. EX1002, ¶235. Claim 4 is therefore unpatentable for the same reasons as claim 1. *Id.*

VII. GROUND 3: CLAIMS 1-5 ARE INDEFINITE

A. "Wnt Surrogate Molecule" Lacks Reasonable Certainty

The challenged claims are directed to a "Wnt surrogate molecule," defined as a molecule that is "biologically active . . . in activation of Wnt signaling, i.e., the molecule is a Wnt agonist." EX1001, 16:52-56; *see supra* § III.E.1. The specification, however, provides both conflicting and necessarily incomplete guidance on how to determine whether a candidate molecule is "biologically active . . . in activation of Wnt signaling" and acts as a "Wnt agonist." EX1002, ¶¶2, 10, 236-46; EX1003, ¶¶4, 9-10, 144-55. Indeed, as further illustrated below, this is classic indefiniteness where "'multiple methods' for determining whether a claim limitation is met 'lead[]' to different results without guidance . . . as to which method should be used." *See Akamai*, 159 F.4th at 1379 (citing *Dow Chem. Co. v. Nova Chem. Corp. (Can.)*, 803 F.3d 620, 634 (Fed. Cir. 2015) and *Teva Pharms. USA, Inc.*

v. Sandoz, Inc., 789 F.3d 1335, 1344-45 (Fed. Cir. 2015)); *see also Nautilus Inc. v. Biosig Instruments, Inc*., 572 U.S. 898, 910-11 (2014).

Multiple Conflicting Assays for Canonical or Noncanonical Wnt Signaling: In 2017, it was known that assays measuring the activation of canonical Wnt signaling (e.g., TOPFlash assay) do not measure the activation of noncanonical Wnt signaling and *vice versa*. EX1003, ¶¶101-02. As such, the same candidate molecule could exhibit opposite responses, depending on the assay and assay conditions. EX1002, ¶¶237-38; EX1003, ¶¶110-11, 136-38. Critically, however, the intrinsic record fails to resolve how to identify a claimed "Wnt surrogate molecule" given the actual and potential conflicting results among the multiple options of assay methods and canonical vs. noncanonical signaling. EX1002, ¶239; EX1003, ¶¶136-38, 144-55. The specification instead exacerbates the problem by (1) defining the Wnt signaling pathway as either "a canonical Wnt signaling pathway ***or*** a non-canonical Wnt signaling pathway" and (2) open-endedly allowing that the "ability of Wnt surrogate molecules of the invention to mimic the activity of Wnt can be confirmed by ***a number of assays***." EX1001, 4:47-51, 16:59-61, 117:28-30.

Wnt5a, discussed above, is exemplary of conflicting, assay dependent measurements that lead to a multiplicity of diametrically different results. EX1003, ¶¶110-11, 136-38; *see supra* §§ II.A.2, VI.A.4. Notably, these conflicting results were obtained notwithstanding prior knowledge regarding Wnt5a's functional

properties. EX1003, ¶136. The potential for conflict results—one molecule appearing to an agonist, ineffective, or an antagonist depending on the assay and conditions used—is further amplified for candidate molecules without this background knowledge. *Id.*

Notwithstanding this known assay dependence, the specification fails to endorse any particular assay or conditions for measuring canonical or noncanonical Wnt signaling. The absence of resolution to the condition-dependence of being a "Wnt surrogate molecule" is "the epitome of indefiniteness." *See Geneva Pharms., Inc. v. GlaxoSmithKline PLC*, 349 F.3d 1373, 1384 (Fed. Cir. 2003); *see also Halliburton Energy Servs., Inc. v. M-I LLC*, 514 F.3d 1244, 1255-56 (Fed. Cir. 2008) (functional limitation was indefinite because different circumstances likely produce differing outcomes as to whether that limitation is met or not).

For canonical signaling, the specification lists at least five different assays: "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, 117:39-44. The specification does not identify ***any*** specific assay for noncanonical signaling. *See generally id.*; EX1002, ¶82; EX1003, ¶¶19, 121. The prosecution history offers no help, as Applicant did not specify any assay to evaluate the claimed Wnt agonism. *See supra* § III.D. Inconsistency among assays and a lack of endorsement for a specific assay is a

hallmark of indefiniteness. *See Dow*, 803 F.3d at 634; *Teva*, 789 F.3d at 1344-45; EX1002, ¶¶236-46; EX1003, ¶¶136-38, 144-55.

Patent Owner may argue that because the Patent used TOPFlash assays, a POSA would have chosen this assay to determine whether a candidate molecule is a Wnt surrogate molecule. However, an argument "that someone skilled in the art could determine which method was the most appropriate" would still be insufficient as a matter of law where "the required guidance is not provided by the claims, specification, and prosecution history." *Dow*, 803 F.3d at 634-35.

Construing the claims as limited to the TOPFlash assay would also be inconsistent with the specification, because it does not measure ***noncanonical*** Wnt signaling purportedly within the scope of the claims. EX1001, 4:49-51. The Patent further disclaimed narrowing to the TOPFlash assay, stating that "the claims ***are not limited*** by" embodiments. *Id.*, 172:52-55; *ImmunoGen, Inc. v. Vidal*, 653 F. Supp. 3d 258, 287-88 (E.D. Va. 2023), *aff'd on other grounds sub nom. ImmunoGen, Inc. v. Stewart*, 130 F.4th 1328 (Fed. Cir. 2025).

That said, as discussed below, the claims are indefinite regardless because TOPFlash and all other disclosed assays are themselves condition dependent. EX1003, ¶¶101-12, 136-38.

Lack of Threshold and Positive Controls in TOPFlash Assay: Although the specification expressly defines that the "Wnt surrogate molecules of the present

invention" must be "biologically active in . . . activation of Wnt signaling," EX1001, 16:52-55, ***none*** of the TOPFlash assays reported in the specification includes either a threshold for being "biologically active" or a biologically relevant positive control, e.g., a Wnt protein. *See id.*, Figs. 2-18; EX1002, ¶240; EX1003, ¶¶145-46. Without a threshold or positive control, a POSA would not be able to determine whether a low-level response corresponds to being "biologically active." EX1003, ¶¶145-46; *see U.S. Well Servs., LLC v. Stewart*, No. 2023-1799, 2025 WL 798863, at *2 (Fed. Cir. Mar. 13, 2025) (affirming PTAB holding of indefiniteness given that "a lack of any clear boundaries for how an ordinarily skilled artisan would interpret" claimed "high pressure" limitation) (citation omitted). As Dr. Kahn explains, the use of positive controls is routine and required to evaluate potential Wnt activity. EX1003, ¶146.

The Patent's "18R5:Fc:1115.3" candidate is exemplary. While characterized as being able to "activate[] Wnt signaling" (EX1001, 159:27-39), its miniscule response in the absence of positive controls makes it impossible to determine whether it's a "biologically active" Wnt surrogate molecule. EX1002, ¶241; EX1003, ¶147.

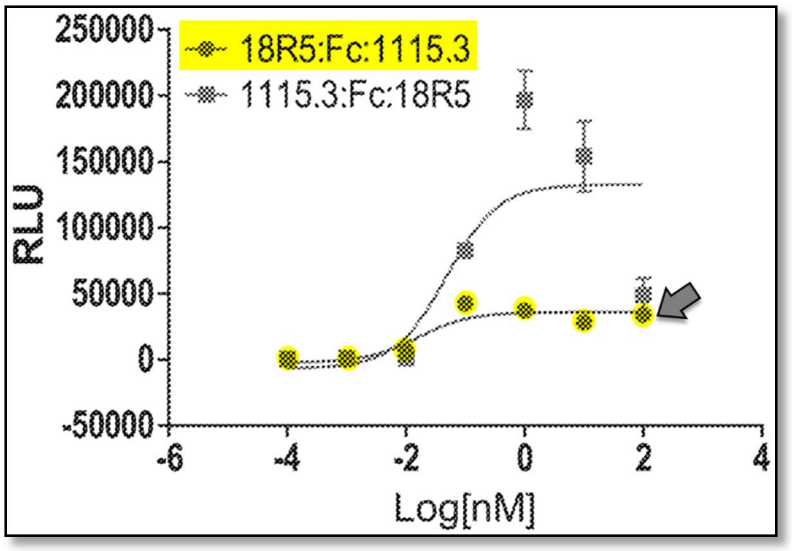


Figure 17. Annotated Patent Figure 14E

R-Spondin Effect: As discussed above, the specification expressly defines that the "Wnt surrogate molecules of the present invention" must be "***biologically active*** in . . . activation of Wnt signaling." EX1001, 16:52-55. The specification further states that "Wnt agonists typically initiate a reaction or activity that is ***similar to or the same*** as that initiated by the receptor's natural ligand." *Id.*, 16:61-64. As Dr. Kahn explained, Wnt and non-Wnt ligands in nature are capable of activating Wnt signaling independent of other potentiating factors such as R-spondin. EX1003, ¶¶36, 88, 148.

As discussed above, several candidate molecules in the specification failed to activate Wnt signaling in the absence of R-spondin, indicating that, unlike natural Wnt and non-Wnt ligands, they are not "biologically active." *Id.*, ¶149; *see supra* § V.A.4. In each instance as reproduced below, the same molecule showed no activity in the absence of R-spondin (grey arrow), while it produced detectable responses in

the presence of R-spondin (red curve). Notably, there is no appreciable difference between the response curves in the absence of R-spondin with the blue curves, the latter of which the specification state "did not induce reporter activity." EX1001, 155:35-36, 155:65. Yet, focusing on the positive responses in the presence of R-spondin only, the specification characterizes these molecules as "induc[ing] canonical Wnt signaling," causing confusion as to whether or not these molecules are "Wnt surrogate molecules." *Id.*, 158:61-63. Given these conflicting condition-dependent results and inconsistent characterization in the specification, a POSA would not be able to determine with reasonably certainty whether these (or other) molecules qualify as Wnt surrogates. EX1002, ¶242; EX1003, ¶¶148-49.

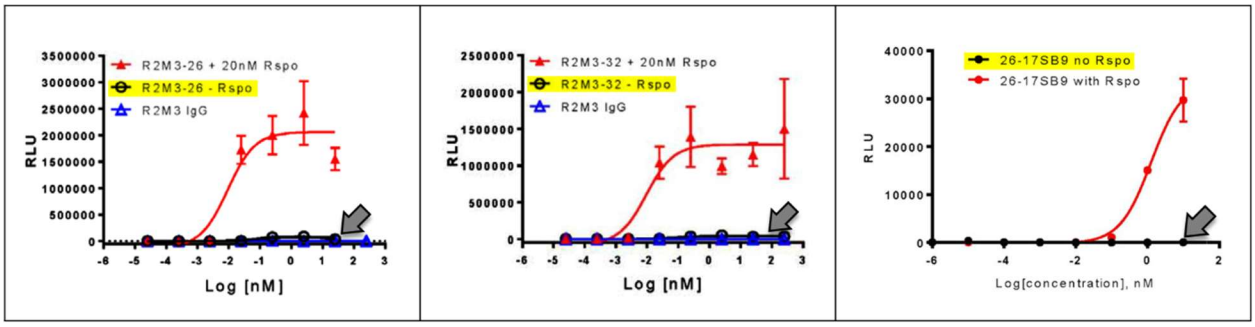


Figure 18. Annotated Patent Figures 2D, 3D, and 13B

Cell-Type Dependency: As discussed above, it was known in 2017 that known Wnt and non-Wnt ligands play tissue-specific roles. EX1003, ¶¶98-99, 131-33, 150-51. As such, the same "Wnt surrogate" molecule could activate Wnt signaling or fail to do so, depending on its biological targets and Fzd/Lrp receptors expressed on a tissue of interest. *Id.*, ¶¶98-99, 131-33, 150-51. This uncertainty is reflected in the

specification, reporting inconsistent responses from one cell type to another. *Id.*, ¶¶150-51; *see Geneva,* 349 F.3d at 1384.

As shown below, a candidate molecule called "18R5-28" in the absence of R-spondin failed to activate Wnt signaling in 293 cells but activated Wnt signaling in A375 cells. EX1002, ¶243; EX1003, ¶151. The specification is silent on how to account for these inconsistent responses from different cell types. *See* EX1001, 156:54-67. Because results are cell-type dependent, a POSA would not be able to determine whether a candidate molecule like this qualifies as a Wnt surrogate molecule. EX1002, ¶243; EX1003, ¶¶150-51.

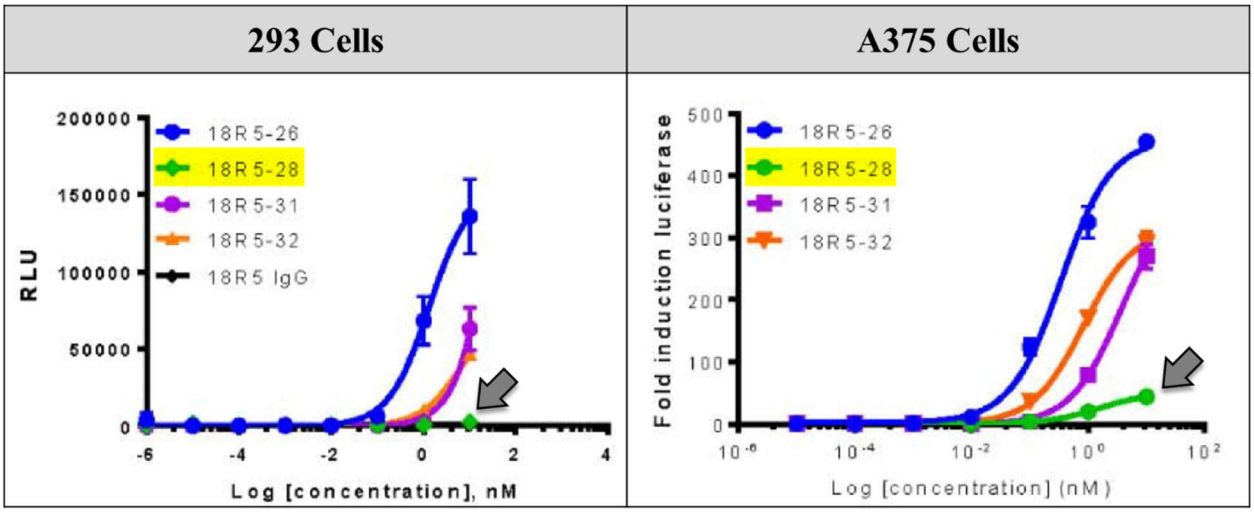


Figure 19. Annotated Patent Figures 6A and 6B

Concentration Dependency: The TOPFlash assays in the specification also show that each assay depends on concentration, and unpredictably in that may or may not be dose-dependent. EX1002, ¶¶244-45; EX1003, ¶¶152-53. This adds further uncertainty, as activity in this assay unpredictably depends on the

concentration tested and the Patent lacks guidance as to whether any one concentration or another is indicative of being a "Wnt Surrogate Molecule." EX1002, ¶¶244-45; EX1003, ¶¶152-53; *Dow*, 803 F.3d at 630 (claims are indefinite in absence of "objective boundaries").

As discussed, several candidate molecules exhibited "hook" effects, illustrating unpredictable responses depending on molecule and concentration. EX1002, ¶245; EX1003, ¶152. Again, the specification does not explain how to account for this, and a POSA would not be able to determine whether these molecules, which unpredictably lost their agonistic effects at higher concentrations, qualify as Wnt surrogate molecules.

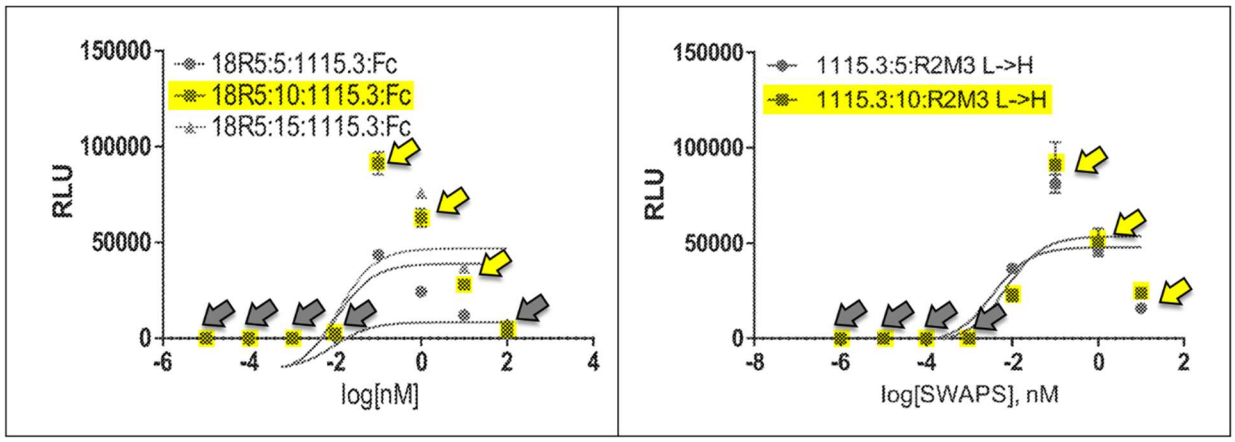


Figure 20. Annotated Patent Figures 14A and 15G

* * *

In sum, while the challenged claims encompass molecules that can activate canonical or noncanonical Wnt signaling, the specification fails to endorse a specific assay that could measure both. The specification also reveals numerous variables

for its primary assay, the TOPFlash assay, and each variable independently affects the results of the assay in an unpredictable manner. EX1002, ¶246; EX1003, ¶154. These variables are also applicable to other disclosed assays, as these stem from the inherent complexity of Wnt signaling pathways. EX1003, ¶¶110, 153 & n.9.

Because the specification fails to specify the conditions for each of these variables for each of these assays, and because whether a candidate molecule is "biologically active" in activating Wnt signaling depends on the assay's results, a POSA would not be able to determine, with reasonable certainty, whether a candidate molecule is a Wnt surrogate molecule. EX1002, ¶¶236-46; EX1003, ¶¶144-55. As such, the challenged claims are indefinite.

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

As discussed above, the last "wherein" clause should be construed as: "each of the two LRP5/6 binding regions is ***connected directly via a linker moiety*** to ***one and only one*** Fzd binding region." *See supra* § III.E.2. To the extent Patent Owner proposes a broader construction that does not require direct connection via the linker to one and only one Fzd binding region, this would further render all claims nonsensical and indefinite. EX1002, ¶¶247-52; *Horizon Pharma, Inc. v. Dr. Reddy's Lab'ys Inc.*, 839 F. App'x 500, 505 (Fed. Cir. 2021) ("One circumstance in which claims are indefinite is where the claims, as properly construed, are nonsensical.").

A construction not requiring "connected directly" makes claim 1 nonsensical for several reasons. EX1002, ¶¶248-52; *see supra* § III.E.2. *First*, the specification's characterization of various formats that fall within the claim scope becomes meaningless. EX1002, ¶249. The format depicted in Figure 1A is illustrative. The specification states that the Nab is "fused" to "the C-terminus of HC" in the left format while the Nab is "fused" to "the C-terminus of LC" in the right format. EX1001, 150:37-44. If the term "fused" encompasses indirect connection, the distinction makes no sense because the Nab would be "fused" to the C-termini of both the heavy and light chains. EX1002, ¶249.

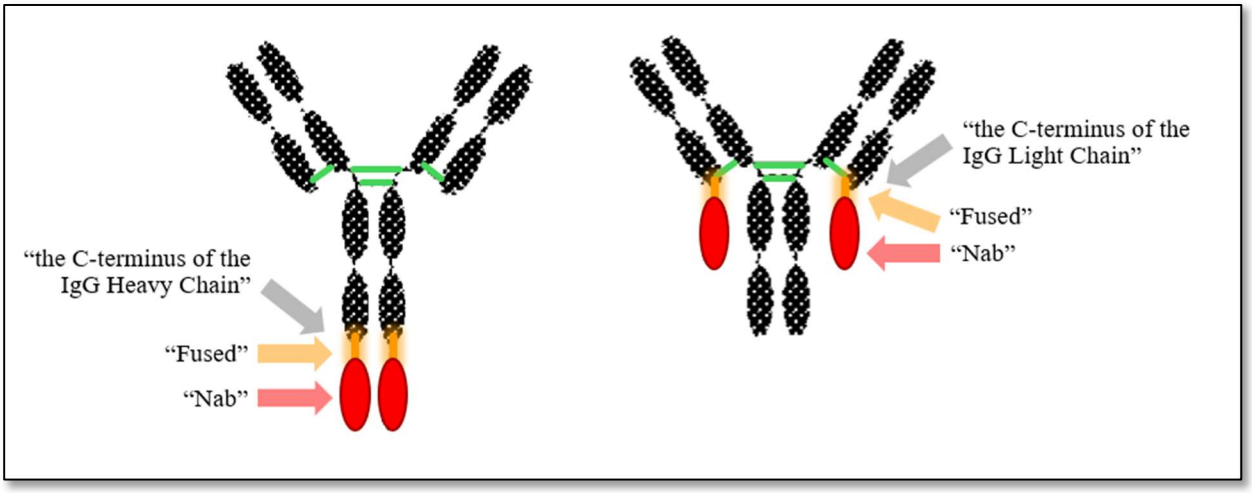


Figure 21. Annotated Patent Figure 1A

Second, a POSA would not be able to determine in any given molecule where the claimed binding regions begin and end or where the claimed linker moiety is located. EX1002, ¶250. For example, a POSA looking at the molecules depicted above would not be able to determine where the binding regions present in the IgG

portion begin or end, e.g., at the C-terminus of the IgG heavy chain, the hinge region, the C-terminus of the IgG light chain, or anywhere in between. *See Infinity Comput. Prods., Inc. v. Oki Data Ams., Inc.*, 987 F.3d 1053, 1062 (Fed. Cir. 2021) (holding the asserted claims indefinite where "[t]here is no reasonable certainty as to [the] boundary" of claimed structure).

Third, if "fused" encompasses connections other than direct connections, the claim becomes nonsensical. EX1002, ¶251. Allowing for indirect connections in the patent's exemplified molecules would mean that all binding regions would be "fused" to each other. This is irreconcilable with the requirement that "each of the two LRP5/6 binding regions" are fused to only "one of the two Fzd binding regions." *See Synchronoss Techs., Inc. v. Dropbox, Inc*., 987 F.3d 1358, 1366-67 (Fed. Cir. 2021) (holding the asserted claims indefinite as nonsensical and requiring an impossibility).

This broader construction would also make the challenged dependent claims incomprehensible. EX1002, ¶252. Claim 3, for example, recites that "the LRP5/6 binding region is fused to the N-terminus or the C-terminus of the heavy chain or is fused to the N-terminus or the C-terminus of the light chain." EX1001, cl. 3. Under a construction allowing indirect connections, the binding region would be simultaneously fused to the N- and C-termini of both the heavy and light chains, rendering the claim limitation meaningless. EX1002, ¶252. The same applies to

claim 5, which recites that "each of the two LRP5/6 binding regions is fused to one of the light chains via a linker moiety." EX1001, cl. 5. Under the broader construction, the LRP5/6 binding region would be fused to both light chains, making "each" and "one" in claim 5 meaningless. EX1002, ¶252.

In essence, a construction that does not require direct connection of each Lrp via a linker to one and only one Fzd binding would turn both the specification and the challenged claims into a "word salad of inconsistent definitions and examples." *IQASR LLC v. Wendt Corp*., 825 F. App'x 900, 905 (Fed. Cir. 2020). To the extent that Patent Owner proposes and the Board adopts such a construction, the challenged claims should be found unpatentable for this additional reason.

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

Claims 1 and 4 cover what was already disclosed in Garcia, a reference published on March 17, 2016. EX1004, item (43). Garcia—the content of which was mischaracterized by Applicant during examination of the '278 Patent and erroneously dismissed by the Examiner as a result—anticipates these claims because it discloses each and every claim element. EX1002, ¶¶2, 11, 253-64.

A. Claim 1 Is Anticipated by Garcia

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

During prosecution, both Applicant and named inventor Dr. Li argued that Garcia does not disclose this limitation because Garcia is limited to "bivalent, bispecific molecules comprised of a single polypeptide and having a stoichiometry of 1:1 Fzd binder:LRP5/6 binder." EX1008, 4005, 4168 (emphasis in original). This argument led to allowance of the '278 Patent. *See supra* § III.D. But contrary to these characterizations, Garcia discloses this limitation. EX1002, ¶¶254-55.

Garcia states that it discloses "water soluble" "Wnt signaling agonist molecules" that can be tetravalent and multispecific. *Id.*, ¶¶256-57; EX1004, Abstract, [0009], [0056]. Specifically, Garcia states that its "wnt surrogate can be ***a polypeptide***, where a binding domain for Fzd is joined to a binding domain for Lrp5/6." EX1004, [0056]. Garcia further states that the "polypeptide wnt surrogate may be a single chain, ***dimer***, or higher order multimer." *Id*. As Dr. McDonnell explains, because each polypeptide in Garcia comprises a binding region for Fzd and a binding region for Lrp5/6, a dimer made of two such polypeptides is a tetravalent molecule having two binding regions for Fzd and two binding regions for Lrp5/6. EX1002, ¶257. As Dr. McDonnell further explains, the dimer is multispecific as it

can bind to at least two different epitopes, one present in Fzd and the other present in Lrp5/6. *Id.*

A prior art reference anticipates if it provides an enabling disclosure of even a ***single*** embodiment within the scope of the claim. *Agilent Techs., Inc. v. Synthego Corp*., 139 F.4th 1319, 1327 (Fed. Cir. 2025). Here, inventor Dr. Li confirmed that Garcia provides such disclosure. EX1002, ¶¶258-59. During prosecution of the '278 Patent, Dr. Li declared that he made compositions comprising a "tandem scFv format" with "a single scFv Fzd binding linked to a single scFv Lrp5/6 binding" as "***described*** by Garcia." EX1008, 4170. Dr. Li declared that the "aggregation of two . . . tandem scFv molecules," corresponding to "***two . . . binding domains for FZD*** and ***two . . . binding domains for LRP*** in ***one molecule***," was "associated with Wnt activity." *Id.*, 4171. In other words, Dr. Li confirmed that a dimer of Garcia comprising two Fzd binding regions and two Lrp5/6 binding regions activated a Wnt signaling pathway. EX1002, ¶259; s*ee Abbott Lab'ys v. Baxter Pharm. Prods., Inc*., 471 F.3d 1363, 1368 (Fed. Cir. 2006) ("a newly-discovered property of the prior art cannot support a patent on that same art").

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

Garcia discloses that each of the two Fzd binding regions present in a dimer Wnt surrogate molecule can comprise an antibody or antigen-binding fragment of

the antibody that specifically binds Fzd. EX1002, ¶260. Garcia states that "[i]n polypeptide embodiments, the Fzd binding domain may be selected from any domain that binds Fzd at high affinity" and that "[s]uitable Fzd binding domains include," for example, "antibody derived binding proteins, e.g., scFv, Fab, etc. and other portions of antibodies that specifically bind to one or more Fzd proteins." EX1004, [0011]. Dr. Li's declaration also confirms that the "dimer" described in Garcia includes two Fzd binding regions specifically binding to two Fzd receptors, each made of an scFv antibody fragment. EX1008, 4170-71.

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

Garcia also discloses this limitation. EX1002, ¶261. Garcia states that "[i]n polypeptide embodiments, the Lrp5/6 binding domain or element may be selected from any domain that binds Lrp5/6 at high affinity" and that "[s]uitable Lrp5/6 binding domains include," for example, "antibody derived binding proteins, e.g. scFv, Fab, etc. and other portions of antibodies that specifically bind to one or more Fzd [sic] proteins." EX1004, [0013]. Dr. Li's declaration also confirms that the "dimer" described in Garcia includes two Lrp5/6 binding regions specifically binding to Lrp5/6, each made of an scFv antibody fragment. EX1008, 4170-71.

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

Garcia's dimer satisfies this limitation. EX1002, ¶262. Garcia explained that in each polypeptide, the "Fzd binding domain and the Lrp5/6 binding domain may be directly joined, or may be separated by a linker, e.g., a polypeptide linker, or a non-peptidic linker, etc." EX1004, [0056]. This teaches that in the dimer each of the two Lrp5/6 binding regions is directly connected to one Fzd binding region with or without a linker in-between. EX1002, ¶262.

B. Claim 4 Is Anticipated by Garcia

Claim 4 recites a "pharmaceutical composition comprising a physiologically acceptable excipient, diluent, or carrier, and the Wnt surrogate molecule according to claim 1." EX1001, cl. 4. Garcia anticipates this claim because it discloses a composition comprising "an effective dose of a wnt signaling agonist in a pharmaceutically acceptable excipient." EX1004, [0019]; *see also id*., cl. 34 (claiming a "pharmaceutical composition comprising a wnt signaling agonist of any one of Claims 1-33, and a pharmaceutically acceptable excipient"); EX1002, ¶264.

IX. MANDATORY NOTICES

A. Real Party-in-Interest

Petitioner Merck Sharp & Dohme LLC is the real-party-in-interest (RPI) to this proceeding. No other party exercised control or could exercise control over Petitioner's participation in this proceeding, the filing of this Petition, the funding of

this Petition, or the conduct of any ensuing trial. Petitioner identifies Merck & Co., Inc. as the corporate parent of Merck Sharp & Dohme LLC. This identification is made without any concession or admission that Merck & Co., Inc. is a real party in interest to this proceeding.

B. Related Matters

To Petitioner's knowledge, the Patent has not been involved in any district court litigations.

The Patent was filed as U.S. Patent Application No. 18/361,782, which is a continuation of U.S. Patent Application No. 16/954,484, filed June 16, 2020, (now U.S. Patent No. 11,773,171); which is a National Stage Entry of PCT/US2018/066616, filed December 19, 2018; which claims the benefits of Provisional Application No. 62/607,875, filed December 19, 2017; Provisional Application No. 62/641,217, filed March 9, 2018; and Provisional Application No. 62/680,522, filed June 4, 2018. The Patent is a parent case of a pending application, U.S. Patent Application No. 19/093,023, filed March 27, 2025.

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Please send all correspondence to counsel at the addresses shown above and to Finnegan-PGR2026-00027@finnegan.com. Petitioner consents to electronic service by email at the email address listed above and to Finnegan-PGR2026-00027@finnegan.com.

X. GROUNDS FOR STANDING

Petitioner certifies that the Patent is available for post-grant review and that Petitioner is not barred or estopped from requesting post-grant review challenging the patent claims on the grounds identified herein.

XI. TIME FOR FILING PETITION

Under 37 C.F.R. §42.202, "[a] petition for a post-grant review of a patent must be filed no later than the date that is nine months after the date of the grant of a patent or of the issuance of a reissue patent." This Petition is filed within nine months of the Patent's issue date (May 13, 2025), and this Petition is therefore timely.

XII. CONCLUSION

For the reasons above, Petitioner requests institution of post-grant review and cancellation of each challenged claim. The Office may charge any required fees to Deposit Account No. 06-0916.

Dated: February 12, 2026

By: / Mark J. Feldstein /
Mark J. Feldstein, Lead Counsel
Reg. No. 46,693

CERTIFICATION OF WORD COUNT

Pursuant to 37 C.F.R. §42.24, Petitioner certifies that the word count of Petitioner's Petition for Post-Grant Review (exclusive of any table of contents, table of authorities, mandatory notices under §42.8, certificates of service and word count, and list of exhibits or claim listing) as measured by Microsoft Word is 18,565.

Dated: February 12, 2026

By: / Mark J. Feldstein /
Mark J. Feldstein, Lead Counsel
Reg. No. 46,693

CERTIFICATE OF SERVICE

Pursuant to 37 C.F.R. §§42.6(e) and 42.205(a), the undersigned certifies that on February 12, 2026, a copy of the foregoing **Petition for Post-Grant Review**, **the associated power of attorney**, and **Exhibits 1001-1014, 1016-1017, 1020, 1022, 1024-1025, 1027-1030, 1033-1034, 1038-1039, 1043-1047, 1049, 1051, 1053-1056, 1059-1060, 1063-1066, 1069-1070, 1072, 1074, 1077-1079, 1081-1082, 1086-1087, 1089-1091, 1093** were served by FedEx Priority Overnight on the correspondence address of record indicated in the Patent Office's public Patent Center system for U.S. Patent No. 12,297,278:

Carol D. Laherty
COOLEY LLP/SURROZEN OPERATING, INC.
Attn: IP Docketing Department
1299 Pennsylvania, Avenue, NW, Suite 700
Washington, DC 20004

Date: February 12, 2026

By: / William Esper /
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