UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

MERCK SHARP & DOHME LLC,

Petitioner,

v.

SURROZEN OPERATING, INC.,
Patent Owner.

Case No. PGR2026-00027

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

DECLARATION OF PROFESSOR KARL WILLERT

TABLE OF CONTENTS

I. Introduction....1

II. Summary of Opinions....1

III. Qualifications....1

IV. Materials Considered....5

V. Level of Ordinary Skill in the Art....5

VI. Claim Construction....7

VII. Response to Dr. Kahn's "Background And State of the Art"....10

A. Wnt Signaling Technology....10

1. Canonical and Noncanonical Wnt Signaling (Paragraphs 80-81, 90-97 of Kahn's Declaration)....14

2. Ligands, Receptors, and Co-receptors (Paragraphs 82-89 of Kahn's Declaration)....19

3. Tissue- and Cell-Dependence (Paragraphs 98-100 in Kahn's Declaration)....25

B. Measuring Canonical Wnt Signaling Activity (Paragraphs 101-112 in Kahn's Declaration)....26

VIII. Analysis of the '278 Patent....35

A. Examples 2-18....36

1. Examples 2 and 3....41

2. Example 4....47

3. Examples 5 and 6....49

4. Example 7....52

5. Example 8....53

Surrozen 2010
Merck v. Surrozen PGR2026-00027
Page 2

6. Example 9 55

7. Examples 10, 11, and 12 59

8. Example 13 61

9. Example 14 65

10. Example 15 68

11. Example 16 70

12. Example 17 71

13. Example 18 73

B. Dr. Kahn's Critiques of Examples 2-18 Are Unpersuasive (Paragraphs 144-155 of Dr. Kahn's Declaration) 74

1. Positive Controls 74

2. R-Spondin 78

3. Cell-Type Dependence 82

4. Dose-Response Behavior 83

C. Response to Dr. Kahn's Contention that the '278 Patent Does Not Resolve Alleged "Unpredictability" of Wnt Signaling (Paragraphs 124-143 of Dr. Kahn's Declaration) 84

D. Dr. Kahn Overstates the Experimentation Required by Claims 1-5 (Paragraphs 113-123 of Dr. Kahn's Declaration) 92

IX. CONCLUSION 94

Surrozen 2010
Merck v. Surrozen PGR2026-00027
Page 3

I. INTRODUCTION

1. My name is Karl Willert, Ph.D. and I have been retained as an independent expert on Wnt signaling by Surrozen Operating, Inc. ("Surrozen" or "Patent Owner") in connection with post-grant review proceedings for U.S. Patent No. 12,297,278 (the "'278 Patent").

2. I have been informed by counsel for Surrozen that Merck Sharp & Dohme LLC ("Merck" or "Petitioner") filed a Petition for post-grant review of the '278 Patent on February 12, 2026, alleging the invalidity of claims 1-5 of the '278 Patent.

II. SUMMARY OF OPINIONS

3. I have been asked by counsel for Surrozen to provide opinions regarding the state of the art of Wnt signaling as of December 2017, and the disclosures and Examples of the '278 Patent. I have also been asked to respond to certain opinions offered in the February 10, 2026, declaration of Professor Michael Kahn, Ph.D.

III. QUALIFICATIONS

4. I am currently a Professor in the Department of Cellular and Molecular Medicine at the University of California, San Diego (UCSD). My research over the past 36 years has focused on Wnt signaling, spanning multiple biological systems (flies, mice, fish, and humans), diverse approaches

Surrozen 2010
Merck v. Surrozen PGR2026-00027
Page 4

(biochemical, cell biological, and genetic), and disciplines (development, stem cell biology, and cancer biology). My research focuses on the fundamental mechanisms of Wnt signaling, with an emphasis on how signaling specificity is established, and the role of Wnt signaling in human embryonic stem cells and the development of various adult tissues, including the central nervous system, kidney, pancreas, skin, blood, mammary gland and intestine. I have also investigated the role of Wnt signaling in tumor initiation and progression and generated a novel therapeutic that targets a Wnt receptor and blocks ovarian and breast cancer growth.

5. One of my key contributions to the field of Wnt signaling was the biochemical characterization and isolation of Wnt, which allowed me to demonstrate for the first time that Wnt proteins are lipid-modified and act as potent stem cell factors. K. Willert et al., *Wnt Proteins Are Lipid-Modified and Can Act as Stem Cell Growth Factors*, 423 NATURE 448-52 (2003). This work, published in the journal Nature and cited nearly 5,000 times, has been transformative and brought Wnt proteins into the limelight of stem cell biology. I was first to show that Wnt proteins are lipid-modified, a discovery that has had far-reaching implications for how Wnt proteins act in development, stem cells, and cancer, and provided a mechanistic insight into Wnt ligands' interactions with their receptors. In addition, this work allowed for countless studies including the description of the first Wnt protein structure in 2012. As a result of my work, Wnt proteins are now

Surrozen 2010
Merck v. Surrozen PGR2026-00027
Page 5

common reagents in many labs. I am also a named inventor on US Patent No. 7,153,832, titled "Compositions of Active Wnt protein," which was issued in 2006.

6. Other publications that address my research on Fzd and LRP receptors and the Wnt pathway include P. R. Sonavane & K. Willert, *Controlling Wnt Signaling Specificity and Implications for Targeting WNTs Pharmacologically*, 269 HANDB. EXP. PHARMACOL. 3-28 (2021) (addressing Wnt signaling specificity, including for Fzd and LRP receptors); D. Gumber et al., *Selective activation of FZD7 promotes mesendodermal differentiation of human pluripotent stem cells*, ELIFE 9:e63060 (2020) (describing a Wnt mimetic binding to Fzd7); S. Grainger et al., *EGFR is required for Wnt9a-Fzd9b signalling specificity in haematopoietic stem cells*, 21(6) NAT. CELL BIOL. 721–730 (2019) (addressing the Wnt9a-Fzd9b-LRP signalosome); and A. Fernandez et al., *The WNT receptor FZD7 is required for maintenance of the pluripotent state in human embryonic stem cells*, 111(4) PROC. NAT'L ACAD. SCIS. U.S.A. 1409–1414 (2014) (addressing the Fzd7 receptor).

7. I obtained a B.A. in Biochemistry from UCSD in 1989 and a Ph.D. in Biochemistry from the University of California, San Francisco in 1996, under the mentorship of Nobel Laureate Professor Harold Varmus. I then joined Professor Roeland Nusse's laboratory at the Howard Hughes Medical Institute at Stanford University as a post-doctoral fellow from 1996 to 2003. During that time, I spent a

Surrozen 2010
Merck v. Surrozen PGR2026-00027
Page 6

year in a mass spectrometry lab at Scripps Research in San Diego. Following my post-doctoral fellowship, I spent two years working in the biotech sector, before returning to UCSD to establish a shared research laboratory focusing on research relating to human embryonic stem cells. In 2008, I became an Assistant Professor in the faculty of the Department of Cellular and Molecular Medicine at UCSD. I was promoted to Associate Professor in 2014, and again to Full Professor in 2018.

8. My laboratory continues to study the role of Wnt signaling in a variety of biological systems, including most recently skin wound repair and breast cancer development. I have published over 50 peer-reviewed articles, many in the field of Wnt signaling, and I am a named inventor on two patents. I have been awarded numerous funding grants from various public and private entities, including the National Institutes of Health (NIH), the California Institute for Regenerative Medicine (CIRM), Pfizer's Centers for Therapeutic Innovation, Takeda Pharmaceuticals, The Mary Kay Foundation, Pedal the Cause, and the National Foundation for Ectodermal Dysplasias.

9. I have served as the Director of UCSD's Human Embryonic Stem Cell Core Facility continuously since 2005 and have served on multiple Advisory Committees for CIRM-sponsored projects. I have organized several international meetings, including in the Wnt field: I organized a Wnt meeting at UCSD in 2007, served as the Vice Chair of the 2017 Wnt Signaling Gordon Research Conference

Surrozen 2010
Merck v. Surrozen PGR2026-00027
Page 7

and Chair of the 2019 Wnt Signaling Gordon Research Conference,[1] and organized a Wnt in Stem Cells Symposium at Stanford University in 2025.

10. My CV is provided as **EX2011**.

IV. MATERIALS CONSIDERED

11. In forming my opinions, I reviewed Merck's Petition, the declaration of Professor James McDonnell, Ph.D. dated February 11, 2026, the declaration of Professor Michael Kahn, Ph.D. dated February 10, 2026 and the materials cited therein, and all materials cited in this Declaration or listed in **Appendix A**.

V. LEVEL OF ORDINARY SKILL IN THE ART

12. I understand from counsel for Surrozen that, in evaluating the disclosures of the '278 Patent, I should apply the perspective of a person of ordinary skill in the art ("POSA") as of December 19, 2017.

13. I also understand that Petitioner has offered the following definition of the person of ordinary skill in the art: "A POSA would have a Ph.D. degree in

[1] I worked together with Roel Nusse to start the series of Wnt Signaling Gordon Research Conferences, first held in 2017. The Wnt Signaling Gordon Research Conference is now a standing international Wnt signaling conference held every two years that brings together leading scholars to present and discuss the latest developments in Wnt signaling.

immunology, molecular biology, chemistry, or biochemistry with at least five years of experience in antibody engineering or Wnt signaling" and "may also have had access to other POSAs with complementary experience in antibody engineering or Wnt signaling." Pet. at 10.

14. I understand that Surrozen has proposed the following modification to Petitioner's definition of the person of ordinary skill in the art: a POSA is an individual with a Ph.D. degree in immunology, molecular biology, chemistry, or biochemistry with at least five years of experience in antibody engineering and who either (i) has, themselves, at least two years of experience with Fzd and/or LRP receptors and/or Wnt signaling, or (ii) has access to someone with at least two years of experience with Fzd and/or LRP receptors and/or Wnt signaling, or is on a team whose members collectively have equivalent experience. A person of ordinary skill in the art may also have access to other POSAs with complementary experience in antibody engineering, Fzd and LRP receptors, and/or Wnt signaling.

15. For a POSA qualified by virtue of their Wnt signaling experience, Petitioner's definition of a POSA would provide an even higher level of Wnt signaling skill than the definition Surrozen has provided.

16. I have applied the perspective of a person of ordinary skill in offering my opinions herein. My opinions in this Declaration are the same under Petitioner's and Surrozen's proposed definitions of the POSA.

17. By virtue of my Ph.D. in biochemistry and my decades of experience with antibody engineering, Fzd and LRP receptors, and the field of Wnt signaling, on December 19, 2017 I qualified as a person of ordinary skill under Petitioner's proposed definition, and also under Surrozen's definition either (i) with access to other persons of ordinary skill in the art with complementary experience in antibody engineering, or (ii) as part of a team that is the person of ordinary skill in the art, with a team member that has at least five years of experience in antibody engineering. I have applied the perspective of a person of ordinary skill in offering my opinions herein.

VI. CLAIM CONSTRUCTION

18. I have been informed that the terms of the '278 Patent claims are given the meaning they would have had to a person of ordinary skill in the art at the time of the invention. I understand that the claim terms must be read in the context of the claims, the patent specification, and the prosecution history of the patent.

19. I have been informed that the time of the invention (also known as priority date) of the '278 Patent is December 19, 2017. I understand that Petitioner does not dispute this date.

20. I have been informed that the Patent Owner and Petitioner have proposed different constructions for two claim terms:

Claim Term	Petitioner's Proposed Construction	Patent Owner's Proposed Construction
"Wnt surrogate molecule" (Claim 1)	Limiting; "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"	Non-limiting; no construction necessary Alternatively, plain and ordinary meaning of "a molecule that binds to both (i) Fzd and (ii) LRP5 or LRP6 receptors"
"wherein each of the two LRP5/6 binding regions is fused to one of the two Fzd binding regions via a linker moiety" (Claim 1)	"wherein each of the two LRP5/6 binding regions is connected directly via a linker moiety to one and only one Fzd binding region"	Plain and ordinary meaning of "wherein each of the two LRP5/6 binding regions is bound to at least one of the two Fzd binding regions via a linker moiety"

21. I have been informed that my opinions in this Declaration may be

Surrozen 2010
Merck v. Surrozen PGR2026-00027
Page 11

relevant to Petitioner's Proposed Construction of "Wnt surrogate molecule," which, contrary to Patent Owner's Proposed Construction, requires "activation of Wnt signaling, i.e., the molecule is a Wnt agonist." I have not been asked to opine on the construction of the term "Wnt surrogate molecule" and I have not been asked to review the complete prosecution history for the '278 Patent. I have been asked to assume that the claims require activation of Wnt signaling as set forth in Petitioner's Proposed Construction in rendering my opinions in this Declaration.

22. While I do not offer an opinion on the construction of "Wnt surrogate," I have reviewed the claims and the specification and understand that the '278 Patent offers the following descriptions in connection with Wnt surrogates. Claim 1 of the '278 Patent requires molecules comprising two Fzd binding regions and two LRP5/6 binding regions. EX1001 at cl. 1. The specification contains a section entitled "Wnt Surrogates," which explains that the patent discloses "Wnt surrogate molecules that bind both one or more Fzd receptors and one or both of LRP5 and/or LRP6." EX1001 at 16:37-39. The specification states Wnt surrogate molecules "may activate Wnt signaling." EX1001 at 117:26. I also note that the specification uses the term "Wnt surrogates" to describe both tetravalent and bivalent molecules, *see, e.g.*, *id.* at 6:35-36, 18:26-28, Fig. 1A, Table 3, and identifies the latter as "ineffective" at activating Wnt signaling, *id.* at 157:55-158:47, 159:40-47, Figs. 10A, 11A, 12A, 14H.

23. In reviewing the specification, I also noted that in the paragraph cited by Dr. Kahn and Petitioner describing Wnt surrogate molecules as "biologically active," the '278 Patent specifically provides that "the Wnt surrogate molecules of the invention enhance the canonical Wnt/β-catenin signaling," where "'enhance[]' refers to a measurable increase in the level of Wnt/β-catenin signaling compared with the level in the absence of a Wnt surrogate molecule of the invention." EX1001 at 117:33-38.

24. I have not been asked to opine on the construction of any other claim term.

VII. RESPONSE TO DR. KAHN'S "BACKGROUND AND STATE OF THE ART"

25. In Section IX (paragraphs 76-112) of his declaration, Dr. Kahn provides a background of his understanding of the state of the art in 2017. Below, I respond to Dr. Kahn's view of the state of the art and provide additional, relevant context to that background. The fact that I do not respond to every aspect of Dr. Kahn's background section does not mean that I agree with Dr. Kahn's opinions or analysis of the state of the art in 2017.

A. Wnt Signaling Technology

26. Wingless-related integration site ("Wnt") signaling pathways "play key roles in the control of development, homeostasis, and regeneration of many

essential organs and tissues," with potential applications in treatment of degenerative diseases, tissue injuries, bone diseases, and cancers, among other conditions. *See, e.g.*, EX1001 at 1:41-50.

27. There are multiple Wnt signaling pathways, but the pathway that is relevant to the '278 Patent is the "canonical" pathway, also known as the Wnt/β-catenin pathway. *Id.* at 119:33-40. This pathway is critical in cell development and regulates gene expression using β-catenin, a protein that binds transcription factors in the nucleus. Without activation of the canonical Wnt signaling pathway, a "destruction complex" phosphorylates β-catenin, leading to degradation of β-catenin and thereby preventing it from entering the nucleus of the cell to activate gene transcription. When a Wnt ligand binds to one or more Fzd receptor and one or more Lrp5/6 coreceptor on the cell surface, the canonical signaling pathway is activated. *See* EX1001 at 1:51-59. These signals inhibit the β-catenin destruction complex, which stops the destruction of β-catenin and allows it to accumulate and enter the nucleus of the cell, where it activates transcription of target genes by binding to TCF/LEF (T cell factor/lymphoid enhancer factor) transcription factors. *See, e.g.*, EX1001 at 119:41-46.

28. The other Wnt signaling pathways are known as "noncanonical" pathways, which are generally thought to act in a β-catenin independent manner. *See id.* at 119:33-40. These noncanonical pathways, while important in many

Surrozen 2010
Merck v. Surrozen PGR2026-00027
Page 14

biological settings, are not relevant in the development of Wnt surrogates, as explained in detail at Paragraphs 32-39, below.

29. Wnt signaling pathways are activated by Wnt ligands, cysteine-rich lipid-modified glycoproteins, that interact with cell-surface Frizzled (Fzd) receptors and other co-receptors, including low-density lipoprotein (LRP) receptor-related protein 5 and 6 and receptor tyrosine kinases (RTK) like Ryk and Ror. *See, e.g.*, EX1001 at 1:51-59, 119:25-31. For canonical Wnt signaling, the relevant receptors are Fzd and LRP5/6. *Id.* at 1:51-59. The formation of these ligand-receptor complexes on the cell surface triggers downstream Wnt signaling cascades that regulate cell proliferation by regulating global changes in the cell's proteome and transcriptome, including regulating transcription of certain target genes. *See id.* at 119:31-32.

30. In the mid-2010s, researchers in the Wnt signaling field began exploring the concept of "Wnt mimetics," engineered antibody-like proteins. For example, the '278 Patent describes tetravalent molecules engineered to have two binding regions that each bind to a Fzd receptor, and two binding regions that each bind to a LRP5/6 coreceptor. By selectively engaging only one or more Fzd and one or more LRP5/6, Wnt mimetics target the canonical Wnt/β-catenin pathway. *See* EX1001 at 1:51-59, 117:35-38.

31. Dr. Kahn's characterization of the "Wnt signaling pathway" as

"bewilderingly complex" and "one of the most, if not the most complicated cellular pathways known" is misleading. *See generally* EX1003, Paragraphs 76-100. First, in characterizing Wnt signaling as "bewilderingly complex," Dr. Kahn quotes from his own review article, which sets forth his characterization of the literature in 2014. *See, e.g.*, EX1003 ¶ 79 (citing EX1043). This fails to capture the significant growth and advances in the field of Wnt signaling in the years preceding 2017, marked by the first Wnt Signaling Gordon Research Conference hosted that year. Contrary to Dr. Kahn's characterization, an article cited by Dr. Kahn (EX1063) explained that, in 2017, "we are now at a point in the history of Wnt signaling where the implications of this pathway for understanding disease are coming into focus" and there are "promising leads" on Wnt-based therapies. EX1063 at 10. Second, Dr. Kahn's characterization fails to account for the context of the tetravalent molecules claimed in the '278 Patent and the disclosures of the '278 Patent, which provide substantial guidance as to the design and use of the claimed tetravalent molecules. The aspects of Wnt signaling relevant to the claimed tetravalent molecules (to the extent it is relevant at all) would not have been mystifying or impenetrable to a person of ordinary skill in December 2017 with the extensive disclosures of the '278 Patent in hand. To the contrary, the '278 Patent, in conjunction with a person of ordinary skill in the art's skill and knowledge, gives a person of ordinary skill in the art a wealth of information.

1. Canonical and Noncanonical Wnt Signaling (Paragraphs 80-81, 90-97 of Kahn's Declaration)

32. In Paragraphs 90-97, and throughout his declaration, Dr. Kahn cites to purported complexities and inconsistencies in the field of Wnt signaling deriving from the existence of ***noncanonical*** signaling pathways. *See, e.g.,* EX1003 ¶¶ 76, 80-81, 90-95, 102-105. Much of this is irrelevant to understanding the claimed tetravalent molecules and related teachings disclosed in the '278 Patent, which, as I noted above, relate to the canonical signaling pathway. But I nonetheless respond to his criticisms below to provide relevant context regarding the state of the art in 2017.

33. At the outset, the '278 Patent is concerned with molecules that bind both Fzd and LRP5/6 coreceptors. Under Petitioner's construction of "Wnt surrogate molecules" requiring Wnt agonism, a person of ordinary skill in the art would understand the claimed molecules, binding to Fzd and LRP5/6, implicate the ***canonical*** pathway, as confirmed by the patent specification. EX1001 at 1:51-59 ("Canonical Wnt signals also involve [LRP5/6] as co-receptors … in addition to Fzds."); *id.* at 117:33-35 ("Wnt surrogate molecules of the invention enhance the ***canonical***[2] Wnt/β-catenin signaling pathway."). Dr. Kahn agrees. *See* EX1003 ¶ 91

[2] Here and throughout this Declaration, unless otherwise noted, emphasis in quotations is my own.

Surrozen 2010
Merck v. Surrozen PGR2026-00027
Page 17

("In 2017, it was thought that canonical Wnt signaling is initiated when a Wnt ligand binds to a Fzd receptor and its co-receptor Lrp5/6 on the cell surface…"). By contrast, the specification only briefly mentions noncanonical signaling pathways to provide context for the term "Wnt signaling." *See* EX1001 at 119:33-40, 119:46-54. And as Dr. Kahn acknowledges, noncanonical signaling involves different co-receptors, including Ryk and Ror, than does canonical signaling. EX1003 ¶ 94.

34. Despite this, Dr. Kahn's analysis of Wnt signaling artificially complicates the state of the art relevant to the '278 Patent by focusing on noncanonical pathways, which he says "were much less understood" than the canonical pathway, EX1003 ¶ 92, and methods of detecting noncanonical signaling activity. *See, e.g.*, EX1003 ¶¶ 76, 80-81, 90-95, 102-105. Dr. Kahn suggests that the boundary between noncanonical and canonical signaling is blurry, but the examples he identifies are not relevant to the context of tailored tetravalent molecules binding both Fzd and LRP5/6 like those claimed in the '278 Patent.

35. For example, Dr. Kahn suggests that natural Wnt ligands can play a role in both canonical and noncanonical signaling and that, in 2017, there was no way of knowing if a given Wnt ligand would activate the canonical or noncanonical signaling pathway. EX1003 ¶ 81, 94. But ***natural*** Wnt ligands are proteins that differ from the engineered tetravalent molecules that are claimed in

the ’278 Patent. Natural Wnt ligands interact with a variety of receptors beyond Fzd and LRP5/6. For example, Mikels and Nusse (2006) (EX1056) explain that Wnt5a, a Wnt ligand family member that both agonizes and antagonizes the canonical pathway, “may be mediating its inhibitory role through the activation of [the Ror2] receptor”—a noncanonical coreceptor—while “Fz 4 and LRP5 coreceptor expression allows Wnt5a to signal in a canonical fashion.” EX1056 at 2, 11. This duality does not extend to the claimed tetravalent molecules, which are designed to bind to both Fzd receptors and LRP5/6 coreceptors, and they therefore do not interact with the coreceptors associated with the non-canonical pathways.

36. Dr. Kahn also refers to purported “overlap” in the canonical and noncanonical signaling processes, referencing certain mediators (calcium and heterotrimeric G-proteins) that act in and/or on both signaling pathways (whether through agonism or antagonism), to suggest that these two signaling pathways were not well understood, or “clear-cut.” EX1003 ¶¶ 92-93. This critique, and Dr. Kahn’s reference to things beyond ligands or molecules that act on the canonical signaling pathways, has no bearing on whether the claimed tetravalent molecules have two Fzd and two LRP5/6 binding regions, as required by the claims, or even whether they are Wnt agonists, as required under Petitioner’s proposed construction of the claims.

37. Dr. Kahn finally suggests that the Fzd and LRP5/6 receptors

individually can play roles in both the canonical and noncanonical pathways. EX1003 ¶¶ 94-95. That again has no bearing on the claimed tetravalent molecules, which bind to ***both*** the Fzd and LRP5/6 receptors simultaneously. Even Dr. Kahn agrees that "Fzd-Lrp interactions primarily mediate the activation of ***canonical*** Wnt signaling," EX1003 ¶ 95, and none of Dr. Kahn's references suggest that this specific combination of receptors somehow ***agonized*** the ***non***canonical pathway.

38. For example, Gray (2013), which Dr. Kahn cites in Paragraph 94, suggests only that mutations in Lrp6 may impact biological processes associated with the PCP noncanonical signaling pathway, such as neural tube closure, through interaction with DAAM1, a formin protein that plays a ***downstream*** role in mediating noncanonical Wnt signaling. *See* EX1029 at 12. It does not suggest that a molecule that binds to both the Fzd and LRP5/6 receptors simultaneously, like the claimed tetravalent molecules, regulates noncanonical signaling (and indeed, that would be contrary to a person of ordinary skill in the art's understanding in 2017). In Paragraph 95, Dr. Kahn cites to an article (EX1066) that he says shows "Fzd8-Lrp6 interactions were shown to inhibit Fzd8-mediated noncanonical pathway activation," seeming to suggest that Fzd-LRP interactions mediate the noncanonical pathway, but Dr. Kahn neglects the full context and conclusions of this reference. The article reported a Wnt-independent basal interaction between a certain LRP6 protein and a Fzd8 receptor and suggested that this interaction can, in

the absence of a natural Wnt ligand, "maintain[] both canonical and non-canonical pathways in an inactive status." EX1066 at 9. But EX1066 does not suggest that a tetravalent molecule that is designed to bind to both LRP5/6 ***and*** Fzd (or a natural Wnt ligand that simultaneously binds to LRP5/6 and Fzd) involves the noncanonical pathway in any manner (whether through agonism or inhibition). None of the articles cited by Dr. Kahn indicate that LRP5/6 or molecules binding to both Fzd and LRP5/6 regulate noncanonical Wnt signaling or transmit noncanonical Wnt signals.

39. Much of the perceived complexity that Dr. Kahn identifies in Wnt signaling processes, stemming from noncanonical signaling, is therefore inapplicable to the context of the '278 Patent. For example, Dr. Kahn focuses on the fact that the 19 identified natural Wnt ligands have different ligand-receptor interactions with "more than 15 receptors and co-receptors distributed over seven protein families." EX1003 ¶¶ 80-81. But unlike natural Wnt ligands, the claimed tetravalent molecules are limited to those that specifically bind both Fzd receptors and LRP5/6 co-receptors.

40. Dr. Kahn's discussion of the ***canonical*** Wnt signaling pathway (¶¶ 96-97), by contrast, is comparatively brief. He points only to downstream processes and interactions by which canonical Wnt signaling activity can be modulated as a potential source of complexity. EX1003 ¶¶ 96-97. But Dr. Kahn's

analysis does not identify any particular unpredictability or uncertainty in these processes, or explain why a skilled artisan would need to assess every step in the downstream process to determine whether a molecule is agonizing the canonical pathway. To the contrary, the processes involved in canonical Wnt signaling were well-understood as of December 2017, and, to the extent necessary, biological activity of a claimed tetravalent molecule could be "readily determined" by assaying for activity of canonical Wnt signaling using assays that were well-known to skilled artisans. *See, e.g.*, EX1001 at 117:39-67, 119:41-58.

2. Ligands, Receptors, and Co-receptors (Paragraphs 82-89 of Kahn's Declaration)

41. Dr. Kahn also spends a significant amount of time discussing the inherent variation among natural Wnt ligands and how they bind receptors, suggesting that this natural variation is evidence of complexity and unpredictability in the field of Wnt signaling. *See* EX1003 ¶¶ 82-89. I disagree. Dr. Kahn's overview of natural Wnt ligands and their interaction with Wnt receptors again goes beyond the claimed tetravalent molecules.

42. Dr. Kahn begins by providing an overview of the cross-reactivity, specificity, and different binding affinities of ***natural*** Wnt ligands with Fzd receptors and LRP5/6 receptors (including at the LRP6-epitope level), and their resulting differences in Wnt signaling activity under different conditions. EX1003

Surrozen 2010
Merck v. Surrozen PGR2026-00027
Page 22

¶¶ 82-84, 95. These principles have nothing to do with the claimed tetravalent molecules, which are not designed to (nor do the claims require them to) replicate the interactions of particular natural Wnt ligands. The claims do not require any specific binding affinity, and Dr. Kahn points to nothing in the claims indicating otherwise. For the same reasons, Dr. Kahn's focus on cross-reactivity is irrelevant.

43. Dr. Kahn's discussion of the "specificity between Wnt ligands and Lrp receptors" (at Paragraph 83 of his declaration) is not only misplaced in its focus on natural Wnt ligands, but mischaracterizes EX1033. The data reported in EX1033 shows only that Wnt11, Wnt5a, and Wnt8, when fused to Fzd5, induced comparatively ***higher*** levels of Wnt signaling in cells that express LRP6 than in cells that express LRP5; it did ***not*** show that the Wnt-Fzd fusion proteins were unable to induce canonical Wnt signaling in cells expressing LRP5. *Compare* EX1003 ¶ 83, *with* EX1033 at 6, Fig. 5. Regardless, even if the claims required activation of Wnt signaling, as is required under Petitioner's construction, and even if "different Wnt ligands require different Fzd and Lrp receptors to induce Wnt signaling" under certain conditions, the specificity and limitations of natural Wnt ligands have no bearing on whether the claimed tetravalent molecules, which are designed to specifically bind two Fzd and two LRP5/6 receptors, will induce Wnt/β-catenin signaling.

44. Dr. Kahn's discussion of Wnt3a's behavior upon binding different

Surrozen 2010
Merck v. Surrozen PGR2026-00027
Page 23

epitopes of LRP6 is likewise inapposite in the context of the claimed tetravalent molecules. EX1003 ¶ 84. ***First***, Dr. Kahn mischaracterizes EX1016. EX1003 ¶ 84. EX1016 reports that when increasing concentrations of purified soluble LRP6 extracellular domains are combined with Wnt3a, "soluble LRP6 directly competes with the cell surface LRP6 receptor for binding to Wnt3a, hence disrupting Fz/Wnt/LRP6 complex formation and resulting in inhibition of cellular β-catenin stabilization." *See* EX1016 at 3-4. EX1016 does ***not*** suggest that Wnt3a binding to cell surface E1E4 LRP6 inhibits canonical Wnt signaling (as Dr. Kahn suggests), but rather that soluble purified LRP6 proteins interfere with Wnt3a binding to cell surface LRP6 and that soluble E1E4 provides more potent interference with Wnt3a's binding to cell surface LRP6 than soluble E1E2 and E3E4. *Id.* ***Second***, assuming Petitioner is correct that the claims require Wnt agonism, Dr. Kahn's observation that certain natural Wnt ligands preferentially bind to different LRP6 domains has no significance to whether or not the claimed tetravalent molecules, binding Fzd and LRP5/6, will activate Wnt signaling, nor does he attempt to explain why it does. *See* EX1003 ¶ 84. ***Third***, the Examples of the '278 Patent (discussed at Paragraphs 75-134, below) establish that the claimed tetravalent molecules can activate Wnt signaling when binding the E1E2 ***or*** E3E4 domains of LRP6. *See, e.g.*, EX1001 at 159:10-39, Figs. 14A-14F (testing molecules incorporating the "LRP6E1E2 binder 1115.3" and the "LRP6E3E4 binder

Surrozen 2010
Merck v. Surrozen PGR2026-00027
Page 24

YW211.31.57," and reporting that all such molecules "were able to activate Wnt signaling"). These results are consistent with a person of ordinary skill in the art's understanding as of 2017 that activation of canonical Wnt signaling was primarily a matter of heterodimerizing Fzd and LRP5/6 receptors expressed on the cell surface, rather than binding particular combinations of epitopes. Dr. Kahn points to no evidence suggesting that the claimed tetravalent molecules may inhibit canonical Wnt signaling when binding certain LRP6 epitopes.

45. Dr. Kahn next contends that, in 2017, there was no "coherent interaction model that applies to Wnt ligands generally." EX1003 ¶ 85. The '278 Patent, however, provides such a coherent interaction model for the claimed tetravalent molecules: a 2:2 stoichiometry with two Fzd binding regions and two LRP5/6 binding regions, backed by the support of 90 embodiments tested *in vitro* that all activated the canonical pathway. *See* EX1001 at 155:14-161:33, cl. 1; Paragraphs 72-134, below. And while Dr. Kahn contends in Paragraph 86 that it "would have been ***helpful***" to have "a complete crystal structure of the full Wnt-Fzd-Lrp complex" to design "therapeutic moieties," he does not say that such a crystal structure would have been necessary. Nor would it have been, with the teachings of the '278 Patent regarding tetravalent molecules in hand showing that heterodimerizing two Fzd receptors and two LRP5/6 receptors via a tetravalent molecule will activate Wnt signaling (as I have been asked to assume is required

Surrozen 2010
Merck v. Surrozen PGR2026-00027
Page 25

under Petitioner's construction). A high-resolution structure of a Wnt-Fzd-Lrp complex, determined by X-ray crystallography or cryo-electron microscopy, would not invalidate the simple fact, first disclosed by the inventors, that heterodimerization of two Fzd and two LRP5/6 with a tetravalent molecule will activate Wnt signaling.

46. Dr. Kahn also points out that "ligands structurally unrelated to Wnt ligands … can activate Wnt signaling and compete for binding to Fzd and Lrp receptors" and that "external potentiators [like R-spondin] … can synergize with Wnt ligands and boost downstream signaling." EX1003 ¶¶ 87-88. But these factors do not affect a person of ordinary skill's ability to make tetravalent molecules binding Fzd and LRP5/6, or even—under Petitioner's proposed construction—those capable of activating Wnt signaling. Similarly, the fact that a non-Wnt ligand, Norrin, was reported to bind Fzd4 and LRP5/6, EX1003 ¶ 87, has no bearing on whether a skilled artisan could make a tetravalent molecule with Fzd4 and LRP5/6 binding regions (as the inventors were able to do, for example, 3SD10-3, 3SD10-26, and 3SD10-36 tested in Example 17, EX1001 at 161:1-17, Table 1B, Table 3, Fig. 17E). The ability of cell surface receptors to interact with multiple ligands is not unique to Fzd and LRP5/6 receptors and, even under Petitioner's proposed construction, does not affect whether simultaneous binding of Fzd and LRP5/6 receptors activates Wnt signaling. And Dr. Kahn does not

identify anything complex or unpredictable about R-spondin, a well-recognized and widely-used biological potentiator commonly used to amplify canonical Wnt signaling, or any other "external potentiator" that "boost[s] downstream signaling." EX1003 ¶ 88. As Dr. Kahn himself straightforwardly explains, "R-spondin inhibits factors that destabilize and degrade Fzd receptors, resulting in … stronger Wnt signaling." EX1003 ¶ 88. R-spondin, a protein occurring naturally in the human body, cannot activate canonical Wnt signaling in the absence of a Wnt agonist. EX2014 at 3 ("Wnt ligands are required for activities of RSpo proteins.").

47. Dr. Kahn finally raises, as a proxy for the complexity of Wnt signaling, the lack of *in vivo* human studies of Wnt signaling and FDA-approved therapies "developed to specifically target Wnt signaling." EX1003 ¶ 89. This is yet another distraction, going beyond the scope of the claimed tetravalent molecules. ***First***, in my experience, the scientific community does not take the absence of an FDA-approved therapy in a specific field as evidence that the field is in its nascency and thus complicated or not well-understood.

48. ***Second***, developing and using the claimed tetravalent molecules of the '278 Patent does not require a "complete understanding of signaling circuitry in the human body" gained through *in vivo* studies in humans. *See* EX1003 ¶ 89. *In vitro* studies in human cells, such as those performed in Examples 2-18, provide the person of ordinary skill with substantial guidance as to the claimed molecules and,

Surrozen 2010
Merck v. Surrozen PGR2026-00027
Page 27

under Petitioner's proposed construction, their activation of Wnt signaling. The Wnt signaling pathway is also a highly conserved system, remarkably consistent across species. *See, e.g.*, EX1034 at 1. Data obtained from *in vivo* studies in non-human cells and organisms provides valuable guidance as to the human Wnt signaling pathways.

3. Tissue- and Cell-Dependence (Paragraphs 98-100 in Kahn's Declaration)

49. Dr. Kahn concludes by discussing how Wnt ligands and their associated receptors (i) are expressed differently in tissues and (ii) among cells in the same tissue, have differing impacts on cellular development. EX1003 ¶ 98-100. It is not clear to me how any of this supports Dr. Kahn's view that the field of Wnt signaling was not well understood.

* * *

50. Overall, Dr. Kahn's efforts to portray Wnt signaling as "bewilderingly complex" focus on aspects of Wnt signaling systems, such as the complexities of natural Wnt ligands and downstream interactions in the canonical Wnt signaling cascade, that would not impact a person of ordinary skill's understanding that the '278 Patent discloses a wide genus of molecules that specifically bind Fzd and LRP5/6 in a 2:2 tetravalent format and that such molecules activate canonical Wnt signaling. The alleged complexity highlighted by Dr. Kahn is irrelevant to whether

Surrozen 2010
Merck v. Surrozen PGR2026-00027
Page 28

a skilled artisan could make tetravalent molecules specific to Fzd and LRP5/6 that activate Wnt signaling, which is all the claims require under Petitioner's proposed construction. EX1003 ¶ 100.

B. Measuring Canonical Wnt Signaling Activity (Paragraphs 101-112 in Kahn's Declaration)

51. In Paragraphs 101-112, Dr. Kahn discusses various methods for measuring Wnt signaling activity that were known in 2017. Below, I provide a brief overview of the assays disclosed in the '278 Patent and respond to Dr. Kahn's criticisms of these known assays.

52. First, I note that under Surrozen's proposed construction, the claims do not require activation of Wnt signaling, let alone a particular level of Wnt signaling. *See* Paragraph 20, above. The claims recite the tetravalent structure and composition of the claimed molecules.

53. Even assuming Petitioner's proposed claim construction is correct, Dr. Kahn's analysis is flawed. Dr. Kahn begins by emphasizing that, in 2017, there was a "lack of a single standardized assay" for "all Wnt signaling activity" (*i.e.*, there was no single assay that measured both canonical and non-canonical Wnt signaling activity). That is irrelevant given the canonical signaling context of the '278 Patent that I discussed above in Paragraphs 27, 33. *See* EX1003 ¶¶ 101-102; *see also* EX1003 ¶ 104, 105. And, as Dr. Kahn appears to acknowledge, *id.* ¶ 103,

Surrozen 2010
Merck v. Surrozen PGR2026-00027
Page 29

there were multiple "[a]ssays frequently used for canonical Wnt signaling by 2017." *Id.* ¶ 103.

54. Dr. Kahn identifies the same five assays that the '278 Patent identifies as "known in the art." *Compare id.* ¶ 103, *with* EX1001 at 117:39-47. The '278 Patent specifically states that the following assays and methods were "known in the art" for "measuring the level of canonical Wnt/β-catenin signaling": "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" and "global transcriptional profiling methods."[3] EX1001 at 117:39-52. While Dr. Kahn goes into great detail about each of the five assays (*see* EX1003 ¶¶ 104-109), he does not actually identify any drawbacks for four of the five assays or identify any scientific evidence that would suggest that "results for a given molecule could and did vary from assay to assay." *Id.* ¶ 103.

55. Dr. Kahn instead focuses his critiques on TCF reporter assays, which are used throughout the '278 Patent. *See* EX1003 ¶¶ 109-111. The '278 Patent specifically uses the SuperTOPFlash ("STF") reporter assay. EX1001 at 117:53-

[3] The '278 Patent also identifies the "BioImage β-Catenin Redistribution Assay" as a "good reflection of the level of Wnt/β-catenin signaling." EX1001 at 118:19-26.

Surrozen 2010
Merck v. Surrozen PGR2026-00027
Page 30

67, 118:37-51, 155:16-161:33. As the patent explains, "[t]he canonical Wnt/[β]-catenin signaling pathway ultimately leads to changes in gene expression through the transcription factors TCF7, TCF7L1, TCF7L2 (a.k.a. TCF4), and LEF." EX1001 at 117:45-47. TCF reporter assays are used to measure the level of Wnt/β-catenin signaling by "assess[ing] changes in the transcription of TCF/LEF controlled genes." *Id.* at 117:53-57. One such TCF reporter assay is TOPFlash, a luciferase reporter assay. When canonical Wnt signaling is activated, β-catenin enters the nucleus of the cell and binds the TCF/LEF transcription factors, resulting in expression of luciferase that is used to measure the level of β-catenin-dependent signaling. The STF reporter assay is another TCF reporter assay, which can be performed in a variety of cell lines, including HEK293 (referred to here simply as "293"), Huh7, A375, and BNL.CL2. *See, e.g.*, EX1001 at 156:43-45.

56. By December 2017, TOPFlash and SuperTOPFlash reporter assays were in widespread use and considered by members of the field as a well-established accurate and reliable indicator of canonical Wnt activity. TCF-based assays, such as TOPFlash assays, have been used across the field for everything from cell culture to whole animal studies in multiple species, and have become the go-to assay for evaluating canonical Wnt signaling in cells. For example, SuperTOPFlash reporter assays have been used in high-throughput screens since the early 2000s to identify Wnt agonists and antagonists: for example, Chen et al.

Surrozen 2010
Merck v. Surrozen PGR2026-00027
Page 31

(2009) used SuperTOPFlash to screen a 200,000-compound synthetic chemical library to identify potent, highly-specific Wnt antagonists. EX2015 at 2-3 (describing use of cells "stably harboring a ***well-characterized*** Wnt/β-catenin pathway-responsive firefly luciferase (FL) reporter plasmid (SuperTopFlash or STF)"). Such studies highlight the robustness and scalability of SuperTOPFlash as a system for measuring canonical signaling activity. Moreover, numerous articles cited by Dr. Kahn use TOPFlash luciferase assays in evaluating activation and inhibition of canonical/β-catenin-dependent signaling. *See, e.g.*, EX1025 at 8; EX1033 at 2, 8; EX1044 at 3, 8, 10, 13; EX1056 at 2-5, 7, 9-10; EX1063 at 6; EX1066 at 2, 4-5, 8-9; EX1082 at 3-8; EX1093 at 3-4. Kahn (2014) explicitly recognizes that "using the TOP-Flash reporter assay as a read-out of β-catenin-TCF activity" is the "strict definition of canonical WNT signalling."[4] EX1043 at 3. In 2017, a person of ordinary skill would have understood a molecule that induced reporter activity in a SuperTOPFlash assay to be an agonist for the canonical Wnt signaling pathway.

[4] While Dr. Kahn's article suggests the TOPFlash assay "might not capture all the important transcriptional changes ***caused*** by activated WNT signalling," it does ***not*** question whether induced reporter activity in a TOPFlash assay reflects activated Wnt signaling. EX1043 at 3.

57. Running a TOPFlash or SuperTOPFlash reporter assay was not a difficult task in 2017 in the Wnt signaling field. While Dr. Kahn suggests the "entire process," from "cell culture" to "reporter readout," "typically takes about a week from start to finish," EX1003 ¶ 108, this significantly overstates the burden of performing a TCF reporter assay. We routinely perform these assays in my laboratory in 96-well formats (and have performed these assays since I established my lab in 2008), and in my experience it is straightforward to assay multiple plates without requiring automation. Cell lines can be engineered to stably carry a SuperTOPFlash transgene so that these experiments involve seeding of cells (Day 0), treating cells (Day 1), and assaying (Day 2). In 2017, a lab with an established SuperTOPFlash cell line could perform assays for hundreds (and even thousands) of conditions in a matter of days. TOPFlash assays are robust and reliable assays extremely well-suited to this kind of high-throughput screening.

58. In my experience, and contrary to Dr. Kahn's suggestion, EX1003 ¶ 109, it is not necessary to use both positive and negative controls to identify whether the tested tetravalent molecules of the '278 Patent are capable of activating Wnt signaling. First and foremost, in 2017 (and today) TOPFlash was a well-established Wnt-dependent assay recognized as a reliable method of monitoring Wnt signaling activity: it was understood in the field that induced reporter activity in a TOPFlash assay indicates that the tested molecule has

Surrozen 2010
Merck v. Surrozen PGR2026-00027
Page 33

activated the canonical Wnt signaling pathway, *i.e.*, is a Wnt agonist.

59. A positive control is used to identify false negatives: if the tested molecules appear inactive, a positive control can be used to confirm whether the assay is working properly. In the ’278 Patent, each of the tetravalent molecules tested induced some level of activity in the SuperTOPFlash reporter assays. Under these conditions, in the context of robust and well-established SuperTOPFlash assays, a positive control is unnecessary for a person of ordinary skill in the art to confirm the assay is working properly. Beyond detecting false negatives, a positive control in the form of a natural Wnt ligand such as Wnt3a serves a very specific purpose, *i.e.*, using the ability of a natural Wnt ligand to activate canonical signaling as the baseline comparator for determining whether a different molecule is activating the canonical signaling pathway to the same or greater extent as a natural Wnt ligand. Where no such comparison is required (and it is not, as I explain at Paragraph 137), there is no need to use a natural Wnt ligand as a positive control.

60. A negative control, like the IgGs binding only to Fzd receptors disclosed in the ’278 Patent, does not activate canonical Wnt signaling and is used to confirm any induced reporter activity is associated with the molecule being assayed. *See, e.g.*, EX1001 at 155:32-36, 156:26-30, 156:45-52, Figs. 4-5. Furthermore, assays conducted at different concentrations necessarily incorporate a

Surrozen 2010
Merck v. Surrozen PGR2026-00027
Page 34

negative control: the tested molecule, diluted to a concentration at which it shows no activity. Each of the STF assays of tetravalent molecules reported in the ’278 Patent used multiple concentrations, including those at which the molecule showed no activity, thereby incorporating an additional negative control. *See* EX1001 at Figs. 2D, 3D, 5-7, 8B, 9, 12B, 13B, 13C, 13E, 13F, 14A-14F, 15B-15G, 16C, 17B-17H, 18B-18C. Dr. Kahn also asserts that “basal reporters such as FOPFlash, which do not contain the TCF/LEF binding elements” should be used “to distinguish true canonical Wnt/β-catenin pathway activity from background or non-specific effects.” EX1003 ¶ 21 n.4. But FOPFlash is an outdated control that has fallen out of common use—use of TOPFlash with the types of negative controls used here by the inventors, without FOPFlash, is well-accepted in the field. I am not concerned, nor would a person of ordinary skill in the art be concerned, about the inventors’ use of negative controls in the SuperTOPFlash assays of the ’278 Patent.

61. A person of ordinary skill in the art would not need ***both*** a positive control and a negative control to understand that the tetravalent molecules tested in the ’278 Patent activated Wnt signaling (which is not required under Surrozen’s proposed construction), or to determine whether a given molecule is activating the canonical pathway, because a person of ordinary skill in the art recognizes that Wnt-dependent TOPFlash assays are a highly reliable method of measuring

Surrozen 2010
Merck v. Surrozen PGR2026-00027
Page 35

canonical Wnt signaling activity and accepts that any induced reporter activity in a TOPFlash assay with appropriate negative controls indicates activation of canonical Wnt signaling.

62. Assuming that Petitioner's claim construction is correct and the claims require that the tetravalent molecules are "biologically active," as I have been asked to assume, Dr. Kahn's criticisms of TCF reporter assays, EX1003 ¶ 110, do not change my opinion that TOPFlash and SuperTOPFlash assays are highly accurate, replicable, and reliable methods of measuring canonical Wnt signaling activity, particularly when applied to the claimed tetravalent molecules of the '278 Patent. The TOPFlash reporter assay is a powerful and widely used tool in cell biology because it is a convenient, highly sensitive, quantitative and scalable assay that distills the complex canonical signaling cascade into a single, quantifiable readout. Contrary to Dr. Kahn's suggestion, TCF reporter assays do not need to capture every transcriptional change caused by canonical Wnt signaling to confirm Wnt signaling activity. EX1003 ¶ 110.

63. ***First***, the fact that β-catenin nuclear translocation and TCF-β-catenin-mediated transcription may in some cases be effected by a ***limited*** number of Wnt-independent factors does not raise concerns in the context of TCF reporter assays of the claimed tetravalent molecules, which do not introduce those factors. *See* EX1043 at 3 (describing, *e.g.*, receptor tyrosine kinases, non-receptor tyrosine

kinases, G protein-coupled receptor signal transduction pathways). ***Second***, TCF reporter assays do not merely measure "β-catenin nuclear translocation," but the resulting transcriptional activity, which ***does*** imply functional Wnt signaling. ***Third***, the fact that β-catenin may be ***underestimated*** by TOPFlash readouts reinforces a person of ordinary skill in the art's confidence that measurable reporter activity is in fact reflective of canonical signaling activity. In the field as of 2017, a person of ordinary skill in the art would have felt confident relying on such readouts. Dr. Kahn makes no attempt to quantify how frequently false negatives might occur, and he ignores that use of biological potentiators like R-spondin would minimize any such occurrences. ***Fourth***, use of biological potentiators like R-spondin (as in Example 5, discussed below at Paragraphs 87, 93) minimizes any "cell-type dependen[cy]" in β-catenin signaling activation in TOPFlash assays.

64. In Paragraph 111, Dr. Kahn points to Wnt5a and Wnt3a as purported examples of Wnt ligands producing different Wnt signaling effects when tested in different cell lines, which Dr. Kahn says highlights the "complexity and uncertainty in measuring Wnt signaling activity." EX1003 ¶ 111. I disagree that this has any bearing on whether one can determine if a molecule exhibits Wnt agonist activity. I also note that Dr. Kahn's cited examples, which rely on references from a decade prior to the '278 Patent, do not support his claim that

Surrozen 2010
Merck v. Surrozen PGR2026-00027
Page 37

"***measuring*** Wnt signaling activity" was "complex[] and uncertain[]." They merely show that a given natural Wnt ligand may activate one or more Wnt signaling pathways, and, even if Wnt signaling activation were required by the claims, a skilled artisan would have been able to determine if a given molecule agonizes the canonical pathway using, *e.g.*, the assays disclosed in the '278 Patent.

65. I strongly disagree with Dr. Kahn's suggestion that "TOPFlash … assays provide, at best, an incomplete and often misleading picture of true Wnt/β-catenin pathway activity." EX1003 ¶ 110. The widespread use of these assays in peer-reviewed research publications, both prior to December 2017 and to date, refutes Dr. Kahn's position. *See, e.g.*, EX2015 at 2-3; EX1025 at 8; EX1033 at 2, 8; EX1044 at 3, 8, 10, 13; EX1056 at 2-5, 7, 9-10; EX1063 at 6; EX1066 at 2, 4-5, 8-9; EX1082 at 3-8; EX1093 at 3-4. In 2017, a person of ordinary skill would have been able to determine with standard TOPFlash assays whether one of the claimed tetravalent molecules activated canonical Wnt signaling.

VIII. ANALYSIS OF THE '278 PATENT

66. The inventors of the '278 Patent made and tested 90 different tetravalent molecules falling within the scope of the claims, which provide significant guidance to a person of ordinary skill in the art seeking to make and use the claimed tetravalent molecules.

67. At Paragraphs 75-134 below, I provide an explanation of Examples 2-

Surrozen 2010
Merck v. Surrozen PGR2026-00027
Page 38

18 of the ’278 Patent (which tested various bivalent and tetravalent molecules incorporating different Fzd and LRP5/6 binders, antibody and antigen-binding fragment types, structures, binder orientations, and linker lengths) and identify the teachings a person of ordinary skill in the art would derive from these examples. At Paragraphs 135-151 below, I also address Petitioner and Dr. Kahn’s mischaracterizations of Examples 2-18, which are set forth in Paragraphs 144-155 of Dr. Kahn’s declaration.

68. Next, at Paragraphs 152-167 below, I respond to the arguments at paragraphs 124-143 of Dr. Kahn’s declaration regarding the alleged unpredictability of the tetravalent molecules claimed by the ’278 Patent.

69. Finally, at Paragraphs 168-172 below, I address Dr. Kahn’s opinions regarding the number of target binding combinations falling within the scope of the ’278 Patent’s claims at paragraphs 113-123 of his declaration.

A. Examples 2-18

70. The ’278 Patent specification contains a wealth of disclosures in Examples 2-18 regarding the claimed tetravalent molecules, which provide a person of ordinary skill with extensive guidance as to how to make the claimed tetravalent molecules. Indeed, even under Petitioner’s proposed construction, which require that the claimed tetravalent molecules be “Wnt agonists” (which is not required by Surrozen’s proposed construction), the ’278 Patent provides 90

Surrozen 2010
Merck v. Surrozen PGR2026-00027
Page 39

examples of tetravalent molecules that activate Wnt signaling.

71. The specification discloses numerous illustrative examples of both the underlying binding regions and the tetravalent molecules that are the invention of the ’278 Patent, which are used in the Examples of the ’278 Patent:

- The ’278 Patent makes clear that “frizzled specific antibodies … are known in the art and are commercially available.” EX1001 at 79:63-80:15 (identifying Fzd-specific antibodies available from, *e.g.*, Biolegend and Abcam and disclosed in numerous U.S. Patent applications). Then, in Table 1B, the patent discloses 91 heavy and light chain sequences for Fzd binders confirmed to bind to one or more Fzd receptors, including binding sequences that are cross-reactive with as many as five different Fzd receptors (for example, binder 001S-A04). EX1001 at Table 1B. The 91 Fzd binding sequences collectively bind all ten Fzd receptors. *Id.*

- Like with the Fzd-specific antibodies, the ’278 Patent notes that “[a]ntibodies that specifically bind to LRP5 or LRP6 are known in the art and are commercially available.” EX1001 at 116:25-27; *see also* EX1001 at 116:29-39 (identifying antibodies commercially-available from Santa Cruz and Cell Signaling Technology, and numerous antibodies disclosed in publications). Table 2A and 2B disclose 211 CDR sequences for confirmed

Surrozen 2010
Merck v. Surrozen PGR2026-00027
Page 40

LRP5/6 binders, binding LRP5 or one of two extracellular domains of LRP6. *Id.* at Table 2A and 2B.

- Table 3 lists 80 illustrative tetravalent molecules that embody the claims, designed in the tetravalent structures described in Example 1 of the '278 Patent. *Id.* at 150:26-152:45, Table 3. Example 1 describes illustrative tetravalent structures (depicted below in Figure 1) for combining binders in a Fab format (which may be converted into a full IgG format) with binders in a Nab or scFv format, several of which are depicted in Figure 1A of the '278 Patent; illustrative tetravalent structures for combining two binders in a Fab format with two additional binders in a Fab format, one of which is depicted in Figure 1B; illustrative tetravalent structures for combining two binders in a Nab or scFv format with two additional binders in a Nab or scFv format, several of which are depicted in Figure 1C; and illustrative tetravalent structures for combining binders linked together in a diabody format, one of which is depicted in Fig. 1D. EX1001 at 150:26-151:28, Fig. 1. The tetravalent molecules listed in Table 3 combine 14 Fzd binding regions and 18 LRP5/6 binding regions in various permutations. *Id.* at 151:29-152:45, Table 3. Together, the 80 illustrative tetravalent molecules listed in Table 3 are designed to bind seven of the ten Fzds, LRP5, and LRP6. *Id.* at Tables 1B, 2A, 3.

Surrozen 2010
Merck v. Surrozen PGR2026-00027
Page 41

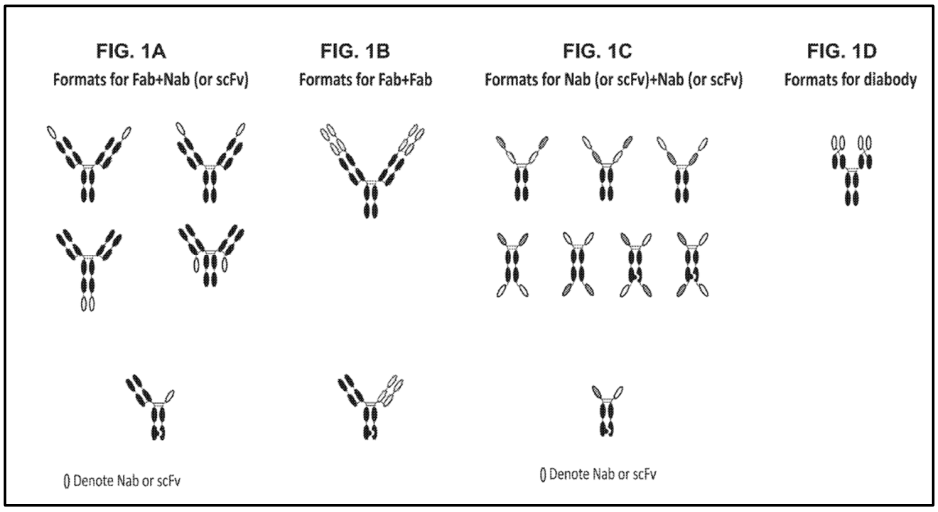


Figure 1: ’278 Patent Figure 1

72. Collectively, Examples 2-18 of the specification provide the structure for and then test 90 different tetravalent molecules, in addition to multiple bivalent molecules, in STF reporter assays to evaluate their activation of canonical Wnt signaling, using various negative controls. *See* EX1001 at 155:14-161:33. The Examples incorporate 16 different Fzd binding regions (collectively binding to seven of the ten different Fzd receptors) and 20 LRP5/6 binding regions (collectively binding to both LRP5 and LRP6). *See* EX1001 at 155:14-161:33.

73. While the claims do not require activation of Wnt signaling under Surrozen’s proposed construction, these Examples, alongside the ’278 Patent specification, teach a person of ordinary skill that every tested tetravalent Wnt surrogate molecule with two Fzd binding regions and two LRP5/6 binding regions activated some level of canonical Wnt signaling, while each of the bivalent (1:1) molecules (*i.e.*, those binding to only one Fzd receptor and one LRP5/6 coreceptor)

tested were "ineffective" at activating canonical Wnt signaling. *Compare* EX1001 at 155:14-156:14 (Examples 2-3), 156:34-157:50 (Examples 5-9), 158:50-159:47 (Examples 13-14), 159:50-161:33 (Examples 15-18), Figs. 2-3, 5-9, 13, 14A-14G, 15-18, *with* EX1001 at 157:54-158:47 (Examples 10-12), 159:7-47 (Example 14), Figs. 10-12, 14H. While Dr. Kahn notes that the 90 tetravalent molecules tested do not include binding regions that bind to Fzd3, 6, or 10, *see, e.g.*, EX1003 ¶ 36, a person of ordinary skill in the art in 2017 would have expected—based on the well-established model of canonical Wnt signaling as involving the dimerization of a Fzd with an LRP5/6 receptor, along with the '278 Patent's teaching that every one of the 90 tetravalent molecules tested activated Wnt signaling—that tetravalent molecules binding Fzd3, 6, and 10 (for which binding sequences are disclosed in Table 1B) would also activate canonical Wnt signaling. *See, e.g.*, EX2016 at 4, Fig. 2(B) (reporting increased Wnt3a-induced TOPFlash activity in the HEK293 cell line when co-transfected with LRP6 ***and*** Fzd3); EX2017 at 4-5 (reporting that "FZD10 positively regulates [] the *Xenopus* WNT-β-catenin-TCF signaling pathway"); *see also* EX2018 at Abstract, 10-12, Fig. 6 (reporting activation of canonical signaling by Wnt1, FZD10, and Lrp6 and explaining "FZD10 requires Lrp6 co-receptor to activate canonical Wnt signaling effectively," confirming a person of ordinary skill's expectation in 2017 that Fzd10 and LRP5/6 will activate canonical Wnt signaling); EX2019 at Abstract, 5-6, 8, Fig. 3 (reporting Wnt10B-

Surrozen 2010
Merck v. Surrozen PGR2026-00027
Page 43

induced FZD6-LRP6 complexes produced "an obvious nuclear accumulation of β-catenin," confirming a POSA's expectation in 2017 that Fzd6 and LRP5/6 will activate canonical Wnt signaling).

74. This result, viewed against the diverse range of antigen-binding fragment types, Fzd and LRP5/6 binding sequences, Fzd-LRP5/6 stoichiometries, tetravalent structures, relative orientations, and spacing / linker lengths of the 90 tetravalent molecules tested in Examples 2-18, teaches a person of ordinary skill that, even if Petitioner's proposed construction requiring "biologically active" "Wnt agonist" molecules were adopted, tetravalent molecules with two Fzd binding regions and two LRP5/6 binding regions will activate Wnt signaling.

1. Examples 2 and 3

75. Examples 2 and 3 test two tetravalent molecules, R2M3-26 and R2M3-32, that embody the claims of the '278 Patent. EX1001 at 155:14-156:14. Both molecules incorporate the R2M3 Fzd binder (001S-A04), which is confirmed to bind Fzd1, Fzd2, Fzd5, Fzd7, and Fzd8. *Id.* at 151:44-152:2, Table 1B. Example 2 combines R2M3 with LRP6 binder 26 (009S-E04) and Example 3 combines R2M3 with LRP6 binder 32 (013S-H04). *Id.* at 155:17-20, 155:47-50, Table 3. The molecules tested in Examples 2 and 3 were designed with the IgG-Nab fusion structures depicted in Figure 2 below. *Id.* at 155:17-20, 155:47-50, Figs. 2A, 3A.

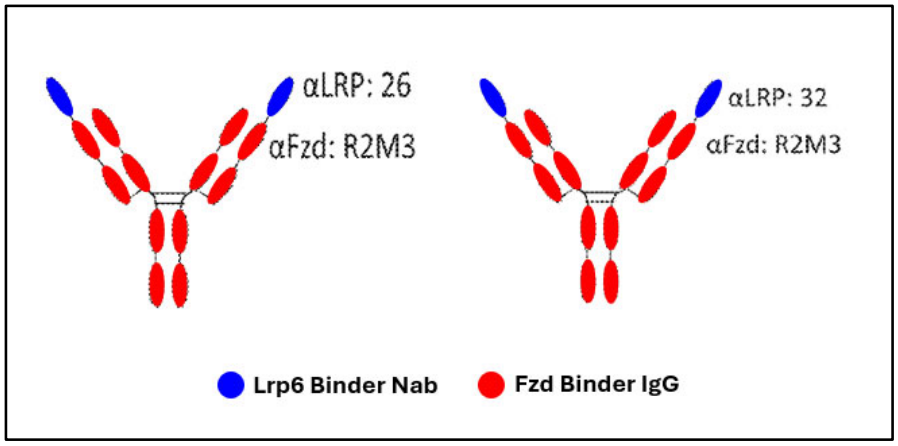


Figure 2: R2M3-26 (left) and R2M3-32 (right) ('278 Patent Figs. 2A and 3A, annotated)

76. In Examples 2 and 3, the inventors purified R2M3-26 and R2M3-32 using a Protein A affinity column and size-exclusion-chromatography (SEC), confirmed through an Octet interaction assay[5] the ability of R2M3-26 and R2M3-32 to bind to a Fzd1 extracellular domain after the fusion of the LRP6 binders to an R2M3 IgG, and tested the ability of R2M3-26 and R2M3-32 to activate canonical Wnt signaling in a 293 cell STF reporter assay. *See* EX1001 at 155:15-156:14. The results for each of these tests are shown in Figure 2C/3C (Octet interaction assay) and 2D/3D (STF reporter assay). EX1001 at Figs. 2C-2D, 3C-3D.

77. The inventors first tested the ability of the molecules to activate canonical Wnt signaling across the identified SEC fractions and confirmed, first,

[5] Octet interaction assays use Bio-Layer Interferometry (BLI), which analyzes light interference patterns on the tip of a biosensor, to measure the binding kinetics and binding affinity of antibody-antigen interactions.

Surrozen 2010
Merck v. Surrozen PGR2026-00027
Page 45

that both molecules activated canonical Wnt signaling and, second, that the "peak of the reporter activity correlated with the peak of the proteins" across the SEC fractions. *Id.* at 155:26-29, 155:54-59. This teaches a person of ordinary skill that the tetravalent molecules tested (rather than larger, higher-valency aggregates or smaller, lower-valency fragments of those tetravalent molecules) were responsible for the canonical Wnt signaling activity detected.

78. The inventors then performed dose-response testing of the R2M3-26 and R2M3-32 molecules in 293STF reporter assays in both the absence and presence of R-spondin, and confirmed that, although not required by the claims under Surrozen's construction, both molecules "induced reporter activity in a dose dependent manner" that was "enhanced by the presence of R-spondin." *Id.* at 155:29-36, 155:59-63, Figs. 2D, 3D.

79. Examples 2 and 3 also included Fzd binder R2M3 in the IgG format, which did not have an attached LRP6 binding arm, as a negative control. The R2M3 IgG "did not induce reporter activity" at any concentration in the STF reporter assay, which a person of ordinary skill in the art would understand means it did not activate canonical Wnt signaling. *Id.* at 155:32-36, 155:62-65, Fig. 2D, Fig. 3D. This confirms for a person of ordinary skill that the Wnt surrogate molecule as claimed (*i.e.*, a molecule comprising two Fzd binding regions and two LRP5/6 binding regions) is what is activating canonical Wnt signaling and that the

induced activity observed with the R2M3-26 and R2M3-32 molecules was not merely a reflection of background activity in the assay.

80. Dr. Kahn criticizes Examples 2 and 3 due to the absence of "a positive control, such as Wnt3A" to support the claim that the molecules "activated Wnt signaling 'similar to a natural ligand.'" EX1003 ¶ 21. But Dr. Kahn's critique mischaracterizes the description offered in Examples 2 and 3. The inventors simply indicated that R2M3-26 and R2M3-32 "induced reporter activity in a dose dependent manner and [were] enhanced by the presence of R-spondin similar to a natural Wnt ligand." EX1001 at 155:32-36, 155:62-65. A positive control is not required to support this observation. Furthermore, as noted, nothing in the claims of the '278 Patent under Surrozen's construction requires activating Wnt signaling, let alone in the same manner as a natural Wnt ligand.

81. Dr. Kahn also criticizes the R2M3 IgG used as a negative control in Examples 2 and 3, asserting without explanation that "R-spondin alone" would offer "a better understanding as to the baseline signal or noise that exists in the absence of any external factor targeting members of Wnt signaling pathways." EX1003 ¶ 21 n.4. I disagree. Fzd binders alone do not activate canonical Wnt signaling, as demonstrated in each of the Examples employing Fzd-binding IgG as negative controls. *See, e.g.*, EX1001 at Figs. 2D, 3D, 5A, 5C, 5D, 5E, 5G, 6A, 6C, 6D. A Fzd-binding IgG is a suitable and well-accepted negative control in the field

Surrozen 2010
Merck v. Surrozen PGR2026-00027
Page 47

and provides an equally as suitable baseline as R-spondin alone, as it is well-established that antibodies directed solely to Fzd receptors harbor no Wnt agonist activity.

82. Petitioner and Dr. Kahn also suggest that R2M3-26 and R2M3-32 "did ***not*** produce responses in a TOPFlash assay in the absence of R-spondin." Pet. at 48-49; EX1003 ¶ 149. I disagree. The claims do not require activation of Wnt signaling under Surrozen's construction, but the data in Figures 2D and 3D for these molecules, as well as the explicit disclosure in Examples 2 and 3 that R2M3-26 and R2M3-32 "induced reporter activity in a dose dependent manner," establish that R2M3-26 and R2M3-32 activated Wnt signaling even in the absence of R-spondin (depicted in black in Figure 3 below). EX1001 at 155:32-36, 155:62-65, Figs. 2D, 3D; EX1005 at 39-40.[6]

[6] Here and for all SuperTOPFlash (STF) assay results provided in this declaration, I have used the figure from the provisional application underlying the '278 Patent (EX1005) as it was provided to the Patent Office in color.

Surrozen 2010
Merck v. Surrozen PGR2026-00027
Page 48

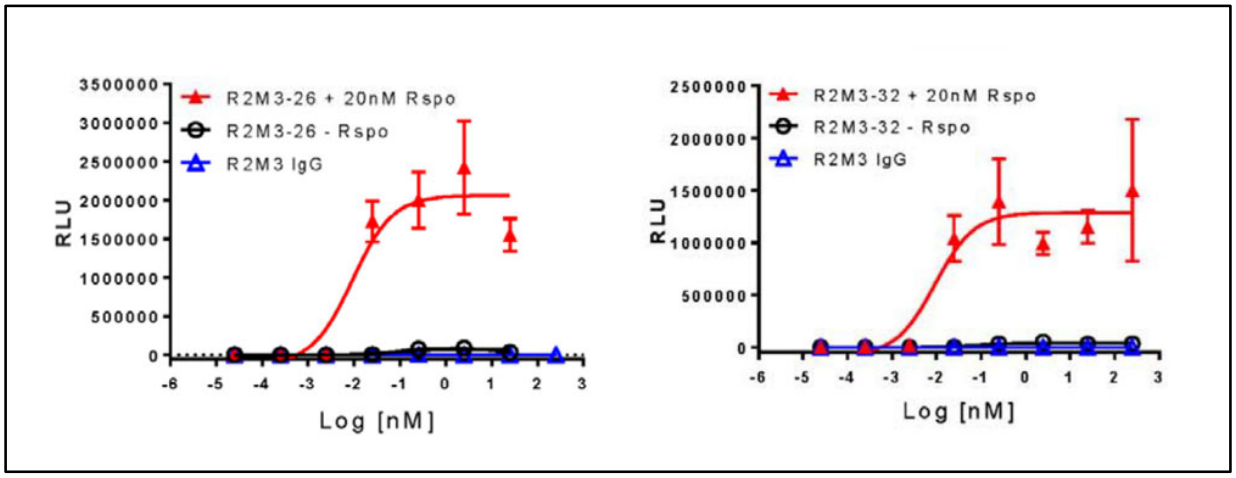


Figure 3: '278 Patent Figures 2D (left) and 3D (right) (EX1005 at 39-40)

83. Figure 5A further confirms the activity of R2M3-26 and R2M3-32 in the absence of R-spondin. In Figure 5 (EX1005 at 42), it is apparent that both R2M3-26 (green) and R2M3-32 (black) produced responses in the TOPFlash assay in the absence of R-spondin. The activities of R2M3-26 and R2M3-32 in the absence of R-spondin are also shown in Figures 2D and 3D but, due to scaling of the y-axes in Figures 2D and 3D (to illustrate the potency of these molecules in the presence of R-spondin), these activities are comparatively obscured. *Compare* EX1001 at Figs. 2D (scaled from 0 to 3,500,000 RLU), 3D (scaled from 0 to 2,500,000 RLU), *with* EX1001 at Fig. 5A (scaled from 0 to 25,000 RLU). Figure 5A of the '278 Patent provides a clearer picture of the activity.

Surrozen 2010
Merck v. Surrozen PGR2026-00027
Page 49

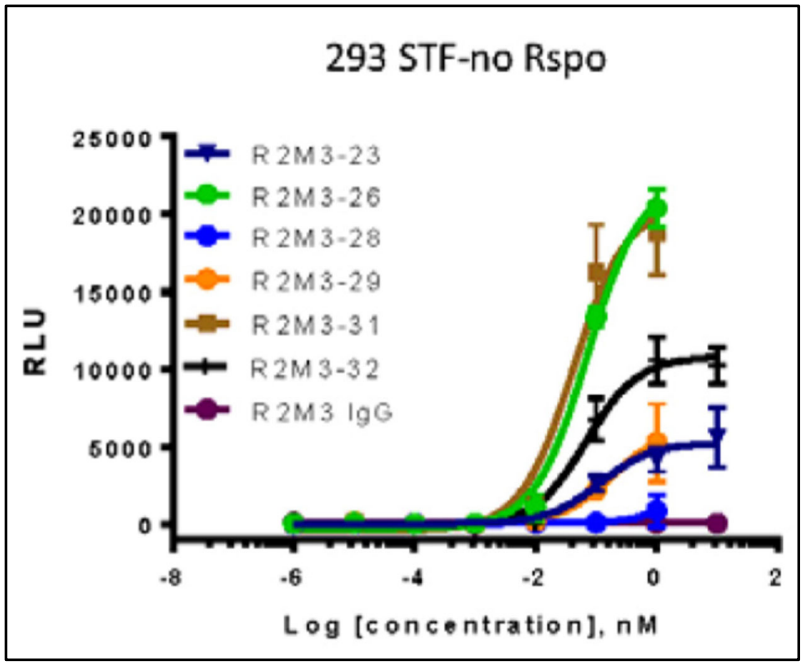


Figure 4: '278 Patent Figure 5A (EX1005 at 42)

2. Example 4

84. In Example 4, the inventors separately tested the molecules of Examples 2 and 3 (R2M3-26 and R2M3-32) in a 293STF reporter assay in the presence of a Fzd1 ECD-Fc (the cysteine-rich domain of the extracellular region of the Fzd1 receptor fused to an Fc region), an R2M3 IgG, and an Fc tag alone (as a negative control molecule). EX1001 at 156:17-30, Figs. 4A, 4B. The inventors found that, "[i]n a dose dependent manner, both Fzd1 ECD-Fc and R2M3 IgG inhibited R2M3-26 (FIG. 4A) and R2M3-32 (FIG. 4B) induced reporter signaling, while the negative control molecule, Fc alone had no impact." *Id.* at 156:26-30.

85. A person of ordinary skill in the art would understand that the R2M3 IgG (which introduces additional Fzd binding regions) inhibited the canonical Wnt

signaling activity induced by the tetravalent molecules in a dose dependent manner because the R2M3 IgG bound to an increasing number of the available Fzd receptors in the 293 cell line, limiting the available binding targets for the Fzd binding regions on the tetravalent molecules. Likewise, a person of ordinary skill in the art would understand that the Fzd1 ECD-Fc (which introduces additional Fzd binding targets) inhibited canonical Wnt signaling activity induced by the tetravalent molecules in a dose dependent manner because the Fzd binding regions of the tetravalent molecules bind to the Fzd1 ECD-Fc, reducing the number of tetravalent molecules binding to both Fzd and LRP5/6 receptors on the surface of the cells in the 293 cell line. By contrast, the Fc negative control provides neither additional binding regions nor additional binding targets that would interfere with the tetravalent molecules' ability to bind two Fzd receptors and two LRP6 receptors on a given cell's surface, and therefore did not inhibit canonical Wnt signaling induced by R2M3-26 or R2M3-32.

86. Example 4 demonstrates to a person of ordinary skill the importance of the tetravalent format with two Fzd binding regions and two LRP5/6 binding regions to the activation of canonical Wnt signaling pathways. Example 4 teaches that when other factors interfere with tetravalent molecules' ability to simultaneously bind two Fzd receptors and two LRP5/6 receptors, the canonical Wnt signaling activity induced by the tetravalent molecule is inhibited.

Surrozen 2010
Merck v. Surrozen PGR2026-00027
Page 51

3. Examples 5 and 6

87. Example 5 tests ten different tetravalent molecules pairing the Fzd binder R2M3 with ten different LRP6 binders in Wnt dependent reporter assays using four different cell lines (293, Huh7, A375, and BNL.CL2), varying the presence of R-spondin. EX1001 at 156:34-52, Figs. 5A-5H. Although Wnt signaling is not required by the claims under Surrozen's construction, the inventors reported that each of the molecules "activated [canonical] Wnt signaling to various levels." *Id.* at 156:43-45. As a comparator, R2M3 was fused to "non-LRP6 binder Nabs, 24 and 34, in the same format as the Lrp6 binders" and tested in the 293 STF reporter assay. *Id.* at 156:45-52. "[N]o activity" was observed for these molecules, which the inventors explain "suggest[s] that Wnt activities observed with R2M3 fusions to [LRP6 binders] are dependent on the presence of both Fzd and Lrp" receptors. *Id.* at 156:47-52, Fig. 5F. The inventors also used R2M3-IgG (without fused LRP5/6 binders) as a negative control, which exhibited no canonical Wnt signaling activity in the various reporter assays regardless of the concentration or presence / absence of R-spondin. *Id.* at Figs. 5A, 5C, 5D, 5E, 5G.

88. Example 6 tests four tetravalent molecules combining the Fzd binder 18R5, which binds Fzd1, 2, 5, 7, and 8, *see* EX2020[7] at 10:10-13, with four

[7] U.S. Patent No. 8,507,442, describing 18R5, is incorporated by reference in the '278 Patent. *See* EX1001 at 79:44-45.

Surrozen 2010
Merck v. Surrozen PGR2026-00027
Page 52

different LRP6 binders in Wnt dependent reporter assays in three cell lines (293, A375, and BNL.CL2), varying the presence of R-spondin. *Id.* at 156:56-67, Figs. 6A-6D. Although Wnt signaling is not required by the claims under Surrozen's construction, the inventors reported that each of the tetravalent molecules "demonstrated ability to activate Wnt signaling." *Id.* at 156:64-67. The inventors also used 18R5 IgG (without fused LRP5/6 binders) as a negative control, which exhibited no canonical Wnt signaling activity in the various reporter assays regardless of the concentration or presence / absence of R-spondin. *Id.* at Figs. 6A, 6C, 6D.

89. The use of multiple cell lines, different R-spondin conditions, and the testing of each molecule at multiple concentrations teaches a person of ordinary skill that the claimed tetravalent molecules' ability to activate canonical Wnt signaling can withstand significant variation in testing conditions.

90. Examples 5 and 6 also teach that diverse Fzd binders and LRP5/6 binders can be combined with one another in tetravalent molecules with the effect of activating canonical Wnt signaling. The R2M3 Fzd binder (001S-A04) was able to activate Wnt signaling under a range of conditions in combination with ten different LRP6 binders, and the 18R5 Fzd binder was similarly able to induce reporter activity under multiple conditions in combination with four different LRP6 binders. Taken together, these examples teach a person of ordinary skill in

the art that R2M3 and 18R5 (and the other Fzd binding regions disclosed in Table 1B) could similarly be combined with any LRP5/6 binder, including those listed in Table 2A, to activate canonical Wnt signaling. On the other hand, the negative controls used in Examples 5 and 6—both the Fzd-binding IgGs and the Fzd binders fused with non-LRP5/6-binding Nabs—confirm for a person of ordinary skill that Fzd binders alone cannot activate canonical Wnt signaling.

91. Furthermore, because R2M3 and 18R5 are cross-reactive Fzd binding sequences, *see* EX1001 at Table 1B, Table 3; EX2020 at 10:10-13, the molecules of Examples 5 and 6 can simultaneously bind to two different Fzd receptor types. A person of ordinary skill would understand from these examples (and all other example molecules incorporating cross-reactive Fzd binders, including Examples 2 and 3) that the claimed tetravalent molecules can activate canonical Wnt signaling when they bind two of the same Fzd ***or*** two different Fzds.

92. Petitioner, but not Dr. Kahn, suggests that R2M3-25 and R2M3-27 in Figure 5B of the ’278 Patent “did not produce responses in a TOPFlash assay even in the presence of R-spondin.” Pet. at 49. This mischaracterizes Example 5. Although Wnt signaling is not required by the claims under Surrozen’s construction, the inventors explicitly disclosed that the molecules tested in Example 5, including R2M3-25 and R2M3-27, “activated Wnt signaling to various levels,” EX1001 at 156:38-45, which Dr. Kahn acknowledges in Paragraph 23 of

his declaration. A person of ordinary skill in the art would understand from this explicit disclosure that R2M3-25 and R2M3-27 ***did*** activate canonical Wnt signaling, and that activity is simply obscured in Figure 5B because of how that figure is scaled. *See* EX1001 Fig. 5B (scaled from 0 to 800,000 RLU).

93. Petitioner, but again not Dr. Kahn, also suggests 18R5-28 in Figure 6A of the '278 Patent "did not produce responses in a TOPFlash assay in the absence of R-spondin." Pet. at 48. But Petitioner ignores that 18R5-28 ***did*** induce canonical Wnt signaling in a TOPFlash assay in the absence of R-spondin when tested in the A375 STF reporter assay, EX1001 at Fig. 6B, and it produced responses in every cell type when tested in the presence of R-spondin, *id.* at Figs. 6C, 6D.

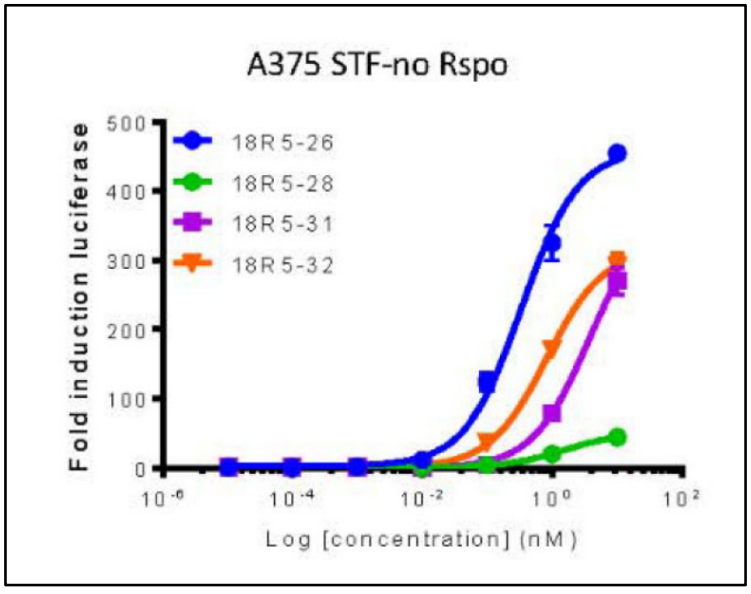


Figure 5: '278 Patent Figure 6B (EX1005 at 43)

4. Example 7

94. Example 7 tests four tetravalent molecules combining the Fzd binder 18R5 with four different LRP5 binders in Wnt dependent 293 STF reporter assays in the presence of R-spondin. EX1001 at 157:1-12. Although Wnt signaling is not required by the claims under Surrozen's construction, the patent specifically states that each molecule was "able to activate Wnt signaling." EX1001 at 157:10-12, Fig. 7.

95. Dr. Kahn criticizes this example for not using "any positive or negative controls," EX1003 ¶ 25, a position with which I disagree at Paragraphs 58-59 above. I note again here that the inventors' conclusion that each molecule activated Wnt signaling does not require a positive control, given the molecules were tested in a "Wnt dependent reporter assay[]," meaning that the activity shown in the assay results in Figure 7 can be attributed to Wnt activation. *See* Paragraph 58, above. With regard to negative controls, Example 7 (like the other STF assays reported in the '278 Patent) included a dose titration from an active high concentration (10 nM) to a low concentration (1 fM) where no activity is detected, thus providing an appropriate negative control. EX1001 at Fig. 7.

96. Example 7 confirms for a person of ordinary skill in the art that tetravalent molecules will activate Wnt signaling when a Fzd binder is combined with a range of LRP5 binders.

5. Example 8

Surrozen 2010
Merck v. Surrozen PGR2026-00027
Page 56

97. Example 8 tests eight IgG-Nab fusion tetravalent molecules combining the LRP6 binder 26 with eight different Fzd binders in Wnt dependent 293 STF reporter assays in the presence of R-spondin. EX1001 at 157:15-29, Fig. 8B. The Fzd binders tested in Example 8 are confirmed to collectively bind to four of the ten Fzd receptors (Fzd1, 2, 7, and 9, including molecules cross-reactive with subsets of three or four of these Fzds). *See id.* at Table 1B, Table 3. Although the claims do not require Wnt signaling activity under Surrozen's construction, the inventors reported that each of the tested molecules "were able to activate [canonical] Wnt signaling." *Id.* at 157:27-29.

98. Alongside Examples 5-7, Example 8 reinforces that Fzd binders and LRP5/6 binders, including those disclosed in the '278 Patent specification, can be combined with one another in different permutations in tetravalent molecules to induce canonical Wnt signaling activity.

99. Dr. Kahn notes that Example 8 reports testing of two tetravalent molecules—1R-H04-26 and 1R-E01-26—that are neither included in Table 3 nor reported in Figure 8. EX1003 ¶ 26.[8] Dr. Kahn does not explain why this matters to his opinions, particularly considering the specification says that the molecules tested in Example 8 "were able to activate Wnt signaling." EX1001 at 157:20-29.

[8] Dr. Kahn incorrectly refers to these tetravalent molecules, binding both Fzd and LRP5/6, as "additional Fzd binders." EX1003 ¶ 26.

To the extent he later provides an explanation, I reserve the right to respond.

100. Petitioner, but not Dr. Kahn, suggests that 1R-G05-26 in Figure 8B of the '278 Patent "did ***not*** produce responses in a TOPFlash assay even in the presence of R-spondin." Pet. at 49. The inventors explicitly disclosed that the molecules tested in Example 8, including 1R-G05-26, "were able to activate Wnt signaling (FIG. 8B)." EX1001 at 157:27-29. This is evident from Figure 8B itself, reproduced below as Figure 6 (1R-G05-26 depicted in grey). EX1001 at Fig. 8B; EX1005 at 45. 1R-G05-26 activates Wnt signaling, and the range of Wnt signaling potencies depicted in Figure 8B again conveys to a person of ordinary skill in the art that the inventors were in possession of a wide range of the claimed tetravalent molecules.

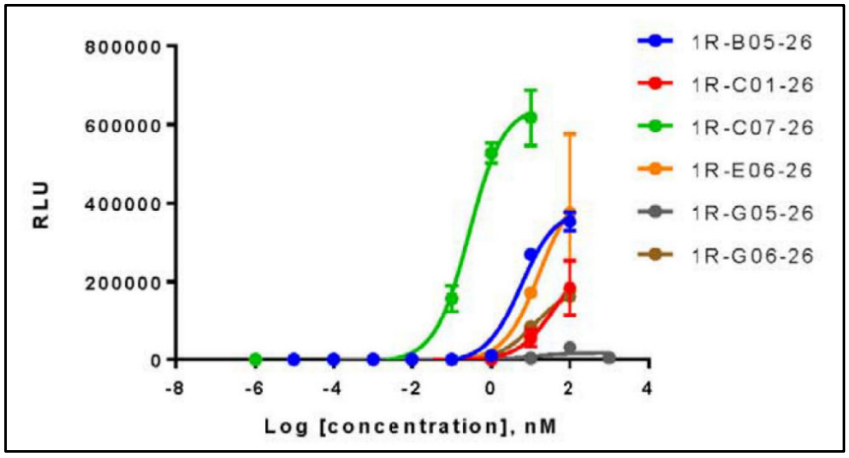


Figure 6: '278 Patent Figure 8B (EX1005 at 45)

6. Example 9

101. Example 9 performs structure-activity relationship (SAR) testing on

twelve different tetravalent molecules: four variations of the IgG-Nab fusion structure with three different Fzd-LRP6 binder combinations (R2M3-26, R2M3-32, and 18R5-26). EX1001 at 157:33-50, Fig. 9. The variety of formats tested in Example 9, depicted in Figure 1A of the ’278 Patent, vary the attachment point of the LRP6 binder Nabs to change their orientation and spacing relative to the Fzd-binding regions. *Id.* at 157:35-42.

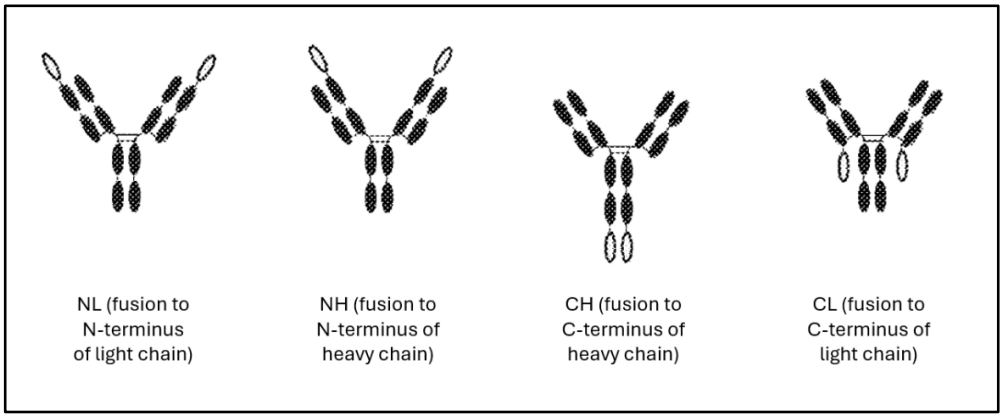


Figure 7: Example 9 Tetravalent Structures (annotated structures from Fig. 1A)

102. Although Wnt signaling is not required by the claims under Surrozen’s construction, the molecules were tested in Wnt dependent 293 STF reporter assays in the presence of R-spondin. EX1001 at 157:44-47. The inventors concluded that the molecules all “activated Wnt signaling to various levels” and that the “attachment location of the fusion and the geometry between the Fzd and LRP binding domains play roles in the ability of the Wnt surrogates to activate Wnt signaling.” *Id.* at 157:47-50. Figures 9A, 9B, and 9C of the ’278 Patent

support this conclusion: each molecule tested induced Wnt signaling activity, although the degree of Wnt signaling activity varied significantly between the molecules. *See id.* at Fig. 9.

103. Although not required by the claims under Surrozen's construction, a person of ordinary skill understands from Example 9 that the claimed tetravalent molecules, which have two Fzd and two LRP5/6 binding regions, are able to activate canonical Wnt signaling despite changes in the attachment point, orientation, and relative spacing among the binding regions.

104. Dr. Kahn states that "the candidate molecules R2M3-26 CL and 18R5-26 CL only produce minimal to no reporter signal even at the highest concentrations tested." EX1003 ¶ 27. The claims do not require activation of Wnt signaling under Surrozen's construction, but to the extent Dr. Kahn is suggesting R2M3-26 CL and 18R5-26 CL did not activate canonical Wnt signaling, I disagree. As shown in Figure 8 below, all molecules tested in Example 9, including R2M3-26 CL and 18R5-26 CL (both in green), induced Wnt signaling activity in the inventors' STF reporter assays. *See* EX1001 at Fig. 9; EX1005 at 46. This is a sharp contrast with the complete absence of activity reported for the molecules used as negative controls. *See, e.g.*, EX1001 at 156:45-49, Figs. 5A, 5C-5G. A person of ordinary skill understands that the comparatively lower level of activity induced by R2M3-26 CL and 18R5-26 CL is *not* a failure to induce canonical

Surrozen 2010
Merck v. Surrozen PGR2026-00027
Page 60

signaling activity, particularly given the scaling of Figures 9A to 9C. *Compare* EX1001 at Figs. 9A, 9C (reporting data at a scale of 0 to 800,000 relative light units ("RLU")), *with, e.g.*, EX1001 at Fig. 5A (reporting data at a scale of 0 to 25,000 RLU). A person of ordinary skill in the art would not understand either R2M3-26 CL or 18R5-26 CL to be an inactive molecule, particularly given the inventors' explicit disclosure to the contrary. EX1001 at 157:44-50.

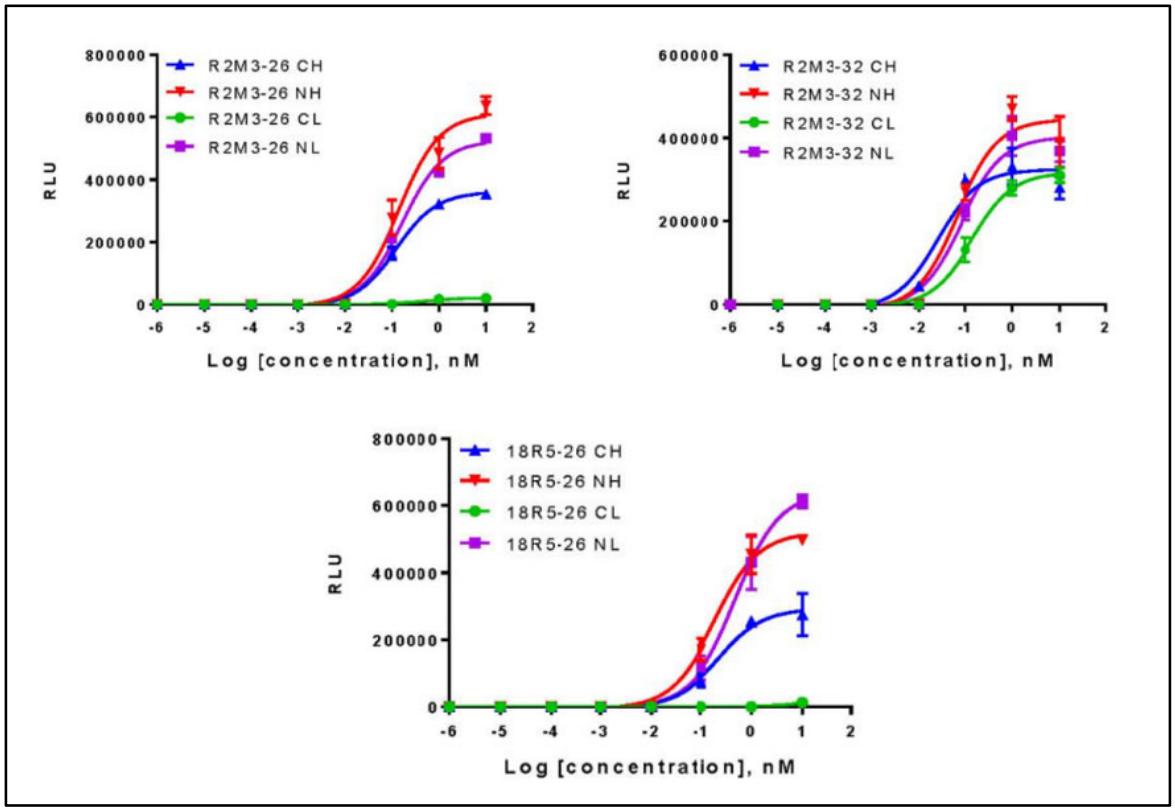


Figure 8: '278 Patent Figs. 9A (top left), 9B (top right), and 9C (bottom) (EX1005 at 46)

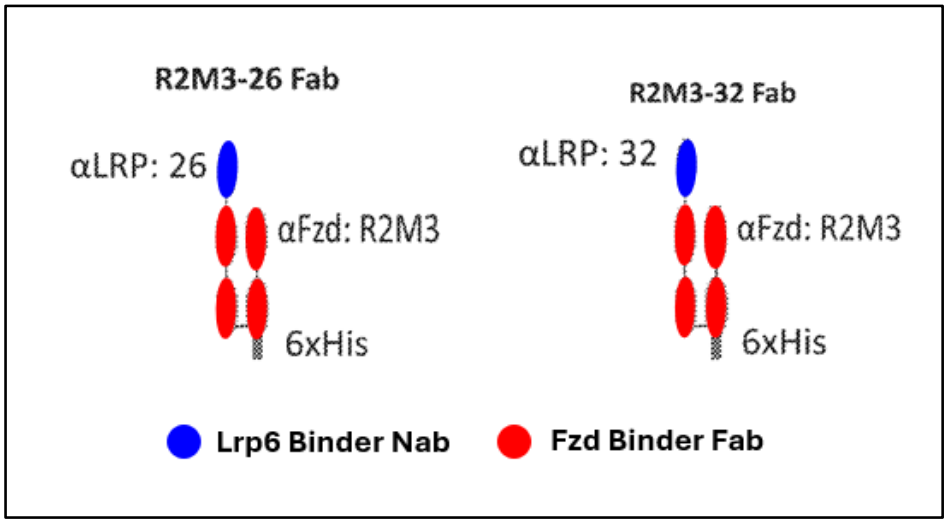
105. Contrary to Dr. Kahn's assertions, a person of ordinary skill would understand from Examples 2-18 that the claimed tetravalent molecules ***will*** induce

some level of canonical Wnt signaling activity in STF reporter assays.

7. Examples 10, 11, and 12

106. Examples 10, 11, and 12 test *bivalent* molecules having only a single Fzd binding region and a single LRP5/6 binding region. *See* EX1001 at 157:54-158:47, Figs. 10A, 11A, 12A. The molecules tested in Examples 10, 11, and 12 do not fall within the scope of the claims.

107. Examples 10 and 11 study two bivalent molecules consisting of one Fzd binding region (R2M3) and one LRP6 binding region (26 and 32, respectively), in the Fab format shown in Figure 9 below. *See id.* at 157:55-59, 158:12-15, Figs. 10A, 11A. These bivalent molecules correspond to the tetravalent molecules studied in Examples 2 and 3, incorporating the same Fzd binder in a Fab format and the same LRP6 binder in Nab format, but altering the valency of the molecule (*i.e.*, including only one of each binder). *Id.*



Surrozen 2010
Merck v. Surrozen PGR2026-00027
Page 62

Figure 9: '278 Patent Figs. 10A (left) and 11A (right) (annotated)

108. The inventors purified these bivalent molecules using size-exclusion-chromatography and tested the molecules in a Wnt dependent 293 STF reporter assay, correlating the results. EX1001 at 157:60-157:67, 158:16-24, Figs. 10B, 11B. The inventors reported that, unlike the tetravalent molecules in Examples 2 and 3, the peak of the reported canonical Wnt signaling activity "did ***not*** correlate with the peak of the proteins" and the bivalent molecules were "ineffective in inducing canonical Wnt signaling." *Id.* at 158:1-6, 158:24-30.

109. Example 12 relates to a bivalent molecule combining the Fzd binder R2M3 and the LRP6 binder 26 in a HeteroIg format, as shown in Figure 10 below. *See id.* at 158:37-39, Fig. 12A. This bivalent molecule contains the same Fzd-LRP6 binder pairing as the tetravalent molecule studied in Example 2, and Example 12 uses the tetravalent R2M3-26 molecule of Example 2 as a comparator. *See id.* at Fig. 12B. The molecule was purified using size-exclusion-chromatography, and the peak fraction was tested at different concentrations in a 293 STF reporter assay in the presence of R-spondin. *Id.* at 158:39-44, Fig. 12B. The inventors reported that the HeteroIg was "ineffective in inducing canonical Wnt signaling" compared to the tetravalent format studied in Example 2. *Id.* at 158:44-47.

Surrozen 2010
Merck v. Surrozen PGR2026-00027
Page 63

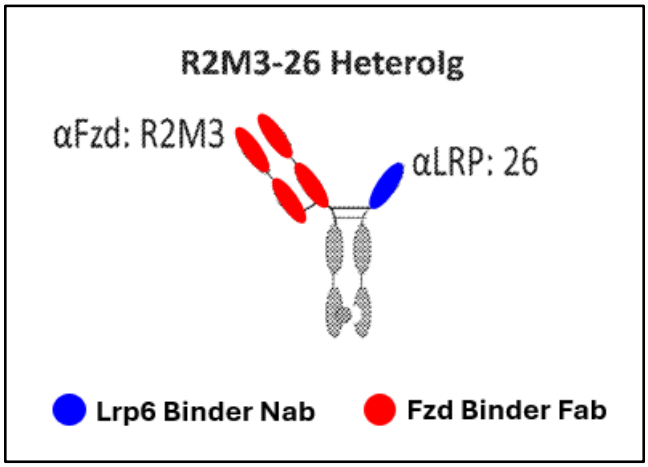


Figure 10: '278 Patent Fig. 12A (annotated)

110. From these results, a person of ordinary skill would understand that any canonical Wnt signaling activity apparently induced by these bivalent molecules is likely a result of aggregation of the bivalent molecules, forming higher-molecular weight species that have two or more Fzd and LRP5/6 binding regions, and spillover of those aggregated species. *See id.* at Figs. 10B, 11B. This is consistent with Dr. Li's description of this experiment to the Examiner during prosecution of the '278 Patent. *See* EX1008 at 4170-71, ¶ 6. Examples 10-12, in combination with the Examples relating to tetravalent molecules, convey to a person of ordinary skill in the art that the tetravalent structure of the claimed molecules induces canonical Wnt signaling activity, whereas the bivalent molecules are ineffective in doing so.

8. Example 13

111. Example 13 tested tetravalent molecules combining the Fzd binder

Surrozen 2010
Merck v. Surrozen PGR2026-00027
Page 64

17SB9 and the LRP6 binder 26 in seven different structures, as depicted in Figure 13D of the ’278 Patent, in 293 STF reporter assays. EX1001 at 158:54-159:3, Fig. 13D.

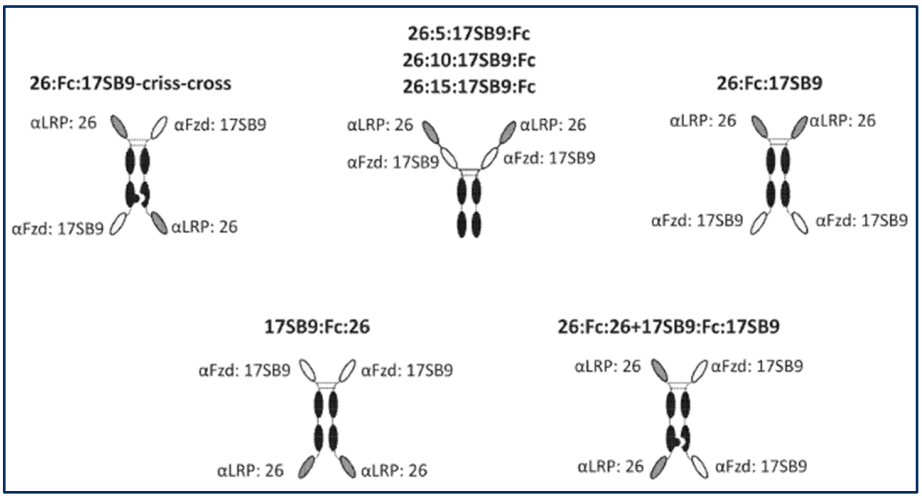


Figure 11: ’278 Patent Figure 13D

112. As shown in Figure 11 above, the structures of 26-17SB9 tested in Example 13 vary significantly across several factors. The molecules collectively embrace five different orientations of the Fzd and LRP6 binders relative to the Fc region. While four molecules locate the binding regions on opposite ends of the fused Fc region, three 26:17SB9:Fc molecules (varied by amino acid linker lengths) place the LRP6 and Fzd binding Nabs on the same end of the Fc region. Five of the molecules tested are symmetrical, while 26:Fc:17SB9-criss-cross and 26:Fc:26+17SB9:Fc:17SB9 are asymmetrical molecules using a knobs-into-holes heterodimer design. 26:Fc:26+17SB9:Fc:17SB9 is not only asymmetrical, but locates the two LRP6 binders and the two Fzd binders on the same polypeptide

Surrozen 2010
Merck v. Surrozen PGR2026-00027
Page 65

chains (rather than attaching one of each binding region type to each polypeptide chain). Example 13 is representative of numerous structures and orientations that can be used to design the claimed tetravalent molecules.

113. The inventors first purified and tested the "26-17SB9 Nab-Fc-Nab" molecule (depicted in Figure 13A of the provisional application underlying the '278 Patent, reproduced below as Figure 12), attaching LRP6 binder Nabs to the N-terminus of a Fc region and attaching Fzd binder Nabs to the C-terminus of a Fc region. *Id.* at 158:54-56; EX1005 at 50.[9]

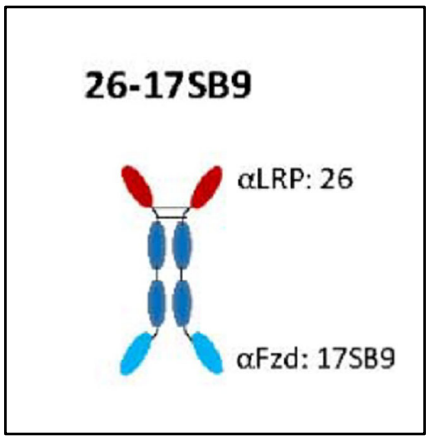


Figure 12: U.S. Provisional Application 62/607,875 at Fig. 13A (EX1005 at 50)

114. Although the claims do not require Wnt signaling under Surrozen's

[9] Figures 13A and 13B of the '278 Patent are misaligned with the description of those figures offered in Example 13. Like Dr. Kahn, I have cited Figures 13A (Figure 12 herein) and 13B (Figure 13 herein) of the underlying provisional application, *see* EX1005 at 50, which match the descriptions offered.

construction, the inventors tested this molecule in the presence and absence of R-spondin, and confirmed that it "induced canonical Wnt signaling as detected in the 293 reporter assay" in the presence of R-spondin. EX1001 at 158:61-63; EX1005 at 50.

115. The remaining formats were also tested in 293 STF reporter assays in the presence of 20 nM R-spondin. *Id.* at 158:58-159:3, Figs. 13E, 13F. The inventors reported that "these various combinations where 26 and 17SB9 were arranged in different tandem formats or on different ends of the Fc fragment ***all*** activated Wnt signaling to various levels." *Id.* at 158:66-159:3 (emphasis added).

116. Example 13 reinforces the teaching of Example 9 (which I discussed above in Paragraphs 101-105) that a given Fzd-LRP5/6 binder pairing is consistently capable of activating canonical Wnt signaling when combined in different tetravalent structures that alter the relative spacing, orientation, and symmetry of the binding regions. A person of ordinary skill in the art reading the specification would understand from Example 13, alongside the other teachings of the specification, that both symmetrical and asymmetrical structures can be used to design a tetravalent molecule that activates Wnt signaling. A person of ordinary skill in the art would also understand the inventors to be in possession of a wide variety of the claimed tetravalent molecules.

117. Petitioner and Dr. Kahn suggest that 26:Fc:17SB9 "did not produce

Surrozen 2010
Merck v. Surrozen PGR2026-00027
Page 67

responses in a TOPFlash assay in the absence of R-spondin." Pet. at 48; EX1003 ¶ 149. Even if 26:Fc:17SB9 does not show a signal on the assay (based upon visual inspection) in the ***absence*** of R-spondin under certain conditions, this does not alter the fact that 26:Fc:17SB9 activates canonical Wnt signaling, as shown in the assay results where R-spondin was present (although again, such activation is not required under Surrozen's construction). *See* EX1005 at 50 (Fig. 13B). R-spondin alone cannot activate Wnt signaling. It is merely a potentiator, requiring the presence of a canonical Wnt agonist to produce reporter activity. EX2014 at 3.

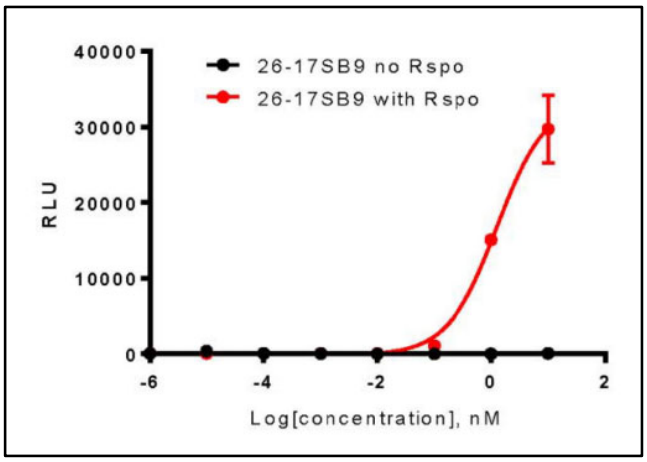


Figure 13: U.S. Provisional Application 62/607,875 at Fig. 13B (EX1005 at 50)

9. Example 14

118. Example 14 tested fifteen different tetravalent molecules incorporating the Fzd binder 18R5 in an scFv format, paired with one of two LRP5/6 binders in scFv format, altering the identity of the LRP5/6 binding region and the relative orientation and spacing of the four binding regions. EX1001 at

159:10-39, Figs. 14A-14G. The molecules tested are depicted in Figure 14 below.

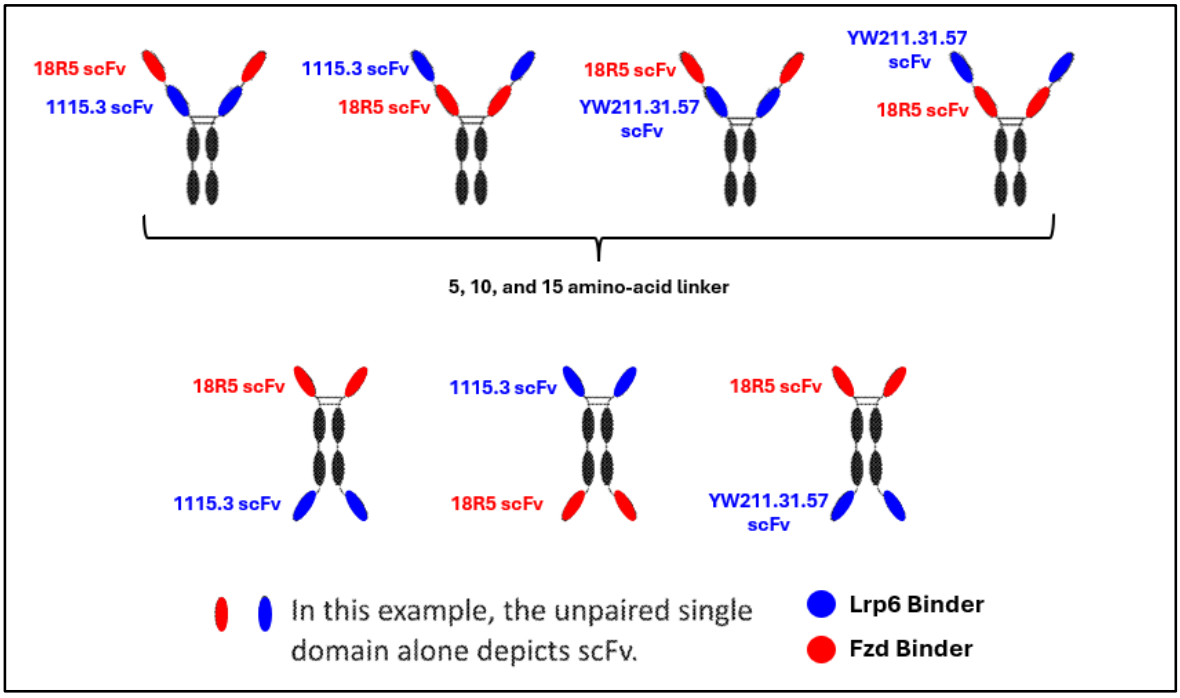


Figure 14: Example 14 Tetravalent Molecules

119. Each of the molecules was tested in a Wnt dependent 293 STF reporter assay. Although Wnt signaling is not required by the claims under Surrozen's construction, the inventors concluded that "all of these scFv formats activated Wnt signaling," and, consistent with Example 9 (*see* Paragraph 102, above), "potency and overall maximal efficacy may differ depend[ing] on the binder combination, linker length, and relative orientation." *Id.* at 159:27-39.

120. Example 14 also tested the same Fzd and LRP5/6 scFv binder pairings in a ***bivalent*** ("bispecific but monovalent," rather than "bispecific bivalent") format with three different linker lengths. *Id.* at 159:40-47, Fig. 14H. Consistent with

Examples 10-12, the inventors determined that the ***bivalent*** molecules "were [ineffective] in activating Wnt signaling" in a 293 STF reporter assay as compared to the activity of a tetravalent molecule, even "in the presence of 20 nM R-spondin." *Id.*

121. Example 14, alongside the other disclosures of the specification, teaches a person of ordinary skill that the claimed tetravalent molecules can be made with binding regions in scFv format and, although not required by the claims under Surrozen's construction, that the claimed tetravalent molecules will consistently activate canonical Wnt signaling activity even when the "binder combination, linker length, and relative orientation" is varied. Example 14 further confirms that ***bivalent*** molecules are comparatively ineffective at activating canonical Wnt signaling activity, even when different structures (in this case, scFv fusions without an Fc region, in contrast with the bivalent molecules of Examples 10-12) are used or biological potentiators like R-spondin are present.

122. Dr. Kahn states that only "miniscule reporter assay activity" was induced by 18R5:Fc:1115.3. EX1003 ¶ 31. This relative range in induced activity among different molecules is informative to a person of ordinary skill, as it reinforces their understanding that tetravalent molecules with two Fzd binding regions and two LRP5/6 binding regions will consistently activate canonical Wnt signaling activity (not required by the claims under Surrozen's construction) when

Surrozen 2010
Merck v. Surrozen PGR2026-00027
Page 70

their binding sequences, binding region orientations, structure, and spacing are altered. A person of ordinary skill in the art reading the specification would understand the inventors to be in possession of several working examples of the claimed tetravalent molecules.

10. Example 15

123. Example 15 tested thirteen tetravalent molecules in a Fab-IgG format, assembled using either a charge pairing or HC-LC crossover design, made up of different pairings of two Fzd binders (R2M3 and 1RC07) and four LRP5/6 binders (421.1, 10SA7, 10SG7, 1115.3). *See* EX1001 at 159:54-160:49, Fig. 15B-15G. Example 15 explains that charge-pairing and HC-LC crossover design are two methods, among others (including knobs-into-holes), of ensuring appropriate pairing between the heavy and light chains of the Fab binding regions in a Fab-Fab or Fab-IgG format. *Id.* at 159:54-59. The molecules of Example 15 vary based on the length of the amino acid linker between the Fzd and LRP5/6 binding regions and the relative orientations of the binding regions. *Id.*

Surrozen 2010
Merck v. Surrozen PGR2026-00027
Page 71

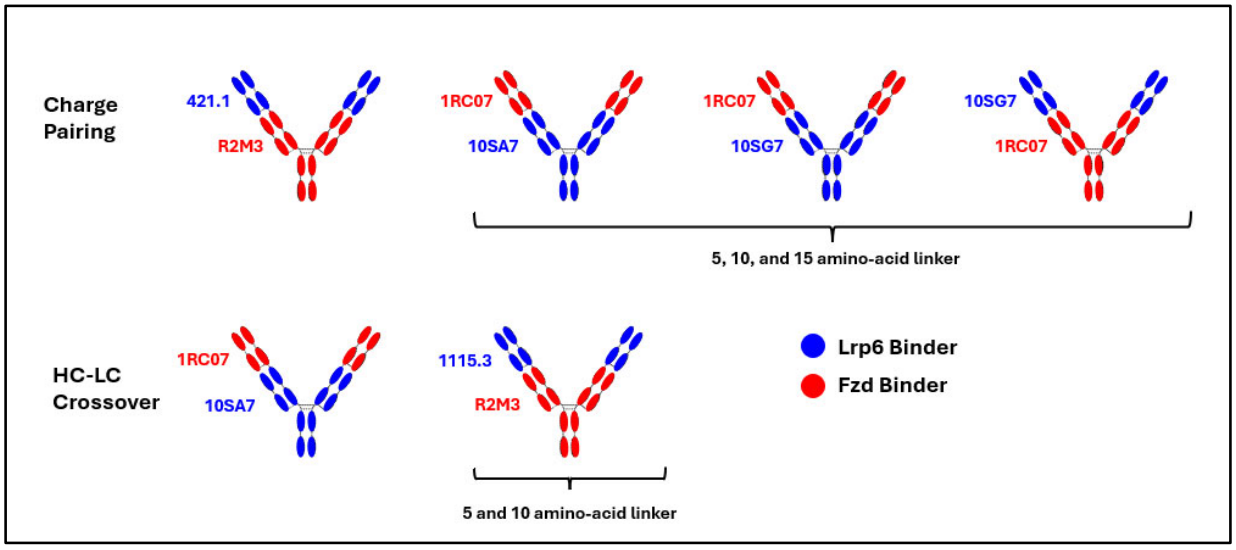


Figure 15: Example 15 Tetravalent Molecules

124. Although the claims do not require Wnt signaling under Surrozen's construction, the molecules were tested in Wnt dependent 293 STF reporter assays. The inventors confirmed that every molecule tested activated canonical Wnt signaling and, consistent with Examples 9, 13 and 14 (*see* Paragraphs 102, 115, 119, above), observed "some preference of orientation and linker length" in the six comparative 1RC07/10SG7 molecules tested. EX1001 at 160:22-40, Figs. 15D-15E.

125. Example 15 teaches a person of ordinary skill that the claimed tetravalent molecules can be designed with Fab format binding regions using multiple different techniques (at least charge pairing, HC-LC crossover, and knob-into-holes) and, although not required by the claims under Surrozen's construction, that the claimed tetravalent molecules will consistently activate canonical Wnt

signaling when their binding regions, spacing, and orientation are varied. A person of ordinary skill in the art reading the specification would understand the inventors to be in possession of a wide variety of the claimed tetravalent molecules.

11. Example 16

126. Example 16 tested a tetravalent molecule comprised of the Fzd binder R2M3 and the LRP6 binder 26 in a F(ab')2 format. *Id.* at 160:55-63, Fig. 16A. R2M3-26 F(ab')2 is comprised of two Fzd-binding Fabs and two LRP6-binding Nabs and it does not have a Fc region. *Id.* Although Wnt signaling is not required by the claims under Surrozen's construction, the inventors tested the molecule in a 293 STF reporter assay and confirmed R2M3-26 F(ab')2 is able to activate canonical Wnt signaling. *Id.* at 160:64-67, Fig. 16C.

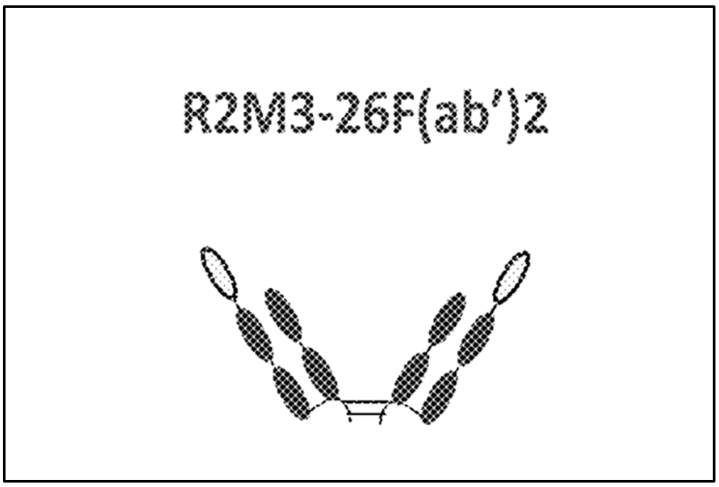


Figure 16: '278 Patent Figure 16A

127. A person of ordinary skill would understand from Example 16, alongside the other disclosures of the '278 Patent, that, although not required by

the claims under Surrozen's construction, tetravalent molecules across a broad range of tetravalent structures activate canonical Wnt signaling. In particular, a POSA would understand that the claimed tetravalent molecules do not require incorporation of or fusion to a Fc region to activate Wnt signaling. A person of ordinary skill in the art reading the specification would understand the inventors to be in possession of a wide variety of the claimed tetravalent molecules.

12. Example 17

128. Example 17 tested nineteen tetravalent molecules in the IgG-Nab format, comprising different permutations of seven different Fzd binders (1RC07, R2M13, R2M3, 3SD10, 4SD1, 14SB6, and R2M9) with three different LRP5/6 binders (3, 26, and 36). *Id.* at 161:6-17, Figs. 17B-17H. The Fzd binders in the molecules of Example 17 collectively bind to seven different Fzd receptors (Fzd1, 2, 4, 5, 8, 7, 9), and each of these Fzd binders was paired with both LRP5 binders (3) and one or more LRP6 binders (26, 36). *See id.* at Table 1B, Table 3.

129. Although the claims do not require Wnt signaling under Surrozen's construction, the nineteen tetravalent molecules were tested in Wnt dependent 293 STF reporter assays in the presence of R-spondin. The three molecules incorporating the Fzd binder 3SD10 (identified in Table 1B as 003S-D10) and the three molecules incorporating 4SD1 (identified in Table 1B as 004S-D01) were tested in a STF reporter assay with "293 cells co-transfected with FZD4 expression

construct," *i.e.*, in a 293 cell line modified to express increased levels of the Fzd4 receptor. *Id.* at 161:11-15, Figs. 17E, 17F; *see id.* at Table 1B, Table 3. Both 003S-D10 and 004S-D01 are confirmed to bind to Fzd4. *Id.* at Table 1B. The three molecules incorporating 14SB6 (identified in Table 1B as 014S-B06) were tested in a STF reporter assay with "293 cells co-transfected with FZD9 expression construct," *i.e.*, in a 293 cell line modified to express increased levels of the Fzd9 receptor. *Id.* at 161:11-15, Fig. 17G; *see id.* at Table 1B, Table 3. 014S-B06 is confirmed to bind to Fzd9. *Id.* at Table 1B. The inventors reported that all of the molecules tested in Example 17 "activated Wnt signaling with varying levels of potency and efficacy." *Id.* at 161:16-17.

130. Example 17 further supports the specification's teaching that different Fzd binders and LRP5/6 binders, including those disclosed in Table 1B and Table 2A of the specification, can be interchangeably paired with one another in tetravalent molecules with the effect of activating canonical Wnt signaling activity (even though such activity is not required by the claims under Surrozen's construction).

131. Dr. Kahn states that the reporter activity induced "is dramatically different between R2M13-3 and R2M13-26, further muddling understanding of whether R2M13-26's reporter activity translates to a biologically significant response." EX1003 ¶ 34. First, Dr. Kahn's emphasis on a "biologically significant

response" is both unclear and misplaced. *See* Paragraphs 137-140, below. Second, the difference in induced canonical Wnt signaling activity among comparator molecules does not change the person of ordinary skill's understanding that, although not required by the claims under Surrozen's construction, the claimed tetravalent molecules will activate Wnt signaling despite changes to the binding regions, structure, relative orientation, and spacing of the tetravalent molecule.

13. Example 18

132. Example 18 studied a tetravalent molecule combining the Fzd binder 1RC07, in an IgG1 form with certain mutations to the constant region, and the LRP6 binder 10SG11. EX1001 at 161:24-29, Fig. 18A. Although the claims do not require Wnt signaling under Surrozen's construction, the inventors tested the molecule in a Wnt dependent 293 STF reporter assay and determined that it had the ability to activate canonical Wnt signaling. *Id.* at 161:29-33.

133. Example 18 reinforces the teaching of the specification, although not required by the claims under Surrozen's construction, that tetravalent molecules combining Fzd binders and LRP5/6 binders, including those disclosed in Table 1B and Table 2A, are capable of activating Wnt signaling in a variety of structures.

134. Dr. Kahn's complaint that the "Lrp specificity [of 10SG11] is not disclosed" is misplaced. EX1003 ¶ 35. Table 2A of the '278 Patent confirms that 10SG11 (010S-G11) binds to "LRP6e3e4." EX1001 at Table 2A (col. 106).

B. Dr. Kahn's Critiques of Examples 2-18 Are Unpersuasive (Paragraphs 144-155 of Dr. Kahn's Declaration)

135. In paragraphs 144-155 of his declaration, Dr. Kahn makes several critiques of the inventors' TOPFlash assays and the data used to evaluate the canonical Wnt signaling activity of the tested molecules of Examples 2-18, focusing on the lack of positive controls, alleged inactivity in the absence of R-spondin, cell-type dependence of Wnt signaling activity, and dose-dependence of Wnt signaling activity. None of these critiques matter under Surrozen's construction because the claims do not require activation of the Wnt signaling pathway. However, assuming Petitioner is correct that the claimed tetravalent molecules must be "Wnt agonists," each of Dr. Kahn's criticisms relates to the degree of Wnt signaling achieved by the tested molecules, rather than whether the molecules are able to activate Wnt signaling.

1. Positive Controls

136. Dr. Kahn repeatedly criticizes the '278 Patent's examples because they do not include a "positive control, such as Wnt3A," in the STF reporter assays, which Dr. Kahn claims means there is no "standard to assess the biological relevance" of the reported activity and therefore "no basis" to conclude the tested molecules activate canonical Wnt signaling. *See, e.g.*, EX1003 ¶¶ 21, 23-27, 30-35, 145-147. I disagree.

137. In making this critique, Dr. Kahn imposes an additional requirement

to Petitioner's construction requiring agonist activity, based on his interpretation of a "biologically active" molecule, "biological relevance," and "biological activity." He appears to define that activity level as "biologically meaningful," *i.e.*, a level of activity that is comparable to a natural Wnt ligand. EX1003 ¶ 145-146. I have reviewed the claims and specification and do not understand, nor would a person of ordinary skill understand, any part of the claims as requiring that the claimed tetravalent molecules must exhibit Wnt agonist activity to the same degree or in the same manner as a natural Wnt ligand, even under Petitioner's construction. To the extent a "biologically active" molecule is required, the '278 Patent specifically provides that "the Wnt surrogate molecules of the invention enhance the canonical Wnt/β-catenin signaling," where "'enhance[]' refers to a measurable increase in the level of Wnt/β-catenin signaling compared with the level in the absence of a Wnt surrogate molecule of the invention." EX1001 at 117:33-38. This would be the appropriate comparator if Petitioner's construction were accepted.

138. As explained above at Paragraphs 58-59, I disagree with Dr. Kahn that a positive control in the form of a natural Wnt ligand is necessary to identify and evaluate canonical Wnt signaling activity (even if such activity were required by the claims). Any level of induced canonical Wnt signaling activity in Wnt-dependent TOPFlash assays, which are recognized in the field as a highly reliable method of monitoring Wnt signaling activity, reflects activation of the canonical

pathway. Such activation will not occur in the absence of a Wnt agonist. A person of ordinary skill understands that a molecule which induces any non-zero level of Wnt/β-catenin signaling in a TOPFlash assay is a Wnt agonist and can be optimized to increase signaling potency for a desired application. A person of ordinary skill in the art therefore would not consider Wnt signaling potency comparable to a natural Wnt ligand a prerequisite for identifying an active molecule. This is consistent with the '278 Patent's "measurable increase" standard. *Id.* at 117:35-38.

139. Dr. Kahn points to the molecules 18R5:Fc:1115.3 and 1115.3:Fc:18R5, tested in Example 14, as "illustrat[ing] the problem with not including a positive control in a TOPFlash assay," because there is no benchmark for determining whether the molecule with lower activity is "biologically active." EX1003 ¶ 147. But again, there is no question that both molecules activated Wnt signaling, they just did so to varying degrees. *See* Paragraphs 119 and 122, above; EX1001 at Fig. 14E. A person of ordinary skill would take from Example 14 that variations in the design of a tetravalent molecule (in this case, inverting the orientation of the Fzd and LRP5/6 binders relative to the Fc region) do not prevent the molecule from activating canonical Wnt signaling activity and that the inventors were in possession of a wide range of the claimed tetravalent molecules. *See* Paragraphs 118-119 and 121, above.

Surrozen 2010
Merck v. Surrozen PGR2026-00027
Page 79

140. As discussed above at Paragraphs 58-59, Dr. Kahn's emphasis on positive controls is unhelpful in the context of the claimed tetravalent molecules. Furthermore, he omits that natural Wnt ligands are notoriously difficult to purify consistently, and therefore difficult to use as positive controls. Native Wnts are non-selective in their binding to Wnt receptors, as emphasized by Dr. Kahn. EX1003 ¶ 82. The claimed tetravalent molecules by their design bypass this limitation and can be tailored to selectively bind a specific Fzd and Lrp5 and/or Lrp6. Since native Wnts, such as Wnt3a, interact with multiple Fzds, they don't serve as appropriate controls for the highly selective and engineered tetravalent molecules claimed. Furthermore, natural Wnts require detergents (*e.g.*, CHAPS) to maintain their solubility in an otherwise aqueous environment. Such detergents are extremely damaging to cells and tissues, and the dilution required to avoid detergent toxicity that would kill the cell line on contact limits the utility of native Wnts as controls, especially at high concentrations (*e.g.*, greater than 10 nM).

141. By contrast, negative controls like Fzd IgGs or Fc tags are easy to purify and more reliable and accessible. *See, e.g.*, EX1001 at 156:26-30, 156:45-47, Figs. 4-5. Furthermore, where a person of ordinary skill seeks to identify the ability to induce any canonical Wnt signaling activity, negative controls (i.e. molecules known ***not*** to activate Wnt signaling activity) are more useful than positive controls. As Dr. Kahn emphasizes, the natural Wnt ligands interact

Surrozen 2010
Merck v. Surrozen PGR2026-00027
Page 80

differently with Fzd receptors and co-receptors and implicate different signaling pathways. *See, e.g.*, EX1003 ¶¶ 80-85. A strict adherence to benchmarking the claimed tetravalent molecules against a specific natural Wnt, e.g. Wnt3a, could result in misleading conclusions that molecules are not "biologically active" when they in fact induce Wnt signaling. Furthermore, demonstrating that a specific tetravalent molecule is either more or less active than a natural Wnt ligand would not provide actionable information about such molecules.

142. As explained above at Paragraph 60, the inventors also used negative controls in several Examples, including Fzd IgG molecules alone and Fzd IgG molecules fused with non-LRP5/6 binders, which are inactive molecules with respect to Wnt signaling. *See, e.g.*, EX1001 at 156:45-52, Figs. 5A, 5C-5G, 6A, 6C, 6D. These negative controls establish a baseline for what failure to activate Wnt signaling activity looks like in the Wnt dependent reporter assays employed by the inventors.

2. R-Spondin

143. Dr. Kahn next argues that molecules which cannot activate Wnt signaling in the absence of the Wnt/β-catenin pathway potentiator R-spondin are "not biologically active in activating Wnt signaling," seemingly because "R-spondin is not required for the activation of Wnt signaling by natural ligands." *See* EX1003 ¶¶ 36, 148-149. On this basis, he criticizes the examples measuring "Wnt

Surrozen 2010
Merck v. Surrozen PGR2026-00027
Page 81

signaling activity only in the presence of R-spondin" as not enabling a determination of whether the molecules activate canonical Wnt signaling. *Id.* at 36.

144. ***First***, this critique is, again, entirely dependent on Dr. Kahn's view that the claims require that the claimed tetravalent molecules be "biologically active" at levels comparable to natural Wnt ligands, which I disagree with for the reasons already explained. The claims do not require Wnt activity under Surrozen's construction, but even under Petitioner's construction, the appropriate comparator is not a natural Wnt ligand. Moreover, none of the articles cited by Dr. Kahn (EX1063, EX1060, EX1053, EX1093) support his broad claim that "R-spondin … is not required for the activation of Wnt signaling by natural ligands" under all circumstances. EX1003 ¶ 36. To the contrary, there are articles showing the use of R-spondin with natural Wnt ligands to amplify the assay signal. As shown by Kim et al. (2008), Wnt3a produces significantly lower amounts of signaling activity in the absence of R-spondin compared to in the presence of R-spondin. EX2014 at 4. Figure 2 illustrates that in the absence of R-spondin, the Wnt3a effect is barely visible, with RLU of less than 10,000, compared to significantly higher RLU when R-spondin is present, even exceeding 250,000 RLU under certain R-spondin conditions. EX2014 at 4. The fact that a limited number of tetravalent molecules may not have a strong signal in the STF reporter assay without R-spondin is no different from natural Wnt ligands, and, even assuming

Surrozen 2010
Merck v. Surrozen PGR2026-00027
Page 82

Wnt signaling activity is required (as is required under Petitioner's proposed construction), it certainly does not mean that the tested molecules are incapable of activating Wnt signaling.

145. ***Second***, Petitioner and Dr. Kahn overstate the number of the embodiments inactive in the absence of R-spondin. Pet. at 48-49 (identifying four supposedly inactive molecules); EX1003 ¶ 149 (identifying three supposedly inactive molecules). The specification offers many examples of embodiments where activity was amplified by the presence of R-spondin, but the molecule remained active even in its absence. *Compare, e.g.*, EX1001 at Fig. 5A, *with* EX1001 at Fig. 5E. In contrast, Petitioner identifies at most four examples of molecules purportedly inactive in the absence of R-spondin, citing Figures 2D (R2M3-26), 3D (R2M3-32), 6A (18R5-28),[10] and 13B (26-17SB9) of the '278 Patent. Pet. at 48-49; EX1003 ¶ 149. As explained above, Petitioner mischaracterizes three of these molecules: R2M3-26, R2M3-32, and 18R5-28 are active in the absence of R-spondin. *See* Paragraphs 82-83 and 93, above. And for

[10] I note that even Dr. Kahn does not seem to agree with Petitioner's claim that 18R5-28 is inactive in the absence of R-spondin, having left this molecule off of his list. *See* EX1003 ¶ 149.

Surrozen 2010
Merck v. Surrozen PGR2026-00027
Page 83

26-17SB9 (Figure 13B),[11] the '278 Patent makes clear that this molecule "induced canonical Wnt signaling" when R-spondin was present. EX1001 at 158:58-63; EX1005 at 50. Dr. Kahn's claim that there is no "appreciable" difference between R2M3-26 and R2M3-32 and the wholly inactive Fzd-binding IgGs used as negative controls in the absence of R-spondin, EX1003 ¶ 149, is also incorrect, as is evident from Figure 5A (which uses a smaller y-axis scale than does Figures 2D and 3D), which I show above in Paragraph 83 and Figure 4 of this Declaration.

146. ***Third***, I disagree that a person of ordinary skill would experience confusion as to whether molecules that activate canonical Wnt signaling only in the presence of R-spondin are Wnt agonists. *See* EX1003 ¶ 149. As explained above at Paragraph 46, R-spondin cannot activate canonical Wnt signaling in the absence of a Wnt agonist. EX2014 at 3. It is only a potentiator and amplifier of canonical Wnt agonists. A person of ordinary skill therefore understands that a molecule which activates canonical Wnt signaling in the presence of R-spondin is a Wnt agonist.

147. Dr. Kahn also briefly critiques the absence of "an R-spondin only control" to detect "background responses or background noise induced by R-spondin in the absence of candidate molecules." EX1003 ¶ 36. But the '278 Patent

[11] Here, like Dr. Kahn, I have reviewed Figure 13B of the underlying provisional application, reproduced above as Figure 13. *See* EX1005 at 50.

confirms no such "R-spondin only" control would have been required. Indeed, the complete lack of reporter activity induced by different negative control molecules in different cell lines, ***even in the presence of R-spondin*** (as in Examples 5 and 6), confirms that the reporter activity of the tetravalent molecules was not attributable to "background responses or background noise induced by R-spondin." *See, e.g.*, EX1001 at Figs. 5D-5G, 6C, 6D. If it were, a person of ordinary skill in the art would have expected to see some level of activity for the negative control molecules (*i.e.*, "background noise" with which Dr. Kahn is concerned). A person of ordinary skill would therefore not be concerned about potential "background responses or background noise," particularly considering the '278 Patent reports the use of negative controls. Additionally, the use of multiple concentrations of the claimed tetravalent molecules in the reported STF assays effectively provides an "R-spondin only control": at the lowest concentrations of the tetravalent molecules used, R-spondin is still present at its fixed concentration.

3. Cell-Type Dependence

148. Dr. Kahn argues that the '278 Patent Examples' TOPFlash assays report "inconsistent … responses across different cell types." EX1003 ¶ 150. Dr. Kahn cites as his only example 18R5-28 from Example 6, which Dr. Kahn alleges activated canonical Wnt signaling without R-spondin in one cell line, but required the presence of R-spondin in another. *Id.* ¶ 151; EX1001 at Figs. 6A, 6B.

Surrozen 2010
Merck v. Surrozen PGR2026-00027
Page 85

149. A person of ordinary skill would not consider these results to be inconsistent; rather, as I have explained, a skilled artisan would have understood that the 18R5-28 activated Wnt signaling in both cell lines, as is plainly stated in the patent. *See* EX1001 at 156:60-67. The purported "inconsistency" only arises because of Dr. Kahn's resistance towards the standard use of R-spondin as a potentiator in Wnt signaling assays to identify molecules that activate Wnt signaling. 18R5-28 activated canonical Wnt signaling in both the 293 cell line (visibly active in the presence of R-spondin in Figure 6D) and the A375 cell line (visibly active without R-spondin in Figure 6B). *See* Paragraph 93, above; EX1001 at Figs. 6B, 6D. Use of R-spondin as a potentiator in these assays is entirely appropriate. 18R5-28 does not provide evidence that certain claimed tetravalent molecules are inactive in some cell lines.

4. Dose-Response Behavior

150. Dr. Kahn finally notes that for some molecules, the dose response in the TOPFlash assay "unexpectedly decreased at higher concentrations," while for others it did not. EX1003 ¶¶ 152-153. Dr. Kahn expresses that a person of ordinary skill in the art's evaluation of a molecule as capable of activating canonical Wnt signaling would be concentration-dependent, with no guidance as to why "some, but not all, candidate molecules deviate from a dose-response curve." *Id.* ¶ 153.

151. Even if the claims required activation of Wnt signaling, it is no

Surrozen 2010
Merck v. Surrozen PGR2026-00027
Page 86

surprise to a person of ordinary skill in the art that molecules behave differently at different concentrations. This is not unique to the claimed tetravalent molecules, but rather affects all molecules binding to cell surface receptors: the molecules may compete for binding to available cell surface receptors at excess concentrations. Even if Wnt signaling activation is required, determining a given molecule's appropriate concentration for activating the desired level of Wnt signaling is not a determinant of whether a molecule activates Wnt signaling. Indeed, it is standard in the field to evaluate a molecule's activation of canonical Wnt signaling at multiple concentrations to determine the molecule's behavior at varying concentrations.

C. Response to Dr. Kahn's Contention that the '278 Patent Does Not Resolve Alleged "Unpredictability" of Wnt Signaling (Paragraphs 124-143 of Dr. Kahn's Declaration)

152. In paragraphs 124-138 of his declaration, Dr. Kahn contends that the '278 Patent does not resolve the "unpredictability" in the field of Wnt signaling and that a skilled artisan would instead have to engage in "undue trial-and-error experimentation to determine which of candidate tetravalent, multispecific molecules could activate the Wnt signaling pathway." EX1003 ¶ 124. I disagree.

153. This argument is again premised on Petitioner's construction requiring Wnt agonism, which is not required by Surrozen's proposed construction. Second, assuming the claims required activation of Wnt signaling, the '278 Patent teaches a

Surrozen 2010
Merck v. Surrozen PGR2026-00027
Page 87

person of ordinary skill that the claimed tetravalent molecules with two Fzd binding regions and two LRP5/6 binding regions will activate canonical Wnt signaling activity. *See* Paragraphs 75-134, above. A skilled artisan would not have to engage in extensive experimentation to confirm as much. Below, I respond to Dr. Kahn's contrary opinion.

154. ***First***, Dr. Kahn argues that the '278 Patent does not "provide meaningful guidance on the target specificity" for the claimed genus (*i.e.*, the Fzd-LRP target combinations capable of activating canonical Wnt signaling), which he then uses to argue that this means a person of ordinary skill in the art would have to test every potential molecule to determine if it activates Wnt signaling. EX1003 ¶ 125-127. Under Surrozen's construction, the claims do not require activation of Wnt signaling. Rather, the claims require that the claimed tetravalent molecules bind to two Fzd and two LRP5/6 receptors, and the specification and Examples collectively provide substantial guidance in this regard, including molecules that incorporate regions binding to seven of the ten Fzds and to both LRP5 and LRP6, combined in various permutations and incorporated into various tetravalent structures, as well as examples of anti-Fzd and anti-LRP5/6 antibodies that bind to all ten Fzds and both LRP5/6 receptors. *See* Paragraphs 70-72, above.

155. Assuming Petitioner is correct that the claims require activating Wnt

Surrozen 2010
Merck v. Surrozen PGR2026-00027
Page 88

signaling,[12] the Examples likewise inform a person of ordinary skill in the art that the claimed tetravalent molecules (2:2) are able to activate canonical Wnt signaling across the scope of the claims, whereas bivalent molecules (1:1) binding Fzd and LRP5/6 are considered "ineffective" at activating canonical Wnt signaling. *See* Paragraphs 106-110 and 120-121, above. Given these teachings, a person of ordinary skill in the art would understand that molecules across the full scope of 400 possible Fzd-LRP target combinations (discussed at Paragraphs 170-171, below) will activate canonical Wnt signaling when in a tetravalent format, as claimed, such that separating out "candidate tetravalent, multispecific Wnt surrogate molecules that lead to Wnt signaling activation from those that do not" would not require "trial-and-error experimentation." *See* EX1003 ¶ 127.

156. ***Second***, Dr. Kahn argues that the specification does not provide guidance "on the stoichiometric relationships between the Fzd and Lrp receptors that are necessary to activate Wnt signaling," or how to ensure "***optimal***" activation of Wnt signaling, but is instead "silent on how these different stoichiometries impact the ability of a tetravalent molecule to activate the Wnt signaling pathway." *See* EX1003 ¶ 128-130. I disagree. Again, the Examples showed that numerous tetravalent molecules, which bound to seven different Fzd

[12] For the remainder of this section, I am making this assumption and I will not make this point every time I respond to one of Dr. Kahn's criticisms.

receptors and both LRP5 and LRP6 receptors in various permutations and topologies, all activated Wnt signaling to varying degrees. If Dr. Kahn's point is to say that a skilled artisan would not know which combinations are *optimal* for activating Wnt signaling, or that some molecules were more potent in activating Wnt signaling, that is irrelevant to the claims, which contain no requirement that the molecule achieve a particular or "optimized" level of Wnt signaling activation, even under Petitioner's proposed construction.

157. As explained above at Paragraph 44, Dr. Kahn identifies no evidence that the claimed tetravalent molecules will inhibit canonical Wnt signaling if they bind to certain LRP5/6 epitopes. *See* EX1003 ¶ 129. To the contrary, his claim that Wnt3a inhibits canonical signaling when binding to certain LRP6 epitopes is itself based on a mischaracterization of EX1016. *See* Paragraph 44, above. Likewise, Dr. Kahn speculates that the LRP5/6 "binding regions [of the claimed tetravalent molecules] may bind to multiple different epitopes on the same Lrp receptor" and that these "different stoichiometries [may] impact the ability of a tetravalent molecule to activate the Wnt signaling pathway," EX1003 ¶¶ 129-30, but offers no evidence or explanation as to why this possibility, even if it occurred, would interfere with the tetravalent molecules' ability to activate canonical Wnt signaling. This provides no support to Dr. Kahn's claim that a person of ordinary skill would need to resort to "undue empirical trial-and-error experimentation," EX1003 ¶ 130,

to identify tetravalent Wnt surrogate molecules that activate Wnt signaling, even if such activation is required by the claims.

158. ***Third***, Dr. Kahn contends that the specification does not provide "meaningful guidance to address the variability and unpredictability of Wnt agonist activity resulted [sic] from tissue- and time-dependent expression profiles" of target receptors. EX1003 ¶ 133. Assuming that such agonist activity is required by the claims, each tetravalent molecule tested in the '278 Patent, incorporating various binders with different target receptors and tested across various cell lines, activated Wnt signaling. *See* Paragraphs 75-134, above. Beyond this, the factors Dr. Kahn identifies (*e.g.*, receptor density, availability across tissues and over time, and linker length to "stretch" the Fzd and LRP5/6 binding arms), EX1003 ¶¶ 131-132, can be accounted for by adjustments a person of ordinary skill could make to the molecules. As Dr. Kahn acknowledges, the specification of the '278 Patent explains that molecules can be adjusted so they have different signaling strengths "'depending on the desired use.'" *Id.* ¶ 133; EX1001 at 116:48-52. Given that every example tetravalent molecule tested in Examples 2-18 successfully activated canonical Wnt signaling, *see* Paragraphs 75-134, above, none of Dr. Kahn's factors render activation of canonical Wnt signaling unpredictable.

159. ***Fourth***, Dr. Kahn claims that the claimed molecules are unpredictable because the patent "provides no meaningful guidance to account for the different

Surrozen 2010
Merck v. Surrozen PGR2026-00027
Page 91

epitopes and binding affinities required for activating the Wnt signaling pathway." EX1003 ¶¶ 134-35. Even if required, again, every tetravalent molecule with two Fzd binding regions and two LRP5/6 binding regions that was tested in the '278 Patent activated canonical Wnt signaling, regardless of the specific epitopes bound or the molecules' binding affinities. *See* Paragraphs 75-134, above. A person of ordinary skill in the art would understand from Examples 2-18 that a tetravalent molecule with two Fzd binding regions and two LRP5/6 binding regions will activate canonical Wnt signaling. And, to the extent Dr. Kahn's argument is motivated by his incorrect understanding that the claimed tetravalent molecules must "mimic the biological activity of Wnt and non-Wnt ligands," EX1003 ¶ 134, I disagree with his premise for the reasons explained above at Paragraph 137.

160. ***Fifth***, Dr. Kahn attempts to bolster his undue "trial-and-error" criticisms by rehashing his complaints about the assays available for detecting Wnt signaling and the alleged "conflicting data" from the '278 Patent's TOPFlash assays regarding activation of Wnt signaling. EX1003 ¶¶ 136-138. I have addressed these criticisms above in Paragraphs 53-65 of this declaration, and I reiterate here that using an assay like the TOPFlash assay to detect Wnt signaling activity was routine in 2017, as confirmed by the '278 Patent itself. EX1001 at 117:39-44.

161. Beyond the arguments addressed above, Dr. Kahn makes a new claim

in paragraph 136 that the claimed tetravalent molecules have a "much greater" "risk of obtaining conflicting results—appearing to be an agonist, ineffective, or an antagonist" than natural Wnt ligands like Wnt5a. *See* EX1003 ¶ 136. He provides no support for this claim. Dr. Kahn points to no evidence that "inconsistent results" are a risk for the claimed tetravalent molecules at all, let alone that such risk is "greater" than for natural Wnt ligands. A person of ordinary skill would not consider TOPFlash assays to be a source of unpredictability.

162. Dr. Kahn also contends that the specification "fails to endorse any particular assay or assay condition for measuring canonical … Wnt signaling." EX1003 ¶ 137. But the specification provides clear guidance to a person of ordinary skill that a TOPFlash assay can and should be used to evaluate canonical Wnt signaling activity. *Id.* at 117:53-67, 118:44, 118:44-51, 155:16-161:33.

163. ***Finally***, I take the opportunity to address Dr. Kahn's sensationalism when it comes to running TOPFlash assays. I disagree with Dr. Kahn's claims that a person of ordinary skill could only evaluate the claimed tetravalent molecules by assaying "520 million reactions" in "1.4 million TOPFlash assay runs" that would take "more than 26,000 years" to perform. EX1003 ¶ 142.

164. Setting aside Dr. McDonnell's estimate of the claims' scope, which I understand will be addressed by Dr. Ravetch, Dr. Kahn's assessment of the effort expended to test the claimed molecules in TOPFlash assays overstates the work

Surrozen 2010
Merck v. Surrozen PGR2026-00027
Page 93

involved.

165. I disagree with Dr. Kahn's suggestion that every molecule would need to be tested in two cell types. EX1003 ¶ 142. A person of ordinary skill in the art could use a single cell line, and test each molecule ***twice*** (at two concentrations) to determine its activity level (which is not required by the claims under Surrozen's construction), cutting Dr. Kahn's estimate of the number of reactions, runs, and expended time in half.

166. Dr. Kahn also overstates the length of time required to perform a TOPFlash assay in 2017. EX1003 ¶ 142. As described above at Paragraph 57, in 2017 a TOPFlash assay could be performed without automation in only two days—far shorter than the week Dr. Kahn claims. Furthermore, during the two-day period required to conduct all steps of an assay, a person of ordinary skill only spends a small amount of time actively performing the highly routine steps of the assay. Finally, Dr. Kahn's calculation that a person of ordinary skill in the art would take thousands of years to perform the necessary assays seems to assume a person of ordinary skill in the art would conduct each assay using a 384-well plate consecutively, one after the other. This does not comport with reality: a person of ordinary skill in the art would be able to run—and would run—multiple assays in parallel.

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Surrozen 2010
Merck v. Surrozen PGR2026-00027
Page 94

167. Not only does Dr. Kahn overcomplicate the state of the art in 2017 relating to Wnt signaling by focusing on concepts irrelevant to the invention of the '278 Patent, but a person of ordinary skill in the art would consider any such unpredictability overcome by the extensive disclosures of the '278 Patent.

D. Dr. Kahn Overstates the Experimentation Required by Claims 1-5 (Paragraphs 113-123 of Dr. Kahn's Declaration)

168. I have been asked by counsel for Surrozen to address Dr. Kahn's estimate of the number of Fzd-LRP target combinations encompassed by the claims of the '278 Patent (Paragraphs 113-123 of Dr. Kahn's declaration).

169. I disagree with Dr. Kahn's estimate that the claims cover molecules binding to "one of at least ***35,721*** Fzd-Lrp target combinations." EX1003 ¶ 118; *see* EX1003 ¶¶ 113-118.

170. Each binding region in the claimed tetravalent molecules binds to only one receptor at a time. Each Fzd binding region in the claimed tetravalent molecule can therefore bind to only one of ten Fzd receptors at a time, and each LRP5/6 binding region can bind to either LRP5 or LRP6 at any given time. Even with the conservative assumption that position matters (*i.e.*, that a molecule in which Fzd binding region 1 targets Fzd1 and Fzd binding region 2 targets Fzd2 is different from the inverse arrangement), this produces at most ***400*** Fzd-LRP target binding combinations (*i.e.*, permutations of Fzd and LRP5/6 receptors that can be bound by

Surrozen 2010
Merck v. Surrozen PGR2026-00027
Page 95

a tetravalent molecule): 10 (Fzd binding region 1) x 10 (Fzd binding region 2) x 2 (LRP binding region 1) x 2 (LRP binding region 2). This figure accounts for bispecific, trispecific, and tetraspecific molecules. Dr. Kahn's figure far exceeds a defensible estimate.

171. Dr. Kahn achieves his estimate by improperly double-counting each cross-reactive binder (*i.e.*, sequences reactive with two or more target Fzd receptors or LRP5/6 coreceptors) as its own binding target. *See* EX1003 ¶ 115. For example, Dr. Kahn would count (i) Fzd1, (ii) Fzd2, (iii) Fzd7, (iv) Fzd1 and Fzd2, (v) Fzd1 and Fzd7, (vi) Fzd2 and Fzd7, and (vii) Fzd1, Fzd2, and Fzd7 as ***seven*** separate "targets" for a single Fzd binding region, despite the fact that the region will ultimately only bind one of Fzd1, Fzd2, or Fzd7. *See* EX1003 ¶ 114. Dr. Kahn provides no reason why a person of ordinary skill in the art would count each of these cross-reactive possibilities as a separate "target." This is inconsistent with how a person of ordinary skill in the field of Wnt signaling would understand the universe of potential binding targets. Cross-reactive binding sequences allow a given molecule in which they are incorporated to bind to more than one of the 400 target combinations, but they do not expand the number of ways in which a tetravalent molecule can bind two Fzd receptors and two LRP5/6 coreceptors.

172. As a result of Dr. Kahn's misleading counting, I also disagree with Dr. Kahn's characterization that the "specification evaluated only 14 of 63 possible

Surrozen 2010
Merck v. Surrozen PGR2026-00027
Page 96

Fzd target combinations" and that, "[o]verall, the tested target combinations are a significantly small fraction of possible 35,721 combinations." EX1003 ¶¶ 119-120.

IX. CONCLUSION

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

Surrozen 2010
Merck v. Surrozen PGR2026-00027
Page 97

Dated: 5/22/2026

Professor Karl Willert, Ph.D.

APPENDIX A:
DR. KARL WILLERT MATERIALS CONSIDERED

In offering my opinions in this Declaration, I considered all materials listed in this Appendix A, as well as all materials cited within my Declaration.

Case Documents

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

Patent Materials

- U.S. Provisional Patent Appl. No. 62/607,875 (Ex. 1005)
- U.S. Provisional Patent Appl. No. 62/641,217 (Ex. 1006)
- U.S. Provisional Patent Appl. No. 62/680,522 (Ex. 1007)
- U.S. Patent No. 8,507,442 (Ex. 2020)
- U.S. Patent No. 12,297,278 (Ex. 1001)
- File History for U.S. Patent No. 12,297,278 (Ex. 1008)
- International Patent Publication WO 2020/010308 (Ex. 1081)

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Surrozen 2010
Merck v. Surrozen PGR2026-00027
Page 101

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

MERCK SHARP & DOHME LLC,

Petitioner,

v.

SURROZEN OPERATING, INC.,
Patent Owner.

Case No. PGR2026-00027

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

ADDENDUM TO MAY 22, 2026 DECLARATION OF PROFESSOR KARL WILLERT

1. My name is Karl Willert, Ph.D. and I have been retained as an independent expert on Wnt signaling by Surrozen Operating, Inc. ("Surrozen" or "Patent Owner") in connection with post-grant review proceedings for U.S. Patent No. 12,297,278 (the "'278 Patent").

2. I signed a Declaration in this matter ("Declaration of Professor Karl Willert") on May 22, 2026.

3. I provide this addendum to note that I am being compensated for my time worked on this matter at my customary hourly rate of $500. My compensation is in no way contingent upon the outcome of this Post-Grant Review proceeding or any other proceeding.

Dated: 5/25/2026

Professor Karl Willert, Ph.D.