

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

BICARA THERAPEUTICS, INC.,
Petitioner,

v.

THE JOHNS HOPKINS UNIVERSITY,
Patent Owner.

Case No. PGR2026-00025
U.S. Patent No. 12,295,968

**PETITION FOR POST GRANT REVIEW OF
U.S. PATENT NO. 12,295,968**

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1092	L. Xu, <i>et al.</i> , “Molecular Mechanisms Regulating TGF- β -Induced <i>Foxp3</i> Expression,” 3:3 <i>Mucosal Immunology</i> 230 (2010) [“Xu 2010”]
1093	Yu-an Yang, <i>et al.</i> , “Lifetime Exposure to a Soluble TGF- β Antagonist Protects Mice Against Metastasis Without Adverse Side Effects,” 109:12 <i>The Journal of Clinical Investigation</i> 1607 (2002) [“Yang 2002”]
1094	Jianhua Zhang, <i>et al.</i> , “Design and Optimization of a Linker for Fusion Protein Construction,” 19:10 <i>Progress in Natural Science: Materials International</i> 1197 (2009) [“Zhang 2009”]
1095	Shuo Tang, <i>et al.</i> , “Challenges and Solutions for the Downstream Purification of Therapeutic Proteins,” 7:1 <i>Antibody Therapeutics</i> 1 (2024) [“Tang 2024”]

I. INTRODUCTION

Petitioner Bicara Therapeutics, Inc. (“Bicara”) requests post grant review of all claims of U.S. Patent No. 12,295,968 (“the ’968 Patent”, EX1001), assigned to The Johns Hopkins University (“JHU”). 35 U.S.C. § 321.

The ’968 Patent broadly discloses genera of targeting moieties and fusion proteins, including fusion antibodies. The ’968 Patent claims priority to nine prior applications, the earliest dating back to March 2010. In December 2024, after prosecuting this family for more than 14 years, JHU abruptly shifted from these broad genera and functional disclosures to narrower subgenus claims that lack any basis in the specification. These claims target, for the first time, a moiety comprising an antibody or antibody fragment comprising only amino acids 1-119 of one sequence (SEQ ID NO: 2) and the entirety of another sequence (SEQ ID NO: 71).

JHU’s sudden change of course was no coincidence. These new claims conspicuously appeared in December 2024, during prosecution, just months after Bicara announced that it would hold an initial public offering, which raised \$362 million. Bicara is clinically developing ficerafusp alfa (a/k/a BCA101). The new claims of the ’968 Patent reflect JHU’s transparent attempt to try to capture Bicara’s BCA101 with these narrower claims, despite never disclosing this species in any patent or application in the ’968 Patent’s alleged priority chain.

JHU's effort to claim a subgenus of fusion antibodies that it did not invent mandates cancellation.

First, all challenged claims are unpatentable for lack of written description under 35 U.S.C. § 112(a). *See infra* Section VI.A. Claims 1-9 are an impermissible attempt to claim fusion antibodies that the named inventors did not invent at any point in time, much less by the pre-2024 filing dates to which JHU alleges priority. *Id.*

Second, all challenged claims are unpatentable for lack of enablement under 35 U.S.C. § 112(a). *See infra* Section VI.B. The '968 Patent does not enable the person of ordinary skill in the art to make and use the full scope of the challenged claims without undue experimentation. *Id.*

Lastly, the contorted claim drafting required for JHU to attempt to capture BCA101 renders claims 2-8 unpatentable for improper dependency under 35 U.S.C. § 112(d) and unpatentable for indefiniteness under 35 U.S.C. § 112(b). *See infra* Section VII.

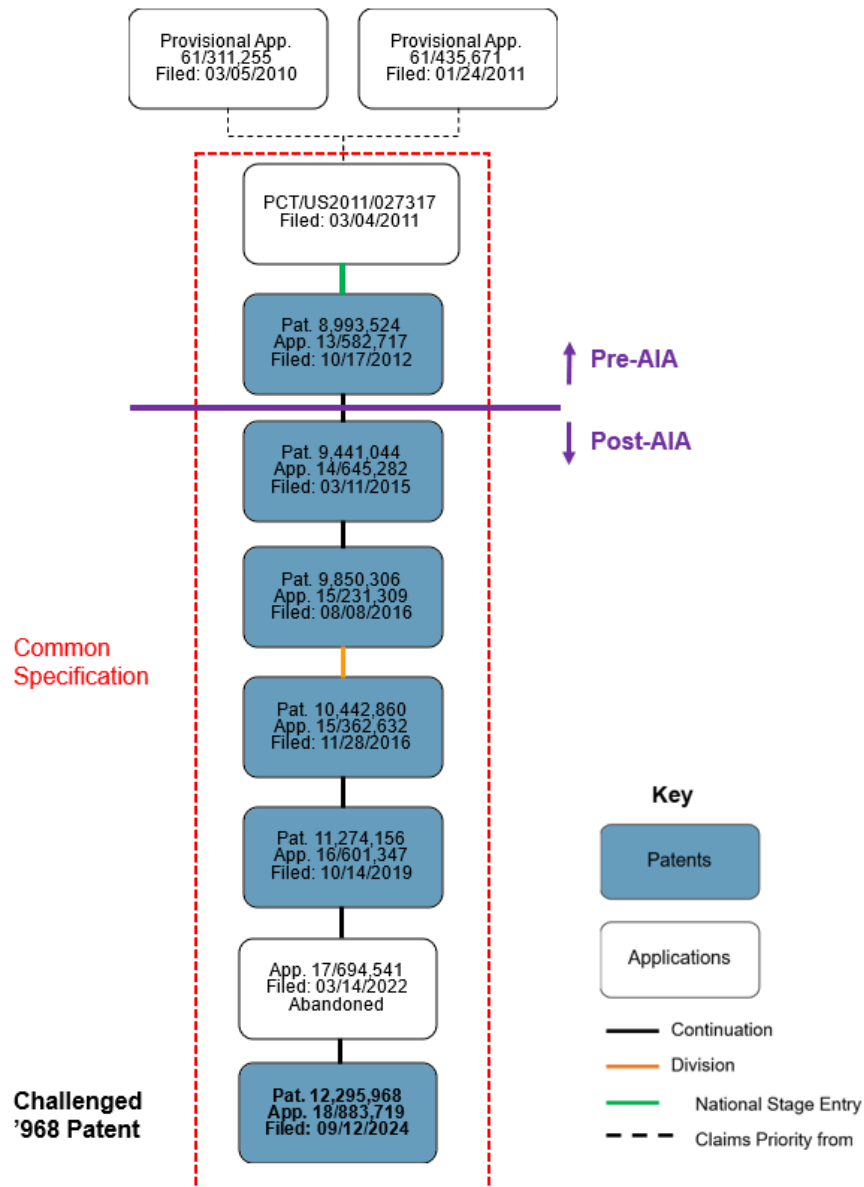
II. GROUNDS FOR STANDING (37 C.F.R. § 42.204(a))

The '968 Patent issued within the past nine months, as required by 37 C.F.R. § 42.202(a). Petitioner certifies that the '968 Patent is available for PGR and that Petitioner is not barred or estopped from requesting a PGR challenging the '968 Patent's claims on the grounds identified below.

The '968 Patent is eligible for PGR because at least one of its claims is not entitled to an effective filing date before March 16, 2013. Despite facially claiming priority to pre-AIA applications filed before 2013, the applications to which the '968 Patent purports to claim priority do not provide sufficient written description support for or enable the claims of the '968 Patent. *E.g.*, *CSIRO v. BASF Plant Sci. GmbH*, PGR2020-00033, Paper-11 at 9 (PTAB Sep. 10, 2020) (“[A] patent claiming the benefit of a priority application filed before March 16, 2013 must have written description support in, and be enabled by, the earlier-filed application to avoid PGR-eligibility.”); 35 U.S.C. § 120.¹

The '968 Patent issued on May 13, 2025 from U.S. Patent Application No. 18/883,719 (“the '719 Application”) filed on September 12, 2024. The '968 Patent issued from a long series of continuation applications and one divisional application that started with International Application No. PCT/US2011/027317 filed Mar. 4, 2011 (“PCT '317 Application”), which purports to claim priority to two earlier provisional applications. A diagram of the claimed priority chain for the '968 Patent is provided for clarity:

¹ *Tricam Indus., Inc. v. Little Giant Ladder Sys., LLC*, PGR2021-00044, Paper-10 at 15 (PTAB Aug. 3, 2021); *Inguran, LLC v. Premium Genetics (UK) Ltd.*, PGR2015-00017, Paper-8 at 16-17 (PTAB Dec. 22, 2015).



With respect to the prior applications within this family, the '968 Patent states:

“The disclosure of each of the prior applications is considered part of and is incorporated by reference in the disclosure of this application.” EX1001, 1:27-30.

The '968 Patent shares a common specification with each of the patent applications in its ancestry from the '719 Application that ultimately issued as the '968 Patent

through the PCT '317 Application.² The only applications in the alleged priority chain that do not share a common specification with the '968 Patent are the two provisional applications. Because the claimed priority applications that share a common specification with the '968 Patent each fail to satisfy the written description and enablement requirements of 35 U.S.C. § 112, the '968 Patent is only entitled to the filing date of the '719 Application, September 12, 2024.

For purposes of priority, and thus eligibility for PGR, the '968 Patent cannot rely on the disclosures of the two provisional applications to support written description or enablement. The '968 Patent and the prior intervening applications to

² “Common specification” refers to the shared disclosure of the '968 Patent through the applications and issued patents in its priority chain back to the PCT '317 Application. Citations to the common specification herein are to the '968 Patent, which correlates to similar citations in each of the prior applications and patents. The disclosures are highly similar but not identical. EX1003, ¶¶72-77; *e.g., compare* EX1001, *with* EX1015. For instance, the sequence listing table in the '968 Patent that spans column 47 to column 98 uses 1-letter amino acid codes, while the prior applications and issued patents use the respective 3-letter code. EX1003, ¶74. Any differences between the disclosures do not alter the unpatentability of the claims. *Id.*, ¶77.

which the '968 Patent claims priority do not include the full disclosure of the two provisionals. *Arthrex, Inc. v. Smith & Nephew, Inc.*, 35 F.4th 1328, 1343 (Fed. Cir. 2022). Rather, each of the intervening applications only include a generic statement attempting to incorporate the two provisionals by reference. *E.g.*, EX1005, p.5. Material from a provisional application incorporated by reference, however, cannot provide written description or enablement support to establish priority, because such material would be deemed “essential material.” 37 C.F.R. § 1.57(d); *see NRG Energy, Inc. v. Midwest Energy Emissions Corp.*, IPR2020-00832, Paper-17 at 29-30 (PTAB Oct. 26, 2020) (analyzing § 1.57 and finding the same).

The current Rule 1.57(d) provides that “essential material”—which includes “material that is necessary to ... [p]rovide a written description of the claimed invention” and enable the claimed invention under § 112—“may be incorporated by reference, but *only by way* of an incorporation by reference to a *U.S. patent or U.S. patent application publication*, which patent or patent application publication does not itself incorporate such essential material by reference.” 37 C.F.R. § 1.57(d) (emphasis added). The three prior versions of this Rule that were in effect from the filing of the first provisional in March 2010 to when the current version took effect on May 13, 2015, provide a similar limitation as to incorporating “essential material.” EX1041 (effective 09/10/2007-09/15/2012); EX1042 (effective 09/16/2012-12/17/2013); EX1043 (effective 12/18/2013-05/12/2015).

A provisional application is neither a “U.S. patent” nor a “U.S. patent application publication” under this rule, meaning the ’968 Patent and the earlier intervening applications cannot incorporate provisional applications by reference for purposes of written description and enablement support. *NRG Energy*, IPR2020-00832, Paper-17 at 29-30; *see Zte (Usa), Inc. v. Cywee Grp. Ltd.*, IPR2019-00143, Paper 87 at 116 (PTAB Feb. 17, 2021) (analyzing § 1.57 and finding “[b]ecause a U.S. provisional application is not a ‘U.S. patent or U.S. patent application publication,’ the ’934 application's incorporation by reference of the ’558 provisional application was ineffective”); 35 U.S.C. § 122 (“An application shall not be published if that application is ... a provisional application filed under section 111(b) ...”); *Nomadix, Inc. v. Second Rule LLC*, 2009 WL 10668158, at *26 (C.D. Cal. Jan. 16, 2009) (analyzing patent before regulation was adopted, “[i]f § 1.57 applied to the [challenged] patent, there would be no question that the ... provisional application was improperly incorporated.”).

As explained in Ground 1 below, none of the claims of the ’968 Patent has written description support in the common specification. Additionally, as explained in Ground 2 below, none of the claims of the ’968 Patent are enabled by the common specification. Accordingly, none of the claims of the ’968 Patent are entitled to a priority date prior to March 16, 2013 as the failures of the common specification are shared by the ’968 Patent and all members of its alleged priority chain through the

PCT '317 Application. The earliest date to which the '968 Patent could claim priority is therefore September 12, 2024, the filing date of the '719 Application, and the patent is thus eligible for PGR.

Additionally, even if the provisional applications supported the claims, the '968 Patent is not entitled to priority before March 16, 2013 because there was a break in the claimed priority chain and, therefore, the patent is not entitled to claim priority to any application preceding that break. The '541 Application³—which immediately precedes, and shares a common specification with, the '968 Patent—does not describe or enable the claims of the '968 Patent for the same reasons discussed in Grounds 1 and 2 below. Because at least the '541 Application does not describe or enable the later-claims of the '968 Patent, any claim of priority is broken, meaning the '968 Patent cannot claim priority to any earlier application. *Arthrex*, 35 F.4th at 1343 (“[E]ach application in the chain leading back to the earlier application must comply with the written description requirement of 35 U.S.C. § 112.” (quoting *Lockwood v. Am. Airlines, Inc.*, 107 F.3d 1565, 1571 (Fed. Cir. 1997)); *Hollmer v. Harari*, 681 F.3d 1351, 1355 (Fed. Cir. 2012) (“[I]f any application in the priority chain fails to make the requisite disclosure of subject matter, the later-filed application is not entitled to the benefit of the filing date of applications preceding the break in the priority chain.”)).

³ Application No. 17/694,541 (EX1005).

III. IDENTIFICATION OF CHALLENGE (37 C.F.R. § 42.204(b))

Petitioner respectfully requests cancellation of all claims of the '968 Patent. The challenged claims should be cancelled as unpatentable on the following grounds:

Ground 1: All claims (claims 1-9) are unpatentable under 35 U.S.C. § 112(a) for failing to satisfy the written description requirement.

Ground 2: All claims (claims 1-9) are unpatentable under 35 U.S.C. § 112(a) for failing to satisfy the enablement requirement.

Ground 3: Claims 2-8 are unpatentable under 35 U.S.C. § 112(d) as improperly dependent.

Ground 4: Claims 2-8 are unpatentable under 35 U.S.C. § 112(b) as indefinite for failing to particularly point out and distinctly claim the subject matter which the inventors regard as the invention.

Ground 5: Claims 3-8 are unpatentable under 35 U.S.C. § 112(d) as improperly dependent.

Ground 6: Claims 3-8 are unpatentable under 35 U.S.C. § 112(b) as indefinite for failing to particularly point out and distinctly claim the subject matter which the inventors regard as the invention.

Petitioner's proposed claim constructions and the precise reasons why the claims are unpatentable are provided below. Petitioner's challenge is supported by

the evidence submitted with this Petition, including an expert declaration by Geoffrey Hale, Ph.D., EX1003. Dr. Hale is an expert in the field of the '968 patent with over 45 years of education, knowledge, and experience in the design, development, and manufacture of antibodies and fusion proteins for research and clinical applications. In this Petition, Petitioner has demonstrated that it is more likely than not that at least one challenged claim is unpatentable, warranting institution. 35 U.S.C. § 324(a); 37 C.F.R. § 42.208(c).

IV. BACKGROUND ON THE CHALLENGED PATENT

A. Field of the Patent

1. Antibodies

(a) Overview of the Immune System and Antibodies

The immune system is a complex network of cells and organs in the human body that protect the body from foreign substances, such as bacteria and viruses. EX1001, 1:60-63. The immune system recognizes abnormal cellular growth within the body, such as cancer cells. *Id.*, 2:1-8. The immune system plays a dual role of identifying and removing foreign or abnormal substances. EX1003, ¶39. Additionally, the immune system can “remember” previously-identified substances, allowing it to respond faster and more effectively. EX1001, 1:63-2:1.

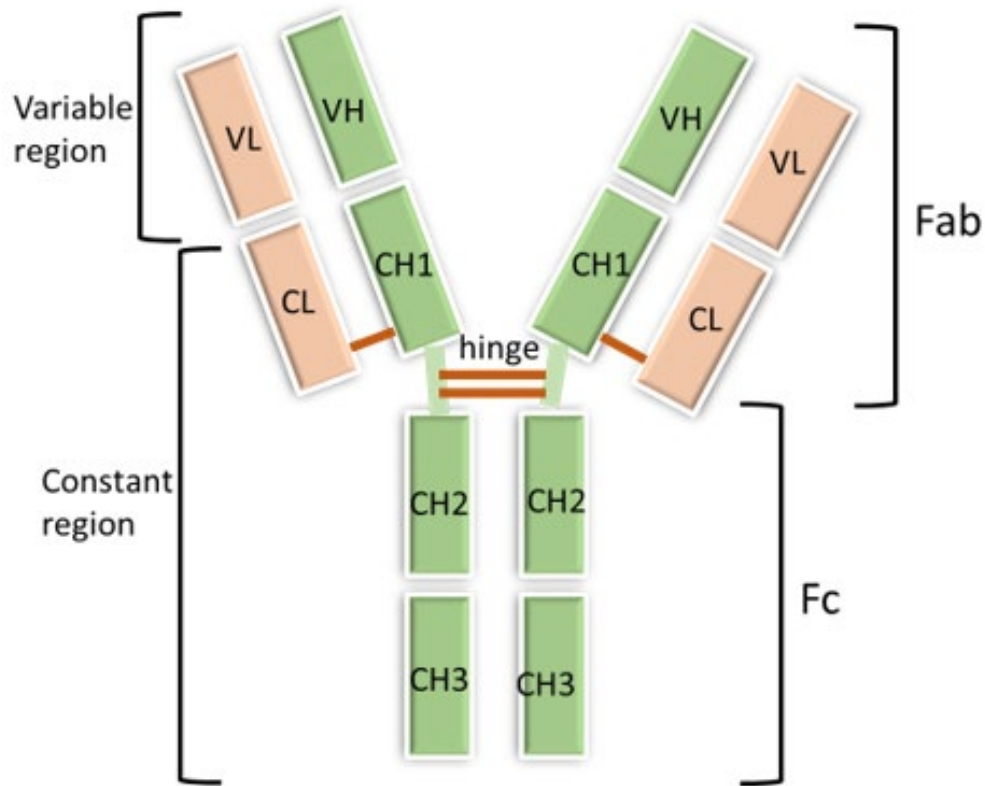
Antibodies—also known as immunoglobulins (Ig)—are proteins of the immune system that bind with specificity to molecular targets, commonly known as antigens. EX1003, ¶¶39-40, 44. The immune system generates antibodies that are specific to

different antigens, and can recognize them by binding to particular structural features on antigens known as epitopes. *Id.*, ¶43. Through this binding interaction, antibodies may directly interfere with antigen activity or promote downstream removal of the antigen by other components of the immune system. *Id.*, ¶¶39, 57.

Antibodies exist as one of five classes based on their structure and function. *Id.*, ¶41. Of these, the antibody class IgG is the most abundant antibody in the blood and plays a key role in the body's immune response to bacteria, viruses, and cancer. *Id.*; EX1001, 1:60-63. As the antibody class IgG is the focus of the '968 Patent, these antibodies are discussed in greater detail below. EX1003, ¶125, Fig.C.

(b) The Structure of IgG Antibodies

IgG antibodies share a conserved overall architecture and are frequently depicted in a simplified fashion as Y-shaped molecules composed of two identical heavy chains and two identical light chains joined by molecular bonds known as disulfide bonds.



Id., Fig.A.

Each heavy chain includes a variable domain and three constant domains, separated by a hinge region. *Id.*, ¶42. Each light chain consists of a variable domain and a constant domain. *Id.* The pairing of heavy and light chain variable domains forms the antigen-binding site, while the paired heavy chain constant domains constitute the Fc region. *Id.* The antigen-binding site is responsible for binding to the antigen target and dictates the specific binding of the antibody molecule, while the Fc region governs interactions with other components of the immune system. *Id.*

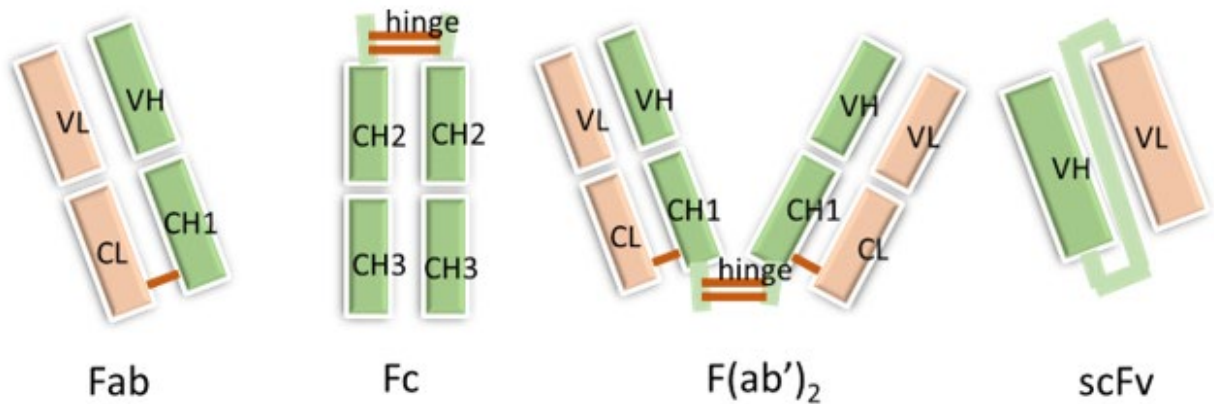
Despite their conserved architecture, IgG antibodies are broadly diverse, which is largely because of the target-specific makeup of the variable region, so

named because the exact amino acid sequence (the specific molecular subunits that make up a protein) of the variable region chain is highly variable and can be fine-tuned to promote target specificity. *Id.*, ¶43. The immune system naturally makes a highly diverse set of IgG antibodies with different variable regions. *Id.* Following antigen exposure, the immune system refines the variable region to be more specific to that antigen. *Id.*

The constant regions of antibodies are comparatively conserved, although minor sequence variations, referred to as allotypes, can occur among individuals. *Id.*, ¶45. Additionally, IgG antibodies can possess different classes of light and heavy chains, defined by specific sequences. *Id.*, ¶¶46-47. This class variation results in four distinct subclasses of IgG antibodies in humans. *Id.*, ¶47. The subclasses of IgG antibodies differ in structure and, as a result, their ability to interact with other molecules in the immune system. *Id.*

While IgG antibodies primarily exist in the complete structure described above, “fragments”—portions of the full-length Y-shaped structure described above—can exist and function. *Id.*, ¶¶48-49. Antibody fragments are often the product of scientific research or therapeutic development. *Id.*, ¶48. Not all antibody fragments are viable, and many potential antibody fragments fail to properly form or maintain their structure or lack any functional ability. *Id.*, ¶49. Known IgG antibody fragments include Fab, Fc, F(ab')₂, and scFv fragments, although the

viability of each fragment is specific to the context of the specific antibody and its corresponding antigen. *Id.*, ¶¶48-51.



Id., Fig.B. The Fab and scFv fragments are most relevant to the challenged claims.

Fab (Fragment antigen-binding): A Fab fragment consists of one complete light chain and the variable and first constant domains of one heavy chain. It can retain a single antigen-binding site and can bind antigen but lacks the Fc region and associated immune effector functions. *Id.*, ¶48.

scFv (Single-chain variable fragment): An scFv is an antibody fragment in which the variable domains of the heavy and light chains are linked by a peptide linker. It retains antigen-binding specificity in a single polypeptide chain but lacks constant regions. *Id.*, ¶¶47, 59.

2. Antibody Therapeutics and Fusion Proteins

Antibodies can be used as targeted treatments that mimic the body's immune proteins to fight diseases like cancer, autoimmune disorders, and infections. *Id.*, ¶39.

Some early therapeutic antibodies targeted cell-surface receptors implicated in cancer biology, such as epidermal growth factor receptor (EGFR), a cell-surface receptor often hijacked in cancer cells to promote cancer cell growth and metastasis. *Id.*, ¶55. To treat EGFR-driven cancer, researchers developed a therapeutic IgG antibody specific to EGFR known as cetuximab (trade name Erbitux®) that binds to EGFR to prevent its activation and limit cancer growth. *Id.*, ¶¶56-57.

Beyond their direct therapeutic use, antibodies' capacity for selective target binding and immune system engagement makes them an effective molecular platform for developing engineered molecules for specific therapeutic applications, a process referred to as antibody engineering. *Id.*, ¶58. Antibody engineering has enabled modification of antibody properties as well as the development of alternative antibody formats, including fragments and fusion proteins. *Id.*

Fusion proteins are engineered polypeptides in which functional domains derived from different proteins are joined into a single molecule. *Id.*, ¶59. Antibody fusion proteins utilize the antibody or antibody fragment as a targeting moiety, while the fused domain contributes an additional biological activity, such as enzymatic function, toxin delivery, or cytokine signaling. *Id.*, ¶60. The domains within fusion proteins are commonly connected by peptide linkers designed to preserve independent folding and biological activity. *Id.*, ¶¶59, 61.

By March 2010, and even to present day, the manufacture of fusion proteins remains very difficult and unpredictable. *Id.*, ¶¶62-64. As Dr. Hale explains, the unnatural combination of two completely different proteins into one polypeptide chain has the potential for many kinds of unexpected interactions, which could lead to instability of the molecule. *Id.*, ¶¶63-64. Dr. Hale has personal experience with the difficulty and unpredictability in manufacturing fusion proteins and fusion antibodies, including failing to reduce to practice particular fusion proteins. *Id.*, ¶¶65-67.

Candidate molecules for coupling to fusion molecules include receptor molecules that can bind to or interact with other proteins to regulate the immune system. *Id.*, ¶¶59, 70. One such molecule was transforming growth factor beta (TGF- β), a cytokine (signaling protein) involved in regulating diverse biological processes that can be coopted by cancer cells to promote cancer growth. *Id.*, ¶¶68, 70.

B. The '968 Patent

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

The POSA for the challenged claims as of the earliest effective filing date would have held a Ph.D. or equivalent (for example, 4 to 5 years of work experience) in biochemistry, molecular biology, immunology, or a closely related field. EX1003, ¶111. The POSA would have had experience that included antibody domain and sequence manipulation, construction, expression, and purification of recombinant

antibodies and/or fusion proteins, and assays for expression levels and activity. *Id.* The POSA would also have collaborated with other individual(s) with experience in the medicinal, pharmaceutical, or biotech industry, *e.g.*, as members of a research team or group. *Id.* For example, the POSA could have worked as part of a team or collaboration to develop antibodies and/or fusion proteins for therapeutic use. *Id.*

Dr. Hale, whose declaration is relied on in this petition, was a POSA from the earliest claimed priority date (March 5, 2010) through the filing of the '968 Patent on September 12, 2024. *Id.*, ¶112.

2. The Challenged Claims

The '968 Patent has two independent claims (claims 1 and 9) and seven dependent claims, each of which depends, directly or indirectly, from claim 1. The independent claims of the '968 Patent are provided in Appendix A.

3. The Common Specification of the '968 Patent

The '968 Patent is titled “COMPOSITIONS AND METHODS FOR TARGETED IMMUNOMODULATORY ANTIBODIES AND FUSION PROTEINS.” The summary of the invention outlines a broad genus of molecules, stating “that targeted immunomodulatory antibodies and fusion proteins can counteract or reverse immune tolerance of cancer cells.” EX1001, 2:12-15; EX1003, ¶¶78-99. The specification broadly describes various molecules, stating “[i]n one embodiment, the present invention provides a molecule including a targeting moiety

fused with an immunomodulatory moiety. The targeting moiety specifically binds a target molecule, and the immunomodulatory moiety specifically binds one of” a list of molecules. *E.g.*, EX1001, 2:32-42.

The targeting moiety is not limited to a complete antibody. The specification states that a “‘targeting moiety’ refers to a molecule that has the ability to localize and bind to a specific molecule or cellular component. The targeting moiety can be an antibody, antibody fragment, scFv, Fc-containing polypeptide, fusion antibody, polypeptide, peptide, aptamer, ligand, nucleic acid, or any combination thereof.” *Id.*, 27:38-43. The specification additionally states an “‘immunomodulatory moiety’ refers to a ligand, peptide, polypeptide, or Fc-containing polypeptide that binds a specific component of a regulatory T cell, myeloid suppressor cell, or dendritic cell and modulates the number or function of Tregs or myeloid suppressor cells.” *Id.*, 31:43-48.

Specific examples are found in Figures 1-57 and Examples 1 and 2. EX1003, ¶¶78-99, Appx.B-C. Figures 2-11, 13-21, 23-30, 32-39, and 41-52 provide prophetic examples of the sequence for fusion proteins. *Id.*, ¶¶80-84, Appx.C. All antibody targeting moieties are full-length antibodies. *Id.* While these Figures disclose 48 exemplary fusion proteins, almost all of them are prophetic examples for which there is no evidence that they were actually made. *Id.* The only working example is Example 1.

Example 1 concerns “[c]ounteracting Tumor Immune Tolerance Via Antibody-Mediated Depletion of CD4⁺ Regulatory T Cells.” EX1001, 38:46-43:34. The only fusion protein agent utilized in Example 1 is “a chimeric protein comprising the extracellular domain of TGFβRII and the Fc portion of the murine IgG1 heavy chain (TGFβRII:Fc).” *Id.* There is no indication of the amino acid sequence of the TGFβRII:Fc protein utilized. This example is not an embodiment of the claims of the ’968 Patent as explained further below.

Example 2 is titled “Exemplary Targeted Immunomodulatory Antibodies and Fusion Proteins.” *Id.*, 43:36-48:10. Example 2 is purely prophetic and in general terms describes: “A targeting moiety, including an antibody, can be coupled to an immunomodulatory moiety.” *Id.*, 43:40-45. Example 2 then cites to FIGS. 1-33 as “[e]xamples of targeted immunomodulatory antibodies and fusion proteins.” *Id.*, 43:50-52. None of the proteins described or cited in Example 2 were made or tested for any functional activity. *Id.*, ¶¶81, 89.

V. CLAIM CONSTRUCTION

The applicable claim construction standard is articulated in *Phillips v. AWH Corp.*, 415 F.3d 1303 (Fed. Cir. 2005) (en banc); 37 C.F.R. § 42.200(b). “[T]he words of a claim ‘are generally given their ordinary and customary meaning,’” which is “the meaning that the term would have to a [POSA] in question at the time of the invention.” *Phillips*, 415 F.3d at 1312-13 (citation omitted). The Board “need

only construe terms ‘that are in controversy, and only to the extent necessary to resolve the controversy.’” *Nidec Motor Corp. v. Zhongshan Broad Ocean Motor Co.*, 868 F.3d 1013, 1017 (Fed. Cir. 2017) (citation omitted); *see Hybrigenics SA v. Forma Therapeutics, Inc.*, PGR2018-00098, Paper-10 at 10-11, 18, 48 (PTAB Mar. 20, 2019); *Groupon, Inc. v. Kroy IP Holdings, LLC*, IPR2019-00061, Paper-12 at 14 (PTAB Apr. 19, 2019) (the Board “do[es] not apply a rule of construction with an aim to preserve the validity of the claims”).

Pursuant to 37 C.F.R. § 42.204(b)(3), Petitioner proposes the following constructions:

No.	Claim Term	Claim(s) of the '968 Patent	Petitioner's Construction
1	“scFv”	Claim 2	“single-chain variable fragment consisting of only the variable regions of the heavy and light chains joined by a linker peptide”
2	“the antibody fragment comprises a light chain domain or a variable heavy chain domain”	Claim 3	“the antibody fragment comprises either a light chain domain or a variable heavy chain domain, but not both”

A. “scFv”

Consistent with the intrinsic and extrinsic record, the term “scFv” in claim 2 means “single-chain variable fragment consisting of only the variable regions of the

heavy and light chain domains joined by a linker peptide.” This is the common meaning of the term to a POSA.

The intrinsic record reflects the common meaning. The specification contains no explicit definition; rather, it uses this term in reference to its common meaning. EX1001, 27: 13-16 (“Unless defined otherwise, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this invention belongs.”). For instance, the specification states that “[a]n antibody as disclosed herein includes an antibody fragment, such as, ... single-chain Fvs (scFv).” EX1001, 34:40-42. The specification uses “scFv” as a POSA would understand it, referring to the “single-chain Fvs” type of antibody fragment.

The extrinsic record further demonstrates that “scFv” is a well-understood term in the art as an abbreviation for “single-chain variable fragment.” EX1003, ¶¶106-10, Fig.F. As Dr. Hale explains, the plain meaning of this term to a POSA is a single-chain variable fragment that consists of only the variable regions of the heavy and light chain domains joined by a linker peptide. *Id.* This accords with the use of this term in the literature. *Id.*, ¶108.

B. “the antibody fragment comprises a light chain domain or a variable heavy chain domain”

Claim 3 recites “[t]he molecule of claim 2, wherein the antibody fragment comprises a light chain domain *or* a variable heavy chain domain.” The proper

construction of the phrase “the antibody fragment comprises a light chain domain or a variable heavy chain domain” in claim 3 is “the antibody fragment comprises ***either*** a light chain domain ***or*** a variable heavy chain domain, ***but not both.***”

The use of “or” in claim 3 is consistent with its common usage designating alternatives and there is no basis in the specification or claims that the use of “or” was intended to embrace “one or both.” *E.g., Game and Tech. Co. v. Activision Blizzard Inc.*, 926 F.3d 1370, 1378-79 (Fed. Cir. 2019) (“The claim’s use of the term ‘comprising,’ combined with the use of the disjunctive conjunction ‘or’ supports the construction that ‘displaying’ and ‘performing game functions’ are two alternatives for layers.”); *SkinMedica, Inc. v. Histogen Inc.*, 727 F.3d 1187, 1199 (Fed. Cir. 2013) (“The disjunctive ‘or’ plainly designates that a series describes alternatives.” (citation omitted)); *Schumer v. Lab’y Computer Sys., Inc.*, 308 F.3d 1304, 1311 (Fed. Cir. 2002) (“We have consistently interpreted the word ‘or’ to mean that the items in the sequence are alternatives to each other.”).

The use of “or” in claim 3 having its common meaning of a disjunctive conjunction specifying alternatives is further confirmed by the specification. When the patentee intended terms to depart from their ordinary meaning, the patentee expressly defined them as such. For instance, the specification states: “As used in this specification and the appended claims, the singular forms ‘a,’ ‘an,’ and ‘the’ include plural references unless the context clearly dictates otherwise.” EX1001,

27:6-8. Unlike the patentee’s clear statements concerning the broadened meaning of these singular forms (a/an/the), there is no special meaning or other evidence that the patentee intended “or” in claim 3 to mean anything other than a conjunction to indicate alternatives, not both.

VI. GROUNDS 1-2: THE ’968 PATENT AND ITS COMMON SPECIFICATION FAIL TO PROVIDE WRITTEN DESCRIPTION AND ENABLEMENT SUPPORT FOR ANY CHALLENGED CLAIM

A. Ground 1: All Claims Lack Written Description Under § 112(a)

All claims of the ’968 Patent fail to meet the written description requirement of § 112(a).

A specification adequately meets this requirement when it “reasonably conveys to those skilled in the art that the inventor had possession of the claimed subject matter as of the filing date.” *Ariad Pharms., Inc. v. Eli Lilly & Co.*, 598 F.3d 1336, 1351 (Fed. Cir. 2010) (en banc) (citation omitted). “[T]he hallmark of written description is disclosure” in the “four corners of the specification.” *Id.*⁴

⁴ As explained above (Section II), to the extent the specification purports to incorporate by reference, there must be a “clear intent to incorporate by reference” that “[c]learly identif[ies] the referenced patent, application, or publication,” and “[e]ssential material”—including material that is necessary to provide written description or to enable—may only be incorporated “by reference to a U.S. patent

The specification must adequately describe both individual claim limitations as well as all of the claim limitations together as a whole. *E.g.*, *Seagen Inc. v. Daiichi Sankyo Co.*, 160 F.4th 1322, 1330 (Fed. Cir. 2025); *Novozymes A/S v. DuPont Nutrition Biosciences APS*, 723 F.3d 1336, 1349 (Fed. Cir. 2013). When there is no express (*ipsis verbis*) disclosure of the claimed subject matter, the written description requirement may be satisfied by the specification providing “sufficient blaze marks” to direct a POSA to the claimed subject matter. *Regents of the Univ. of Minn. v. Gilead Scis. Inc.*, 61 F.4th 1350, 1358 (Fed. Cir. 2023); *Duke Univ. v. Sandoz Inc.*, 160 F.4th 1305 (Fed. Cir. 2025) (“To meet the written description requirement in this manner, the patent must ‘provide sufficient blaze marks’ to direct a skilled artisan to the claimed subgenus.” (citation omitted)); *Seagen*, 160 F.4th at 1332.

“As [the Federal Circuit has] consistently held, a patent’s disclosure of a ‘broad genus,’ without more, is inadequate to satisfy the written description requirement for claims directed to a ‘particular subgenus or species contained therein.’” *Seagen*, 160 F.4th at 1330. “A patent owner cannot show written description support by picking and choosing claim elements from different

or U.S. patent application publication.” 37 C.F.R. § 1.57(c)-(d). As addressed above, U.S. provisional applications are neither U.S. patents nor U.S. patent application publications under § 1.57.

embodiments that are never linked together in the specification.” *Flash-Control, LLC v. Intel Corp.*, 2021 WL 2944592, at *4 (Fed. Cir. July 14, 2021) (nonprecedential). “The written description requirement is not met when ... the specification provides at best disparate disclosures that an artisan might have been able to combine in order to make the claimed invention.” *Id.*; *Samsung Elecs. Co. v. Ward Participations B.V.*, PGR2022-00007, Paper-33, at 9-21 (PTAB April 21, 2023) (similar), *aff’d*, No. 23-2080 (Fed. Cir. Jan. 13, 2025).

“[A] description that merely renders the invention obvious does not satisfy the [written description] requirement.” *Ariad*, 598 F.3d at 1352 (citation omitted); *Lockwood*, 107 F.3d at 1572 (insufficient “that the disclosure, when combined with the knowledge in the art, would lead one to speculate as to modifications that the inventor might have envisioned, but failed to disclose.”). “A ‘mere wish or plan’ for obtaining the claimed invention is not adequate written description.” *Centocor Ortho Biotech, Inc. v. Abbott Labs.*, 636 F.3d 1341, 1348 (Fed. Cir. 2011) (citation omitted).

Finally, “hindsight” is not permitted—a patent lacks written description for a claim, even where the patent “provides formal textual support for each individual limitation recited in the claims,” if the patent “nowhere describes the actual functioning [invention] ... that those limitations together define.” *Novozymes*, 723 F.3d at 1349 (prohibiting “[w]orking **backward** from a knowledge of [the claims]”

and “finding if there’s a written description for that”). Instead, the written description analysis must be “view[ed] ... from the proper vantage point ‘of one with no foreknowledge of the specific [claimed invention].’” *Id.* at 1349 (citation omitted).

Here, all claims lack written description for several reasons. **First**, there is no disclosure of a specific limitation required by each independent claim—the incomplete “targeting moiety” which comprises only part of SEQ ID NO: 2 (amino acids 1-119) and the entirety of SEQ ID NO: 71, and which binds EGFR. There is no express disclosure of this limitation anywhere in the ’968 Patent or its common specification. EX1003, ¶¶116-23. There are also no blaze marks that would lead a POSA to arrive at this “targeting moiety” limitation. *Id.* Instead, the ’968 Patent broadly discloses a genus of targeting moieties without any direction or suggestion to arrive at this limitation. **Second**, there is no disclosure of the specific combination of all the limitations as an integrated whole for each claim. *Id.*, ¶¶124-54. The Federal Circuit prohibits “picking and choosing” among disclosures in the patent to cobble together written description based on hindsight or obviousness. There is no evidence whatsoever that the inventors actually possessed the specific combination of limitations required by each of the challenged claims.

**1. No Written Description for Specific “Targeting Moiety”
Limitation Required by Independent Claims 1 and 9 (All Claims)**

The incomplete antibody fragment required by each of the two independent claims as a “targeting moiety” is not disclosed anywhere in the ’968 Patent. Without any basis in the common specification, this limitation in both independent claims requires a targeting moiety comprising an antibody fragment that includes only part of one sequence (amino acids 1-119 of SEQ ID NO: 2) and the entirety of another sequence (SEQ ID NO: 71). To satisfy the written description requirement, each and every element of the claims must be adequately described by the disclosure. *E.g.*, *Juno Therapeutics, Inc. v. Kite Pharma, Inc.*, 10 F.4th 1330, 1335, 1341-42 (Fed. Cir. 2021) (lack of adequate written description as to “the claimed functional binding element”); *Seagen*, 160 F.4th at 1332 (lack of adequate written description as to the subgenus of tetrapeptides claimed). At best, the common specification only discloses a full-length antibody, not an antibody fragment, comprising the full sequences of SEQ ID NOS: 2 and 71. Including this partial targeting moiety in “comprising” claims reflects JHU’s clear attempt to capture Bicara’s BCA101. The ’968 Patent neither expressly discloses nor provides sufficient blaze marks for a POSA to arrive at the claimed “targeting moiety” limitation.

With respect to the targeting moiety limitation, each independent claim requires:

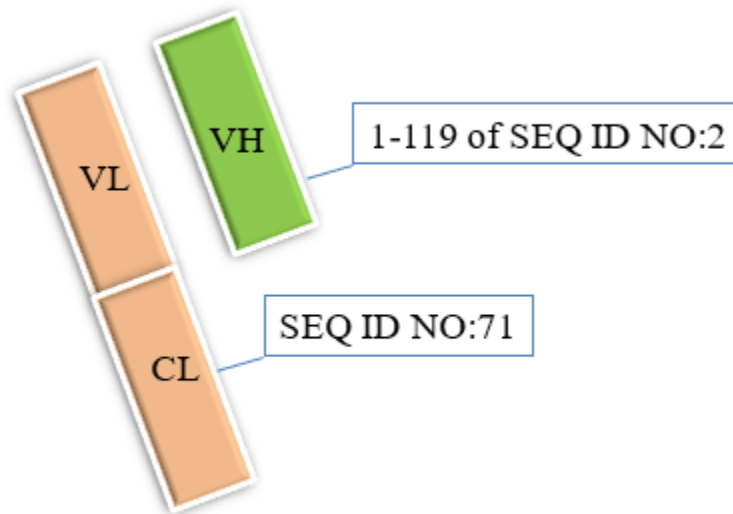
- Claim 1: “a targeting moiety comprising an antibody or antibody fragment thereof, comprising amino acids 1-119 of SEQ ID NO: 2 and the amino acid sequence of SEQ ID NO: 71, which specifically binds Epidermal Growth Factor Receptor (EGFR).”⁵
- Claim 9: “a targeting moiety comprising an antibody fragment which specifically binds Epidermal Growth Factor Receptor (EGFR) comprising a light chain domain comprising the amino acid sequence of SEQ ID NO: 71 and a variable heavy chain domain comprising amino acids 1-119 of SEQ ID NO: 2.”

Independent claims 1 and 9 both require targeting moieties comprising *antibody fragments* with these two claimed sequence components. Both independent claims thus require, at a minimum, just parts of a targeting moiety—*i.e.*, a targeting moiety that specifically binds EGFR and includes, but is not limited to, antibody fragments comprising amino acids 1-119 of SEQ ID NO: 2 (variable heavy chain domain) and

⁵ As explained below in this section, amino acids 1-119 of SEQ ID NO: 2 is referred to as the variable region of a heavy chain domain. EX1001, Fig. 3; EX1003, ¶97. SEQ ID NO: 71 is referred to as the full light chain domain in the '968 Patent, including both the variable region and constant region. EX1001, Fig. 3; EX1003, ¶98.

the amino acid sequence of SEQ ID NO: 71 (full light chain).⁶ EX1003, ¶¶117-18.

The figure below depicts the minimum requirements of this limitation:



Id., Fig.G (“VH” refers to the variable region of the heavy chain; “VL” and “CL” refer to the variable and constant regions, respectively, of the light chain).

There is no express disclosure of such an incomplete targeting moiety required by independent claims 1 and 9 anywhere in the ’968 Patent. *Id.*, ¶¶117-22. The first time this specific targeting moiety was referenced was when the patentee amended

⁶ Unlike claim 9, the targeting moiety of claim 1 also covers full-length antibodies and the two sequence components are not limited to the light chain domain or variable heavy chain domain. This section addresses the antibody fragment targeting moiety required by both independent claims. The lack of written disclosure of the integrated wholes of claims 1 and 9 is addressed in the next section.

the claims during prosecution of the application underlying the '968 Patent. EX1002, p.434; EX1003, ¶¶102-05. Beyond that amendment and the issued claims, there is no other explicit reference to this specific limitation anywhere in the disclosure of the '968 Patent. EX1003, ¶118. Indeed, there is no disclosure in the common specification of *any antibody fragment* with this portion of SEQ ID NO: 2 and the entirety of SEQ ID NO: 71, let alone an antibody fragment consisting of only these components. *Id.*, ¶119.

The '968 Patent also does not provide sufficient blaze marks to direct a POSA to the claimed subgenus requiring this incomplete targeting moiety. *Id.*, ¶¶94-99, 120-22. To arrive at the claimed subgenus, the POSA would have to start from this laundry list regarding a generic targeting moiety and make a myriad of selection steps without any direction or guidance from the disclosure to do so. While the common specification discloses the full sequences for both SEQ ID NO: 2 and 71, there are no blaze marks to arrive at a targeting moiety comprising specifically amino acids 1-119 of the full 601 amino acid sequence of SEQ ID NO: 2 paired with the full sequence of SEQ ID NO: 71. EX1003, ¶¶120-22.

The common specification discloses 124 sequences, including the full sequences for SEQ ID NOS: 2 and 71. *E.g.*, EX1001, 47:13-98:36 (table titled "Sequence Listing" and providing sequences for SEQ ID No: 1 through SEQ ID NO:

124); *id.*, 1:37-45 (referencing the sequence listing text file);⁷ EX1003, ¶¶82-84, 121. The common specification discloses the full sequence of SEQ ID NO: 71 in four places—in three of the Figures and in the “Sequence Listing” table. EX1001, Figs. 3, 14, 24; *id.*, 77:60-79:4; EX1003, ¶¶94-99. The common specification discloses the full sequence of SEQ ID NO: 2 in two separate places in the specification—Figure 3 and the same “Sequence Listing” table. EX1001, Fig. 3, 47:35-51. The claimed portion of SEQ ID NO: 2 is nowhere disclosed.

The sequence listing discloses the entire sequence for SEQ ID NO: 2 in an undifferentiated list of all 601 amino acids in the sequence.

```

SEQ ID NO: 2          moltype = AA  length = 601
FEATURE
source               Location/Qualifiers
                    1..601
                    mol_type = protein
                    organism = synthetic construct

SEQUENCE: 2
QVQLKQSGPG LVQPSQSLSI TCTVSGFSLT NYGVHWVRQS PGKGLEWLGV IWSGGNTDYN 60
TPFTSRLSIN KDNSKSQVFF KMNSLQSDNT AIYYCARALT YYDYEFAYWG QGTLVTVSAA 120
STKGPSVFPL APSSKSTSGG TAALGCLVKD YFPEPVTVSW NSGALTSGVH TPPAVLQSSG 180
LYSLSSVVTV PSSSLGTQTY ICNVNHKPSN TKVDKRVEPK SCDKTHTCPP CPAPELLGGP 240
SVFLFPPKPK DTLMISRTPE VTCVVVDVSH EDPEVKFNNY VDGVEVHNAK TKPREEQYNS 300
TYRVVSVLTV LHQDWLNGKE YKCKVSNKAL PAPIEKTISK AKGQPREPQV YTLPPSRDEL 360
TKNQVSLTCL VKGFYPSDIA VEWESNGQPE NNYKTTTPVL DSDGSFFLYS KLTVDKSRWQ 420
QGNVFSCSVM HEALHNHYTQ KSLSLSPGKG GGGSGGGGSG GGGSTIPPHV QKSVNNDMIV 480
TDNNGAVKFP QLCKFCDVRF STCDNQKSCM SNCSITSICE KPQEVCAVAV RKNDENITLE 540
TVCHDPKLPY HDFILEDAA S PKCIMKEKKK PGETFFMCSC SSDECNDNII FSEEYNTSNP 600
D                                                                 601

```

EX1001, 47:30-45; EX1003, ¶¶46, 82-84. Nothing in the sequence listing suggests taking only a portion of SEQ ID NO: 2, nor that only some portion of that sequence

⁷ The Sequence Listing table provides the same 124 sequences as the sequence listing file. EX1003, ¶83.

could be combined with SEQ ID NO: 71 to form a targeting moiety. EX1003, ¶¶120-22. Nor that, if that portion of SEQ ID NO: 2 and SEQ ID NO: 71 were combined, it would bind to EGFR. *Id.*, ¶¶120-22, 167-70.

While Figure 3 discloses a complete “fusion protein” that includes all of SEQ ID NO: 2 and all of SEQ ID NO: 71, plus other sequences, nothing in Figure 3 (provided below) provides a blaze mark to require only the portions now selected in the independent claims. EX1003, ¶¶94-99, 120-22.

Fusion proteins comprising Anti-EGFR1 antibody and Transforming growth factor-beta receptor II (TGF β -RII) Extracellular domain (ECD).

Anti-EGFR1 heavy chain + TGF β -RII ECD fusion amino acid sequence

(SEQ ID NO: 2):

QVQLKQSGPGLVQPSSQLSITCTVSGFSLTNYGVHWVRQSPGKGLEWLGVIWSSGNTDYNTPTFSR
LSINKDNSKSQVFFKMNSLQSNDAIYYCARALTYDYEFAYWGQGLTVTSAASTKGPSVFPLAP
SSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVPSSSLGTQ
TYICNVNHKPSNTKVDKRVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCV
VVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKAL
PAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTT
PPVLDSDGSFFLYSKLTVDKSRWQQGNVFCFSVMHEALHNHYTQKSLSLSPGK
GGGGSGGGSGGGGS TIPPHVQK SVNNDMIVTD NNGAVKFPQL CKFCDVRFST
CDNQKSCMSN CSITSICEKP QEVCVAVWRK NDENITLETV CHDPKLPYHD FILEDAASPK
CIMKEKKKPG ETFFMCSCSS DECNDNIIFS EYNTSNPD

Anti-EGFR1 light chain amino acid sequence (SEQ ID NO: 71):

DILLTQSPVILSVSPGERVSFSCRASQSIGTNIHWYQORTNGSPRLLIKYASESISGIPSRFSGSG
SGTDFTLINSVESEDIADYYCQNNNWPTTFGAGTKLELKRTVAAPSVFIFPPSDEQLKSGTASV
VCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKSDSTYLSSTLTLSKADYEKHKVYACEVTH
QGLSSPVTKSFNRGEC

Underlined: Anti-EGFR antibody variable region

Plain: Anti-EGFR antibody constant region

Italic: Linker

Bold: TGF β RII ectodomain

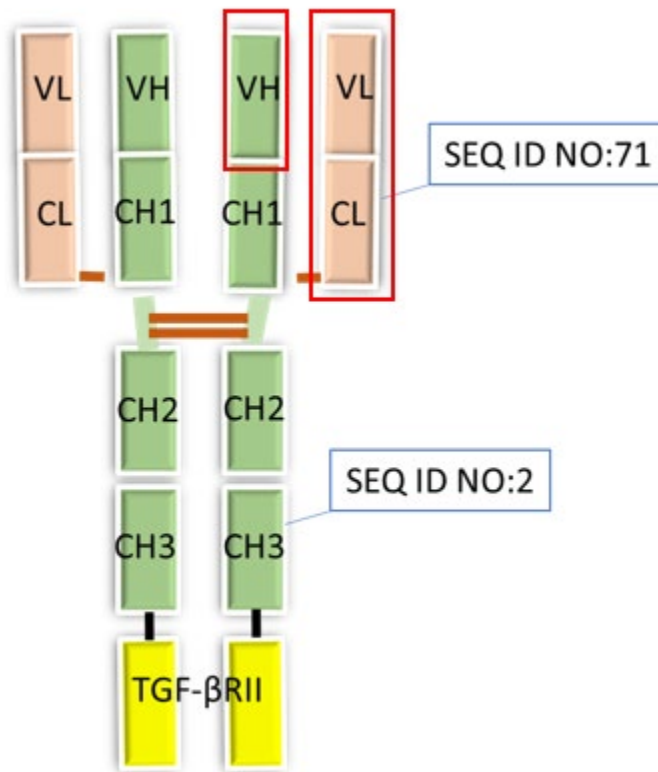
FIG. 3

EX1001, Fig. 3 (highlighted). The heading above SEQ ID NO: 2 in Figure 3 states “Anti-EGFR1 heavy chain + TGF β -RII ECD fusion amino acid sequence.” *Id.*, Fig. 3. The key at the bottom of Figure 3 states that “Underlined” means “Anti-EGFR antibody variable region.” *Id.* The first 119 amino acids in SEQ ID NO: 2 in Figure

3 (*i.e.*, amino acids 1-119) are underlined. *Id.*⁸ Beyond this, there is no further indication of amino acids 1-119 of SEQ ID NO: 2 as the variable region in the specification. Indeed, there is no mention of “amino acids 1-119 of SEQ ID NO: 2” anywhere in the specification. The first time the phrase “amino acids 1-119 of SEQ ID NO: 2” appeared was in the claims filed on September 12, 2024 with the continuation application that led to the '968 Patent. EX1002, pp.93-94.

Even if a POSA were to focus on just Figure 3 where SEQ ID NO: 2 is listed in its entirety for the first time, this figure discloses a targeting moiety that is a full-length antibody with *all* of SEQ ID NO: 2 paired with *all* of SEQ ID NO: 71, using a specific linker and immunomodulatory moiety connected in a specific alignment. EX1003, ¶¶94-99, 120-22. The fusion protein disclosed in Figure 3 is depicted below with the elements required by this limitation annotated in red:

⁸ The Sequence Listing table provides numbering for the sequences. EX1001, 47:35.



EX1003, Fig.C (annotated). Nothing in Figure 3 or elsewhere suggests to a POSA to only pick part of SEQ ID NO: 2 (the claimed amino acids 1-119) and pair it with entirety of SEQ ID NO: 71. To the contrary, Figure 3 discloses (according to its heading) “Fusion proteins comprising Anti-EGFR antibody and Transforming growth factor-beta receptor II (TGFB-RII) Extracellular domain (ECD).” Figure 3 thus requires the entirety of SEQ ID NO: 2 and SEQ ID 71 and nowhere suggests a POSA could take only a portion of these sequences.

Instead of blaze marks directing toward the claim, the common specification simply includes a laundry list of potential options among its broad disclosures. The

broad genera and laundry lists described in the common specification are insufficient to constitute the blaze marks needed to direct a POSA to specifically amino acids 1-119 of SEQ ID NO: 2 paired with the full sequence of SEQ ID NO: 71. *E.g., Regents*, 61 F.4th at 1358 (lack of written description even where the priority documents blaze a trail “that runs close by the later-claimed tree,” but “do[] not direct one to the proposed tree in particular, and do[] not teach the point at which one should leave the trail to find it.” (citation omitted)). Indeed, the ’968 Patent never ties any of its optional generic language of possible antibody fragments to Figure 3, SEQ ID NO: 2, or SEQ ID NO: 71, let alone amino acids 1-119 of SEQ ID NO: 2 as required by the independent claims.

Contrary to the required blaze marks to the claimed targeting moiety, the patent contains general disclosures that would cover a nearly uncountable number of embodiments. EX1003, ¶¶78-93, Appx.B. For example, the ’968 Patent broadly explains that “[t]he targeting moiety can be an antibody, antibody fragment, scFv, Fc-containing polypeptide, fusion antibody, polypeptide, peptide, aptamer, ligand, nucleic acid, or any combination thereof.” EX1001, 27:40-43; EX1003, ¶85. With such a disclosure, the ’968 Patent includes a vast, uncountable number of targeting moieties. EX1003, ¶86.

The broad general disclosures do not direct a POSA to include only the sequence and portions of a sequence as the “targeting moiety.” Instead, the optional

concept of what the targeting moiety can include is only generally disclosed. The common specification uses the word “include(s)” over 235 times. The specification specifically states over 60 different times that “the targeting moiety includes” in one aspect or another. *E.g.*, EX1001, 2:43-47, 3:13-17, 3:35-38.

Moreover, while both independent claims cover a targeting moiety that is a fragment of an antibody, no such examples are disclosed. EX1003, ¶¶81, 84, 120-22. Out of the 35 specific (and only prophetic) examples of fusion proteins containing antibody targeting moieties disclosed in the common specification, each one is made up of a ***full-length antibody***. EX1003, ¶¶81, 84, 120-22, Appx.C. Put differently, the specification provides no specific examples, even prophetic examples, of ***any antibody fragments*** used as the targeting moiety, ***only full-length antibodies***. *Id.* For each of these examples, there is also no “fragment thereof” or similar language used in the headings describing the sequences referenced in the respective figure. This is in contrast to other figures that use such language. *Contrast*, Figs. 1A, 1C, 12, 22, 31, 40 (figures of immunomodulatory proteins specifically referencing “or a fragment thereof”).

Moreover, such an interpretation that these broad, optional disclosures of the common specification could provide direction to arrive at specific optional items themselves has been rejected by one of the named inventors. Dr. Atul Bedi—the named inventor of the ’968 Patent and its ancestors—provided an affidavit to try to

overcome a rejection for an application in a different patent family. EX1044, pp.1-

2. In that affidavit, the named inventor of the '968 Patent described the disclosures of the '524 Patent, which shares a common specification with the '968 Patent. Specifically, Dr. Bedi agreed with the examiner that the "524 [Patent] does not disclose an [sic] anti-PD1 antibody." *Id.*

The common specification of the '524 and '968 Patents contains broad, optional disclosures that the targeting moiety can be made up of an antibody that binds PD-1 (*i.e.*, an anti-PD-1 antibody). *E.g.*, EX1015 ('524 Patent), 2:55-57 ("In one aspect, the targeting moiety includes an antibody, antibody fragment, or polypeptide that specifically binds to Programmed Death-1 (PD-1)"); EX1001 ('968 Patent), 3:22-24 (same); EX1015 ('524 Patent), 30:6-12 ("Examples of antibodies which can be incorporated into compositions and methods disclosed herein include, but are not limited, to antibodies such as ... MDX-1 106 (anti-PD1 mAb)");⁹ EX1001 ('968 Patent), 31:13-19 (same). The named inventor of the '968 Patent agreed that such broad and optional language in the common specification is insufficient for disclosing an anti-PD-1 antibody itself. In like manner, the broad and optional disclosures in the common specification concerning

⁹ "mAb" stands for monoclonal antibody. EX1003, ¶¶52-54.

targeting moieties are insufficient to disclose or provide blaze marks to the incomplete and partial targeting moiety required by the independent claims.

In sum, to arrive at this limitation of a targeting moiety comprising amino acids 1-119 of SEQ ID NO: 2 and the entirety of SEQ ID NO: 71 that binds EGFR, a POSA would need to make a myriad of selection steps from the broad generic disclosure, without guidance or direction to do so. EX1003, ¶¶78-93, 117-22. A POSA would have to start from a generic disclosure of potential targets and a laundry list of options regarding a generic targeting moiety. The POSA would then have to select Figure 3 out of the 35 figures providing prophetic examples of fusion proteins containing antibody targeting moieties. Then, a POSA would need to further select only amino acids 1-119 of SEQ ID NO: 2 but still combine it with all of SEQ ID NO: 71 while ignoring that Figure 3 discloses a full antibody, a linker, and an immunomodulatory moiety combined together in a specific structure. This is far from the blaze marks required to arrive this limitation. *E.g., Seagen*, 160 F.4th at 1332 (“no adequate blaze marks that would lead a [POSA] to the [claimed] subgenus”); *Purdue Pharma L.P. v. Faulding Inc.*, 230 F.3d 1320, 1326 (Fed. Cir. 2000) (“[O]ne cannot disclose a forest in the original application, and then later pick a tree out of the forest and say here is my invention.”).

As such, independent claims 1 and 9 of the '968 Patent are unpatentable for lack written description. Claims 2-8, which depend from claim 1, are unpatentable for lack of written description for the same reasons. EX1003, ¶¶123, 135-46.

2. No Written Description for All of the Claim Requirements Together (All Claims)

All claims suffer from a separate, independent failure to satisfy the written description requirement. Written description does not only require support for each individual limitation in the claims, but requires the specification provide support for the entirety of the claimed invention—*i.e.*, the ***combination*** of elements of each claim as ***an integrated whole***. *Flash-Control*, 2021 WL 2944592, at *3 (“the specification must present each claim as an ‘integrated whole’” (citation omitted)); *Novozymes*, 723 F.3d at 1349 (written description analysis requires “[t]aking each claim ... as an integrated whole rather than as a collection of independent limitations”). The challenged claims are also unpatentable for lack of written description when taking each claim as an integrated whole. Indeed, the lack of written description for the challenged claims is highlighted when assessing the combinations of limitations required by each of the claims, rather than as collections of independent limitations. There is no express disclosure of, and no blaze marks that would lead a POSA to arrive at, the ***specific combination*** of all the limitations required by each claim. Instead, the '968 Patent provides precisely the type of broad generic disclosures with a laundry list of options that the Federal Circuit has

repeatedly held does **not** satisfy the written description requirement for narrower subgenus claims such as those included in the patent. *Seagen*, 160 F.4th at 1330; *Flash-Control*, 2021 WL 2944592, at *4 (“cannot show written description support by picking and choosing claim elements from different embodiments that are never linked together in the specification.”).

(a) No Written Description for Integrated Whole of Independent Claim 1

The '968 Patent fails to provide written description support for the combination of limitations required by claim 1. As a whole, claim 1 is directed to a subgenus that requires (i) a targeting moiety comprising a full-length antibody or antibody fragment thereof, which comprises amino acids 1-119 of SEQ ID NO: 2 and the full sequence of SEQ ID NO: 71, which specifically binds EGFR and (ii) an immunomodulatory moiety comprising the amino acid sequence of SEQ ID NO: 87. The figure below illustrates those three sequence components that are required by claim 1:



EX1003, Fig.H.

As discussed above (Section VI.A.1), there is no express disclosure of, or blaze marks leading a POSA to, the antibody pieces required by this claim—a targeting moiety comprising amino acids 1-119 of SEQ ID NO: 2 and the full sequence SEQ ID NO: 71. For the same reasons, when adding in the additional limitation of an immunomodulatory moiety comprising SEQ ID NO: 87 required by the full claim, the lack of express disclosure and blaze marks applies with even more force. EX1003, ¶¶124-34.

Adding an additional limitation introducing an immunomodulatory moiety to the integrated whole adds another step to the myriad of steps the POSA would need to make to arrive at the claimed combination of claim 1. *Id.* As with its disclosures of targeting moieties, the '968 Patent likewise broadly discloses genera of immunomodulatory moieties. *Id.*, ¶87, Appx.B. The common specification states:

As used herein, “immunomodulatory moiety” refers to a ligand, peptide, polypeptide, or Fc-containing polypeptide that binds a specific component of a regulatory T cell, myeloid suppressor cell, or dendritic cell and modulates the number or function of Tregs or myeloid suppressor cells.

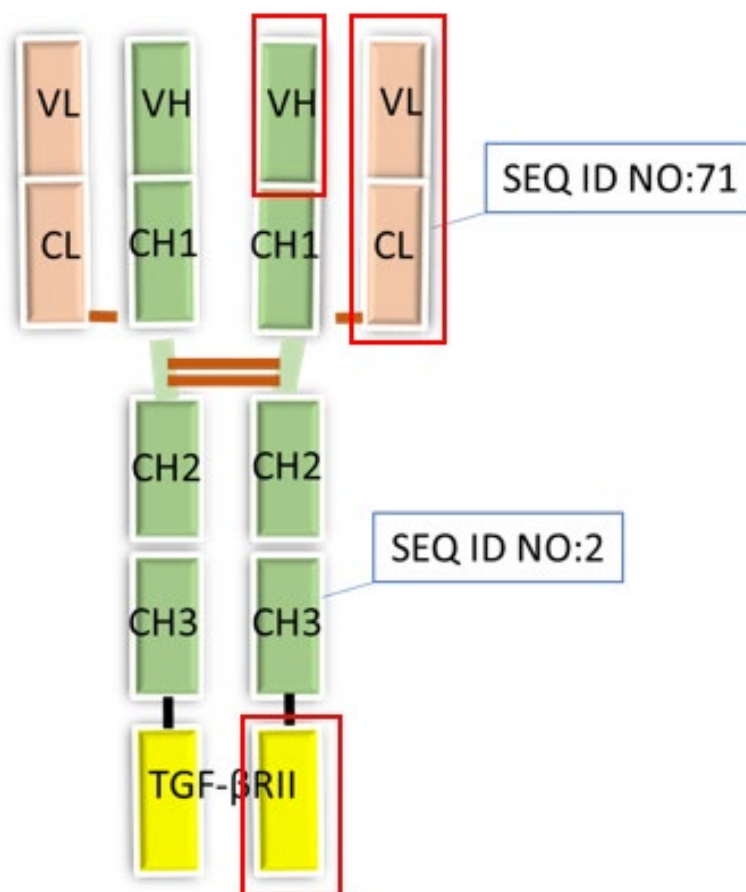
EX1001, 31:43-48. The specification specifically states over 60 times different items that “the immunomodulatory moiety includes” in one aspect or another. *E.g.*, EX1001, 4:5-11, 4:12-14. The breadth of the disclosure of potential immunomodulatory moieties is further evidenced by the at least 23 possible immunomodulatory moieties that Dr. Hale counted in a portion of the common specification alone. EX1003, ¶89. From Dr. Hale’s conservative estimate, the common specification’s broad disclosures gives rise to a minimum of 227,332 candidate molecules comprising a targeting moiety and an immunomodulatory moiety, not including fragments or variables thereof. *Id.*, ¶¶86-90, Appx.B.¹⁰ The specification fails to provide blaze marks leading to the specific minimum integrated whole required by claim 1. For this additional reason, claim 1 is unpatentable for lack of written description.

¹⁰ Adding to the complexity, the specification suggests immunomodulatory moieties can also be targeting moieties. EX1003, ¶88.

Beyond the minimum integrated whole, the specification also fails to adequately describe the breadth of the subgenus. As discussed more below (Section VI.B.1.(a)), the breadth of this subgenus is reflected by claim 1 only requiring the presence of three structural components—a targeting moiety comprising (i) amino acids 1-119 of SEQ ID NO: 2 and (ii) the full sequence of SEQ ID NO: 71, with (iii) an immunomodulatory moiety comprising the amino acid sequence of SEQ ID NO: 87—and the functional limitation of the targeting moiety specifically binding EGFR. EX1003, ¶¶124-26. Moreover, the claimed targeting moiety ranges from a full-length antibody to any type of antibody fragment thereof.

The only species disclosed in the common specification that falls within the large subgenus of claim 1 is that disclosed in Figure 3. *Supra* Section VI.A.1 (providing full figure). As seen in Figure 3, Figure 3 discloses a fusion protein with (a) a targeting moiety that is a ***full-length antibody*** comprising ***all*** of SEQ ID NO: 2 and ***all*** of SEQ ID NO. 71; (b) an immunomodulatory moiety comprising SEQ ID NO: 87; (c) a specific “Linker;” and (d) the immunomodulatory moiety connected

to the end of SEQ ID NO: 2 by the Linker.¹¹ EX1003, ¶¶94-99, 131-34. The fusion protein disclosed in Figure 3 is depicted below:



¹¹ Although SEQ ID NO: 87 is not identified explicitly in Figure 3, the bolded sequence at the end of SEQ ID NO: 2 is the same sequence as SEQ ID NO: 87. EX1003, ¶97.

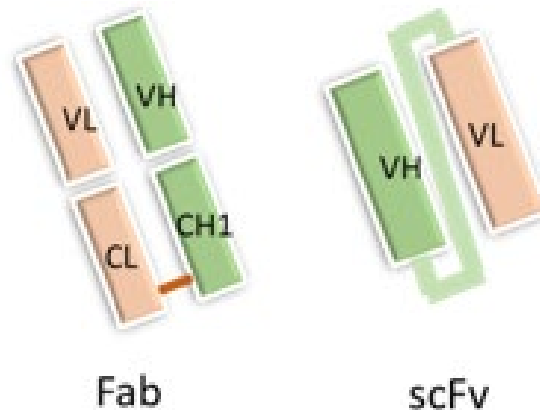
EX1003, Fig.C (annotated). The disclosure of this single species is not enough to describe the full breadth of the claim 1, nor to direct a POSA to select only the three claimed portions of the figure. EX1003, ¶¶94-99, 129-34. Claim 1 comprises only the three sequence components annotated in red in the above figure. In comparison, Figure 3 only discloses a *full-length antibody*. *Id.* Indeed, there is no disclosure of *any antibody fragment* as a targeting moiety with the components required by claim 1 in the common specification. *Id.* Thus, the '968 Patent is unpatentable for lack of written description for the additional reason of failing to adequately describe the full breadth of the subgenus of claim 1.

(b) No Written Description for Integrated Whole of Dependent Claim 2

Claim 2 depends from claim 1 and limits the targeting moiety to “an antibody fragment selected from a Fab or scFv.” The '968 Patent fails to provide written description support for the integrated whole of claim 2. The same reasons discussed above regarding the lack of written description for the integrated whole of claim 1 apply in greater force to the integrated whole of claim 2. There is no express disclosure or blaze marks in the '968 Patent that would lead a POSA to the specific combination of limitations required by claim 2. EX1003, ¶¶135-37.

Claim 2 limits the targeting moiety of the molecule of claim 1 to one of two specific types of antibody fragment—a Fab (fragment antigen-binding fragment) or a scFv (single-chain variable fragment). As depicted in the figure below, a Fab (left)

consists of one complete light chain and the variable and first constant domains of one heavy chain, and a scFv (right) consists of only the variable regions of the heavy and light chain domains joined by a linker peptide.



EX1003, Fig.B (excerpted). There is no express disclosure in the '968 Patent of a Fab or scFv with the elements required by claim 2; indeed, there is no example at all of a targeting moiety that is a Fab or scFv. EX1003, ¶¶135-37.

The lack of blaze marks discussed above with claim 1 applies with even more force to claim 2, which further narrows the claims to require one of two specific types of antibody fragments. All of the examples, including prophetic examples, of fusion proteins containing antibody targeting moieties disclosed in the common specification are made up of a *full-length antibody*, not an antibody fragment, let alone a Fab or scFv. *Id.* Thus, dependent claim 2 is unpatentable for lack of written description of the integrated whole of this claim.

(c) No Written Description for Integrated Wholes of Dependent Claims 3, 4, and 8

There is no written description support for the combinations of limitations required by claims 3, 4, and 8 for the same reasons discussed above for claims 1 and 2. Claim 3 recites “The molecule of claim 2, wherein the antibody fragment comprises a light chain domain or a variable heavy chain domain.” Claims 4 and 8 each depend directly from claim 3 and recite the following, respectively, “wherein the antibody fragment comprises a light chain domain comprising the amino acid sequence of SEQ ID NO: 71” (claim 4) and “wherein the variable heavy chain domain comprises amino acids 1-119 of SEQ ID NO: 2” (claim 8).

Claim 3 thus requires that the targeting moiety antibody fragment of claim 2 comprise a light chain or a heavy chain (but not both). EX1003, ¶¶138-39. Claim 4 requires if claim 3 has a light chain domain, that it comprises SEQ ID NO: 71. Claim 8 requires if claim 3 has a variable heavy chain domain, that it comprises amino acids 1-119 of SEQ ID NO: 2. *Id.* There is no express disclosure in the '968 Patent of a Fab or scFv with the elements required by claims 3, 4, or 8. *Id.* To the extent these claims are not improperly dependent or indefinite for the reasons below (Section VII), the lack of blaze marks discussed above with claims 1 and 2 apply with even more force to claim 3, 4, and 8.

(d) No Written Description for Integrated Wholes of Dependent Claims 5-7

There is no written description support for the combinations of limitations required by each of dependent claims 5-7. For the same reasons discussed above with claims 1-4, when adding in the additional limitations required by each of claims 5-7, the lack of express disclosure and blaze marks is amplified. Adding in each of the additional limitations required by the these claims adds even more steps the POSA would need to make to arrive at the claimed combinations of these claims without sufficient blaze marks in the specification to direct a POSA to make these choices. EX1003, ¶¶140-46.

Dependent Claim 5: Claim 5 requires that the molecule of claim 4 “further compris[e] a polypeptide linker comprising the amino acid sequence of SEQ ID NO: 104.” There is no express disclosure or blaze marks to the integrated whole required by claim 5. EX1003, ¶¶140-43. The choice of which linker to use for the fusion protein is another choice the POSA would need to make to arrive at this claimed combination. *Id.*, ¶¶87, 140-43, Appx.B. The specification identifies numerous linkers for the prophetic fusion proteins. *Id.* In fact, as for this specific linker of SEQ ID NO: 104, the specification repeatedly states that “the linker GGGGSGGGGSGGGGS SEQ ID NO: 104” “is optional and can be replaced with” SEQ ID NO: 105 “or another linker sequence well known in the art.” *E.g.*, EX1001, 8:27-30, 9:40-43, 10:35-38, 11:12-15, 11:36-39. The specification denotes the

breadth of possible linkers that could be used, which are optional and can be replaced with any linker well known in the art. EX1003, ¶¶141-43, Appx.B.

Moreover, claim 5 does not specify what, if anything, this linker is attached to. A POSA would understand the scope of this claim to include molecules which have a linker peptide that is independent of the other three claimed sequence components as well as the linker peptide being attached to any one or two of them at different orientations. EX1003, ¶¶140-43.

Dependent Claims 6 and 7: Claim 6 depends directly from claim 5 and further requires “wherein the light chain domain comprising the amino acid sequence of SEQ ID NO: 71 is fused to an N-terminus of the polypeptide linker comprising the amino acid sequence of SEQ ID NO: 104.” Claim 7 depends directly from claim 6 and further requires “wherein the immunomodulatory moiety comprising the amino acid sequence of SEQ ID NO: 87 is fused to a C-terminus of the polypeptide linker comprising the amino acid sequence of SEQ ID NO: 104.” As discussed above with claim 5, dependent claims 6 and 7 require a POSA to arrive at even more specific structural limitations of what and where the linker of claim 5 is connected. EX1003, ¶¶144-46.

The disclosures of the common specification do not direct the POSA to the integrated wholes of these claims, particularly an antibody fragment with a linker linked to the light chain. *Id.* The common specification does not disclose a single

example, not even a prophetic example, of a fusion antibody fragment linked through the light chain. *Id.* In particular, the fusion protein disclosed in Figure 3 of the common specification is a ***full-length*** antibody targeting moiety that is linked through the ***heavy chain***. EX1001, Figure 3; EX1003, Fig.C, ¶¶132-33.

The lack of blaze marks discussed regarding the claims above applies even more so for the additional limitations required by dependent claims 5-7. Claims 5-7 are therefore unpatentable for lack of written description of the combination of limitations required by each claim.

(e) No Written Description for Integrated Whole of Independent Claim 9

There is no written description support for the combination of limitations required by independent claim 9. Claim 9 requires many of the elements of claim 1 as narrowed by claims 5-7, and lacks written description for similar reasons. Claim 9 requires: (a) a targeting moiety antibody fragment that binds EGFR comprising a light chain domain comprising SEQ ID NO: 71 and a variable heavy chain domain comprising amino acids 1-119 of SEQ ID NO: 2; (b) an immunomodulatory moiety comprising SEQ ID NO: 87; (c) a polypeptide linker of SEQ ID NO: 104 that is connected through a specific orientation to the light chain, as depicted in the following figure:



EX1003, Fig.I, ¶¶147-49.

Claim 9 is similar to claim 1 by requiring the presence of the three same sequence components for the targeting and immunomodulatory moieties, but is narrower in several aspects including by limiting the targeting moiety to only antibody fragments, not full-length antibodies. *Id.* Similar to the limitations in dependent claims 5-7, claim 9 is also narrower than claim 1 by requiring specific orientations for the claimed components, including requiring a specific linker linked through the light chain. There is no express disclosure of the integrated whole of claim 9 anywhere in the '968 Patent. EX1003, ¶¶150-52. Even Figure 3 does *not* fall within the scope of claim 9. Additionally, claim 9 adds in a single claim the

myriad of steps a POSA would need to consider and make discussed above for claim 1 and claims 5-7 as well as additional steps. *Id.*, ¶¶150-54. Indeed, as discussed above, the common specification does not provide a single example of a targeting moiety comprising an antibody fragment of any kind (Sections VI.A.1, VI.A.2.(a)) nor any example of a light chain-linked antibody construct (Section VI.A.2.(d)-(e)). The lack of blaze marks leading a POSA to the claimed combination of claim 9 is thus even greater than the claims discussed above individually. EX1003, ¶¶147-54. Claim 9 is therefore unpatentable for lack of written description of the combination of limitations required by the claim.

B. Ground 2: All Claims Are Unpatentable for Lack of Enablement Under § 112(a)

All claims of the '968 Patent fail to meet the enablement requirement of § 112(a).

Section 112(a) requires that the specification must describe “the manner and process of making and using [the invention], in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains ... to make and use the same.” 35 U.S.C. § 112(a).

To satisfy this requirement, “the specification must enable the full scope of the invention as defined by its claims,” allowing for “a reasonable amount of experimentation.” *Amgen v. Sanofi*, 598 U.S. 594, 610, 612 (2023). “Put differently, ‘[t]o be enabling, the specification of a patent must teach those skilled in the art how

to make and use the full scope of the claimed invention without undue experimentation.”” *Seagen*, 160 F.4th at 1332 (citation omitted). “The more one claims, the more one must enable.” *Amgen*, 598 U.S. at 610. “[A] patentee ‘cannot simply rely on the knowledge of a [POSA] to serve as a substitute for the missing information in the specification.’” *Enzo Life Scis., Inc. v. Roche Molecular Sys., Inc.*, 928 F.3d 1340, 1348 (Fed. Cir. 2019) (citation omitted). The Supreme Court has repeatedly addressed enablement to “reinforce the simple statutory command. If a patent claims an entire class ..., the patent's specification must enable a person skilled in the art to make and use ***the entire class***”—i.e., “the specification must enable ***the full scope*** of the invention as defined by its claims.” *Amgen*, 598 U.S. at 610.

Here, the '968 Patent discloses the concept of certain fusion proteins with little to no actual demonstration of which ones to make, how to make them, or whether they will work for their claimed function of binding a particular target (EGFR). For the subgenus of claim 1, the '968 Patent discloses at best one prophetic embodiment—the fusion protein of Figure 3 that is made up of a full-length antibody including the required sequence components. This singular, limited disclosure is insufficient to enable a POSA how to make and use ***the full scope*** of the claimed invention, which is much broader, without undue experimentation. The lack of enablement is even more problematic for claims 2-9, which only cover certain

targeting moieties made up of antibody fragments, not full-length antibodies. The '968 Patent does not disclose, let alone enable a POSA how to make and use, even a single example of the claimed antibody fragments. Thus, the '968 Patent does not enable a POSA how to make and use the full scope of the claimed invention without undue experimentation. EX1003, ¶¶155-86. An analysis of the optional “*Wands* factors” compels the same conclusion.¹²

1. Independent Claim 1 Is Not Enabled

The '968 Patent does not enable the subgenus of claim 1, which claims a diverse set of “isolated molecule[s].” Instead, the '968 Patent provides no clear

¹² Although not required, enablement may be assessed using the *Wands* factors, which consider: “(1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims.” *In re Wands*, 858 F.2d 731, 737 (Fed. Cir. 1988); *Idenix Pharms. LLC v. Gilead Scis., Inc.*, 941 F.3d 1149, 1156 (Fed. Cir. 2019) (listing the *Wands* factors). “[I]t is not necessary that a court review all the *Wands* factors” to assess enablement; “[t]hey are illustrative, not mandatory.” *Amgen, Inc. v. Chugai Pharm. Co.*, 927 F.2d 1200, 1213 (Fed. Cir. 1991).

guidance or working examples of how to produce the claimed fusion antibodies nor how to identify whether they meet the functional limitation of binding EGFR. From the earliest claimed priority date to the present, the manufacture of fusion proteins remains difficult and unpredictable.

**(a) Diverse Subgenus of “Isolated Molecule[s]” Are Claimed
(*Wands* Factor 8)**

As discussed above, because claim 1 is limited to three structural sequences and the functional limitation that the targeting moiety binds to EGFR, it encompasses a substantial subgenus—all molecules, no matter the connections or orientations that contain these structures. That is, claim 1 is directed to a substantial subgenus of “isolated molecule[s]” that require (i) a targeting moiety comprising a full-length antibody or antibody fragment thereof, which comprises amino acids 1-119 of SEQ ID NO: 2 and the full sequence of SEQ ID NO: 71, which specifically binds EGFR and (ii) an immunomodulatory moiety comprising the amino acid sequence of SEQ ID NO: 87. Any molecule with these three components—two claimed sequences for the targeting moiety and one claimed sequence for the immunomodulatory moiety—and the functional limitation that the targeting moiety specifically bind EGFR is covered. EX1003, ¶¶124-26, 162-63. This is illustrated in the following figure:

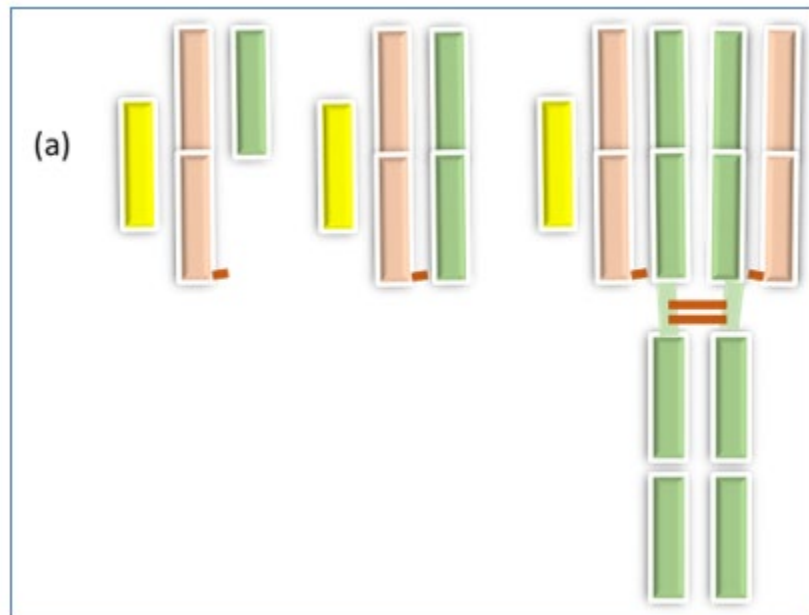


EX1003, Fig.H.

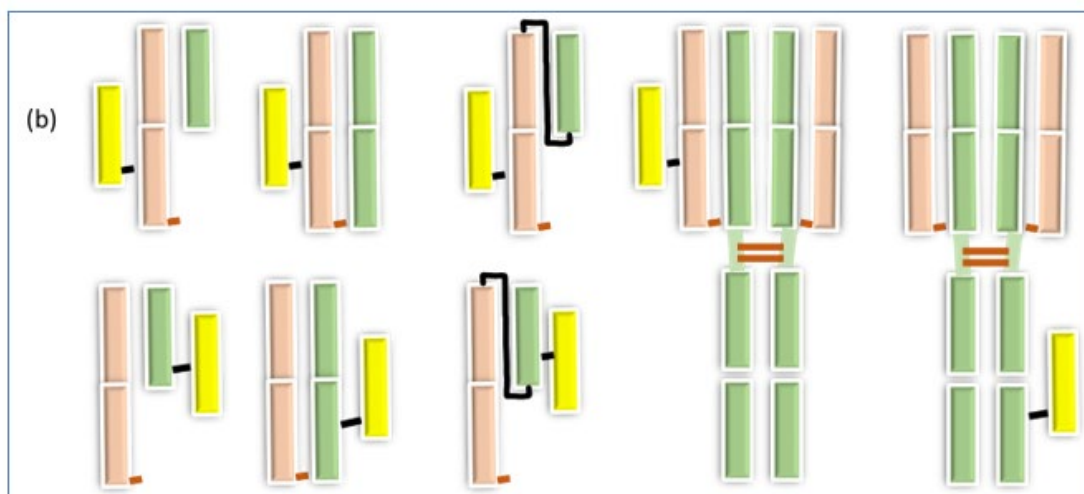
An immense number of “isolated molecule[s]” are covered by this claim. For example, the targeting moiety limitation alone covers a *full-length antibody* to *any antibody fragment*. This broad range of targeting moieties includes, for instance, various forms of intact antibodies, fragment antigen-binding (Fab) regions, molecules that include multiple separate peptides, molecules where the various separate peptides are linked by covalent bonds, and molecules where the various separate peptides are variously fused together in different orientations. EX1003, ¶¶162-63. Further, the orientation of the claimed components is nowhere specified in claim 1, and as such each of the above types of molecules could be assembled in several different ways that would be covered under the claim. Indeed, claim 1 is so broad as to allow the components to be associated in essentially any random orientation.

To demonstrate the breadth of claim 1, Dr. Hale provides just a sampling of the type of molecules covered by claim 1. EX1003, ¶¶162-63, Fig.K. As Dr. Hale describes and provides exemplary depictions of, these include:

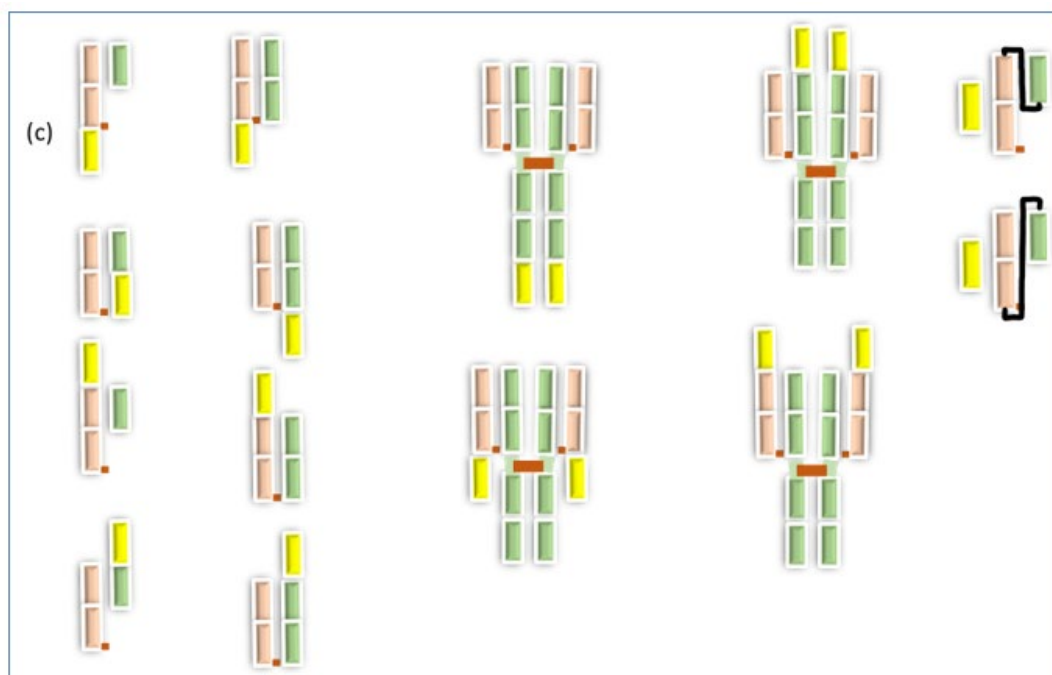
- (a) Molecules where the three claimed sequence components exist as three polypeptides (*i.e.*, amino acid chains, the basic structural unit of proteins);



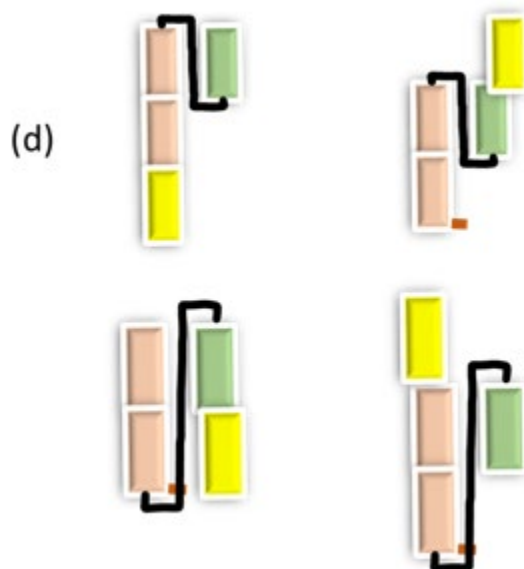
- (b) Molecules where the three claimed sequence components exist as polypeptides which are chemically bound together;



- (c) Molecules where the three claimed sequence components exist as two polypeptides, where two of the three the claimed components are genetically fused together into a continuous polypeptide chain using any number of different genetic linkers, or no linker at all; and



- (d) Molecules where all three of the claimed components exist as one polypeptide genetically fused together using any number of different genetic linkers, or no linker at all.



Id. These examples represent just one high-level structuring of the types of the molecules that fall within the scope of claim 1. Each of these subclasses include further subtypes of molecules distinguishable by how the claimed components are variously arranged, how they are fused or attached together (or not), and what other subunits the molecule contains. *Id.*, ¶¶162-63.

The breadth of claim 1 is further emphasized by amendments made during prosecution, the surrounding issued claims, and broad statements in the specification describing the claimed components. First, during prosecution of the '968 patent, the patentee specifically amended claim 1 to remove the requirement of “a targeting moiety fused with the immunomodulatory moiety.” EX1002, p.434. This further

demonstrates that claim 1 does not require the claimed components be fused together; rather, claim 1 covers various associations of the claimed components so long as they are isolatable as a molecule

Second, the surrounding claims demonstrate the breadth of independent claim 1. Claims 4 and 8, which depend indirectly from claim 1, specify that the antibody fragment targeting moiety comprises a light chain domain comprising amino acid sequence SEQ ID NO: 71 and a variable heavy chain domain comprising amino acids 1-119 of SEQ ID NO: 2, respectively. To be properly dependent, claims 4 and 8 must add a further limitation. 35 U.S.C. § 112(d). As such, these two claimed sequence components in claim 1 comprise more than just these sequences structurally limited as a light chain and a variable heavy chain domain, respectively. This is further evidenced by comparing independent claim 1 to independent claim 9, with the latter requiring the two claimed sequence components have the structural limitations added to claim 1 by dependent claims 4 and 8. *Compare with* '968 Patent, claim 9 (independent claim requiring “a light chain domain comprising the amino acid sequence of SEQ ID NO: 71 and a variable heavy chain domain comprising amino acids 1-119 of SEQ ID NO: 2”).

Third, as noted above (Section VI.A.2.(a)), the '968 Patent broadly defines the terms “targeting moiety” and “immunomodulatory moiety” and repeatedly states broad genera of what these moieties can include in one aspect or another. By way

of example, the '968 Patent notes that in certain embodiments, the targeting moiety can be a “chimeric” antibody. EX1001, 34:23-39, 34:61-35:9, 35:16-30. “A chimeric antibody combines DNA encoding regions from more than one type of species. For example, a chimeric antibody may derive the variable region from a mouse and the constant region from a human.” *Id.*, 35:18-21. The '968 Patent also explains that “[t]he antibody may be monospecific, bispecific, trispecific, or of greater multispecificity.” *Id.*, 34:58-60. The breadth and diversity of claim 1 is further exemplified by the antibody components ranging from a single species to combination of parts from different species and ranging from monospecific to multispecificity. EX1003, ¶163.

The breadth of claim 1 supports the lack of enablement for this claim. *Id.*, ¶¶162-63, 174-76. Indeed, “[t]he more one claims, the more one must enable.” *Amgen*, 598 U.S. at 610.

(b) Producing the Claimed “Isolated Molecules” and Identifying Whether They “Specifically Bind [EGFR]” Is Unpredictable and the '968 Patent and the Prior Art Provide No Guidance to the POSA to Navigate that Uncertainty (*Wands* Factors 2-7)

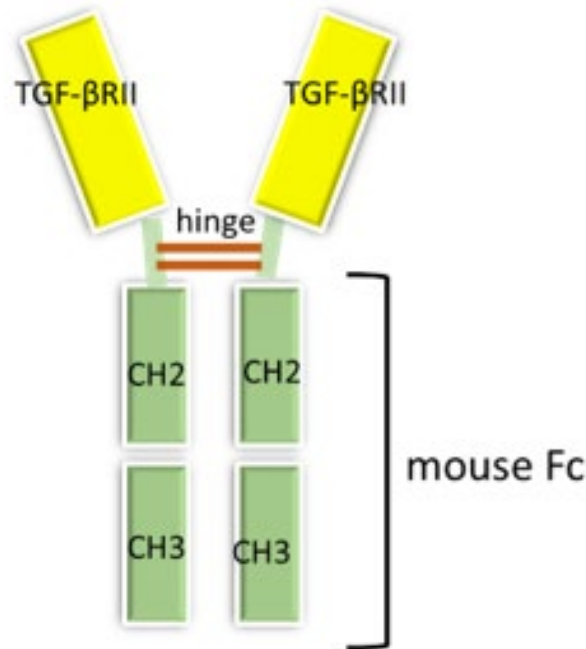
The '968 Patent provides no clear guidance to a POSA that would enable them to make the entire genus of isolated molecules claimed in claim 1, particularly in light of *Wands* factors 2-7. The additional *Wands* factors direct consideration of “(2) the amount of direction or guidance presented, (3) the presence or absence of

working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art.” *Wands*, 858 F.2d at 737. Specifically, the ’968 Patent provides no examples or clear guidance on (i) how to produce any of the claimed molecules or (ii) how to discern if any such molecules are capable of specifically binding EGFR. Moreover, its attempts to refer the POSA to known methods in the art creates more uncertainty than clarity.

i. Lack of Clear Guidance on, and Unpredictability of, Producing the Claimed “Isolated Molecules”

First, the ’968 Patent provides no working examples or clear guidance on *how to make* any of the molecules covered by the diverse subgenus of claim 1. Of the examples of fusion proteins in the ’968 Patent, only one is described as actually having been made—the TGFβRII:Fc fusion protein in Example 1, which bears no relation to the molecules claimed in claim 1. Otherwise, all of the other examples of fusion proteins are prophetic with no evidence in the specification that they were actually made. Even more problematic, the ’968 patent does not disclose how to make any of the fusion proteins.

The ’968 Patent discloses only a single working example of a fusion protein, “a soluble chimeric protein comprising the extracellular domain of TGFβRII and the Fc portion of the murine IgG1 heavy chain (c).” EX1001, 40:42-44; EX1003, ¶¶160-61. This example is depicted in the following figure:



EX1003, Fig.J.

TGFβRII:Fc bears almost no relation to the components claimed in claim 1 of the '968 Patent. EX1003, ¶¶160-61. The TGFβRII:Fc fusion protein comprises a TGFβRII extracellular domain fused to a Fc portion of a mouse IgG heavy chain. *Id.* This fusion protein does **not** include an antibody targeting moiety as required by claim 1, and indeed lacks an antibody light chain sequence altogether. *Id.* This fusion protein has no relation to components required by claim 1 beyond the shared use of the TGFβRII extracellular domain. Additionally, TGFβRII:Fc suggests fusing a TGFβRII extracellular domain to a mouse IgG heavy chain Fc sequence, while no heavy chain Fc sequence is required by claim 1. The '968 Patent fails to describe at any level how to actually make the TGFβRII:Fc fusion protein, or even disclose its

source. *Id.* As such, the '968 Patent fails to provide any working examples of any isolated molecule within the immense subgenus of claim 1.

Beyond this singular disclosure of a working example of an unrelated fusion protein, the '968 Patent provides *no examples*, not even prophetic examples, of any type of antibody fragment comprising amino acids 1-119 of SEQ ID NO: 2 and SEQ ID NO: 71, as required by claim 1. EX1003, ¶¶157-64, 184-85. Aside from the TGFβRII:Fc fusion protein, all of the exemplary fusion molecules disclosed in the '968 Patent are prophetic examples. *Id.*, ¶¶80-84, 160, 185. Moreover, all of the exemplary fusion molecules that include antibody targeting moieties are full-length antibodies. *Id.* Claim 1 covers molecules including a targeting moiety comprising a full-length antibody to any antibody fragment thereof. Yet, there is not a single exemplary disclosure of a targeting moiety comprising an antibody fragment of any kind, let alone a targeting moiety comprising an antibody fragment comprising this specific portion of SEQ ID NO: 2 and the full sequence of SEQ ID NO: 71.

No known antibody fragment would be made up of only the claimed sequences. As Dr. Hale explains, he is not aware of the minimum antibody fragment covered by this claim—an antibody fragment targeting moiety that is made up of only amino acids 1-119 of SEQ ID NO: 2 and the entirety of SEQ ID NO: 71—ever being made or referred to in the literature. EX1003, ¶119. Indeed, as far as Dr. Hale

is aware, many of the claimed molecules have never been produced before 2010 (and to this day, have never been produced). *Id.*, ¶182.

Instead, there is only a single prophetic disclosure of a fusion protein that falls within the scope of claim 1 by comprising amino acids 1-119 of SEQ ID NO: 2, SEQ ID NO: 71 and SEQ ID NO: 87—the fusion protein with a full-length antibody targeting moiety that is disclosed in Figure 3. *Id.*, ¶¶94-99, 120-22. This single disclosure is insufficient to enable the full breadth of claim 1. Of note, this example is of a full-length antibody targeting moiety, not an antibody fragment. This example also does not approximate the myriad of other full length antibody fusion proteins that are covered by claim 1, and provides no guidance on the entire class of antibody targeting moiety fragments also covered by claim 1. *Id.* ¶¶167-71. At most, Figure 3 represents a single prophetic example of one species within the immense subgenus of molecules covered by claim 1. *Amgen*, 598 U.S. at 610–16 (lack of enablement where specification disclosed limited number of exemplary antibodies but claimed entire functional genera); *Baxalta Inc. v. Genentech, Inc.*, 81 F.4th 1364-67 (Fed. Cir. 2023) (lack of enablement for broad functional claims where specification disclosed 11 working examples of antibodies); *Idenix*, 941 F.3d at 1161 (“Where, as here, working examples are present but are ‘very narrow, despite the wide breadth of the claims at issue,’ this factor weighs against enablement.” (citation omitted)).

While broadly disclosing genera of fusion proteins, the '968 Patent strikingly provides no clear instruction or direction on how to make any of the molecules claimed in claim 1, including the prophetic example disclosed in Figure 3. The '968 Patent attempts to refer the POSA to “methods known in the art” and “familiar to one of skill in the art,” but this fails for several reasons. *E.g.*, EX1001, 37:34-35; *id.*, 38:34-36 (“Any methods and materials similar or equivalent to those described herein can be used in the practice or testing of the invention.”). First, “a patentee ‘cannot simply rely on the knowledge of a [POSA] to serve as a substitute for the missing information in the specification.’” *Enzo*, 928 F.3d at 1348 (citation omitted). Second, the description of so-called known and familiar methods in the '968 Patent creates more confusion than clarifying instruction. In short, the '968 Patent provides a POSA with no actual guidance on how to generate any isolated molecule within the vast subgenus of claim 1. EX1003, ¶¶157-64.

For instance, the '968 Patent provides no useful instruction on how to design the DNA constructs required to make such fusion proteins in cells, or how to introduce the constructs into a cell so that the antibody fusion proteins are properly expressed by the cell. Indeed, as Dr. Hale describes, it is unclear that the singular reference to an antibody-producing cell line in the specification (at 35:54-55) could produce a fusion protein, and at best, would be a cell line a POSA would be unfamiliar with using for such a task. EX1003, ¶¶157-58.

The limited description of protein synthesis described in the '968 Patent also appears to be inaccurate and would likely confuse a POSA, compounding the uncertainty. *Id.*, ¶159. As Dr. Hale explains, the '968 Patent's description of polypeptide synthesis methods is misleading to the extent it suggests that the claimed fusion proteins can be made via these methods. *Id.* For instance, to Dr. Hale's knowledge, one of the *preferred* methods cited in the specification—solid-phase Merrifield-type synthesis (at 37:4-10)—has never been used to make such complex polypeptides. *Id.* To the extent these methods were attempted, a POSA would be skeptical of their success in making a viable peptide, their ability to make them to the required level of purity, and their ability to make them without extensive, and therefore undue, experimentation. *Id.* A POSA would view the limited description of protein synthesis described in the '968 Patent with caution, and would likely find the description more confusing than instructive. *Id.*

The lack of clarity with the examples and methods referred to in the '968 Patent is further evidenced by the patentee's attempt to refer the POSA to examples of antibodies. The specification states: "Examples of antibodies include those disclosed in U.S. Pat. Nos. 5,736,167, 7,060,808, and 5,821,337." EX1001, 30:10-12. The first referenced patent in this sentence is titled "Mold Device for Making Safety Shoe." EX1045, cover. The '968 Patent's reference to this patent appears to be a miscite as the term antibody is not found once in this patent. EX1045.

The '968 Patent not only fails to provide guidance on how to make the claimed molecules, it adds to the uncertainty to this already unpredictable field. EX1003, ¶¶63-67, 178-83. In his declaration, Dr. Hale explains his significant personal experience trying to make and test fusion proteins and how unpredictable this field is with respect to both production and functionality. *Id.*, ¶¶63-67. In his experience, he was able to make certain fusion proteins, but others proved extremely difficult to make and some unable to ever be made for unapparent reasons. *Id.* Dr. Hale further explains how the unpredictability he personally encountered with fusion proteins accords with the difficulties emphasized in the literature. *Id.*, ¶¶63-67, 178-79, 183; *Amgen*, 598 U.S. at 610–13 (failure to teach how to make claimed antibodies across scope rendered claims not enabled); *Baxalta*, 81 F.4th at 1364-67.

ii. Lack of Clear Guidance on, and Unpredictability of, Identifying Whether They “Specifically Bind [EGFR]”

Second, in addition to the '968 Patent's lack of guidance on how to make any molecule claimed by claim 1, the '968 Patent fails to provide a POSA with any working examples or guidance on how to determine if such a molecule ***satisfies the functional requirement*** of claim 1 that the targeting moiety “specifically binds [EGFR].” Where the scope of the claims is large, few to no working examples are disclosed, and the only guidance to practice “the full scope of the invention [is] to use trial and error to narrow down the potential candidates to those satisfying the claims’ functional limitations—the asserted claims are not enabled.” *Baxalta Inc. v.*

Genentech, Inc., 579 F. Supp. 3d 595, 615-16 (D. Del. 2022) (Dyk, J., sitting by designation), *aff'd* 81 F.4th 1362 (Fed. Cir. 2023).

The '968 Patent provides no information on how to test this functionality—not even an assay or a working example of how to screen for the targeting moiety binding EGFR as part of the claimed fusion protein. EX1003, ¶172; *Baxalta*, 81 F.4th at 1367 (“[I]t is undisputed that to practice the full scope of the claimed invention, skilled artisans must make candidate antibodies and screen them to determine which ones perform the claimed functions This is the definition of trial and error and leaves the public no better equipped to make and use the claimed antibodies than the inventors were when they set out to discover the antibodies over which they now have an exclusive right.”). Moreover, “a patentee ‘cannot simply rely on the knowledge of a [POSA] to serve as a substitute for the missing information in the specification.’” *Enzo*, 928 F.3d at 1348 (citation omitted).

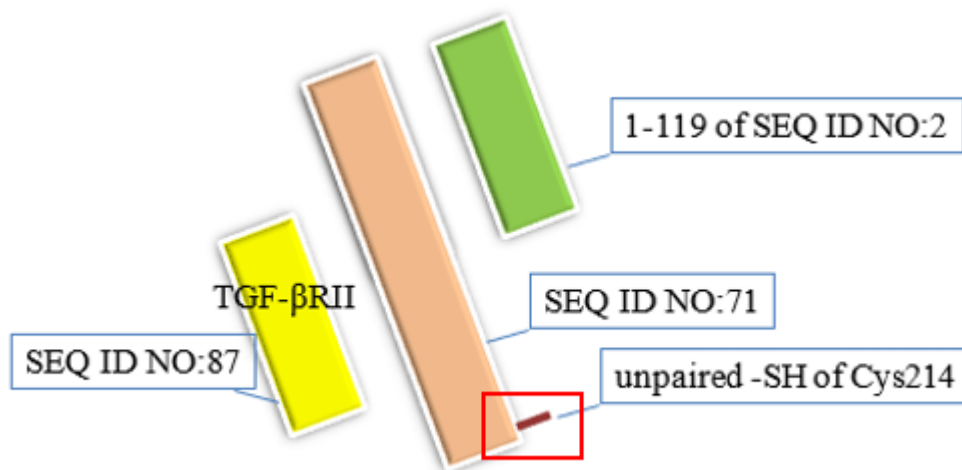
This absence of information is particularly glaring given the inherently unpredictable nature of antibody binding known in the art. EX1003, ¶¶168-71. Antibody-antigen binding is unpredictable by nature, requiring that the antibody targeting moiety having not only specific sequences but also a protein structure to facilitate selective binding of the antigen target. *Id.* This is particularly true when designing fusion proteins, which do not naturally occur in nature. *Id.* Like the unpredictability in making fusion proteins, the functionality of fusion proteins is also

unpredictable, which Dr. Hale explains based on the literature as well as his personal experience. *Id.*, ¶¶63-67, 168-71.

The unpredictability of the art for fusion proteins is exacerbated by the nature of the invention claimed by claim 1. A POSA would not expect that all of the claimed molecules incorporating the two sequence components of the targeting moiety would be able to specifically bind EGFR. EX1003, ¶¶167-71. In particular, the POSA would be concerned that many, if not most, molecules having only the minimal sequence components recited in claim 1 would fail to bind EGFR. *Id.* Here, the common specification provides “no disclosures—such as ‘a quality common to every functional embodiment’ ... —that would allow a skilled artisan to predict which antibodies will perform the claimed functions.” *Baxalta*, 81 F.4th at 1366. Instead, the common specification leaves the POSA with nothing more than the extensive and random trial-and-error experimentation that is undue under *Amgen*. 598 U.S. 594; *Baxalta*, 81 F.4th at 1367 (“Under *Amgen*, such random trial-and-error discovery, without more, constitutes unreasonable experimentation that falls outside the bounds required by § 112(a).”); *Seagen*, 160 F.4th at 1333 (similar).

For example, a POSA would not predict that a minimally claimed molecule would properly dimerize to form a binding pocket—which is the antibody targeting moiety structure required to bind to the antigen, in this case EGFR. EX1003, ¶¶168-69. Similarly, a POSA would not predict that molecules comprising only the

minimal components recited in claim 1 would associate with each other to form the binding pocket, as a molecule with only the minimal components recited in claim 1 would lack a second cysteine residue (normally present in the Fc region of an IgG antibody heavy chain) that facilitates light chain-heavy chain association. *Id.* The figure below depicts the unpaired cysteine residue in red:



EX1003, Fig.D (annotated).

A POSA would also not predict that molecules comprising only the minimal components recited in claim 1 would be able to successfully fold into the secondary protein structure required to function due to the lack of a full IgG heavy chain. *Id.*, ¶169. A POSA would be uncertain as to how the folding process would work in the absence of the majority of the IgG heavy chain sequence. *Id.* Similarly, a POSA would be uncertain that molecules comprising only the minimal components recited in claim 1 would complex together at all. *Id.* A POSA would be further uncertain how the various post-translational modifications that occur during full-length

antibody development would translate to these molecules with only the minimal components and what effect these processes could have on their form and function. *Id.* These uncertainties further exacerbate the issues presented by the complete lack of working examples and guidance on how to determine if such a molecule could in fact bind EGFR as required by the claim and would impose additional experimental burdens on the POSA. *Id.*, ¶¶167-73.

**(c) Taken Together with the Quantity of Experimentation
Necessary (*Wands* Factor 1), Undue Experimentation Would
Be Required to Practice the Full Scope of Claim 1**

The analysis of the *Wands* factors above coupled with the amount of experimentation necessary to practice the full scope of claim 1 demonstrates that claim 1 of the '968 patent is not enabled. In light of the varied and broad subgenus of molecules claimed in claim 1 of the '968 Patent, the lack of guidance and working examples in the specification for either making or testing any of the claimed molecules, the inherent uncertainty in the art for the nature of this invention, and the amount of experimentation required, a POSA would not be able to make and use the full scope of the claimed invention without undue experimentation.

The extent to which a POSA would have to conduct undue experimentation to practice the full scope of claim 1 is illustrated in Dr. Hale's declaration. EX1003, ¶¶167-73, 186. As Dr. Hale describes, for a POSA to determine whether a single molecule falls into the scope of claim 1, the POSA would have to engage in at least

a 9-step process including designing the initial manner in which the molecule would be expressed, designing the system to express the molecule, producing and properly purifying the molecule, and assaying the molecule to determine whether it can specifically bind to EGFR as required by claim 1. *Id.* Each of these 9 steps requires weighing multiple factors that would require decision-making from the POSA and trial and error to determine how to conduct the step successfully. *Id.*

To take just one example, a POSA would have to decide not only what kind of expression vector (DNA introduced into cells to provide them with the instructions to make the claimed molecule) and its exact contents, but also what type of cells to use to make the claimed molecule. *Id.*, ¶172(B)-(C); *id.*, ¶71. The POSA would then have to conduct an experiment to determine whether the cells are capable of making the claimed molecule using that particular expression vector, and to the extent they could not would have to troubleshoot any of 1) the expression vector, 2) the design of the expression vector, and 3) the cell line used to determine what the issue is. *Id.*, ¶172. Similar interrelated experimenting would have to be conducted for all of the steps in this process, presenting a POSA with an extensive matrix of design choices to navigate with next to no guidance or instruction from the specification. *Id.*, ¶¶167-73, 186.

Additionally, the lack of guidance is accentuated by the inherent unpredictability of the art. EX1003, ¶¶63-67, 168-71, 178-83. The same

unpredictability with regard to EGFR binding discussed above applies here as well, and would require additional experimentation from the POSA to navigate. *Supra* Section VI.B.1.(b).ii. Even with a research plan such as the one outlined by Dr. Hale—using no information from the specification, a POSA would need to undertake extensive experimentation to attempt to actually create a molecule as claimed in claim 1. And a POSA would have to do the same amount of experimentation for *each* molecule covered by claim 1.

In light of the breadth of claim 1, the unpredictable nature of the art, the lack of guidance to a POSA on how to practice claim 1, and the resulting experimental demand amounting to undue experimentation, claim 1 of the '968 patent is therefore unpatentable for lack of enablement.

2. Dependent Claim 2 Is Not Enabled

Claim 2 narrows the scope of independent claim 1 by limiting the targeting moiety to an antibody fragment selected from a Fab or an scFv. This narrowing, however, does not cure the fundamental enablement defects discussed above for claim 1. Although claim 2 excludes full-length antibodies, it still encompasses a broad subgenus of antibody fragment-based targeting moieties that the common specification does not enable a POSA to make and use without undue experimentation.

While claim 2 narrows the breadth of the claims (*Wands* factor 8), the claims remain expansive. EX1003, ¶¶165, 175-76. Claim 2 still covers any Fab or scFv targeting moiety that satisfies the requirements of claim 1, including the presence of amino acids 1-119 of SEQ ID NO: 2, the full sequence of SEQ ID NO: 71, and the immunomodulatory moiety comprising SEQ ID NO: 87. As discussed above (Section VI.B.1.(a)), this still encompasses a wide array of possible molecular architectures, orientations, and modes of association, none of which are specified or constrained by the claims.

Additionally, the common specification does not disclose a single working example or prophetic example of a Fab or scFv targeting moiety at all, much less a Fab or scFv incorporating the three specific claimed components of claim 1 (amino acids 1-119 of SEQ ID NO: 2, SEQ ID NO: 71, and SEQ ID NO: 87). EX1003, ¶¶135-37, 165, 185. All disclosed antibody-based targeting moieties in the specification are full-length antibodies. *Id.*, ¶165. The complete absence of any disclosure directed to Fab or scFv formats weighs heavily against enablement under *Wands* factors 2 and 3 (lack of guidance and lack of examples), particularly given the acknowledged unpredictability of antibody fragment design and function. *Amgen*, 598 U.S. at 610–16 (lack of enablement even when specification disclosed limited number of exemplary antibodies); *Baxalta*, 81 F.4th at 1364-67 (similar); *Enzo*, 928 F.3d at 1348-50.

Moreover, one of the embodiments ostensibly encompassed by claim 2 is internally contradictory and scientifically incoherent: an scFv comprising SEQ ID NO: 71 as a full light chain. As understood by a POSA, an scFv consists solely of the variable regions of the heavy and light chains joined by a linker peptide—meaning it expressly excludes constant regions. However, SEQ ID NO: 71 is referred to in the '968 Patent as the full light chain sequence that includes both variable and constant domains. This contradiction not only renders claim 2 improperly dependent and indefinite (as addressed in Section VII.A), but also underscores the lack of meaningful guidance to a POSA attempting to practice the full scope of claim 2. A POSA would be left to guess how to reconcile these apparently incompatible structural requirements, further exacerbating the need for undue experimentation. EX1003, ¶¶187-93.

Finally, aside from the narrowing of claim scope, all other *Wands* factors discussed above for claim 1 apply with equal force to claim 2. The art remains unpredictable; the specification provides no instruction on how to construct, express, assemble, or test Fab or scFv-based fusion molecules with the claimed components; and there is no guidance on how to determine whether any such molecule would specifically bind EGFR as required. EX1003, ¶¶135-37, 157-65, 172, 174-86. A POSA would still be required to engage in extensive experimentation across multiple

design variables simply to determine whether any given Fab or scFv embodiment falls within the claim. *Id.* Claim 2 is therefore unpatentable for lack of enablement.

3. Dependent Claims 3, 4, and 8 Are Not Enabled

Claims 3, 4, and 8 further narrow the scope of claim 2 by limiting the antibody fragment-based targeting moiety to particular component configurations. Specifically, claim 3 recites that the antibody fragment comprises a light chain domain or a variable heavy chain domain; claim 4 further limits the molecule of claim 3 to include a light chain domain comprising the amino acid sequence of SEQ ID NO: 71; and claim 8 further limits the molecule of claim 3 to include a variable heavy chain domain comprising amino acids 1-119 of SEQ ID NO: 2. While these limitations further narrow the breadth of the claims (*Wands* factor 8), they do not render the claimed subgenus enabled. EX1003, ¶¶165, 175-76.

As described above (Section VI.A.1), the common specification does not disclose any working or prophetic examples of *any* antibody fragment comprising only a light chain domain, only a variable heavy chain domain, or any combination thereof covered by claims 3, 4, and 8. EX1003, ¶¶138-39. As discussed above, every disclosed antibody-based targeting moiety in the specification is a full-length antibody. The specification provides no guidance on how to design, assemble, express, or validate antibody fragments limited to only one chain or one variable region, let alone fragments incorporating the specific claimed sequences. *Id.*, ¶¶138-

39, 157-65, 167-71. The complete absence of examples weighs strongly against enablement under *Wands* factors 2 and 3. *Cf. Idenix*, 941 F.3d at 1161 (“Where, as here, working examples are present but are ‘very narrow, despite the wide breadth of the claims at issue,’ this factor weighs against enablement.” (citation omitted)).

Moreover, one embodiment encompassed by claims 3, 4, and 8 is internally contradictory and highlights the lack of meaningful guidance provided by the specification. As explained below (Section VII.B), claim 3 contradicts claim 1 by requiring that the antibody fragment have a complete light chain *or* a variable heavy chain domain, but not both, but both is covered by claim 1. This contradiction not only renders the claims improperly dependent and indefinite, as discussed below, but also reinforces the absence of a coherent, enabled disclosure that would allow a POSA to practice the full scope of the claims. EX1003, ¶¶194-98.

Additionally, the specification provides no instruction as to how an antibody fragment comprising only a single light chain or single variable heavy chain domain could function as a targeting moiety that specifically binds EGFR, as required by the claims. As explained above (Section VI.B.1.(b).ii), antigen binding by antibodies depends on the paired interaction of heavy and light chain variable regions to form a binding pocket. The claims here encompass fragments that lack one of these essential components, yet the specification provides no guidance on how such fragments could be made functional, stabilized, expressed, or tested. EX1003,

¶¶167-72. This absence of guidance is particularly significant given the unpredictable nature of antibody structure-function relationships and fusion protein engineering (*Wands* factors 4 and 7). *Amgen*, 598 U.S. at 610–16 ; *id.* at 600 (“aspects of antibody science remain unpredictable”); *Baxalta*, 81 F.4th at 1364-67; *Enzo*, 928 F.3d at 1348-50 (similar).

Finally, beyond the narrowing of claim scope, the remaining *Wands* factors continue to weigh decisively against enablement. The specification offers no direction on how to make or use the claimed antibody fragments; no assays or criteria for determining EGFR binding; no discussion of expected success rates; and no roadmap for navigating the extensive experimentation that would be required to practice the full scope of the claims. EX1003, ¶¶167-86. A POSA would be required to engage in undue experimentation simply to determine whether any given embodiment falling within claims 3, 4, or 8 could be successfully constructed and would meet the functional limitations of the claims. *Id.* Accordingly, claims 3, 4, and 8 are not enabled.

4. Dependent Claims 5-7 Are Not Enabled

Claims 5-7 further narrow the scope of the asserted subgenus by introducing a specific polypeptide linker and by requiring that the linker be fused to the light chain domain and the immunomodulatory moiety in particular orientations. Claim 5 further limits claim 4 by requiring a polypeptide linker comprising the amino acid

sequence of SEQ ID NO: 104; claim 6 further limits claim 5 by requiring that the light chain domain comprising SEQ ID NO: 71 be fused to the N-terminus of that linker; and claim 7 further limits claim 6 by requiring that the immunomodulatory moiety comprising SEQ ID NO: 87 be fused to the C-terminus of the linker. While these limitations narrow the breadth of the claims (*Wands* factor 8), they do not cure the specification's fundamental enablement deficiencies. EX1003, ¶¶165, 175-76.

As with the claims discussed above, the common specification does not disclose a single working or prophetic example of a light chain-linked antibody construct, nor a light chain-linked Fab or scFv incorporating the claimed sequences. *Supra* Section VI.A.2.(d); EX1003, ¶¶140-46. All disclosed antibody-based targeting moieties in the specification are full-length antibodies, and none are described as being linked through the light chain, much less through a defined linker sequence in a specified orientation. *Id.*, ¶¶140-46, 153-54, Appx.C. In particular, the fusion protein disclosed in Figure 3 of the common specification is a full-length antibody targeting moiety that is linked through the heavy chain. *Id.*, ¶¶94-98, 153. The complete absence of any disclosure addressing light chain-linked antibody in the common specification weighs heavily against enablement under *Wands* factors 2 and 3. *Id.* ¶¶146, 153-54, 157-66, 184-85.

Moreover, the specification provides no guidance to a POSA regarding whether, or how, fusing a linker to the light chain domain would affect folding,

stability, assembly, protein secretion, or antigen binding. Light chain-linked constructs present distinct structural and functional challenges compared to conventional antibody or fusion protein designs, yet the specification offers no discussion of these challenges, no design principles to address them, and no indication that the inventors had successfully contemplated or reduced such constructs to practice. EX1003, ¶¶62-67, 166, 169. This lack of guidance is particularly significant given the acknowledged unpredictability of antibody fragment engineering and fusion protein design (*Wands* factors 4 and 7). *Id.*, ¶¶62-67, 167-73, 183.

Additionally, the remaining *Wands* factors continue to weigh strongly against enablement. The specification provides no instruction on how to construct or express the claimed linker-containing molecules; no examples demonstrating that such constructs can be made to function; and no assays or criteria for determining whether the resulting molecules would specifically bind EGFR as required by the claims. *Id.*, ¶¶167-73, 177-86. A POSA would therefore be required to engage in extensive experimentation across multiple variables such as linker placement, orientation, expression systems, and folding behavior simply to determine whether any embodiment within the scope of claims 5-7 is operable. Accordingly, claims 5-7 are not enabled.

5. Independent Claim 9 Is Not Enabled

Independent claim 9 is not enabled for the same reasons discussed above for independent claim 1 and dependent claims 5-7. Claim 9 recites additional structural detail requiring: (a) a targeting moiety antibody fragment that binds EGFR comprising a light chain domain comprising SEQ ID NO: 71 and a variable heavy chain domain comprising amino acids 1-119 of SEQ ID NO: 2; (b) an immunomodulatory moiety comprising SEQ ID NO: 87; (c) a polypeptide linker of SEQ ID NO: 104 that is connected through a specific orientation to the light chain. However, these additional structural limitations do not cure the specification's failure to enable the full scope of the claimed invention without undue experimentation. EX1003, ¶¶166, 174-86.

While the breadth of claim 9 is narrower relative to claim 1—for instance by limiting the targeting moiety to an antibody fragment, specifying a particular linker (SEQ ID NO: 104) and defined fusion orientations—the scope of claim 9 remains substantial (*Wands* factor 8). *Id.*, ¶¶166, 175-76. Claim 9 still encompasses antibody fragment-based fusion molecules that must be designed, assembled, expressed, folded, and validated to functionally bind EGFR, but the specification provides no guidance or working examples sufficient to enable a POSA to accomplish these tasks across the full scope of the claim. *Id.*, ¶¶166-86.

Critically, the common specification does not disclose any working or prophetic examples of an antibody fragment comprising the claimed components in the configuration required by claim 9. *Id.*, ¶¶150-54. The specification contains no guidance or examples of: (i) an antibody fragment incorporating SEQ ID NO: 71 and amino acids 1-119 of SEQ ID NO: 2; (ii) antibody fragments linked through the light chain domain; and (iii) antibody fragment-based fusion proteins incorporating the claimed linker sequence and orientations. *Id.* As discussed above (Section VI.A.1), all disclosed antibody-based targeting moieties in the specification are full-length antibodies. The complete absence of any guidance or example approximating the claimed architecture weighs heavily against enablement under *Wands* factors 2 and 3. *Id.* ¶¶150-54, 157-66, 184-85.

Further, the specification provides no instruction to a POSA on how to construct or express an antibody fragment comprising both a light chain domain and a truncated variable heavy chain domain in the claimed configuration, nor does it explain how such a construct would assemble into a functional antigen-binding structure. *Id.*, ¶¶167-73, 177-86. As explained above (Section VI.B.1.(b).ii), antibody binding depends on precise pairing and folding of heavy and light chain variable regions. Claim 9 requires a non-standard antibody fragment architecture that departs from conventional full-length antibodies and well-characterized antibody fragments, yet the specification offers no guidance on how to ensure proper

folding, stability, secretion, or assembly of such a construct. EX1003, ¶166. This lack of guidance is particularly significant given the unpredictable nature of antibody fragment engineering and fusion protein design (*Wands* factors 4 and 7).

Additionally, the specification provides no guidance on how to determine whether a molecule within the scope of claim 9 “specifically binds” EGFR, as required by the claim. The specification does not disclose any binding assays, acceptance criteria, or experimental benchmarks for assessing EGFR binding by antibody fragment-based fusion proteins. *Supra* Section VI.B.1.(b).ii. As with claim 1, a POSA would be forced to rely on extensive experimentation simply to determine whether any given embodiment within the scope of claim 9 satisfies the functional limitation of EGFR binding (*Wands* factors 1 and 2).

Finally, as discussed above for claims 5-7 (Section VI.A.2.(d)), the specification provides no guidance regarding the functional consequences of linking the immunomodulatory moiety to the light chain domain via a defined linker in a specified orientation. The specification does not address whether such a configuration would interfere with antigen binding, folding, or stability, nor does it provide any examples demonstrating that such constructs are viable. A POSA would therefore be required to engage in extensive experimentation to assess linker placement, orientation, expression systems, and folding behavior, further

underscoring the undue experimental burden required to practice the full scope of claim 9. EX1003, ¶¶140-46.

Accordingly, notwithstanding the additional structural detail recited in claim 9, the specification fails to teach a POSA how to make and use the full scope of the claimed invention without undue experimentation. Claim 9 is unpatentable for lack of enablement.

VII. GROUNDS 3-6: CLAIMS 2-8 ARE UNPATENTABLE FOR IMPROPER DEPENDENCY UNDER § 112(d) AND INDEFINITENESS UNDER § 112(b)

Claims 2-8 are unpatentable for improper dependency and indefiniteness because claims 2 and 3 contradict, and do not narrow, the respective claim(s) from which they depend, resulting in nonsensical claims. The claims which depend from claims 2 and 3, respectively, are unpatentable for the same reasons. *E.g., Samsung Elecs. Co. v. Ouraring, Inc.*, PGR2024-00030, Paper-57, at 53-54 (PTAB Nov. 25, 2025); *In re Gamble*, 2025 WL 1341621, at *3 (Fed. Cir. May 8, 2025).

Under 35 U.S.C. § 112(d), “[a] claim in dependent form shall be construed to incorporate by reference all the limitations of the claim to which it refers.” Section 112(d) further requires that “a claim in dependent form shall contain a reference to a claim previously set forth and then specify a further limitation of the subject matter claimed.” *Id.* A dependent claim is invalid if it “does not narrow the scope of” the claim it depends upon. *Pfizer, Inc. v. Ranbaxy Lab ’ys. Ltd.*, 457 F.3d 1284, 1291-

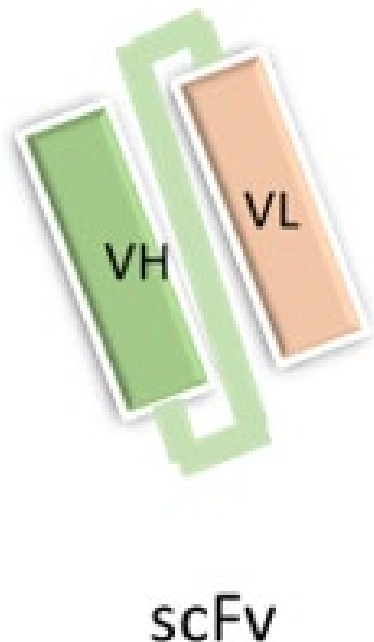
92 (Fed. Cir. 2006); *Alcon Research, Ltd. v. Apotex Inc.*, 687 F.3d 1362, 1367 (Fed. Cir. 2012); *Samsung*, PGR2024-00030, Paper-57, at 53-54. Indeed, “[a] dependent claim that contradicts, rather than narrows, the claim from which it depends is invalid.” *Multilayer Stretch Cling Film Holdings, Inc. v. Berry Plastics Corp.*, 831 F.3d 1350, 1362 (Fed. Cir. 2016) (dependent claim invalid where “[i]ndependent claim 1 excludes LDPE from the inner layers, while dependent claim 10 includes it”).

A claim is indefinite under 35 U.S.C. § 112(b) if it fails to “inform those skilled in the art about the scope of the invention with reasonable certainty.” *Nautilus, Inc. v. Biosig Instruments, Inc.*, 572 U.S. 898, 910 (2014). Claims that are “contradictory” or “nonsensical” are indefinite. *In re Shafovaloff*, 2025 WL 1779173, *1-2 (Fed. Cir. June 27, 2025) (“Contradictory limitations within a single claim or between different claims can render a claim indefinite.”); *Trs. of Columbia Univ. v. Symantec*, 811 F.3d 1359, 1367 (Fed. Cir. 2016). “[S]emantic indefiniteness of claims ‘is not rendered unobjectionable merely because it *could* have been corrected.’” *Allen Eng’g Corp. v. Bartell Indus.*, 299 F.3d 1336, 1349 (Fed. Cir. 2002) (citation omitted). Indeed, “it is not [the court’s] function to rewrite claims to preserve their validity,” including claims that are otherwise “nonsensical.” *Synchronoss Techs., Inc. v. Dropbox, Inc.*, 987 F.3d 1358, 1366-67 (Fed. Cir. 2021) (citation omitted) (claims indefinite as “nonsensical and require[ing] impossibility”).

A. Grounds 3-4: Claims 2-8 Are Improperly Dependent and Indefinite

Claim 2 is invalid for improper dependency because it does not incorporate all the limitations of claim 1 nor specify a further limitation. Instead of narrowing, claim 2 contradicts claim 1. Claim 1 requires a targeting moiety comprising an antibody or antibody fragment “comprising [i] amino acids 1-119 of SEQ ID NO: 2 and [ii] the amino acid sequence of SEQ ID NO: 71.” The ’968 Patent refers to SEQ ID NO: 71 as the full light chain domain, including both the variable region *and constant region*. EX1001, Fig. 3; *id.*, claim 9; EX1003, ¶¶95-100. Figure 3 makes clear that SEQ ID NO: 71 contains both a variable region (underlined) and constant region (plain).

Claim 2 depends directly from claim 1 and recites “wherein the targeting moiety comprises an antibody fragment selected from a Fab or scFv.” As discussed above (Section V.A), properly construed, the plain and ordinary meaning of “scFv” is a “single-chain variable fragment consisting of only the variable regions of the heavy and light chains joined by a linker peptide.” EX1003, ¶¶108-11; EX1001, 34:42. This well-understood antibody fragment is depicted in the following figure:



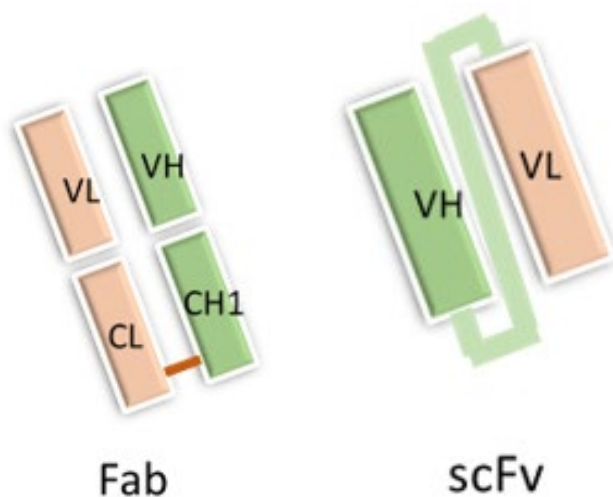
EX1003, Fig.B (excerpted). A POSA would understand an “scFv” to exclude the constant regions of the light and heavy chains. EX1003, ¶¶107-110. By claiming an scFv, which excludes the constant region of the heavy chain, claim 2 contradicts claim 1. *Id.*, ¶¶190-92. The antibody fragment of claim 1 covers the full light chain of SEQ ID NO. 71, including the constant region, while the scFv antibody fragment of claim 2 excludes the constant region. *Id.*

Claim 2 violates § 112(d) because it does not incorporate all the limitations of claim 1 nor specify a further limitation. Claim 2’s contradiction of claim 1 also renders claim 2 indefinite. The contradictory requirements make claim 2 nonsensical and fail to inform a POSA about the scope of the invention with reasonable certainty. EX1003, ¶¶190-93, 199-201.

Thus, claim 2 is unpatentable as both improperly dependent and indefinite. Claims 3-8, which depend from claim 2, are unpatentable for the same reasons. *Id.*

B. Grounds 5-6: Claims 3-8 Are Improperly Dependent and Indefinite

Claim 3 depends directly from claim 2, which itself depends directly from claim 1. Claim 3 recites “The molecule of claim 2, wherein the antibody fragment comprises a light chain domain *or* a variable heavy chain domain” (emphasis added). As explained above (Section VI.A.2.(a)), claim 1 covers an antibody or antibody fragment that comprises *both* amino acids 1-119 of SEQ ID NO: 2 (which is described as the variable heavy chain domain) *and* SEQ ID NO: 71 (which is described as the complete light chain). Additionally, claim 2 requires that the antibody fragment be a Fab or scFv, both of which require at a minimum the presence of the variable light chain domain (VL) and the variable heavy chain domain (VH), as depicted below:



EX1003, Fig.B (excerpted).

Claim 3 contradicts the requirements of claims 1 and 2 by specifying that the claimed antibody fragment comprises “a light chain domain *or* a variable heavy chain domain” (emphasis added). As discussed above (Section V.B), properly construed, the term “or” in claim 3 is used in its common usage designating alternatives. In other words, ‘or’ in claim 3 means “either/or,” not “one or both.”

Claim 3 contradicts claim 1 by requiring that the antibody fragment have a complete light chain *or* a variable heavy chain domain, but not both, while claim 1 covers the presence of sequences that are described as both. EX1003, ¶¶194-95. Claim 3 likewise contradicts claim 2, which requires an antibody fragment with at least both the variable light chain domain and variable heavy chain domain. *Id.*, ¶196.

Claim 3 violates § 112(d) because it does not incorporate all the limitations of claims 1 and 2 nor specify a further limitation. Claim 3’s contradiction of claims 1 and 2 also renders claim 3 indefinite. The contradictory requirements make claim 3 nonsensical and fail to inform a POSA about the scope of the invention with reasonable certainty. EX1003, ¶¶194-201.

Thus, claim 3 is unpatentable as both improperly dependent and indefinite. Claims 4-8, which depend from claim 3, are unpatentable for the same reasons. *Id.*

VIII. PETITIONER'S MANDATORY NOTICES**A. Real Parties-in-Interest (37 C.F.R. § 42.8(b)(1))**

The real party in interest is the Petitioner, Bicara Therapeutics, Inc.

B. Related Matters (37 C.F.R. § 42.8(b)(2))

Petitioner in this action is currently a party in a pending litigation: *Y-Trap, Inc. v. Biocon Ltd. and Bicara Therapeutics, Inc.*, No. 1:24-cv-12678 (D. Mass.). In this litigation, the '968 Patent is not being asserted for infringement nor is its validity being challenged. However, Defendant Biocon Ltd. has brought a counterclaim seeking correction of inventorship of certain U.S. patents, including the '968 Patent, pursuant to 35 U.S.C. § 256. None of the grounds of unpatentability raised in this Petition will be addressed or decided in the district court litigation.

Petitioner is not aware of any *ex parte* or *inter partes* reexaminations for or petitions for *inter partes* or post-grant review of the '968 Patent. Petitioner is further not aware of any patent application or patent claiming the benefit of the priority of the filing date of the '968 Patent.

C. Lead and Back-up Counsel (37 C.F.R. § 42.8(b)(3))

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D. Service Information (37 C.F.R. § 42.8(b)(4))

Petitioner consents to service via email at the email addresses listed above for lead and back-up counsel for Petitioner.

IX. CONCLUSION

Petitioner respectfully requests Trial be instituted and all claims of the '968 Patent be cancelled as unpatentable for the above grounds.

Dated: February 10, 2026

Respectfully Submitted,

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APPENDIX A – LISTING OF INDEPENDENT CLAIMS ('968 PATENT)

1. An isolated molecule comprising:
 - (a) a targeting moiety comprising an antibody or antibody fragment thereof, comprising amino acids 1-119 of SEQ ID NO: 2 and the amino acid sequence of SEQ ID NO: 71, which specifically binds Epidermal Growth Factor Receptor (EGFR); and
 - (b) an immunomodulatory moiety comprising an amino acid sequence of the extracellular domain of Transforming growth factor-beta receptor II (TGF- β RII) comprising the amino acid sequence of SEQ ID NO: 87.

9. An isolated molecule comprising:
 - (a) a targeting moiety comprising an antibody fragment which specifically binds Epidermal Growth Factor Receptor (EGFR) comprising a light chain domain comprising the amino acid sequence of SEQ ID NO: 71 and a variable heavy chain domain comprising amino acids 1-119 of SEQ ID NO: 2;
 - (b) an immunomodulatory moiety comprising an amino acid sequence of the extracellular domain of Transforming growth factor-beta receptor II (TGF- β RII) comprising the amino acid sequence of SEQ ID NO: 87; and
 - (c) a polypeptide linker comprising the amino acid sequence of SEQ ID NO: 104;

wherein the light chain domain comprising the amino acid sequence of SEQ ID NO:

71 is fused to an N-terminus of the polypeptide linker comprising the amino acid of SEQ ID NO: 104, and

wherein the immunomodulatory moiety comprising the amino acid sequence of SEQ ID NO: 87 is fused to a C-terminus of the polypeptide linker comprising the amino acid sequence of SEQ ID NO: 104.

CERTIFICATE OF COMPLIANCE

I hereby certify that this petition complies with the type-volume limitations of 37 C.F.R. § 42.24 (a)(1)(ii) (“18,700 words”) because it contains 18,577 words (as determined by the Microsoft Word word-processing system used to prepare the petition), excluding the parts of the petition exempted by 37 C.F.R. § 42.24(a)(1).

Dated: February 10, 2026

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*Counsel for Petitioner Bicara
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CERTIFICATE OF SERVICE

I hereby certify that on February 10, 2026, a copy of this Petition, including all exhibits, and a copy of Petitioner's Power of Attorney and Designation of Lead and Back-Up Counsel has been served in its entirety by FedEx Express Next Business Day Delivery on the following correspondence address of record for Patent Owner as listed on Patent Center:

100899 - The John Hopkins University
c/o DLA Piper LLP (US)
4365 Executive Drive, Suite 1100
San Diego, CA 92121-2133
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Dated: February 10, 2026

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